Revisiting KDIGO clinical practice guideline on chronic kidney disease—mineral and bone disorder: a commentary from a Kidney Disease: Improving Global Outcomes controversies conference

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In October 2013, the Kidney Disease: Improving Global Outcomes (KDIGO) initiative convened a Controversies Conference in Madrid, Spain, titled ‘CKD-MBD: Back to the Future’. The title was reminiscent of the 2005 KDIGO Controversies Conference on Definition, Diagnosis, and Classification of Renal Osteodystrophy in Madrid. The term ‘chronic kidney disease—mineral and bone disorder’ (CKD-MBD) was coined at the 2005 conference and replaced the bone-centric concept of ‘renal osteodystrophy’ worldwide following the publication of this conference report.¹ CKD-MBD was defined as a systemic disorder and a trinity of bone abnormalities, laboratory abnormalities, and vascular calcification that are linked to hard outcomes such as fractures, cardiovascular morbidity, and mortality. Accordingly, an initiative to create a new global guideline on the diagnosis and therapy of CKD-MBD was set in motion.

The publication of the subsequent KDIGO CKD-MBD guideline in 2009 raised public awareness, fostered discussion, and created controversy.² The KDIGO guideline Work Group had to contend with the reality that high-quality evidence for CKD-MBD-associated outcomes was surprisingly sparse. Narrow target levels for laboratory parameters including calcium, phosphate, and parathyroid hormone (PTH), as proposed in 2003 by the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease,³ were no longer recommended because such levels were not grounded in solid evidence. Rather, recommendations should
be based on trends in laboratory markers as therapeutic goals. A key criticism of this guideline was the deliberate vagueness of some recommendations as reflected by the lack of provision of laboratory target levels and that these trends were not numerically defined. During discussions in society meetings and nephrology conferences, it was repeatedly expressed that these new guidelines could potentially contribute to diagnostic and therapeutic nihilism. Position papers and commentaries were written by peer groups, such as KDOQI and the European Renal Best Practice. Nevertheless, the KDIGO CKD-MBD guideline was translated into many languages and endorsed by nephrology societies around the world (http://kdigo.org/home/mineral-bone-disorder/).

In 2013, the KDIGO Board of Directors concluded that the CKD-MBD guideline may require updating. The systematic review for the 2009 guideline included studies published through 2007, with a few selected papers published in 2008. A significant body of new literature has accumulated since then with potential impact to change CKD-MBD diagnostic and therapeutic decision-making. As a result, the objective of this 2013 KDIGO Controversies Conference was to determine whether sufficient new data had emerged to support a reassessment of the CKD-MBD guideline and if so to determine the scope of these potential revisions. The conference’s goal was not to draft new guideline statements or to formally reappraise the evidence grade for each statement. These tasks will be reserved for a future Work Group and Evidence Review Team to undertake.

CONFERENCE STRUCTURE AND APPROACH
The conference was attended by 74 participants from 5 continents and 19 countries, representing adult, pediatric, and transplant nephrologists, as well as endocrinologists, cardiologists, pathologists with expertise in bone histomorphometry, and epidemiologists. Before the meeting, the participants were assigned to one of the four groups on the basis of the availability of new evidence. These topic areas were (i) vascular calcification, (ii) bone quality, (iii) calcium and phosphate, and (iv) vitamin D and PTH. Each participant identified salient new publications in their topic area, and these publications were distributed to participants before the meeting.

The criteria for guideline updating and approaches to guideline revision were outlined for all participants (Figure 1). A focused catalog of questions specific to their content area and a defined, homogeneous and general list of questions for each guideline statement, as depicted in Table 1, was prepared in advance of the meeting to facilitate targeted discussions. The ultimate goal of the conference was to determine which recommendations require follow-up and reevaluation. These assessments were reported and discussed in the plenum, and a condensed summary of these appraisals is presented in this commentary.

TOPIC 1: VASCULAR CALCIFICATION
This working group had a focused task limited to reviewing two guideline recommendations (3.3.1 and 3.3.2, see Supplementary Table S1 online). 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. However, they concluded that there was insufficient new evidence to warrant a reassessment of these statements. Specifically, no high-quality data have been published to justify routine screening for cardiovascular calcification in chronic kidney disease (CKD) patients, and no new data comparing different imaging methods have emerged.

Additional new data have now become available from CKD patients not on dialysis. Studies comparing the associated risks of treatment with calcium-containing vs. calcium-free phosphate binders in this group emphasized previous concerns that calcium load may be a risk factor for progression of calcification in adult CKD patients. For example, Russo et al. underlined the powerful cardiovascular and mortality risk prediction based on the magnitude of coronary artery calcium in a cohort of 181 CKD patients not on dialysis. In the INDEPENDENT study, a decreased mortality rate with sevelamer vs. calcium carbonate treatment was observed in 212 CKD stages 3–4 patients and linked to a reduced progression of coronary artery calcification.

The ADVANCE trial comparing cinacalcet vs. standard treatment on secondary hyperparathyroidism failed to demonstrate a significant effect on the primary end point (coronary calcification progression according to Agatston scores) but showed positive signals concerning some predefined secondary end points (coronary calcification progression according to volume scores, valvular calcification progression). The overall perception of the working group...
Table 1 | How and when to update a clinical practice guideline: Overarching questions discussed in the second breakout session by each of the four topic groups

**Questions to be addressed for all guideline recommendations under review**
- Has there been new evidence since the original report that better substantiates or conflicts with current recommendations? Are there large-scale studies that may significantly improve the certainty or magnitude of net benefit/harm?
- Should any of the guideline statements be modified/created or removed because of new data or new interventions, strategies, or techniques not previously considered?
- Should any of the guideline statements be modified/created to address specific CKD populations by levels of severity or CKD populations not previously covered (e.g., elderly, pediatric, transplant recipients)?
- Should any of the guideline statements be modified/removed because they are difficult to implement?

**Questions to be discussed as appropriate**
- Which laboratory and imaging outcomes are appropriate surrogate end points for CKD-MBD? Are there new surrogate end points to consider?
- What are desirable patient-level outcomes in CKD-MBD?
- Are there new topic areas the next guideline update should include?
- What are the existing controversial questions and how can future research or improved trial design better resolve them?

Abbreviations: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease—mineral and bone disorder.

was that the available data may indeed strengthen the existing clinical practice guideline. Given that systematic review was not performed on this issue a priori, the question of upgrading the evidence rating was outside the scope of the conference.

**Special populations**
The group also believed that there were insufficient data to support special considerations for CKD subgroups including predialysis CKD, transplant recipients, children, and the elderly.

**Research recommendations**
See Supplementary Table S5 online.

**TOPIC 2: BONE QUALITY**
Guideline recommendations related to bone quality reviewed by the working group are summarized in Supplementary Table S2 online. Treatment strategies to prevent fractures in patients with CKD include pharmacologic agents that have been approved for the treatment of post-menopausal osteoporosis. There is a growing consensus that in CKD stages 1 to 3, in the absence of abnormalities of mineral metabolism such as elevated phosphorus or hyperparathyroidism, one can use therapies that are approved for osteoporosis. At the time of the KDIGO guideline, the evidence was largely limited to bisphosphonates as reflected in recommendations 3.2.1 and 4.3.4 (Table 2). The bone quality working group identified multiple publications reporting post hoc analyses of clinical trials in otherwise healthy post-menopausal women with CKD, including studies of denosumab and teriparatide. Accordingly, these guidelines should be revisited to consider antiresorptive and anabolic therapies besides bisphosphonates.

At the time of the 2009 KDIGO guideline, publications addressing the relations between dual energy X-ray absorptiometry, bone mineral density (BMD), and fracture risk in CKD were limited to cross-sectional studies comparing BMD in CKD patients with and without a prevalent fracture. The working group identified multiple new studies, including two recent prospective studies demonstrating that femoral neck BMD was associated with the future risk of fractures in people with CKD. In a study of 485 adult hemodialysis patients at a single center, lower femoral neck and total hip BMD was associated with excess risk of incident fractures, independent of age, sex, dialysis vintage, and diabetes status. Supplementary Figure S1 online illustrated the receiver operating characteristic curves for dual energy X-ray absorptiometry BMD at multiple sites. A study of 2754 older participants in the Health, Aging, and Body Composition (Health ABC) cohort demonstrated that lower femoral neck BMD was associated with greater fracture risk in participants with and without CKD. After adjustment, the hazard ratios (HRs; 95% confidence intervals) were 2.74 (1.99–3.77) and 2.15 (1.80–2.57) per standard deviation (s.d.) lower BMD for those with and without CKD, respectively. The HR per s.d. lower BMD did not differ for those with or without CKD (test for interaction P value = 0.68). Taken together, these data demonstrated that lower BMD (as assessed by dual energy X-ray absorptiometry) is associated with higher fracture risk in multiple CKD populations. Hence, the working group believed recommendations 3.2.2, and those of 5.5 and 5.7 applicable to the transplant recipients, should be reexamined (Table 2).

**Special populations**
The working group noted that none of the studies addressing bone therapies or dual energy X-ray absorptiometry BMD fracture prediction included children, but given the unique characteristics of the growing skeleton, the future updating Work Group may elect to examine this issue more closely with the hope to provide some pediatric guidance. The group also concluded that there are multiple important patient-level outcomes besides fracture. These include quality of life, physical function, pain and growth, skeletal deformities, and achievement of peak bone mass in children.

**Research recommendations**
See Supplementary Table S5 online.
5.7 In patients with CKD stages 4–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).

3.2.2 In patients with CKD stages 3–5D with evidence of CKD–MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).

4.3.4 In patients with CKD stages 4–5D having biochemical abnormalities of CKD-MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (2C).

5.5 In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m², we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (2D).

5.7 In patients with CKD stages 4–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease (2B).

**TOPIC 3: CALCIUM AND PHOSPHATE**

This working group largely focused on the treatment-related clinical practice guideline statements 4.1.1–4.1.8 but also discussed the diagnosis-related statements 3.1.1, 3.1.2, and 3.1.5 and the transplantation-related statements 5.1 and 5.2 (Supplementary Table S3 online). The group identified two major developments relevant to these recommendations. First, there were new safety signals with regard to liberal exposure to calcium in both predialysis and dialysis populations in adults. Second, there were some unexpected new insights concerning different consequences of phosphate lowering approaches in predialysis vs. dialysis patients.

One of the key publications in this context was the recent meta-analysis by Jamal et al., which examined all-cause mortality data from a total of 11 randomized controlled trials, mostly in patients on dialysis, comparing calcium-containing vs. calcium-free phosphate binders in CKD patients.16 The primary end point of most of these studies was progression of vascular calcification, but all contained a complete data set on mortality during the course of the investigation. In summary, this meta-analysis identified a 22% mortality risk reduction associated with the use of the non-calcium-based binders sevelamer and lanthanum carbonate (n = 4622 patients; Supplementary Figure S2 online). However, in some of the included studies, binders were titrated to high doses because of protocol-driven targets and these results should be extrapolated with caution to situations of low-dose calcium exposure, including therapy combining calcium-containing binder with non-calcium-based binder.

One small but potentially important study on the issue of calcium and phosphate balance was performed in patients in CKD stages 3b-4 (n = 148, mean eGFR 30–33 ml/min per 1.73 m², mean serum phosphate 4.2 mg/dl within each treatment arm). This study compared the effect of active treatment with one of the three phosphate binders (calcium acetate, lanthanum carbonate or sevelamer carbonate; 'active treatment') vs. placebo on several laboratory parameters and cardiovascular (coronary and aortic) calcification progression.7 Surprisingly, CKD patients on active treatment demonstrated increased calcification progression in comparison to patients treated with placebo. In a post hoc analysis of the active treatment group, this pro-calcifying effect was most strongly associated with the calcium-containing binder; however, the sample sizes in each group precluded binder-specific conclusions.

In another recent study specifically evaluating CKD patients not on dialysis, di Iorio et al.10 demonstrated a significant survival advantage and slowing down of progression to end-stage renal disease for those who were treated with sevelamer (n = 107) vs. calcium carbonate (n = 105) over a period of 36 months. In contrast to the pilot study by Block et al.,7 however, no placebo arm was included and patients were moderately hyperphosphatemic on average (4.84 vs. 4.2 mg/dl, respectively). This study was included in the recent meta-analysis by Jamal et al.16

The working group concluded that five of their assigned guideline recommendations should be reevaluated on the
### Table 3 | Recommendations related to calcium and phosphate requiring literature reassessment

4.1.1 In patients with CKD stages 3–5, we suggest maintaining serum phosphorus in the normal range (2C). In patients with CKD stage 5D, we suggest lowering elevated phosphorus levels toward the normal range (2C).

4.1.2 In patients with CKD stages 3–5D, we suggest maintaining serum calcium in the normal range (2D).

4.1.3 In patients with CKD stage 5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/L (2D)).

4.1.4 In patients with CKD stages 3–5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, the presence of other components of CKD-MBD, concomitant therapies, and side effect profile (not graded).

4.1.5 In patients with CKD stages 3–5D, we suggest using calcium supplements, calcium-free binders, and other therapies that impact calcium balance and load reviewed by the working group are summarized in Supplementary Table S4 online. The discussions for this topic were largely informed by recent clinical trials, chiefly OPERA and PRIMO for recommendation 4.2.2, both indicating hypercalcemia risks, and EVOLVE for recommendation 4.2.3. Concerns about treatment to lower PTH values to within the normal range in CKD stages 3–5, while moderate PTH elevations may serve as a beneficial adaptive response (e.g., phosphaturia, bone turnover), as well as concerns relating to calcium balance and load reviewed by the Calcium and Phosphate working group, further supported revisiting guidelines 4.2.1. and 4.2.2 (Table 4). Concerns about the wide PTH range and that acceptance of high values may negatively impact bone quality, result in the progression of parathyroid hyperplasia and decrease the efficacy of treatment strategies.

**Research recommendations**

See Supplementary Table S5 online.

### TOPIC 4: VITAMIN D AND PTH

Guideline recommendations related to vitamin D and PTH reviewed by the working group are summarized in Supplementary Table S4 online. The discussions for this topic were largely informed by recent clinical trials, chiefly OPERA and PRIMO for recommendation 4.2.2, both indicating hypercalcemia risks, and EVOLVE for recommendation 4.2.3. Concerns about treatment to lower PTH values to within the normal range in CKD stages 3–5, while moderate PTH elevations may serve as a beneficial adaptive response (e.g., phosphaturia, bone turnover), as well as concerns relating to calcium balance and load reviewed by the Calcium and Phosphate working group, further supported revisiting guidelines 4.2.1. and 4.2.2 (Table 4). Concerns remain about the wide PTH range and that acceptance of high values may negatively impact bone quality, result in the progression of parathyroid hyperplasia and decrease the efficacy of treatment strategies.

The PRIMO21 and OPERA22 randomized controlled trials failed to show a beneficial effect of lowering PTH with...
paricalcitol on cardiac structure and function but did demonstrate an increased risk of hypercalcemia. The PRIMO placebo-controlled clinical trial evaluated the effect of paricalcitol on cardiac magnetic resonance imaging measures of the left ventricular mass index (LVMI) and diastolic function over 48 weeks in 227 participants with CKD stage 3 and 4 and moderate left ventricular hypertrophy. Although treatment with paricalcitol promptly reduced PTH levels and maintained them within the normal range, the change in LVMI did not differ between treatment groups and Doppler measures of diastolic dysfunction also did not differ. However, episodes of hypercalcemia (defined as serum calcium >10.5 mg/dl) were more frequent in the paricalcitol group (20.9%) compared with the placebo (0.9%) group. The subsequent OPERA study was a placebo-controlled trial of the effect of 52 weeks of paricalcitol on magnetic resonance imaging measures of LVMI and echocardiographic measures of cardiac function in 60 participants with non-dialysis CKD stages 3–5 and left ventricular hypertrophy. Paricalcitol was associated with prompt reductions in PTH but was not associated with changes in LVMI or cardiac function. Hypercalcemia (serum calcium >10.5 mg/dl) occurred in 43.3% and 3.3% of participants randomized to paricalcitol and placebo, respectively. The primary differences in the OPERA and PRIMO studies were the smaller sample size in OPERA and the fact that the LVMI of the OPERA subjects was at least 70% greater compared with those in PRIMO. Thus, OPERA provided important evidence in a cohort with more severe CKD, more severe secondary hyperparathyroidism, and frank left ventricular hypertrophy that paricalcitol had no effect on reduction of left ventricular mass over 52 weeks. In both PRIMO and OPERA, cardiovascular-related hospitalizations were lower in the treated groups but these were secondary or post hoc analyses requiring further confirmation. In addition, whether low-dose treatments, avoidance of hypercalcemia, and targeting a higher range for PTH values might have long-term non-cardiac benefits were not assessed in these studies.

The EVOLVE trial was the topic of a plenary session and the results of its secondary analyses engendered substantial discussion. A total of 3883 hemodialysis patients with moderate-to-severe secondary hyperparathyroidism were randomized to cinacalcet or placebo. The participants were followed for up to 64 months with a median duration of 21.2 and 17.5 months in the cinacalcet and placebo groups, respectively. The primary composite end point was time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event. In an unadjusted intention-to-treat analysis, the primary composite end point was reached in 938 of 1948 patients (48.2%) in the cinacalcet group and 952 of 1935 patients (49.2%) in the placebo group (relative HR in the cinacalcet group vs. the placebo group, 0.93; 95% confidence interval, 0.85–1.02; P = 0.11). After adjustment for baseline characteristics (including a 1 year older age in the participants randomized to cinacalcet), there was a significant 12% reduction in risk (P = 0.008). Hypocalcemia and gastrointestinal adverse events were significantly more frequent in patients receiving cinacalcet. In light of these results, the working group did not feel there was sufficient evidence to reassess recommendations 4.2.3 and 4.2.4 (Supplementary Table S4 online). However, the working group noted the following important considerations. First, in the placebo group, 20% began receiving commercially available cinacalcet before the occurrence of the primary event, and participants in the cinacalcet group discontinued the drug at an annual rate of 27%. In an analysis with censoring of data 6 months after study drug discontinuation, the reduction in the primary composition end point (HR = 0.85, P = 0.003) and mortality (HR = 0.83, P = 0.009) were significant. Second, 47 and 148 of participants in the cinacalcet and placebo arms, respectively, underwent parathyroidectomy during the study interval. Sensitivity analyses with censoring for kidney transplantation, parathyroidectomy, or commercially available cinacalcet yielded a HR of 0.90 for the primary composite end point (P = 0.03).

Special populations
The working group reported that currently there are no data to support varying PTH targets by race. Target PTH levels may also differ during growth and development; however, there are insufficient data to provide pediatric-specific recommendations.

Research recommendations
See Supplementary Table S5 online.

CONCLUSIONS
In summary, a consensus was reached by the participants of the Controversies Conference calling for a ‘selective update’ of the 2009 KDIGO clinical practice guideline on the diagnosis and treatment of CKD-MBD. Although most of the recommendations were still considered to be current, a total of 12 recommendations were identified for reevaluation based on new data. In addition, the conference concluded with a few additional topic questions that the guideline

**Table 5** Potential new topic questions that merit review by guideline updating group

- Is there new evidence to merit recommendation statement(s) on the diagnosis and management of calciphylaxis?
- What are the effects of physical function (e.g., exercise programs, muscle strength, sarcopenia) and the influence of gonadal hormones on bone quality?
- What is the impact of amenorrhea in pre-menopausal women?
- Because of the current broad use of magnesium-based binders, can we issue recommendations regarding monitoring of magnesium, including in dialysate? Some studies have reported potential cardiac benefits in maintaining normal magnesium levels, and there are also findings suggesting the frequent occurrence of hypomagnesemia in the post-transplant period.
updating group may consider (Table 5). The task of this selective update should be performed by a new guideline Work Group and again supported by an independent evidence review team in the near future. Despite the completion of several pivotal trials since the 2009 guideline publication, large gaps of knowledge still persist in the field of CKD-MBD as reflected by the relatively small number of recommendation statements deemed for revisiting. It is hoped that the research agenda set forth in this report and in the upcoming guideline update will prompt for improved trial design with the use of meaningful ‘hard’ and clinical patient outcomes to better assess new potential CKD-MBD therapies.

DISCLOSURE
MK declared having received consultancy fees and speaker honoraria from Abbvie, Amgen, Fresenius, Medice, Mitsubishi, Sanofi, Shire, and Vifor. GJE declared having received consultancy fees from Amgen, Shire, and Vifor Australia; speaker honoraria from Amgen, Sanofi and Shire; research support from Amgen. JHL declared having received consultancy fees from AstraZeneca and Keryx; speaker honoraria from Shire. SAJ declared having received consultancy fees from Amgen and Sanofi; speaker honoraria from Amgen, Bayer, Sanofi/Genzyme, and Warner Chilcott/Actavis. MHLP declared having received research support from Servier. RIT declared having received consultancy fees from Fresenius and research support from Kaneka. MAT declared having received research support from Abbott Laboratories through a peer reviewed grant to the Canadian Institutes of Health Research. DCW declared having received consultancy fees from Abbvie, Amgen, Astellas, Baxter, F Hoffmann-La Roche, Janssen, Merck Sharp & Dohme, Otsuka, and Vifor; research funding from AstraZeneca/UK, British Heart Foundation, Kidney Research UK, Medical Research Council, Healthcare Quality Improvement Partnership; speaker honoraria from Amgen and Otsuka. BLK, MBL and RS reported no relevant disclosures.

SUPPLEMENTARY MATERIAL
Figure S1. Receiver operating characteristic (ROC) analysis on the prediction of any time of fracture.
Figure S2. Comparing 11 RCTs with full data sets on all-cause mortality identify a 22% mortality risk reduction when hyperphosphatemia was treated with a calcium-free versus a calcium-containing phosphate binder.
Figure S3. In CKD patients in stages 3b-4 (n = 8), daily dietary intake of 1000 mg calcium and 1500 mg phosphate equals a neutral calcium (and phosphate balance).
Table S1. Guideline recommendations related to vascular calcification.
Table S2. Guideline recommendations related to bone quality.
Table S3. Guideline recommendations related to calcium and phosphate.
Table S4. Guideline recommendations related to vitamin D and PTH.
Table S5. Research recommendations.

REFERENCES