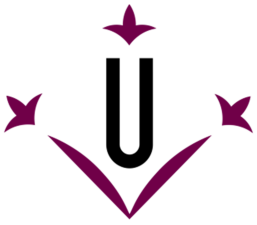

INTEGRAL PHARMACOLOGICAL MANAGEMENT OF BONE MINERAL DISORDERS IN CHRONIC KIDNEY DISEASE (part II): *From treatment of phosphate imbalance to control of PTH and prevention of progression of cardiovascular calcification*

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ABSTRACT

INTRODUCTION: Chronic kidney disease-mineral and bone disorders (CKD-MBD) are associated with costly complications and dismal hard-outcomes.

AREAS COVERED: In two comprehensive articles we review contemporary and future pharmacological options for treatment of phosphate (P) imbalance (part 1) and hyperparathyroidism (this part 2), taking into account CKD-accelerated cardiovascular calcification (CVC) processes.

EXPERT OPINION: Improvements in CKD-MBD require an integral approach, addressing all three components of the CKD-MBD triad. Here, initial guidance to control hyperparathyroidism is provided, taking into account the presence/absence of CVC. We include also measures for patients at risk of adynamic bone disease or suffering from calciphylaxis. Many epidemiological studies (relating to vitamin D) and thorough analyses of recent randomized clinical trials (of cinacalcet) point towards benefits of attempting to improve biochemical parameters while trying to, at least, avoid progression of CVC by more rational use of intestinal P-binders and low-dose vitamin D derivatives and/or calcimimetics. This approach does not seem to be far away from significantly improving hard-outcomes, at least in the dialysis population. The availability of new drugs and the performance of randomized clinical trials should ultimately lead to define earlier, clearer, and more cost-effective patient stratification and biochemical targets with consequent significant clinical improvements.

1) INTRODUCTION

As previously mentioned in part 1 of this review[1], accelerated atherosclerosis and premature ageing are closely associated with chronic kidney disease (CKD) and particularly with end-stage renal disease (ESRD)[2–5]. The term chronic kidney disease-mineral and bone disorder (CKD-MBD) was introduced eleven years ago to define a triad of laboratory and bone abnormalities and tissue (mainly vascular) calcifications, all of which are linked to poor hard-outcomes [6,7]. Currently, bone is considered a new endocrine organ at the heart of CKD-MBD, while there is ongoing controversy as to whether CKD-MBD should be regarded as a real syndrome or not[8,9].

The increasing availability of new phosphate (P)-binders (reviewed in reference 1), vitamin D (VD) receptor activators (VDRA) and the innovative development of modulators of the calcium (Ca)-sensing receptor (CaSR) –calcimimetics- have significantly increased our therapeutic armamentarium[10,11]. Furthermore, the appearance of sevelamer and recognition of the fibroblast growth factor-23 (FGF23)/klotho axis have helped to review paradigms in the pathophysiology of secondary hyperparathyroidism (SHPT)[12,13], and to increase awareness of the presence of cardiovascular calcification (CVC) and the need to quantify it[14,15]. These developments have given rise to the concept that CKD-MBD-related drugs such as non-Ca-based P-binders may attenuate the accelerated progression of CVC in CKD patients and potentially improve survival[15–18]. Consequently, other agents such as anti-parathyroid drugs have also been analyzed in this regard.

In order to control the increasing parathyroid hormone (PTH) levels, new VDRA and calcimimetics were introduced that allowed not only medical treatment of previously calcitriol-resistant patients with severe forms of SHPT[19] but also earlier and more effective control of CKD-MBD-related laboratory parameters. Experimental and

clinical studies have also shown that some anti-parathyroid agents may attenuate the progression of CVC[20,21], potentially leading to improved survival[22–24]. The number of parathyroidectomies (PTX) has also markedly dropped[25,26], and it should not be forgotten that PTX (and PTX-related percutaneous injections of ethanol or VD in parathyroid glands) are not exempt from important risks, especially in the perioperative period and during the year after the procedure[27], including permanent hypoparathyroidism.

Against this background, the purpose of this article is to provide an update on the contemporary pharmacological control of PTH in the context of CKD-MBD. The first part focused on agents that aim to control P imbalance and this second part covers anti-parathyroid drugs such as VD derivatives and calcimimetics emphasizing their differential effects not only on biochemical parameters but also on tolerance, CVC, and/or hard-outcomes. Related issues such as the very frequent adynamic bone disease (ABD), usually neglected in drug -reviews, and the rare calciphylaxis will also be briefly discussed.

2) VITAMIN D

SHPT is a common consequence of CKD, which not only leads to bone disease but also plays a role in reducing quality of life and increasing mortality of CKD patients[28–31]. Calcitriol (1,25-$(OH)_2$-VD), as an anti-parathyroid agent, decreases the synthesis of PTH independently of its known hypercalcemic action by acting through its specific receptor (the VD receptor)[32]. The desirable serum PTH target levels and the variability of PTH assays are matters of intense current debate[7,33–38]. For instance, Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that in CKD stage 5 and 5D,

serum PTH levels should be maintained at between 2 and 9 times (2X-9X) the upper normal limits for the used assay[7], based on the poor quality as a biomarker of PTH in relation to underlying renal bone disease[7,36]. Other national guidelines continue to support the 2003 National Kidney Foundation (NKF)/Kidney Dialysis Outcomes Quality Initiative (KDOQI™) recommendation of 150-300 pg/ml (2X-5X)[39,40,35], mainly based on some epidemiological studies describing the lowest mortality rates in this PTH interval [30,31]. Agreement exists regarding the need for treatment when laboratory values show an increasing trend over time, even within the aforementioned ranges, and the fact that values exceeding 9 times the upper normal limit must be avoided because they represent extremes of risk[7,34,39]. As a matter of fact, questions remain about the wide PTH range suggested in the KDIGO guidelines[26,36], and there is concern that the acceptance of "very high" values may negatively impact bone quality, result in the progression of parathyroid glands to uncontrollable monoclonal-growth tumor-like nodular hyperplasia and decrease the efficacy of treatment strategies[36]. In this respect, it is well known that higher than normal serum PTH levels are required to maintain bone remodelling in CKD due to the presence of resistance to the action of PTH[41], while PTH levels above the 150-300 pg/ml range are associated with increases in hospitalizations[26,29] , fractures[29,42,43] and, as mentioned before, mortality rates[30,31].

Recent changes in therapeutic approaches and their impact on outcomes among patients with SHPT on chronic hemodialysis have been described by Tentori et al[26]. Using data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS), these authors analyzed trends in PTH levels and SHPT therapies over the past 15 years and studied the associations between PTH and clinical outcomes. A total of 35,655 participants from the DOPPS phases 1-4 (1996-2011) were included, and it was found that median PTH increased from phase 1 to phase 4 in all regions except Japan, where it

remained stable. Importantly, compared with the 150-300 pg/ml range, in adjusted models all-cause mortality risk was higher for PTH=301-450 pg/ml (hazard ratio, 1.09; 95% CI, 1.01-1.18) and >600 pg/ml (hazard ratio, 1.23; 95% CI, 1.12-1.34). PTH >600 pg/ml was also associated with a higher risk of cardiovascular mortality and all-cause and cardiovascular hospitalizations. Prescriptions of intravenous VDRA (and cinacalcet) increased and PTX rates decreased in all regions over time. In a subgroup analysis of 5,387 patients not receiving anti-parathyroid agents and without prior PTX, very low serum PTH levels (<50 pg/ml) were associated with increased mortality risk (hazard ratio, 1.25; 95% confidence interval, 1.04-1.51).

On the other hand, there are also serious concerns about normalizing serum PTH levels in CKD stages 3-5 since moderate elevations of PTH may serve as a beneficial adaptive response (with improvements in phosphaturia or bone turnover)[36]. All these results underline the urgent need for additional research into PTH targets, both in dialysis and non-dialysis patients, as well as the concomitant use of other risk factors and biomarkers in order to better define appropriately individualized clinical practice. Thus, it seems clear that old protocols using just serum PTH levels for correlation with bone turnover and/or survival are inadequate in terms of sensitivity and specificity. Other factors such as Ca, P, CVC should also be taken into account; nevertheless, in patients with CKD and elevated or rising PTH, it is still suggested that VD derivatives, calcimimetics or a combination thereof may be used to lower PTH (evidence 2B)[7]. Monitoring of alkaline phosphatase activity (especially bone-specific) in combination with PTH may also be helpful to increase specificity[44,45].

2.1) NATIVE VITAMIN D

It is well known that VD deficiency is common both in the general population and in patients with CKD[46,47]. It is usually due, among other factors, to inadequate

exposure to sunlight and/or a VD deficient diet. The importance of its diagnosis has been increasingly recognized because of the reported association between circulating calcidiol levels [25-(OH)-VD, the storage form of VD] and survival in both the general population and dialysis patients[48,49]. In fact, many beneficial pleiotropic effects beyond bone have been attributed to VD and VD receptor activation, including with regard to CKD-MBD laboratory markers, inflammation and even risk of falls (if high doses are avoided)[50,51]. However, to date no definitive proof is available regarding a benefit for hard-outcomes, although the use of cholecalciferol (VD_3), or ergocalciferol (VD_2) (real forms of "native" VD) and 25-(OH)-VD supplementation have been shown to be able to correct calcidiol levels in CKD patients, including those receiving dialysis[52,53]. Thus, calcidiol measurement (and supplementation in deficient states) is recommended for CKD patients in most guidelines[5,7,39,40]. In a retrospective study, treatment with *active* forms of VD significantly abolished the relationship between survival and calcidiol levels[48], and thereby the significance of calcidiol levels in patients treated with active forms of VD remains unclear. The dual combination of cholecalciferol and active VD (e.g. paricalcitol) has also been safely tested in hemodialysis patients[54]. Finally, traditional measures of VD status may need to be revisited to account for levels of VD-binding protein and albumin ("bioavailable VD"), since both can bind circulating VD[55].

2.2) CALCITRIOL AND SELECTIVE VDRA

In CKD, the synthesis of calcitriol by 1-α-hydroxylase is limited by the dual inhibitory and catabolic effect of elevated FGF23 levels and the progressive reduction in renal mass, contributing to the development and progression of SHPT. Calcitriol is also needed to improve the cellular uptake of calcidiol[56]. Consequently, 1-α-hydroxylated alfacalcidol and doxercalciferol (1-α-VD_3 and 1-α-VD_2 pro-hormones, respectively) and

the physiologically active calcitriol represent classical elements of the strategy to prevent and control uremic SHPT. Survival benefits have been consistently associated with the use of different active VD compounds in retrospective studies in CKD, including dialysis patients and even patients with low PTH levels[57–60], highlighting the importance of VDR activation in CKD. Nevertheless, there is still the possibility that unrecognized confounding variables may account for the observed benefits, and the lack of prospective trials diminishes the strength of these results. On the other hand, high doses of VDRA may cause increased serum Ca and P levels, especially in patients with ABD, and increased CVC has commonly been demonstrated in experimental animals with CKD fed high P diets[20,61,62]. *Selective* VDRA (e.g., paricalcitol or maxacalcitol) seem to have more selective effects on the parathyroid glands as compared with bone and the gastrointestinal (GI) tract (decreasing the risk of high serum Ca, Ca x P, and/or P levels)[63–65], as well as reduced experimental procalcifying effects on vessels[20,61,62], thereby theoretically providing a wider therapeutic window as compared with calcitriol[63]. Clinical improvement of endothelial function has also been shown in a small randomized controlled trial (RCT) in which patients with stage 3-4 CKD were treated with paricalcitol (vs placebo)[66]. Nevertheless, it has to be recognized that despite the robustness of the data regarding the beneficial clinical effects of VD, including experimental restoration of klotho, clinical improvement of residual proteinuria in RCTs and meta-analyses, and improved survival in retrospective studies and meta-analyses[67–70], hard-outcome benefits have not been proven and no positive effects on left ventricular hypertrophy have been demonstrated in RCTs (secondary or post-hoc analyses only)[71–73]. Moreover, distinctions among specific vitamin D compounds remain a matter of great controversy[20,68,74,75].

2.3) NEW VDRA

Several VDRA for the treatment of SHPT are in the early stages of development (i.e. CTAP101, CTAP201, 2MD, CTA018/MT2832, CTA091)[10,76]. CTAP101, a modified-release capsule formulation of calcifediol, has been designed to raise serum 25-(OH)-VD in a gradual manner to physiological levels, avoiding excessive induction of CYP24; it has now reached Phase III development in CKD patients with vitamin D insufficiency[77]. Results from a Phase I trial of intravenous CTAP201 in hemodialysis patients revealed decreased PTH levels similar to those obtained with doxercalciferol but with lower serum Ca and P levels[10,78].

Although developed for osteoporosis treatment, 2MD demonstrated reduction of PTH levels without concomitant increases in serum Ca and P in both preclinical and postmenopausal women[79]. Lunacalcipol (CTA018/MT2832) is the first compound in a new class of vitamin D hormone analogs having a novel dual mechanism of action. (http://www.prnewswire.com/news-releases/cytochroma-regains-rights-to-lunacalcipol-156261375.html). Similarly to other compounds such as CTA091, it is a potent CYP24 inhibitor (increasing the half-life of active VD by decreasing its clearance)[76]. Lunacalcipol differs from CTA091 in that it also has the ability to activate VDR-mediated transcription and suppresses PTH synthesis at doses which do not affect experimental Ca and P levels[76]. However, changes in US market dynamics relating to dialysis treatment seem to delay its clinical development.

3) CALCIMIMETICS.

3.1) CINACALCET

As mentioned before, most traditional therapies for SHPT have entailed correction of reduced Ca intake and absorption in CKD patients, correction of

hypocalcemia and excessive production of PTH by administration of Ca salts, supraphysiological Ca levels in the dialysate, use of VDRA, and prevention of hyperphosphatemia by means of Ca-based P-binders[1,80]. However, these therapies have been limited by the occurrence of hyperphosphatemia (VDRA) and hypercalcemia, a lack of specificity, restricted long-term efficacy, and potential vascular toxicity[11,24,81] . On the other hand, surgical PTX is not exempt from risks[27]. The identification and cloning of CaSR in the 1990's prompted the development of calcimimetics and calcilytic agents[82]. Cinacalcet, the first clinically available activator of the CaSR (calcimimetic), represents a completely new mechanism of action and extends the armamentarium against SHPT in dialysis patients and primary hyperparathyroidism[24,83] (Table 1).

It has been shown that cinacalcet, when tolerated, is very effective in reducing abnormal circulating levels of PTH, Ca, P, CaxP product and, importantly, FGF23[24,81,84]. Furthermore, two important prospective RCTs evaluated both the efficacy of cinacalcet in preventing the progression of CVC (ADVANCE)[21] and its effect on all-cause mortality and cardiovascular events (EVOLVE)[22]. First, the ADVANCE trial suggested that cinacalcet plus low doses of VD may attenuate the progression of coronary, aortic, and valvular calcification compared with flexible VD therapy[21]. Although significant changes in the *volume* of coronary artery calcifications were described, results with respect to the predefined primary end-point of the study (*surface*) did not strictly reach statistical significance (p=0.07). Two recent *post-hoc* analyses suggested that cardiac valve calcification was a predictor of coronary artery calcification progression and, potentially, of greater cardiovascular vulnerability[85] and demonstrated that treatment with cinacalcet had statistically significant beneficial effects among participants who adhered to the prespecified protocol[86]. Second, the

EVOLVE RCT did not reach its primary composite end-point (all-cause mortality and cardiovascular events) after an *unadjusted* intention to-treat (ITT)–based analysis[22]. These results were supported by a recent meta-analysis, mainly driven by this negative EVOLVE primary result, which included other heterogeneous studies with different designs[87]. However, we do believe that it is important to emphasize that *prespecified* secondary ITT *adjusted* analysis revealed a nominally significant improvement in survival in the cinacalcet group[24,22]. Thus, the effect of cinacalcet was significantly more pronounced among patients aged ≥65 years in secondary and *post-hoc* analyses[22,88]. Lag-censoring and other prespecified companion analyses also suggested a nominally significant beneficial effect of cinacalcet on the primary composite end-point[22], and accepting the limitations of non-primary analysis, patients randomized to cinacalcet experienced fewer non-atherosclerotic cardiovascular events (including sudden death and heart failure), a decreased incidence of PTX, fewer episodes of calciphylaxis, and a reduction in clinically-reported fractures[22,23,89]. The excessive rate of drop-ins and drop-outs and the loss of statistical power, among other factors, probably seriously hindered the interpretation of the primary end-point and rendered the EVOLVE study inconclusive[24]. Consequently, cinacalcet may not be warranted in all dialysis patients and it cannot be recommended in order to improve their survival[90]; however, it unquestionably improves the achievement of target levels for all metabolic abnormalities associated with CKD-MBD and mortality[91,92]. A summary of negative and positive aspects of the EVOLVE study is presented in Table 2.

It has been recently reviewed the practical use of calcimimetics in dialysis patients assessing and advising how to circumvent the most frequent adverse events such as nausea and vomiting (Table 3), hypocalcemia, PTH oversuppression and QT-prolongation, among others, with the goal of potentially improving clinical practice and

patient adherence[24]. Beyond the influence of cost in prescription rates[93], persistence of treatment among patients remains low despite all the beneficial effects associated with cinacalcet[93,92,94].

3.2) ETELCALCETIDE (AMG416)

Etelcalcetide (AMG416 or, as previously confusingly named, velcalcetide) is currently in development and undergoing regulatory review. It represents a novel, third generation intravenous (i.v.) long-acting selective peptide agonist of the CaSR[95,96]. Etelcalcetide allows i.v. administration in the dialysis setting and may improve drug monitoring and adherence. A multicenter, double-blind, placebo-controlled, dose-escalation study designed to evaluate the safety and efficacy of etelcalcetide administered thrice weekly by i.v. bolus at the end of hemodialysis for up to 4 weeks for the treatment of SHPT in hemodialysis patients has recently been published[97]. It was observed that a substantial proportion of subjects treated with etelcalcetide achieved PTH ≤300 pg/mL and a ≥30% reduction in PTH from baseline, supporting the continued development of etelcalcetide. The observed decreases in serum-corrected Ca were well tolerated and serum P levels also tended to decrease. Etelcalcetide pharmacokinetics have also been recently published[98].

The results of a second placebo-controlled Phase III study in dialysis patients evaluating the effect of etelcalcetide on the treatment of SHPT were recently announced[99,100]. The study's primary endpoint was the proportion of patients with a > 30% reduction from baseline in PTH levels during an efficacy assessment phase defined as weeks 20-27 of the study. In the etelcalcetide group, 74% of patients achieved the primary endpoint, compared with 8.3% of patients in the placebo group. Secondary endpoints included the percentage change in serum P (-7.7% and -1.3% in the

etelcalcetide and placebo arms, respectively) and corrected Ca concentrations (-7.3% and 1.2%, respectively). Both of these secondary endpoint results were statistically significant. Treatment-emergent adverse events were reported in 92% of patients who received etelcalcetide and 79% of patients receiving placebo. The most frequently reported adverse event was asymptomatic reduction in Ca; symptomatic hypocalcemia was reported in 7.2% of patients who received etelcalcetide compared with 0.4% in the placebo group [100]. The proportions of patients reporting muscle spasms, diarrhea, nausea, and vomiting were higher in the etelcalcetide group than in the placebo group [99,100].

Another Phase III, head-to-head, double-dummy, placebo-controlled study of etelcalcetide and cinacalcet has also been conducted to compare their efficacy and tolerability. It has been announced that treatment with i.v. etelcalcetide achieved >50% and >30% reductions in PTH in more patients compared with cinacalcet, while, somewhat surprisingly, nausea and vomiting did not seem to differ[101]. Thus, it is currently unclear whether etelcalcetide will have fewer adverse GI effects compared with oral cinacalcet. The i.v. route may also offer a potential reduction in the risk of drug-drug interactions[96]. A numerical imbalance in cardiac failure was observed in this study, for which a causal relationship to etelcacetide could not be established[101]. Hypocalcemia was seen more frequently with etelcalcetide and the safety profiles appeared to be comparable although more prolonged clinical experience is definitely required[101].

3.3) NEW CALCIMIMETICS

Two other oral CaSR modulators are in Phase II development (KHK-7580 and ASP7991)[10]. ASP7991 has been shown to significantly decrease PTH levels in a rat

model of SHPT and may have less potential for CYP-enzyme-mediated drug-drug interactions than cinacalcet[10]. Another calcimimetic compound, LEO 27847, has been evaluated in a Phase I study for the treatment of SHPT, but no additional information regarding its development is available[10].

4) ADYNAMIC BONE DISEASE

Adynamic bone disease (ABD) is a well-recognized clinical entity in the CKD-MBD complex[102,103]. Although the gold-standard diagnostic method is bone biopsy, the presence of low circulating PTH and low bone-specific alkaline phosphatase levels may be suggestive of ABD[44]. In the most recent bone histomorphormetry study before and after long-term treatment with an antiparathyroid agent (cinacalcet), no ABD was observed among patients with PTH ≥ 300 pg/ml, Ca ≥ 8.4 mg/dl and bone-specific alkaline phosphatase > 20.9 ng/ml, although 22 out of 146 patients had normal bone histology[45].

ABD is increasing in prevalence relative to other forms of renal osteodystrophy and is becoming the most frequent type of bone lesion in some series[7,102] It is potentially linked to fracture risk and progression of CVC. Among many other factors (recently reviewed in reference 103), drug-induced oversuppression of PTH may contribute to this low-turnover bone state[45]. Thus, prevention of sustained PTH levels <2 times the upper limit of normality, especially in the steadily growing proportions of diabetic, white, and elderly patients, is of the outmost importance (Table 4). In the recent COSMOS study, in patients with baseline PTH levels below 168 pg/ml (mean 89 pg/ml), increases in PTH were associated with a lower risk of mortality[34]. Recombinant PTH has been used in case-reports[104]. The potential use of Natpara®, released to control hypocalcemia in patients with hypoparathyroidism**,** or antisclerostin monoclonal antibodies remains to be tested[103].

5) CALCIPHYLAXIS

Calciphylaxis, or calcific uremic arteriolopathy, is a rare condition and continues to represent a clinical challenge[105,106]. In addition to existing pharmacological treatments, and that cinacalcet appears to reduce the incidence of calciphylaxis in hemodialysis patients[107], sodium thiosulfate has recently been introduced in the armamentarium against calciphylaxis. It may also attenuate the rate of progression of CVC but at the expense of reduced bone mineral density at the hip[108]. Vitamin K deficiency is common in ESRD, and vitamin K antagonists (e.g. warfarin) may promote calciphylaxis as well as CVC[109]. Thus, several prospective RCTs are currently evaluating the effect of vitamin K supplementation on the progression of CVC[110]. Beyond osteoporosis treatment, different bisphosphonates have also been used off-label in the treatment of calciphylaxis; however, since their potentially positive effects on CVC cannot be separated from an adequate bone formation, administration of these drugs to patients with CKD stage 4/5 may be unsafe[7]. A novel approach with an i.v. formulation (SNF472) of myo-inositol-hexaphosphate (phytate), a selective calcification inhibitor, is being developed as an orphan drug, and Phase II studies are being developed to analyze its influence on the progression of CVC in dialysis patients [111].

6) CONCLUSION

Improvements in the management of CKD-MBD require an integral approach that addresses all 3 components of the CKD-MBD triad. Individualization of P-binders and reasonable combinations of anti-parathyroid agents may provide the best biochemical control with the lowest incidence of undesirable effects. Despite the

absence of level 1A evidences from RCTs on whether any treatment or a combination of treatments should be preferred in order to control CKD-MBD[81,90] and the lack of consensus among nephrologists on the best diagnostic parameters or treatment laboratory goals, there is general agreement that CKD-MBD and SHPT are common and costly manifestations of CKD. Clear *associations* with negative quality of life, CVC, cardiovascular complications, and worse patient outcomes have been repeatedly reported.

We have already mentioned that avoidance of an excessive P load is currently considered one of the key issues in the management of CKD-MBD[1]. We also previously reported that best treatment remains to be defined, especially considering the low efficiency, poor patient adherence, potential toxicity and cost of P-binders[1]. Retail prices are currently decreasing due to the advent of generic drugs after expiry of patent protection, and this may change some subjective perceptions.

In this second part of the article we have reviewed specific anti-parathyroid treatment, including several VDRA (some of which are described as *selective* VDRA), calcimimetics, and combinations thereof. Guidelines suggest that VDRA treatment may be used in patients with stage 3-5 CKD who are not on dialysis and in whom PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors. On the other hand, VDRA and/or calcimimetics are suggested in patients with CKD stage 5D and elevated or rising PTH, bearing in mind that it is reasonable for the initial drug selection to be based on Ca and P levels as well as on other aspects of CKD-MBD such as cardiovascular calcification.

Determination of CVC fits into the paradigm of personalized medicine[112], and we believe that an assessment for CVC is therefore warranted at least in some patients, including any in whom the carying physician decides that knowledge of the presence of

CVC may impact therapeutic decisions (i.e., Ca- vs non-Ca based P-binders; calcitriol or alfacalcidol vs paricalcitol or maxacalcitol; VDRA vs calcimimetics)[1,112,113]. Actually, in the recent commentary from a KDIGO controversies conference[36], it was stated that "the group was unanimous in their assessment of the clinical significance of cardiovascular calcification and the conclusion that cardiovascular calcification should be considered for guidance of CKD-MBD management".

Although the link between intervention and outcomes when progression of CVC is attenuated has not been conclusively demonstrated, cheap and readily accessible plain X-rays and/or echocardiography may help to define the initial best and safest treatments, at least until we are able to use other therapeutic means at earlier stages of the accelerated atheromatosis process[112,114].

7) EXPERT OPINION

PTH is a poor biomarker in relation to underlying bone disease, at least partially due to the presence of *multifactorial* resistance to the renal and skeletal actions of PTH in uremia and the variability of PTH assays. For the moment and until deciphering the way to circumvent these problems, it is clear that serum PTH levels should be maintained higher than normal in dialysis patients. Thus, KDIGO guidelines suggest that ″serum PTH levels should be maintained at between 2X-9X the upper normal limits for the used assay" in patients with CKD stage 5D; nevertheless, we follow the Spanish adaptation of the KDIGO guidelines which initially aim at 2-5 times the upper limit of normality to free up space and safely avoid KDIGO extremes of risk (<2 or >9 times the upper normal limit) [35,39,40]. This narrower PTH interval has been chosen from some important epidemiological studies describing that the lowest mortality rates in dialysis patients are found in this PTH range[26,30,31]. Nephrologists should not react to any minor PTH variation by instituting "urgent" changes in treatment. On the other hand, there are

also serious concerns about normalizing serum PTH levels in CKD stages 3-5 since moderate elevations of PTH may serve as a beneficial adaptive response (with improvements in phosphaturia or bone turnover)[36].

VD receptor is ubiquitous and can be directly or indirectly activated by different forms of native and active VD . We usually supplement with native vitamin D as suggested in different guidelines, using treatment goals and strategies recommended for the general population. Many beneficial pleiotropic global class effects have been described for active forms of VD, including survival benefits in observational studies and meta-analyses. Selective VDR activation, identified by its low calcemic, low phosphatemic profile, may yield specific differential beneficial effects at the tissue and molecular levels (e.g. slower CVC progression), but this has only been shown under experimental conditions, and no RCT has ever been performed. We believe that although it has not been proven that VDRA improve hard-outcomes, it would be insensitive to completely dismiss the accumulated robust data. In this regard, paricalcitol shares, and sometimes has been shown to selectively improves, pleiotropic VD-related systemic effects[68,75]. Questions about costs in relation to benefits may be raised, but it is to be borne in mind that expiry of patent protection will decrease retail prices.

Practical issues regarding the use of VDRA have recently been reported[115,116]. Briefly, we use paricalcitol as the first-line VDRA due to its wider therapeutic window as compared with calcitriol, especially in patients with CVC, diabetics, and patients treated with coumadin derivatives. In adults, in order to avoid unacceptably and unnecessarily rapid PTH suppression, we calculate the initial dose based on baseline serum intact PTH (iPTH) levels (µg of paricalcitol iv /dialysis session = baseline iPTH in pg/mL / 100-120) instead of the common iPTH/80 reported in the summary of

product characteristics. Conversion of intravenous paricalcitol from calcitriol is smoother using a 1:3 calcitriol to paricalcitol conversion ratio[117]. In patients not undergoing dialysis, we usually convert oral calcitriol to paricalcitol on a 1:4 basis according to the most commonly marketed dose (0.25 μg of calcitriol/1 μg of paricalcitol). Further dose adjustment is necessary according to PTH response and during the concomitant use of calcimimetics (in dialysis patients). We generally prefer non-Ca-based P-binders, especially when using VDRA; while VDRA and/or paricalcitol may be administered with Ca-based P-binders, there is an increased risk of hypercalcemia and, potentially, progression of CVC[20,81]. If not a first choice, cinacalcet may be used as a rescue drug in the event of hypercalcemia[118].

On the other hand, the use of cinacalcet is fully justified at least as a component of a multitargeted intervention in dialysis patients with SHPT, including P-binders and VD**.** Among patients with *hypercalcemia* or significant *hyperphosphatemia*, calcimimetics are probably the best first-line treatment since hypercalcemia and hyperphosphatemia occur more often with VDRAs[7,81,119]. Calcimimetics should not be started if basal serum Ca level is less than 8.4 mg/dl but mild hypocalcemia is clinically acceptable during the maintenance phase (normality for Ca levels will probably be soon revisited by KDIGO in patients treated with calcimimetics)[36]. In any case, in order to avoid unnecesary positive Ca balances, Ca should not be pushed up when patients develop assymptomatic mild hypocalcemia (i.e. 8.0 mg/dl), especially if no significant changes are observed in the QT-interval. Calcimimetics may also allow a safer concomitant use of VDRA, benefiting patients as a result of their credited pleiotropic effects. Crossed positive, bidirectional and additive interactions between calcimimetics and VDRA have been described in experimental studies[120,121]. An important difference between calcimimetics and VDRA is that two important RCTs relating to the former at

least show a nominally significant benefit over standard therapy with respect to hard-outcomes in dialysis patients. Emerging i.v. calcimimetics may promote patient compliance and improve achievement of treatment goals. On the other hand, various maneuvers, including decreasing or withdrawing Ca-based P-binders, VD derivatives and/or calcimimetics as well as decreasing the dialysate-bath Ca content will help to increase PTH levels to safer levels in those patients at risk of ABD.

Finally, many believe that a combination of P-binders and a combination of anti-parathyroid agents is probably the best current clinical option, as in other areas of Nephrology such as the treatment of hypertension or albuminuria and the use of immunosuppressive protocols in transplantation (Table 5). Combinations of different drugs decrease high doses and associated adverse effects of any individual drug, counterbalance negative effects and facilitate additive positive effects by acting on different pathophysiological pathways; they probably also decrease costs or increase the cost/benefits ratio. The absence of indisputable evidences in Nephrology should not lead to the acceptance of attitudes of therapeutic nihilism while awaiting results from difficult confirmatory and definitive studies. Multi-interventional RCT and the development of reliable risk estratification scores seems distant aspirations; in the meantime, it would appear prudent at least not to increase the CVC burden in CKD patients, in compliance with the Hippocratic principle “first, do not harm”. As a matter of fact, it is known that the “absence of evidence” does not equate to “evidence of absence”[122]. All these considerations should prompt the design of new prospective RCTs to better define the potential direct relationship between CVC and outcomes and the institution of other better, earlier, and more cost-effective clinical actions in the field, including new studies with clinically relevant hard-outcomes (rather than

biochemical or radiological), and head-to-head comparisons that also take patient-reported outcomes into account[123].

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CONFLICTS OF INTEREST

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Article highlights

- CKD is linked to an extremely important and independent increase in mortality, and mineral and bone disorders (MBD) explain at least part of this disproportionate risk
- Treatment of CKD-MBD requires an integral approach, addressing all 3 components of the CKD-MBD triad (including the presence of CVC)
- CKD-MBD and secondary hyperparahtyroidism are common and costly manifestations of CKD
- Vitamin D deficiency is common both in the general population and in patients with CKD, and it is associated with poor outcomes
- There is no proof that supplementation with vitamin D improves survival, although guidelines recommend treatment of vitamin D deficiency
- Vitamin D receptor activators are used to reduce PTH secretion and have been associated with improved outcomes in observational studies and meta-analyses, but not in RCTs
- Selective activators of the vitamin D receptor (i.e. paricalcitol vs calcitriol) seem to have a wider therapeutic window (less hypercalcemic and hyperphosphatemic episodes) and have also been associated with improved survival in dialysis patients in retrospective studies
- Calcimimetics provide a completely different means to control secondary hyperparathyroidism in dialysis patients, controlling PTH synthesis and secretion and decreasing calcium and phosphate levels.

- The ADVANCE and EVOLVE RCTs provide important clues towards improvement of hard outcomes in dialysis patients
- Etelcalcetide represents a novel iv agonist of the calcium-sensing receptor
- Combination of anti-parathyroid agents is a feasible clinical option
- Low PTH levels (< 2 times the upper limit of normality for the assay) should be avoided since adynamic bone disease is associated to poor outcomes
- Increasing trends in PTH levels should be treated and PTH levels > 9 times the upper limit of normality should be definitely avoided
- Therapeutic nihilism while awaiting the results of new RCTs does not seem to be justified

This box summarizes key points contained in the article

CKD: chronic kidney disease; MBD: mineral and bone disorders; CKD-MBD: chronic kidney disease-mineral and bone disorder; CVC: cardiovascular calcification; PTH: parathyroid hormone; RCT: randomized clinical trial

Table 1. General comparison between vitamin D derivatives and cinacalcet

	ADVANTAGES	DISADVANTAGES
ACTIVE VITAMIN D Calcitriol Alfacalcidol Paricalcitol (SVDRA) Maxacalcitol (SVDRA)	• Very good tolerance • Oral and intravenous routes • Decreases PTH synthesis • Improves bone • Can be given both in dialysis and non-dialysis patients • Association with improved survival in retrospective studies and meta-analyses	• Increased Ca, P and Ca x P level • Increased FGF-23 • Cost and availability of SVDRA • Lack of hard end-point prospective RCTs
CINACALCET	• Oral (an intravenous calcimimetic is in Phase III) • Decreases PTH synthesis and secretion • Improves bone • Decreases Ca, Ca×P, and FGF-23 levels • May decrease P levels • May be given with high serum Ca and/or P levels	• Hypocalcemia (rarely symptomatic) • Relatively poor tolerance (especially frequent nausea and vomiting among other secondary effects) • NOT indicated in non-dialysis patients (only primary hyperparathyroidism and parathyroid carcinoma)

	• Nominally significant attenuation of the progression of valvular and vascular calcification (RCT) • Nominally significant survival benefits (secondary adjusted predefined analysis of RCT)	because of hypocalcemia and hyperphosphatemia • Cost and availability

SVDRA: selective vitamin D receptor activators; Ca: calcium; P: phosphate; PTH: parathyroid hormone; FGF23: fibroblast growth factor 23; RCT: randomized clinical trial

Table 2. Negative and positive aspects of the EVOLVE study (EValuation Of Cinacalcet HCl therapy to Lower CardioVascular Events)

NEGATIVE

Nonsignificant primary composite endpoint by unadjusted ITT analysis

Too many drop-ins (20% in the placebo group)

Too many drop-outs (almost 2/3 in the cinacalcet group)

Unacceptable loss of statistical power (re-estimated power, 54%)

Very frequent secondary effects

Complex statistics

Inconclusive trial

POSITIVE

Clear positive tendencies with a single drug in the complex dialysis setting

Nominally significant PRESPECIFIED analysis:

Adjusted multivariable analysis

Lag-censoring analysis

Inverse probability of censoring weighting (IPCW)

Nominally significant decreases in heart failure, parathyroidectomy, clinically reported bone fractures, and calciphylaxis (secondary endpoints)

Known and expected secondary effects

Table 3. Strategies to control gastrointestinal symptoms related to cinacalcet

• Inform patients about the importance of controlling CKD-MBD and its impact on cardiovascular outcomes • Inform patients that although cinacalcet may cause GI effects, it is not an ulcer-inducing drug • Give cinacalcet after the main meal or in the evening • Do not withdraw cinacalcet immediately if only mild/moderate symptoms are present • Start with the minimum dose and adjust the dose according to PTH and tolerance (combination with vitamin D may be helpful) • Decrease or fractionate the dose if symptoms appear after a dose escalation • Caution is advised with the use of antiemetics (including metoclopramide) in patients with hypocalcemia-related QT prolongation

CKD-MBD: chronic kidney disease and mineral bone disease; GI: gastrointestinal; PTH: parathyroid hormone; QT: QT interval on electrocardiogram

Table 4. Considerations for adynamic bone disease

• Avoid an excessive Ca load (Ca-based P-binders, active forms of vitamin D) and consider non-Ca based P-binders • Avoid an excessive PTH oversuppression (active forms of vitamin D, calcimimetics) and consider native vitamin D • Decrease Ca-dialysate content • Avoid trace metal exposure • Avoid bisphosphonates and other antiresorptive agents without a bone biopsy ruling out low-turnover bone disease • Potential for recombinant PTH and antisclerostin monoclonal antibodies (?)

Ca: calcium; P: phosphate; PTH: parathyroid hormone

Table 5. Summary of the treatment of secondary hyperparathyroidism and CKD-MBD

Use knowledge of CVC to guide treatment of CKD-MBD, use drugs in combination, and individualize treatment.

Phosphate (and/or FGF23) control: (P-binders) (see Part I)[1]

- Achieve P levels as close to normality as possible with reasonable measures, including optimization of dialysis*
- Avoid additives by all possible means, prioritize a balanced vegetarian vs animal dietary protein source and limit ↑ P/protein index foods
- Prioritize P-binder prescription over unsupervised non-specific protein diet restriction
- If very high serum PTH and P levels are present, consider the possibility that P may NOT be of intestinal origin.
- Personalize choice of P-binder prescription depending on patient preferences, CKD stage (dialysis vs non-dialysis), presence/absence/degree of VC, concomitant therapies (i.e., VDRA, calcimimetics) and side effect profile (i.e., palatability, constipation, diarrhea)
- Avoid Ca-based P-binders in patients with hypercalcemia, low PTH levels, and/or ABD. Avoid or limit Ca-based P-binders in diabetics, patients with VC, and patients treated with coumadin.

- Combination of P-binders is possible and inhibition of intestinal transporters may soon become an alternative or add-on therapy to improve clinical effectiveness.

PTH control (specific anti-parathyroid treatment)

- Aim for iPTH levels between 2 and 5 times the upper limit of normality and avoid extremes of risk (<2X or >9X).
- Treat tendencies and do not respond to minor variations in PTH.
- Initial drug selection may be based on CKD stage, Ca and P levels as well as on other aspects of CKD-MBD (e.g., CVC).
- Cinacalcet is not approved for the treatment of secondary hyperparathyroidism in CKD stages 3-5
- In CKD stage 5D, use vitamin D and calcimimetics in combination to improve efficacy with fewer secondary effects, eventually always considering the Ca and P levels
- Selective VDRA (paricalcitol) may provide a wider therapeutic window, especially in those with a trend toward hypercalcemia or hyperphosphatemia, diabetic patients, and those prone to VC (experimental).
- Cinacalcet is considered first-line treatment in hypercalcemic (and perhaps significantly hyperphosphatemic) dialysis patients.
- I.V. etelcalcetide may improve compliance

CKD-MBD: chronic kidney disease-mineral and bone disorder; P: phosphate; Ca: calcium; CVC: vascular calcification; ABD: adynamic bone disease; VDRA: vitamin D receptor activators; iPTH: intact parathyroid hormone; i.v.: intravenous; <2X->9X: less than 2 times or more than 9 times the upper limit of normality for the assay.

*Curiously, just in the summary of product characteristics of *non-Ca based* P binders it is stated that they are indicated for the control of hyperphosphatemia in adult patients with CKD not on dialysis only with serum P > 1.78 mmol/l (5.5 mg/dl).