COMPARISON OF EXISTING ANEMIA GUIDELINES WORLDWIDE

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The Kidney Disease: Improving Global Outcomes website: Comparison of guidelines as a tool for harmonization

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Chronic kidney disease (CKD) is a worldwide public health problem with significant comorbidity and mortality. Improving quality of life and survival of CKD patients necessitates a large number of preventive and therapeutic interventions. To resolve these issues several organizations have developed guidelines, which are difficult to compare comprehensively. The Kidney Disease: Improving Global Outcomes website at http://kdigo.org compares five major guidelines. The section ‘compare guidelines’ covers 41 topics distributed over five major subjects: (1) general clinics; (2) hemodialysis (HD); (3) vascular access for HD; (4) peritoneal dialysis; and (5) chemistries. The tables compare guideline recommendations and the evidence levels on which they are based, with direct links to each of the guidelines. These data show that the different guideline groups tend to propose similar targets, but that nuances in the guideline statements, their rationale, and grading of evidence levels present some discrepancies, although most guidelines are based on the same literature. We conclude that there is an urgent need to harmonize existing guidelines, and for a global initiative to avoid the parallel development of conflicting guidelines on the same topics. The tables displayed on the website offer a basis for structuring this process, a procedure which has recently been initiated by a body composed of the five guideline development groups.
Mission Statement:
To improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines.

KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES (KDIGO)

Clinical Practice Guidelines Survey
Please take the time to complete our short online survey.

Participate in the Review Process
Participate in the Review Process
Sign up to review the KDIGO Clinical Practice Guidelines currently under development

KDIGO News
Meetings & Events
- NEW: KDIGO Position Statement on CKD as a Global Public Health Problem: Approaches and Initiatives Published in KI
- Compilation of International Guidelines for Immunization in CKD
- KDIGO Board Completes Review of Clinical Practice Guidelines on Hepatitis C in Chronic Kidney Disease
- KDIGO Controversies Conference on CKD as a Global Public Health Problem

About Us
Kidney Disease Improving Global Outcomes (KDIGO) was established in 2003 as an independently incorporated non-profit foundation governed by an international board with the stated mission to "improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines."

KDIGO is managed by the National Kidney Foundation, a U.S. foundation with 11 years of experience in developing and implementing guidelines.

Click on the article below for a more detailed description of why and how KDIGO was created.

October 2004 - The burden of kidney disease: Improving global outcomes

Authors: Garabed Eknoyan, Norbert Lameire, Rashad Barssoum, Kai-Uwe Eckardt, Adeera Levin,
CLINICAL PRACTICE GUIDELINES

KDIGO is pleased to announce the development of three global clinical practice guidelines in nephrology:

- Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in Chronic Kidney Disease, under the leadership of Drs. Michel Jadhoul and David Roth. (Anticipated Publication - 2007)
- Diagnosis, Evaluation, Prevention and Treatment of Chronic kidney Disease related Mineral and Bone Disorders (CKD-MBD), under the leadership of Drs. Tilman Druke and Sharon Mox (Anticipated Publication - 2008)
- Care of the Kidney Transplant Recipient, under the leadership of Drs. Bertram Kasiske and Martin Zierer (Anticipated Publication - 2008)

Guiding principles for the KDIGO guideline development process include:

- Scientific and methodological rigor: The process will be evidence-based. The grading of the evidence and recommendations will adhere to the position statement of KDIGO on the grading evidence and recommendations for clinical practice guidelines.
- Interdisciplinary approach: Work Group members will be chosen for leadership in their respective fields, commitment to quality of care and expertise in clinical practice, with due consideration of international representation reflecting the mission statement of KDIGO.
- Independence of Work Groups: The workgroup will have independence and final responsibility in the formulation of recommendations. This will assure an unbiased approach to guideline development, without influence of organizations or industry.
- Openness of the guideline development process: Following their initial review by KDIGO Executive Committee and Board of Directors the draft guidelines will be subjected to an organizational and peer review process that invites comment from international groups and professionals whom the guidelines will affect. Comments submitted at each phase of the review process will be carefully reviewed and considered by the Work Group prior to publication of the final guidelines.

The development process will take 18-24 months for each guideline.

We invite you to be part of the clinical practice guideline development by:

- Participating in the guideline development process by registering in the peer review phase of the guidelines. (Sign up)
- Submitting your suggestions on future guideline topics and activities that KDIGO should undertake. (Take Clinical Practice Guidelines Survey)

We look forward to your participation in this important initiative.

Sincerely,
Garabed Eknoyan
Norbert Lomeire
KDIGO Co-chairs
COMPARE GUIDELINES

Compare Guidelines

The Kidney Disease: Improving Global Outcomes has created summary tables listing the key features of the currently-available dialysis clinical practice guidelines in Europe, Canada, Australia, UK and US. The ultimate goal is to create an interactive and searchable database, available on the Internet, to facilitate comparison of the guidelines.

Choose from the list below for a guideline comparison table showing recommendations, evidence, and notes from the 5 international groups.

General Nephrology
- target hemoglobin
- mineral metabolism targets: stage 3
- mineral metabolism targets: stage 4
- target blood pressure
- preferred nephroprotective agents
- protocol for hepatitis B vaccination
- time referral to the nephrologist (Rationale)
- cardiovascular screening in kidney disease

Hemodialysis
- target hemoglobin (Rationale)
- Kt/V urea (Rationale)
- mineral metabolism targets: stage 5
- target blood pressure
- middle molecule removal
- bacteriological dialysate purity
- anticoagulation (HD) with bleeding risk
- anticoagulation (HD) without bleeding risk
- anticoagulation for HFT
- time to start dialysis
- chemical dialysate purity

Vascular Access for HD
- preferred vascular access (Rationale)
- prevention of infection general prevention of infection AV-fistulae
<table>
<thead>
<tr>
<th>Source</th>
<th>Hemoglobin Level</th>
<th>Evidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARD-Australia 2005</td>
<td>≤12 g/dl for patients with proven or likely CV disease</td>
<td>Evidence level I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥11 g/dl recommended minimum</td>
<td>Evidence level III-IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb between 12-14 g/dl has beneficial effect when no CV disease</td>
<td>Evidence level III-IV</td>
<td></td>
</tr>
<tr>
<td>CSN-Canada 1999</td>
<td>11-12 g/dl (Target Rationale)</td>
<td>Guideline 2.5 Assessing for Erythropoetin Therapy PDF page S294</td>
<td>Opinion</td>
</tr>
<tr>
<td>ESPO Europe 2004</td>
<td>&gt;11 g/dl (Target Rationale)</td>
<td>II.1 What are the appropriate hemoglobin targets for anemia treatment? Not allowed to go higher than 12 g/dl in severe cardiovascular disease. A global value in excess of 14 g/dl is not recommended. Evidence Level B</td>
<td>Targets recommended are for erythropoietin administration and not for blood transfusion therapy. Evidence Level B</td>
</tr>
<tr>
<td>KDOQI-US 2001</td>
<td>11 to 12 g/dl (Target Rationale)</td>
<td>Guideline 4: Target Hemoglobin/Hematocrit for Epoetin Therapy.</td>
<td></td>
</tr>
<tr>
<td>UK-Guidelines 2002</td>
<td>&gt;10 g/dl (Target Rationale)</td>
<td>7. Anemia in patients with chronic renal failure Article 126-129 of 204 website PDF pages.</td>
<td>Evidence level A</td>
</tr>
</tbody>
</table>
## Comparative data regarding target Hgb levels

<table>
<thead>
<tr>
<th>Origin</th>
<th>Year</th>
<th>Target</th>
<th>Comments</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARI</td>
<td>2005</td>
<td>≥ 11 g/dl</td>
<td>≤ 12 g/dl in CVD</td>
<td>III-IV; comment: I</td>
</tr>
<tr>
<td>CSN</td>
<td>1999</td>
<td>11-12 g/dl</td>
<td></td>
<td>Opinion</td>
</tr>
<tr>
<td>EBPG</td>
<td>2004</td>
<td>&gt; 11 g/dl</td>
<td>Not &gt; 12 g/dl in severe CVD</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not &gt; 14 g/dl globally</td>
<td></td>
</tr>
<tr>
<td>K/DOQI</td>
<td>2001</td>
<td>11-12 g/dl</td>
<td>Targets for EPO, not for transfusion</td>
<td>Evidence</td>
</tr>
<tr>
<td>UK</td>
<td>2002</td>
<td>&gt; 10 g/dl</td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>

Abbreviations of guideline names (origin): see Table 5. CVD, cardio-vascular disease; EPO, erythropoietin.

For comparison of different evidence scoring systems, please refer to Table 5.
DISSECTION: YEAR OF PUBLICATION

- CARI 2005
- CSN 1999
- EBPG 2004
- K/DOQI 2001 (update 2006/2007)
- UK 2000
DISSECTION: MINIMUM TARGET

• CARI / CSN / EBPG / K/DOQI:
  • = or > 11 g/dL

• Only exception: UK
  • > 10 g/dL
DISSECTION: MAXIMUM TARGET

- For CSN and K/DOQI:
  - 12 g/dL

- For CARI, EBPG, and UK:
  - No maximum in proper guideline

- For CARI in comments:
  - 12 g/dL in severe cardiovascular disease
  - 12-14 g/dL beneficial if no CV disease

- For EBPG in comments:
  - 12 g/dL in severe cardiovascular disease
  - 14 g/dL globally
DISSECTION: EVIDENCE LEVELS

- CARI: III-IV
  (comment < 12 in CVD: I)
- CSN: Opinion
- EBPG: B (= III-IV)
- K/DOQI: Evidence (can be I, II, III or IV)
- UK: A (I-II)
All these conclusions seem to be based on the same literature.

For minimum: a series of non-randomized studies, suboptimal RCT’s and a meta-analysis based on these suboptimal studies (Cochrane 2003).


Besarab et al: restricted to severe CVD (+ elderly and graft as access) – conclusions extrapolated to general population.
DISSECTION: FURTHER REFLECTIONS (2)

• Not much evolution in the literature between 1999 and 2004-2005
• Extra argument for target of 10 in UK guidelines: cost
• Reason for absolute maximum of 14 in EBPG: concern for hemoconcentration in hemodialysis
• Nevertheless no separate recommendations for CKD 3-4, PD and transplantation
## K/DOQI UPDATE 2006 vs. 2001*

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>11 g/dL</td>
<td>11 g/dL</td>
</tr>
<tr>
<td>Maximum</td>
<td>12 g/dL</td>
<td>“insufficient evidence to recommend routinely maintaining Hb levels above 13g/dL”</td>
</tr>
</tbody>
</table>

*: guidelines endorsed by EBPG and generated by a committee also containing European experts, formerly involved in EBPG anemia
CONCLUSIONS (1)

- Among existing guidelines, subtle differences in target Hb levels exist.
- Most guidelines give a minimum target of 11 g/dL with one exception at 10 (UK).
- The maximum fluctuated between 12 and 14 g/dL.
- The most striking differences were regarding evidence levels.
CONCLUSIONS (2)

- Advent of two new RCT’s, showing an outcome disadvantage for high target Hb, shed a new light on our attitude towards threshold values
- Up till now, only K/DOQI issued an update
- Their committee contained also EBPG members
- The target was set at 11-12 g/dL, with a warning against targets > 13 (previous update 2006)
K/DOQI UPDATE 2006 vs. 2001

• Arguments for defining the minimal level at 11 g/dL:
  – Essentially RCT’s with a benefit
    • QoL
    • LVH

• Arguments for generating a warning for Hb> 13 g/dL
  – Again Besarab et al (higher target 14 g/dL)
  – Parfrey, JASN 2005: more CVA (higher target 13.5 g/dL)
K/DOQI UPDATE 2006 vs. 2001

• “Similarly, the Work Group considered, but rejected, identifying a target Hb level bounded by narrow upper and lower values (e.g. 11 to 12 g/dL). Such a target affords neither clarity nor simplicity, is possible to achieve in only a minority of patients, discourages flexibility in treating individual patients, and likely promotes cycling of Hb results greater than and less than the target.”
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National Kidney Foundation Releases Preliminary Anemia Guideline Update

New Evidence Spurs Re-examination of 2006 Recommendations

Orlando, Florida
April 12, 2007

After reviewing new information about anemia management in chronic kidney disease (CKD), a National Kidney Foundation Kidney Disease Outcomes Quality Initiative™ (KDOQ™) work group is today issuing a draft update to its 2006 Clinical Practice Guidelines on Anemia and CKD. The draft is being sent to over 1000 stakeholders for review and comment, prior to being finalized and published.

A key aspect of the new update is that the work group was able to clarify key aspects of a Hemoglobin (Hb) target for patients receiving Erythropoiesis Stimulating Agent (ESA) therapy. In the new statements, the work group recommends factors that should be considered in selecting a Hb target and states that the selected Hb target should generally be in the range 11.0 to 12.0 g/dL. They point out that because of natural fluctuations, actual Hb results will vary widely from Hb targets.

Also, after reviewing the latest results from six new randomized controlled trials about anemia management in chronic kidney disease (which doubled the number of CKD patients studied), the work group was able to upgrade one of its opinion-based statement to an evidence-based guideline recommending that, in dialysis and non-dialysis CKD patients receiving Erythropoiesis Stimulating Agent (ESA) therapy, the Hb target should not be above 13.0 g/dL.

“We want all clinicians who treat patients with chronic kidney disease to have guidelines based on the most up-to-date and reliable science available,” says Mike Rocco, MD, Vice-chair of KDOQ™.

The work group -- made up of 16 volunteer experts in nephrology,
“The work group clearly felt that the evidence is even stronger now that their original recommendation to choose Hb targets below 13 g/dL is very appropriate for CKD patients,” says Dr Michael Rocco.

“The US FDA has placed an upper limit for target Hb at 12.0 g/dL. Recently the agency issued a black boxed warning … that Hb above 13 g/dL had a higher risk of death, blood clots, strokes and heart attacks.”
2.1.2. In the opinion of the Work Group, in dialysis and non-dialysis CKD patients receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL (Clinical Practice RECOMMENDATION)

- **Target**: distinguishes between a targeted and an achieved value
- **Generally**: emphasizes flexibility in medical decision making
K/DOQI UPDATE ANEMIA GUIDELINES (DRAFT)

- 2.1.3. In dialysis and non-dialysis CKD patients receiving ESA therapy, the Hb target should not be above 13 g/dL (Clinical Practice GUIDELINE - MODERATELY STRONGLY EVIDENCE)
• Limitations of evidence
  – Singh et al
    • Greater proportion of patients with higher Hb target had a history of hypertension and coronary bypass
    • After adjustment for baseline cardiac condition, significance for high Hb disappeared
    • High rates of premature study termination
  – Drüeke et al
    • Event rate much lower than predicted