The editorial by Dr Bostom in this issue of the American Journal of Kidney Diseases poses an interesting narrative regarding the 2009 KDIGO (Kidney Disease: Improving Global Outcomes) chronic kidney disease–mineral and bone disorder (CKD-MBD) guideline. The author points out that the compounds niacin and nicoretrol are potential therapeutic agents for a variety of clinical indications in CKD such as preventing disease progression, decreasing proteinuria, and improving lipoprotein metabolism. Their ability to lower serum phosphorus has also been noted in several studies in animals as well as humans. Dr Bostom notes that the recent KDIGO CKD-MBD guideline failed to comment on the utility of niacin as a phosphate-lowering agent, citing this as an omission. Indeed, the CKD-MBD guideline did not comment on this phosphate binder (nor several other potential binders) because the currently available evidence is not of sufficiently high quality to support a guideline recommendation for using niacin to lower phosphate in CKD patients. As key participants in the KDIGO CKD-MBD guideline process, our objectives for this editorial are to describe the purpose and goal of the KDIGO CKD-MBD guideline and the methodological approach taken in evidence review, which explains that the omission was not an accident but the result of a purposeful and systematic process. Finally, we will discuss the options for a guideline work group when evidence is not adequate to support a recommendation.

**PURPOSE AND GOAL OF THE KDIGO CKD-MBD GUIDELINE**

A clinical practice guideline aims to guide clinical decisions regarding evaluation and management towards improving patient outcomes. Discovery in medicine occurs through various forms of observation and research. However, research can inform clinical practice more or less directly. The directness with which studies inform clinical practice usually increases from experimental laboratory research to observational clinical studies to clinical trials, among which randomized controlled trials (RCTs) remain the “gold standard” to evaluate an intervention. Thus all research does not a guideline make! The emphasis for the CKD-MBD guideline was in the critical review of the most directly informative and applicable evidence rather than in the comprehensive review of the state of the science in the field of bone and mineral metabolism in CKD.

**THE KDIGO CKD-MBD GUIDELINE APPROACH TO EVIDENCE REVIEW**

Over the 2-year development period of the KDIGO CKD-MBD guideline, an international work group comprising experts in the field collaborated closely with an evidence review team with methods expertise. Together, they defined clinically relevant questions. For topics related to treatments they conducted systematic reviews after defining populations, interventions, comparators, and outcomes of interest. Outcomes of interest were divided into 3 tiers: (1) those of critical importance included all patient-centered outcomes, such as death, clinical events from cardiovascular disease, kidney failure, or fractures; (2) those of high but not critical importance included surrogate outcomes for bone and cardiovascular disease; and (3) those of moderate importance were biochemical outcomes related to kidney function and laboratory components of CKD-MBD. Adverse events specific to certain treatments were also reviewed.

Only studies in humans with CKD-MBD were subjected to systematic evidence review. It was decided to include only data from studies published as full articles in peer-reviewed journals. Also, prior to any knowledge of the search results, the Work Group decided that for questions relating to treatments directed at MBD, only RCTs with a minimum of 25 patients per treatment arm and of more than 6 months’ duration would be included. These criteria were based on methodological and clinical considerations. Treatment trials of interventions for CKD-MBD with fewer than 25 patients per arm would be unlikely to have sufficient power to find significant differences in patient-centered outcomes. This is espe-
cially true for dichotomous outcomes such as deaths, events from cardiovascular disease, or fractures. A minimum duration of follow-up of 6 months was chosen since for the treatments under review, it would not be plausible to see effects on patient-centered outcomes before several months of exposure to the intervention. For surrogate outcomes, effects might become apparent in smaller samples or after shorter treatment durations, but none of the surrogate outcomes reviewed for the CKD-MBD guideline have been unequivocally validated so far. Unfortunately, the number of RCTs in the nephrology field lags well behind other medical specialties. Furthermore, the number of nephrology RCTs providing clinically meaningful estimates for patient-centered outcomes represents only a small subset.

Many data on treatments of CKD-MBD derive from observational studies rather than RCTs. Historically, observational data for treatment effects are not always confirmed by RCTs. This has been especially true in the dialysis population, where consistent observational associations exist between higher achieved dialysis dose, higher hemoglobin levels, or the use of statins and better survival, but RCTs failed to show treatment benefits. How one should incorporate observational data into reviews of interventions, especially in the setting of limited RCT evidence, remains a methodological challenge. The KDIGO CKD-MBD guideline followed the guidance from the GRADE (Grading of Recommendations Assessments, Development and Evaluation) Working Group, which specifies that observational studies should be considered to be low quality, but that their quality can be “upgraded” to moderate or high quality if they have no serious methodological flaws and show a consistent and strong association for a patient-centered outcome, for example a statistically significant relative risk of $<0.5$ or $>2$.14,15

After screening thousands of citations, these stringent criteria lead to the exclusion of many studies for the systematic reviews conducted for the KDIGO CKD-MBD guideline. None of the articles cited by Dr Bostom met our inclusion criteria. Reasons for exclusion included laboratory experimental studies in animals, studies in individuals who do not have CKD-MBD, uncontrolled trials and controlled trials of small size or short duration, and abstracts or articles from journal supplements. Does this rigorous approach miss important information? It may be reassuring to compare the conclusions of the guideline systematic reviews with those from recent Cochrane reviews on corresponding topics.16,17 Cochrane systematic reviews follow a more comprehensive and inclusive approach in evidence review. Yet the conclusions of the respective KDIGO guideline questions and the Cochrane reviews for clinical outcomes appear congruent, precisely because the criteria employed by the guideline focus its systematic reviews on those studies that evaluate critical patient-centered end points or surrogates of high importance.

**WHEN EVIDENCE IS NOT ADEQUATE TO SUPPORT A GUIDELINE RECOMMENDATION**

Besides the potential role of niacin as a phosphate binder, there have been attempts to study magnesium salts, chitosan, as well as other compounds for this indication. From the perspective of the KDIGO CKD-MBD guideline Work Group, research evidence on these agents was not definitive enough to be considered for issuing a guideline recommendation. Prematurely recommending treatments of yet indeterminate utility in a guideline may be counterproductive as even weak recommendations are often adopted without considerations of the nuance of the attached guideline grade, which provides an expression of the confidence that following the guideline recommendation will do more good than harm. In fact, premature guideline recommendations may even hinder further research in the field. As an example, the recruitment of CKD patients into studies of 25-hydroxyvitamin D repletion has been impeded by widespread adoption of a liberal repletion practice. From a patient perspective, recommending drugs and formulations not yet ready for “prime time” may expose patients to the risk of adverse effects that may become apparent with more extensive evaluation. In the nephrology community we must be cautious not to discourage further research by issuing clinical practice guidelines before the research that should support them is completed. In response to the limitations of the evidence in the field of CKD-MBD, the KDIGO guideline
Work Group formulated many research recommendations which provide a plan to expand knowledge that can directly inform clinical practice.

CONCLUSION

We agree with Dr Bostom that abnormalities of mineral metabolism parameters are associated with significant disease burden in CKD patients. There is an acute need to study phosphate-lowering approaches in CKD patients, including studying the effects of different phosphate targets as well as the relative effectiveness of established and newer phosphate-lowering agents. Niacin is one of many agents that require further study. We hope that high-quality research in CKD-MBD as well as in other realms of nephrology will contribute to more definitive evidence upon which to base guideline updates.

Ranjani N. Moorthi, MD, MS
Indiana University School of Medicine
Indianapolis, Indiana

Sharon M. Moe, MD
Indiana University School of Medicine/
Roudebush Veterans Administration Medical Center
Indianapolis, Indiana

Tilman Drüeke, MD
Picardie University
Amiens, France

Katrin Uhlig, MD, MS
Tufts Medical Center
Boston, Massachusetts

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