COMPARISON OF EXISTING ANEMIA GUIDELINES WORLDWIDE

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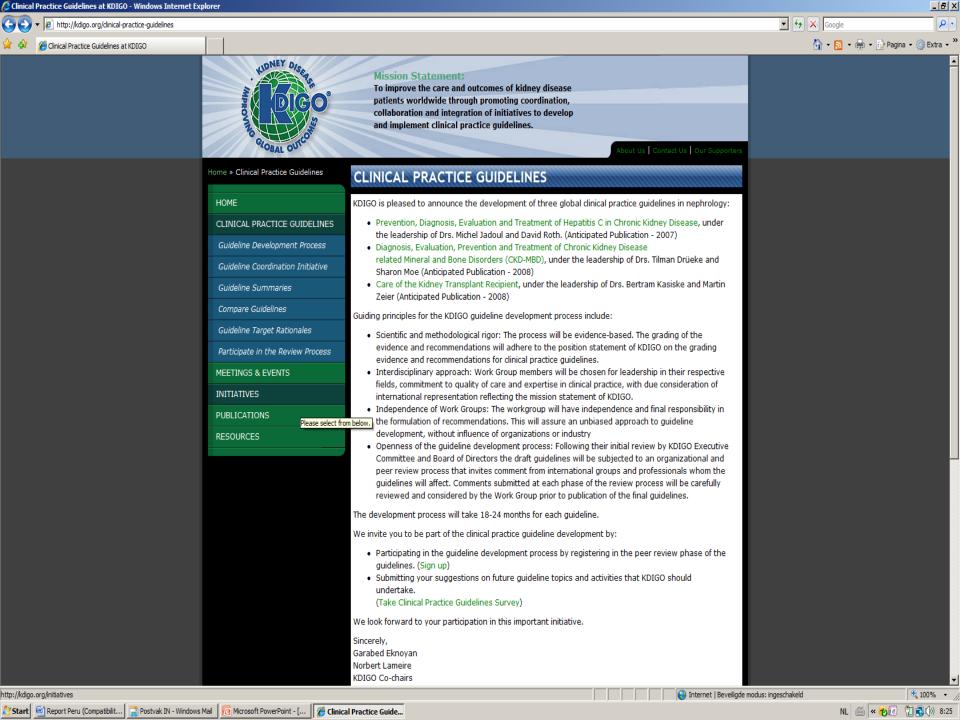
The Kidney Disease: Improving Global Outcomes website: Comparison of guidelines as a tool for harmonization

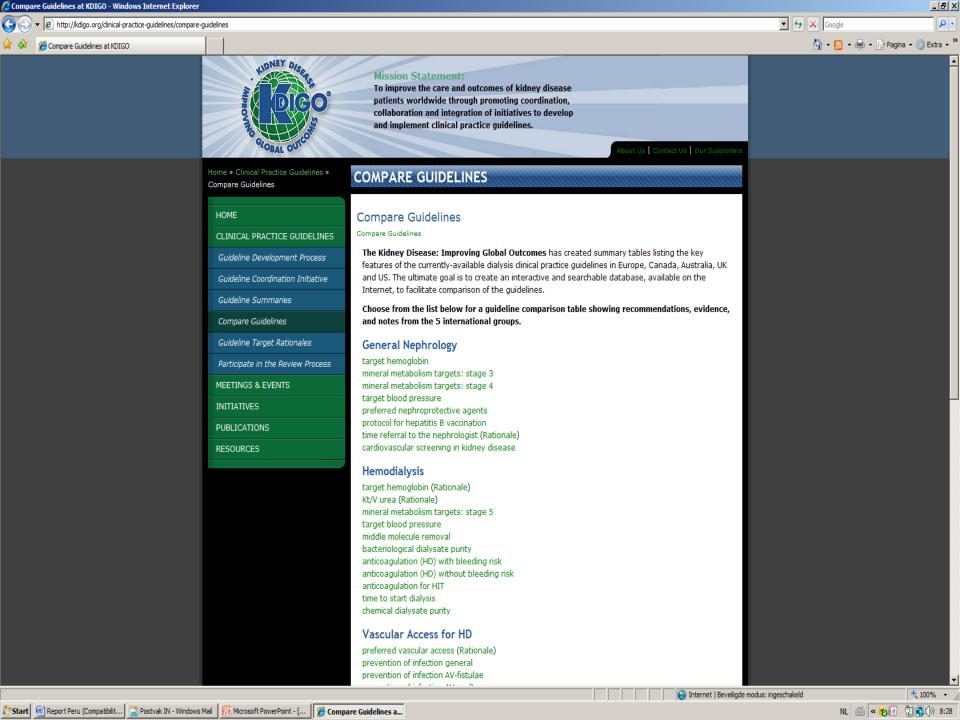
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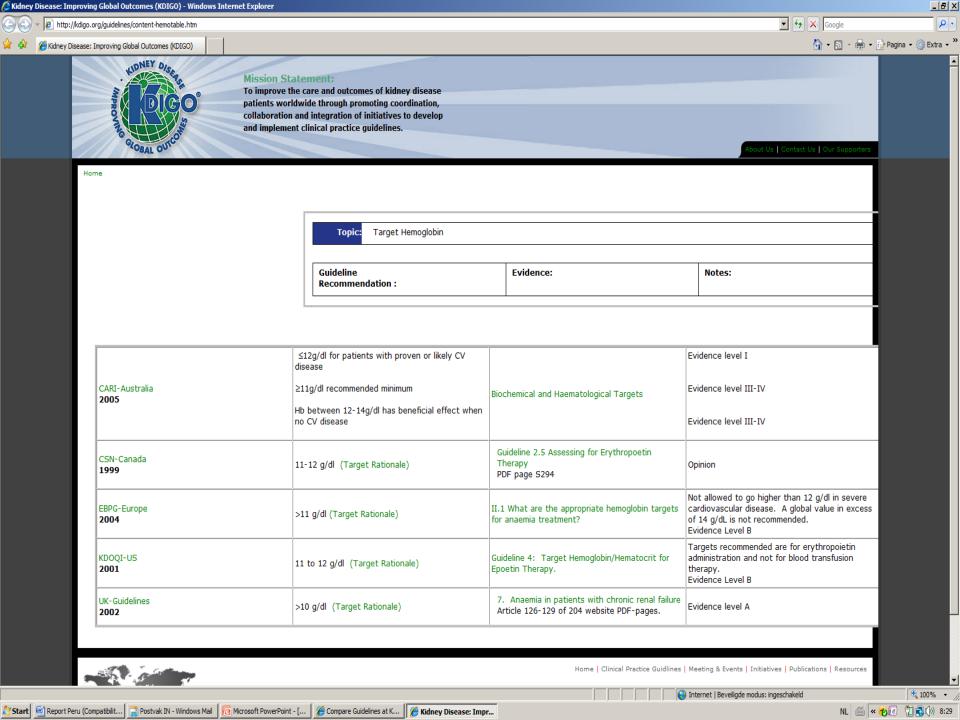
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Chronic kidney disease (CKD) is a worldwide public health problem with significant comorbidity and mortality. Improving quality of life and survival of CKD patients necessitates a large number of preventive and therapeutic interventions. To resolve 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.









Comparative data regarding target Hgb levels

Origin	Year	Target	Comments	Evidence
CARI	2005	≥ 11 g/dl	≤ 12 g/dl in CVD	III-IV; comment: I
CSN	1999	11-12 g/dl		Opinion
EBPG	2004	> 11 g/dl	Not > 12 g/dl in severe CVD Not > 14 g/dl globally	В
k/doqi UK	2001 2002	11-12 g/dl > 10 g/dl	Targets for EPO, not for transfusion	Evidence A

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)

DISSECTION: FURTHER REFLECTIONS (1)

- All these conclusions seems to be based on the same literature
- For mimimum: a series of non-randomized studies, suboptimal RCT's and a meta-analysis based on these suboptimal studies (Cochrane 2003)
- For maximum: Besarab et al, NEJM, 1998
- 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*

	2001	2006
Minimum	11 g/dL	11 g/dL
Maximum	12 g/dL	"insufficient evidence to recommend routinely maintaining Hb levels above 13g/dL"

*: 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)

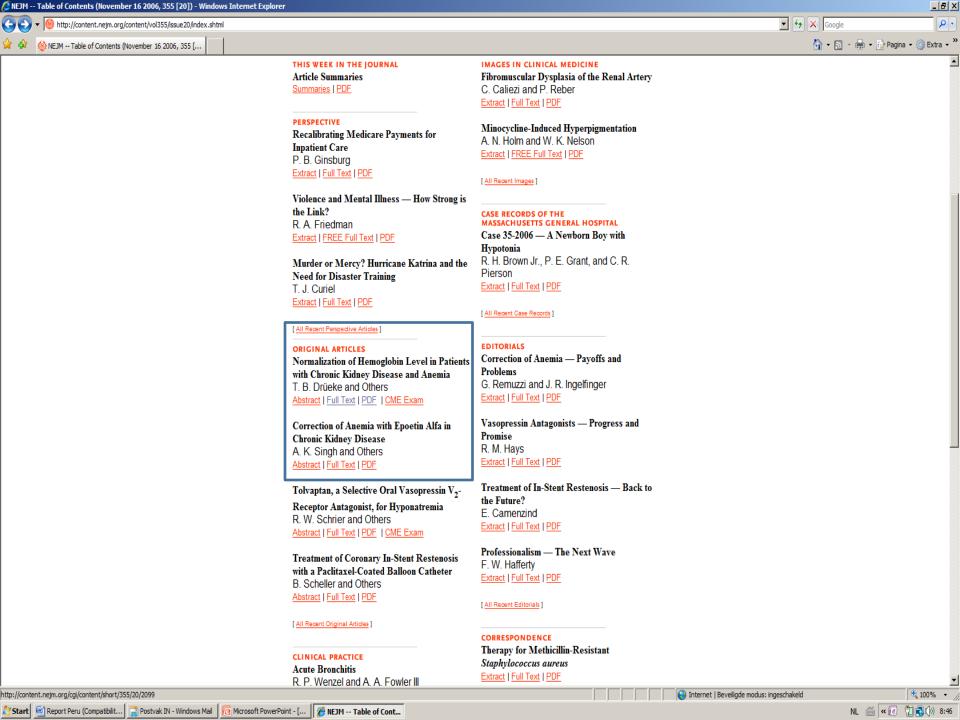
- Advent of two new RCT's, showing an outcome disadvantage for high target Hb, shed a new light on our attitude towards threshold values
- Up till now, only K/DOQI issued an update
- Their committee contained also EBPG members
- The target was set at 11-12 g/dL, with a warning against targets > 13 (//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

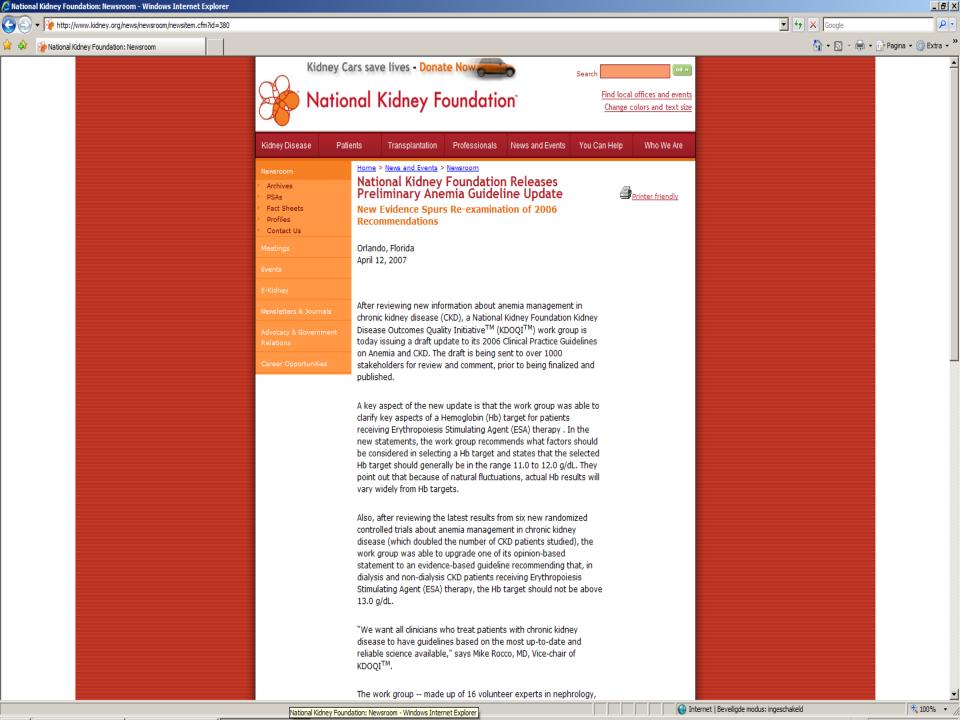
K/DOQI UPDATE 2006 vs. 2001

- 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 afforts 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."





COMMUNICATION K/DOQI APRIL 12 2007

- "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."

K/DOQI UPDATE ANEMIA GUIDELINES (DRAFT)

- 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 STRONG EVIDENCE)

K/DOQI UPDATE ANEMIA GUIDELINES (DRAFT)

- 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