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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A new definition and classification of chronic kidney disease–mineral and bone disorder (CKD-MBD) was proposed in 2005 and it was later followed by a guideline publication on this topic from Kidney Disease: Improving Global Outcomes (KDIGO) in 2009. This work recognized that CKD-MBD is a syndrome of bone abnormalities, laboratory abnormalities, and vascular calcification linked to fractures, cardiovascular disease, and mortality. Because of limited data at the time of the original guideline systematic review, many of the recommendations were cautiously vague. KDIGO convened a Controversies Conference in October 2013 to review the CKD-MBD literature published since the 2009 guideline. Specifically, the objective of this 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. This report summarizes the results of these proceedings, highlighting important new studies conducted in the interval since the original KDIGO CKD-MBD guideline.

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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.[4–6] 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 their expertise. 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.

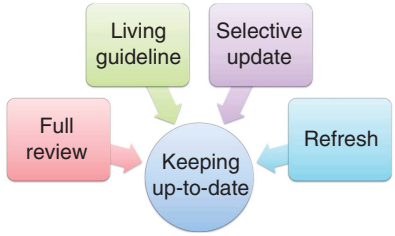

Figure 1 | Different potential options for updating clinical practice guidelines. A full review involves beginning guideline production from scratch, with or without retaining the existing analytical framework. A living guideline implies a document that is constantly under revision and could be revised at any point on the basis of the availability of new evidence. A selective update uses specific methods to update only those parts of the guideline in need of update (which can be quite extensive in some cases). A refresh implies a quick change to a small, circumscribed part of a guideline, without the need to assemble new multidisciplinary Work Group (e.g., new evidence necessitating an update of no more than two key questions or a policy/licensing change that would affect the whole guideline). Adapted with permission from Roberta James.

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.[7,8] For example, Russo *et al.* underlined the powerful cardiovascular and mortality risk prediction based on the magnitude of coronary artery calcifications in a cohort of 181 CKD patients not on dialysis.[9] 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.[10]

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).[11] The overall perception of the working group