David C Wheeler

- David's current positions include Professor of Kidney Medicine at University College London, UK and Honorary Consultant Nephrologist at the Royal Free London NHS Foundation Trust.
- He is Clinical Lead for Division 2 of the North Thames Clinical Research Network and heads a team of eight clinical trials nurses/practitioners at the Centre for Nephrology, Royal Free Hospital in London. He has been involved in clinical practice guideline development for several organisations, most recently for KDIGO, of which he is currently Co-Chair.

KDIGO 2016 Clinical Practice Guideline Update

GUIDELINE OVERVIEW AND OBJECTIVES

WHY UPDATE?

Clinical Practice Guidelines should be updated if:

- new evidence shows that a recommended intervention causes previously unknown substantial harm;
- a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or
- a recommendation can be applied to new populations.

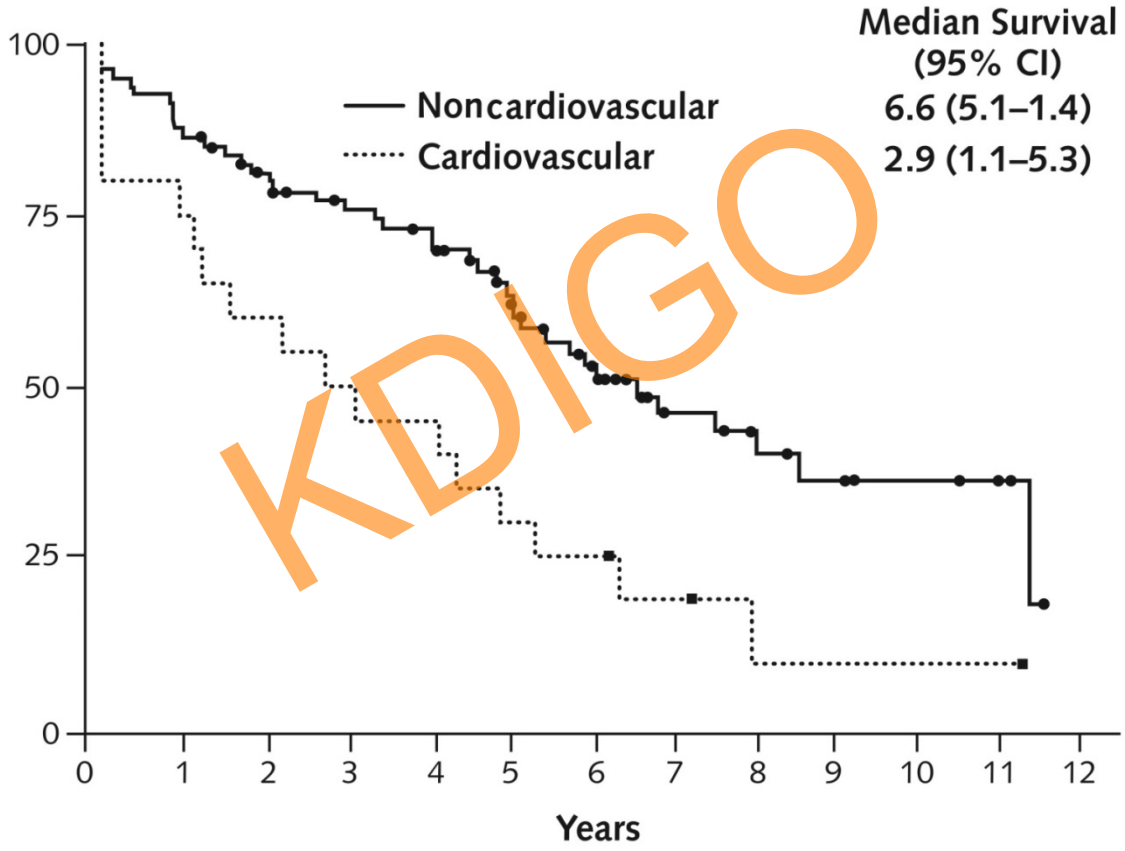
Institute of Medicine, 2011
Clinical Practice Guidelines We Can Trust

WHY UPDATE?

Additional considerations for updating:

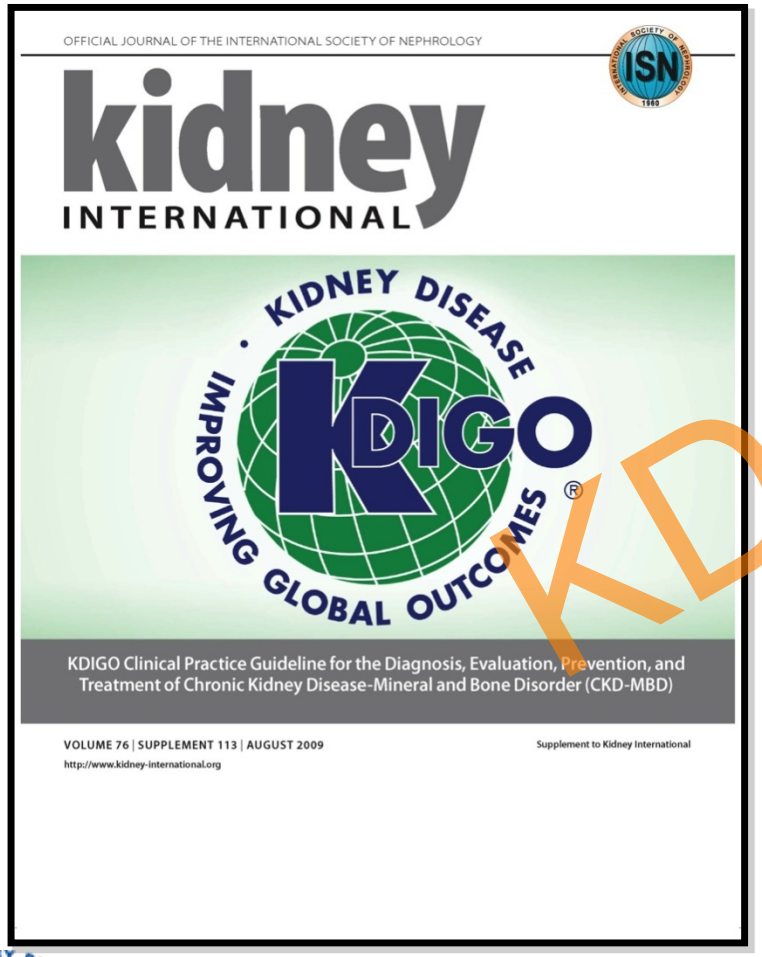
- Changes in the relevance of a clinical question to the practice of medicine
- Changes in available interventions (e.g. new drugs or devices)
- Changes in evidence on the existing benefits and harms of interventions
- Changes in outcomes considered important
- Changes in values places on outcomes
- Changes in evidence that current practice is optimal
- Changes in resources available for health care

How long does it take until clinical practice guidelines are out of date?



Shojania KG et al. Ann Intern Med 2007

KDIGO 2009 CKD-MBD GUIDELINE



The first KDIGO clinical practice guideline on CKD-MBD was published in August 2009.

Shojania KG et al. Ann Intern Med 2007

KDIGO Controversies Conference on CKD-MBD, 2013 (Madrid, Spain)

- **74 attendees** from **5 continents** and **19 countries**
- Represented experts in adult, pediatric and transplant nephrology, endocrinology, cardiology, bone histomorphometry, and epidemiology
- Divided into 4 Breakout Groups
  - Bone Quality
  - Calcium and Phosphate
  - Vitamin D and PTH
  - Vascular Calcification

CONTROVERSIES CONFERENCE OBJECTIVE

The overall goal was to provide a suggested roadmap for the next guideline update group by identifying which recommendations potentially warrant revisions (or deletions) and what new scope topics or recommendations could be considered in a future systematic review.

CONTROVERSIES CONFERENCE OBJECTIVE

Questions to be addressed for all guideline recommendations under review by topic groups:

- 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)?

CONTROVERSIES CONFERENCE PUBLICATION

meeting report

http://www.kidney-international.org

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

Markus Ketteler[1], Grahame J. Elder[2,3], Pieter Evenepoel[4], Joachim H. Ix[5,6,7], Sophie A. Jamal[8], Marie-Hélène Lafage-Proust[9], Rukshana Shroff[10], Ravi I. Thadhani[11], Marcello A. Tonelli[12,13], Bertram L. Kasiske[14], David C. Wheeler[15] and Mary B. Leonard[16]

GUIDELINE RECOMMENDATIONS TO REVISIT

Bone Quality

3.2.1 In patients with CKD stages 3–5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD-MBD (Not Graded).

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).

GUIDELINE RECOMMENDATIONS TO REVISIT

Bone Quality

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/1.73m2, 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).

Guideline Recommendations to Revisit

Bone Quality

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/1.73m2, 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).

BONE QUALITY: WHY UPDATING?

- 2009 Guideline was largely limited to bisphosphonates
- Clinical trial data are now available for denosumab and teriparatide
- There are recent data from at least two studies suggesting that low BMD is associated with higher risk of fractures; whether this is applicable to transplant recipients is unknown and awaits formal systematic review by the Evidence Review Team (ERT)

GUIDELINE RECOMMENDATIONS TO REVISIT

Calcium and Phosphate

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).

Guideline Recommendations to Revisit

Calcium and Phosphate

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, presence of other components of CKD–MBD, concomitant therapies, and side-effect profile (not graded).

4.1.7 In patients with CKD stages 3–5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D).

Calcium and Phosphate: Why Updating?

- Renewed safety concerns concerning liberal exposure to calcium in both predialysis and dialysis patients
- Effect of calcium balance on endpoints such as vascular calcification, mortality, and progression to ESRD
- Potential new data on dialysis calcium mass transfer during hemodiafiltration/nocturnal hemodialysis. Any benefits for use of low calcium dialysate?
- New evidence suggesting that calcimimetics may alter clinical significance of low calcium

Calcium and Phosphate: Why Updating?

- Relevance of above issues for the pediatric populations as calcium balance is expected to be more dynamic for this group?
- Relevance of above issues for the transplant recipients? Any data on management of hypercalcemia for this patient group?
- Data to support separate recommendations on use of phosphate binders for management of hyperphosphatemia in predialysis and dialysis patients?
- Data to provide more guidance on limiting dietary phosphate intake by targeting specific phosphoprotein sources?

Guideline Recommendations to Revisit

Vitamin D and PTH

4.2.1 In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH (iPTH) above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C). It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).

4.2.2 In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

VITAMIN D AND PTH: WHY UPDATING?

- Both PRIMO and OPERA failed to show a beneficial effect of lowering PTH with paricalcitol on cardiac structure and function, but did demonstrate an increased risk of hypercalcemia.

- There are also concerns about treatment to lower PTH values to within the normal range in CKD stages 3 to 5, while moderate PTH elevations may serve as a beneficial adaptive response (e.g., phosphaturia, bone turnover). For this reason, along with issues mentioned previously relating to appropriate calcium balance and load, supported revisiting these two recommendations

What About Vascular Calcification?

3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).

3.3.2 We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD–MBD (not graded).

What About Vascular Calcification?

3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, if reasonable alternatives to computed tomography-based imaging are unavailable.

3.3.2 We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (2A). It is reasonable to use this information to guide the management of CKD–MBD (not graded).

What No Update for Vascular Calcification?

- No high quality data to justify routine screening for cardiovascular calcification in CKD
- No new data comparing different imaging methods have emerged

Conference Recommendations

- Selective update of the 2009 CKD-MBD Guideline.
- Most of the 2009 guideline recommendations were unchanged.
- 12 recommendations were identified for re-evaluation.
- Additional recommendations were proposed for revisiting since complete trial data analyses (e.g., EVOLVE) were published after the Madrid conference and are now available for formal systematic review.
- Large gaps of knowledge still persist, despite the completion of several RCTs since 2009.

CKD-MBD Guideline Update 2016

Guideline Chairs

Markus Ketteler (Germany)

Mary B Leonard (USA)

Work Group

- Geoffrey Block (USA)
- Pieter Evenepoel (Belgium)
- Masafumi Fukagawa (Japan)
- Charles A. Herzog (USA)
- Linda McCann (USA)
- Sharon M. Moe (USA)
- Rukshana Shroff (UK)
- Marcello A. Tonelli (Canada)
- Nigel D. Toussaint (Australia)
- Marc G. Vervloet (The Netherlands)

Evidence Review Team

Leader

Karen A. Robinson
Director, Johns Hopkins University
AHRQ Evidence-Based Practice Center

Evidence Review Team

Casey M. Rebholz, PhD, MPH MS
Lisa M. Wilson, ScM
Ermias Jirru, MD, MPH
Marisa Chi Liu, MD, MPH
Jessica Gayleard, BS
Allen Zhang, BS

METHODOLOGY

- Refine and update guideline clinical questions
- Review prior search strategy, inclusion/exclusion criteria, and amend if necessary
- Perform data extraction on studies fulfilling inclusion criteria
- Relevant outcomes and evidence appraisal are summarized in the form of Evidence Matrices and Evidence Profiles
- Work Group reviewed ERT data and revised relevant guideline recommendations
- Work Group revisited the strength of the recommendation
- ERT assisted with the evidence grading of the individual recommendations

GRADING RECOMMENDATIONS

		Implications	
Grade	**Patients**	**Clinicians**	**Policy**
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	Most patients should receive the recommended course of action.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

Ungraded recommendations are also issued to provide guidance based on common sense or where the topic does not lend itself for systematic review. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. recommendations.

THE GRADE SYSTEM

Step 1: Starting grade for quality based on evidence based on study design	Step 2: Reduce grade	Step 3: Raise grade	Final grade for quality of evidence for an outcome[a]
High for randomized controlled trials Moderate for quasi-randomized trial Low for observational study Very low for any other evidence	Study quality -1 level if serious limitations -2 levels in very serious limitations Consistency -1 level if important inconsistency Directness -1 level if some uncertainty -2 levels if major uncertainty Other -1 level if sparse or imprecise data -1 level if high probability of reporting bias	Strength of association +1 level is strong,[b] no plausible confounders, consistent and direct evidence +2 levels if very strong,[c] no major threats to validity and direct evidence Other +1 level if evidence of a dose-response gradient +1 level if all residual confounders would have reduced the observed effect	High Moderate Low Very low

GRADE, Grades of Recommendations Assessment, Development, and Evaluation; RR, relative risk.

[a]The highest possible grade is 'high' and the lowest possible grade is 'very low'.

[b]Strong evidence of association is defined as 'significant RR of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders

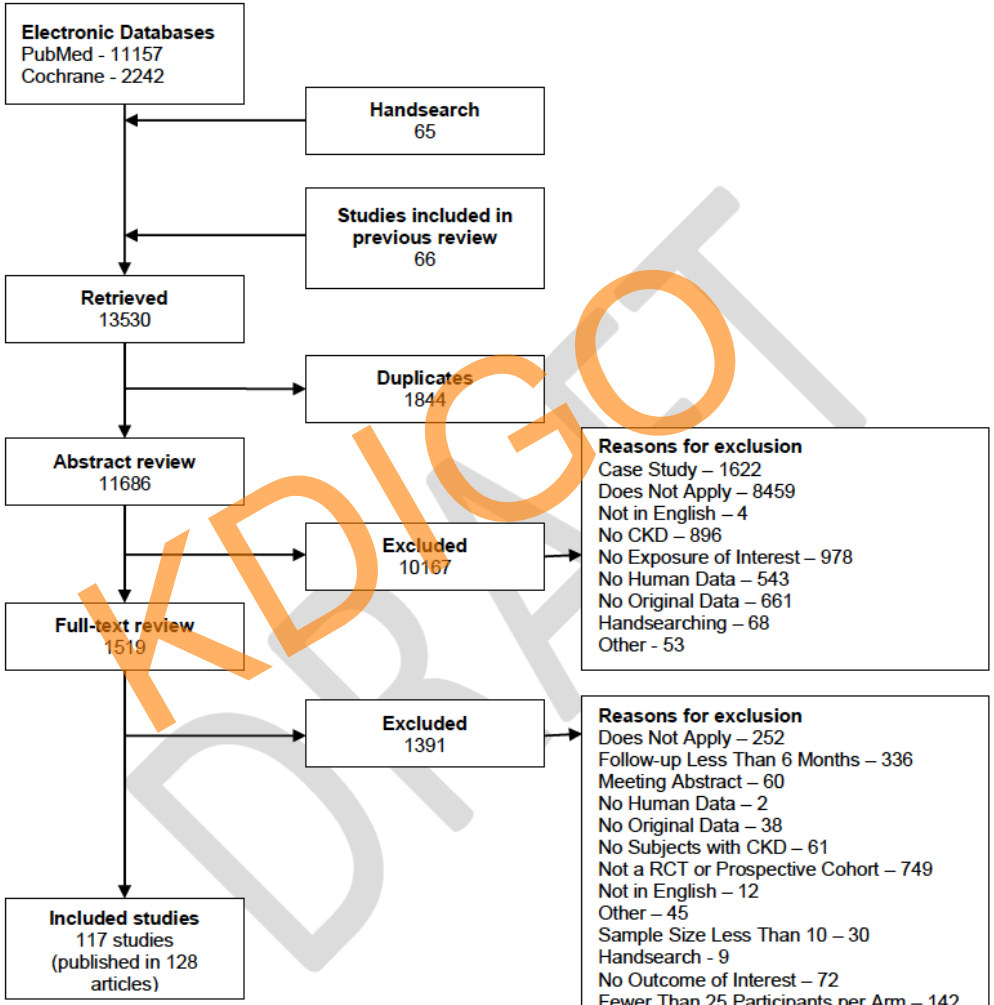
[c]Very strong evidence of association is defined as 'significant RR of >5 (<0.2)' based on direct evidence with no major threats to validity.

Modified with permission from Uhlig (2006)[152] and Atkins (2004).[153]

Final Grade for Overall Evidence Quality

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

SUMMARY OF ERT SEARCH YIELD



SIGN UP TO REVIEW CKD-MBD GUIDELINE UPDATE DRAFT

KDIGO 2016 CLINICAL PRACTICE GUIDELINE UPDATE
ON DIAGNOSIS, EVALUATION, PREVENTION AND
TREATMENT OF CKD-MBD

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