What have we learned about CKD-MBD From the EVOLVE and PRIMO trials?

Sharon M. Moe, MD and Ravi Thadhani, MD, MPH

1Indiana University School of Medicine and Roudebush Veterans Administration Medical Center, Indianapolis, IN
2Massachusetts General Hospital, Harvard Medical School, Boston MA

Abstract

Purpose of Review—The treatment of CKD-MBD (Chronic Kidney Disease-Mineral Bone Disorder) has traditionally focused on improvement in biochemical parameters of the disease. However, studies evaluating hard clinical end points or surrogate end points are limited.

Recent Findings—Two randomized trials have recently been published. In the EVOLVE study (EValuation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) cinacalcet was compared to placebo in 3883 hemodialysis patients with secondary hyperparathyroidism. The primary end point (death, myocardial infarction, unstable angina, heart failure, or peripheral vascular disease) in an unadjusted intention to treat analysis was not significant (HR 0.93; 95% CI 0.85 – 1.02, p = 0.11). However, the a priori defined secondary end points of an adjusted intention to treat analysis (HR 0.88; 95% CI 0.79–0.97, p = 0.008). In the PRIMO (Paricalcitol Capsule Benefits in Renal Failure Induced Cardiac Morbidity), 227 patients with CKD stage 3–4 and left ventricular hypertrophy by echocardiography were randomized to paricalcitol or placebo. The primary end point of change in left ventricular mass index by MRI after 12 months was not different between the two groups, but the pre-specified end point of cardiovascular related hospitalizations were reduced in the paricalcitol treated group (p=0.04).

Summary—The results of these two randomized trials leave clinicians with the difficult choice of therapies for secondary hyperparathyroidism.

Keywords
cinacalcet; paricalcitol; heart; mortality; cardiovascular disease; dialysis; CKD; hyperparathyroidism

Introduction

Chronic Kidney Disease-Mineral Bone Disorder is a systemic disease with three components: abnormalities in biochemical tests related to disordered mineral metabolism in CKD, abnormal bone, and extra skeletal calcification [1,2]. The pathophysiology of the disorder is complex and each year its complexity grows with the addition of a new feedback loop, new hormone, or new organ involvement. At the center of this complexity is the kidney, with kidney-bone, kidney-vascular, kidney-intestine, and bone-vascular and bone-intestine loops. In essence, the system (Figure 1) is designed to ensure that calcium and
phosphorus are jointly regulated, with an ultimate goal of appropriate skeletal mineralization, and to avoid nephrolithiasis and extra-skeletal calcification. For example, the urinary calcium excretion is reduced while the excretion of phosphorus is increased in late stage CKD. Parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) regulate each other and have opposing effects on the conversion of 25-hydroxy vitamin D to 1,25(OH)2-vitamin D (calcitriol). Indeed the system is very efficient, until kidney disease prevents the normal function of these homeostatic loops. As kidney function declines, the expression of the co-receptor for FGF23, Klotho, is decreased in the kidney and the parathyroid glands [3–5] rendering these organs ‘FGF-23 resistant’. Therefore, multiple components of the feedback loops shown in Figure 1 become dysfunctional.

As Nephrologists, we have tried various treatments for CKD-MBD to compensate for the role of the failed kidney, including phosphate binders, calcitriol and its analogues, and calcimimetics. Unfortunately, the vast majority of clinical trials of these agents have only studied the efficacy of treating one or more components of the biochemical manifestations of CKD-MBD. While these changes are an important component of CKD-MBD, as detailed in the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines, biochemical changes alone are low level end points on which to guide therapy, as opposed to intermediate/surrogate end points (such as heart, vascular or bone measures), or on hard clinical end points such as cardiovascular or all-cause mortality [6]. This limitation is critically important, as unlike hypertension, dyslipidemia, or diabetes, there is no CKD-MBD in the general population from whom studies can be extrapolated. Thus, studies that attempt to look beyond the biochemical changes of CKD-MBD to intermediate (surrogate) or hard clinical should be applauded when conducted, and demanded when absent.

In the last year, we have seen two important studies that evaluate currently administered therapies for the treatment of secondary hyperparathyroidism: cinacalcet, a calcimimetic and paricalcitol, a vitamin D analog, both FDA approved for the lowering of parathyroid hormone. Both studies looked beyond control of the biochemical manifestations of CKD-MBD. In the EVOLVE study (EValuation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) cinacalcet was compared to placebo in patients with secondary hyperparathyroidism, the vast majority already on phosphate binders and vitamin D derivatives [7–9]. The hypothesis was that cinacalcet had a unique mechanism of action that would lower PTH, and simultaneously lower calcium and phosphorus, thereby improving vascular calcification, cardiac hypertrophy, bone and ultimately mortality. The PRIMO (Paricalcitol Capsule Benefits in Renal Failure Induced Cardiac Morbidity) study was based on the premise that not only does paricalcitol lower PTH but it also directly reduces the adverse effects of the renin-angiotensin system on cardiac remodeling by activation of the vitamin D receptor present in cardiac myocytes in animal models [10,11]. Unfortunately, the unique approach of testing a secondary benefit of the drug in each case was hampered by an inability to alter the usual use of the drugs in the treatment of secondary hyperparathyroidism as discussed below.

**EVOLVE**

The EVOLVE trial was the largest trial ever conducted in hemodialysis patients: 3,883 patients with moderate to severe secondary hyperparathyroidism from around the world were studied for up to 64 months (event driven duration). The primary end point was a composite of death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular disease. The primary analysis was an unadjusted intention to treat analysis which found no difference between cinacalcet versus placebo on top of conventional therapy (HR 0.93; 95% CI 0.85 – 1.02, p = 0.11). However, the *a priori* defined secondary end points of an adjusted intention to treat analysis (HR 0.88; 95% CI
0.79–0.97, p = 0.008) was positive. This was very important given that there was an age imbalance in the two arms despite randomization, and age is one of the strongest predictors of death in dialysis patients. The unfortunate decision when designing the trial to not adjust the primary end point for critical factors converted this large, long study from positive to negative. Overall, the study had only a 2.1% of subjects lost to follow up. This does prove that studies can be done in dialysis patients. Unfortunately, the results of the trial must be declared non-definitive at best, given the primary end point was negative.

Other *a priori* planned secondary end points included an analysis censoring of data after 6 months of study drug discontinuation, to assess drug effect in those taking the medication (HR 0.83, 95% CI 0.73 to 0.96, p = 0.009). The rationale for 6 months was the executive committee felt the mechanisms of action for a benefit of cinacalcet was hypothesized to be a reduction in arterial calcification, and that the efficacy of drug on vascular calcification would last 6 months. This *a priori* decision appeared appropriate as there was a gradual increase in HR from 9 to 12 months after discontinuation of drug with the lag-censoring analysis [9]. While it makes sense to determine if a drug works when the patients take it (as we would evaluate in clinical practice), this approach is always somewhat biased as the true test of a drug is its benefit:risk ratio.

In the EVOLVE trial, the median duration of study drug exposure was 21.2 months for cinacalcet and 17.5 months for placebo. In the cinacalcet arm, 66.7% of subjects discontinued study drug, 22.1% for protocol specified reasons, 20.6% for ‘administrative reasons’, and 15.8% for adverse events. In the placebo arm, 70.5% of subjects discontinued study drug, 30.7% for protocol specified reasons, and 11.8% for adverse events. In the placebo arm, 80% of patients achieved the maximum dose suggestive of appropriate titration and 19.8% of subjects received commercial cinacalcet (versus 2.1% in the cinacalcet arm). Thus, the drug exposure and ultimate power of the study was impaired by drop-outs and drop-ins to the randomized arms. In addition, parathyroidectomy was reduced with cinacalcet compared to placebo (HR 0.43, 95% CI 0.35–0.53, p < 0.001). With these drop ins, drop outs, and parathyroidectomies, the ultimate power of the study to show a difference was only 54% using the original assumption of 20% treatment effect. A sensitivity analysis censoring the data for patients at the time of kidney transplantation, parathyroidectomy, or use of commercial cinacalcet found the HR was 0.90 (95% CI 0.82 to 0.90, p = 0.03) for the primary end point. These data demonstrate the difficulty of conducting trials in dialysis patients, especially when the agent of interest is commercially available, the drug needs to be discontinued when PTH levels are low, and when an alternative to the therapy (parathyroidectomy) can be utilized.

Many important findings should be taken from this trial. First, cinacalcet had adverse effects with nearly twice as many gastrointestinal side effects as the placebo arm, and 12.4% of patients developed hypocalcemia. Second, cinacalcet did lower PTH, calcium, and phosphorus in a population with very high PTH levels, including those on and off vitamin D therapy. Thus, cinacalcet is effective in the treatment of secondary hyperparathyroidism either as mono therapy or with vitamin D therapy. Third, there was a significant effect on heart failure, but not angina, peripheral vascular disease, or stroke suggesting that CKD-MBD may not impact traditional atherosclerotic disease. Instead, CKD-MBD may be more causative in medial calcification, arteriosclerosis, endothelial dysfunction, and/or cardiac hypertrophy. Finally, the incidence of fractures was lower than expected, in part due to the fact the only clinically symptomatic fractures were reported and adjudicated. This indicates that very large trials would be needed to test any traditional anti-fracture agents and such trials should evaluate both clinical and non-clinical (spine) fractures.
Unfortunately, we will almost certainly not see an “EVOLVE 2” trial and thus clinicians are left to determine how best to interpret such an inconclusive trial. This phenomenon is all too common in the ESRD population: the HEMO trial [12], DCOR [13,14], 4D [15] and many other trials have failed to show that we can significantly impact outcomes in our patients. Does that mean we should abandon such trials? Absolutely not. Instead it may mean that we need to look at multiple therapies given against placebo rather than a single agent. ESRD patients have multi organ involvement, why would we think that one drug would be a cure-all? Perhaps we need a statin, with cinacalcet, and an ACE or ARB, and increased dialysis to really impact the care of these patients. After all, that is our approach clinically. Such a trial would be very difficult to design, but likely worth the effort.

PRIMO

In the PRIMO trial [10], patients with stage 3 and 4 CKD, mild left ventricular hypertrophy but normal systolic function were randomized to paricalcitol compared to placebo. The study screened 811 patients, with 227 randomized to paricalcitol or placebo. Of those who failed screening, 297 did not meet laboratory criteria, and 195 did not meet echocardiographic criteria. Baseline demographics, laboratory results, and echocardiography and MRI findings were not different between the two groups. The primary end point was a change in ventricular mass over 48 weeks assessed by the gold standard MRI. The results demonstrated no significant difference (p = 0.06 between the two group (change in LVMI was 0.34 [95% CI = −0.11 to 0.83] in the paricalcitol group, and −0.07 [95% CI = −0.55 to 0.42]). Thus, the trend was in favor of placebo albeit the net change/difference was clinically negligible (2 to 4 gram difference in heart weights). The results did not differ if the LVMI was adjusted for height. Other measures of LV dysfunction including end-systolic index, end-diastolic index, ejection fraction, aorta compliance and aorta volume were also not different. The dose of paricalcitol was adequate to suppress PTH to 30% of baseline in 85.7% of patients in the paricalcitol arm versus 16.5% of the placebo group (p < 0.001), but this was associated with significant increases in serum calcium (0.45 vs. 0.32 mg/dl, p < 0.001), serum phosphorus (0.23 vs 0.04 mg/dl p = 0.05), hypercalcemia (20.9 vs 5.4%, p < 0.001) and a decrease in eGFR by MDRD (−9.5 vs 3.8 ml/min/1.73 m² p < 0.001), but not in changes in cystatin C in the paricalcitol treated patients compared to placebo.

Interestingly, the risk of hospitalizations was lower in the paricalcitol group (1.1 per 100 person years vs. 8.8 per 100 person years, p=0.04). The primary difference was in episodes of congestive heart failure. In a post-hoc analysis, there was a reduction in atrial enlargement in the paricalcitol treated patients [16].

Why was this trial negative? Several possibilities exist, including that the hypothesis was not true in humans, that the blood pressure was so well controlled that it masked any effect of paricalcitol, or that the patients already had LVH (or that the LVH was not bad enough or patients not followed long enough). These results are also in contrast to several animal models of LVH, including Dahl salt sensitive rats [17–19], spontaneously hypertensive heart failure prone rat [20], and pressure overload rat [21]. Clearly the heart expresses the VDR and in rodents, selective deletion of the VDR in cardiomyocytes results in LVH [22].

Presumably, based on animal models, paricalcitol should have had a direct effect on the heart and thus should be effective with and without CKD. Unfortunately, none of the above animal studies examined animals with CKD. One study in a 5/6th nephrectomized rat found that treatment with calcitriol led to an improvement in fibrosis, but no change in heart weight (a surrogate animal indicator of LVH) [23]. One potential explanation for why results may be different in CKD is FGF23. Calcitriol (and presumably paricalcitol) also increase FGF23 expression from bone [24] and FGF23 directly induces cardiomyopathy in animal models [25,26]. But this is not certain, as another study in a mouse model of CKD, calcitriol actually reduced FGF23 levels, presumably by increasing soluble klotho and
making the animal less ‘FGF resistant’ [27]. Paricalcitol also increases klotho expression in human arteries ex vivo [28], and should improve endothelial dysfunction [29]. These results demonstrate the importance of studying therapies in the setting of different stages of CKD in rodent animals to determine the effect on all of the homeostatic loops shown in Figure 1 and to optimize clinical trial design. Ultimately, all therapies must be examined in randomized controlled trials in patients.

Conclusion

So where do the results of these trials leave us in the management of CKD-MBD. One could argue that in the absence of any hard end point trials that we should do nothing. Let PTH rise, not replete 1,25D, don’t give phosphate binders. After all, if we demand hard end point evidence this may seem the right thing to do. However, as physicians caring for patients we see symptoms of CKD-MBD and secondary hyperparathyroidism- the non-STEMI heart attacks due to calcification of small arteries, elevations in pulse pressure with duration on dialysis, amputations, strokes, myopathies, and even itching! An alternative approach is to assume that lowering blood levels of PTH, phosphorus and maybe calcium with whatever is cheapest warrants the best approach. But these therapies have not been subjected to long term trials evaluating hard end points and may also be negative or lead to adverse events. How should we interpret studies such as EVOLVE in which the primary end point of an unadjusted intention to treat analysis is negative but the secondary end point of an adjusted intention to treat analysis is positive? Or PRIMO in which LV mass did not differ but there seemed to be a difference in CVD related hospitalizations? This requires a frank discussion with the patient. Clearly, we need more studies, perhaps with combination therapies, rather than fewer. Unfortunately, the call for more studies directly comparing agents in clinical practice guidelines, in the concluding paragraph of manuscripts describing cross sectional observational studies, and by governing bodies has failed to lead to increased funding for such studies. The answer at the present time is to individualize the approach and discuss the benefit-risk with each patient given the results of these and other studies. Clearly, the lack of evidence by not asking the question at all is worse than a negative trial.

Acknowledgments

SMM has research funding from the NIH (R01 AR058005), Veterans Administration, Genzyme-Sanofi, Novartis, and has served as a consultant to Amgen (and was a member of the EVOLVE executive committee), Genzyme-Sanofi, and Litholink-CKD/LabCorp. RT has research funding from NIH (K24 DK 094872 and R01 HL 11274602), Abbott Laboratories for the PRIMO Trial, and is a consultant to Fresenius Medical Care North America.

References


Key Points

1. Studies that evaluate hard clinical end points for treatments commonly used for CKD-MBD are limited.

2. In the EVOLVE study, the primary end point of (death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular disease) was negative (HR 0.93; 95% CI 0.85 – 1.02, p = 0.11).

3. In the EVOLVE study, the a priori defined secondary end points of an adjusted intention to treat analysis was positive (HR 0.88; 95% CI 0.79–0.97, p = 0.008) as were other sensitivity type analyses suggesting that decisions to use cinacalcet require individualization.

4. In the PRIMO trial, the primary end point of differences in LVMI by MRI after 12 months was negative and the adverse effects of paricalcitol were greater but CVD related hospitalizations were fewer in the paricalcitol treated arm (p=004).
Figure 1. The homeostatic control of phosphorus and calcium

The regulation of these ions involves three major hormones, parathyroid hormone (PTH) synthesized in the parathyroid glands, vitamin D (1,25(OH)2D) made from the kidney, and fibroblast growth factor 23 (FGF23) secreted from bone. A series of homeostatic feedback loops exist that involve the kidney via vitamin D conversion or phosphate excretion. Thus, in the setting of CKD, these homeostatic loops are disturbed. Adapted from Brenner & Rector’s: The Kidney. Editors: Taal, Maarten; Chertow, Glenn; Marsden, Phillip; Skorecki, K; Yu, Alan; Brenner, Barry. Chapter “Chronic Kidney Disease-Mineral Bone Disorder” by Moe, Sharon and Sprague, Stuart. Elsevier, 2012, chapter 54, page 2023.