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KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease

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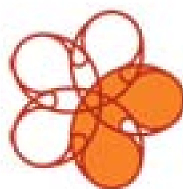

National Kidney Foundation®

KDIGO Clinical Practice Guideline

for Anemia in Chronic Kidney Disease

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Additional information in the form of supplementary materials can be found online at http://www.kdigo.org/clinical_practice_guidelines/anemia.php

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Reference Keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1**, **Level 2**, or **Not Graded**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	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.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
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 substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

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.

STAGES OF CHRONIC KIDNEY DISEASE

CKD Stage	Description	GFR (ml/min per 1.73 m^2)
1	Kidney damage with normal or increased GFR	$\geq$90
2	Kidney damage with mild decreased GFR	60–89
3	Moderate decreased GFR	30–59
4	Severe decreased GFR	15–29
5[a]	Kidney failure	$<$15 (or dialysis)

CKD, chronic kidney disease; GFR, glomerular filtration rate.
CKD 1–5T notation applies to kidney transplant recipients.
[a]5D if dialysis (HD or PD).

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD Categories	Definition
CKD	CKD of any stage (1–5), with or without a kidney transplant, including both non-dialysis dependent CKD (CKD 1–5ND) and dialysis-dependent CKD (CKD 5D)
CKD ND	Non-dialysis-dependent CKD of any stage (1–5), with or without a kidney transplant (i.e., CKD excluding CKD 5D)
CKD T	Non-dialysis-dependent CKD of any stage (1–5) with a kidney transplant
Specific CKD Stages	
CKD 1, 2, 3, 4	Specific stages of CKD, CKD ND, or CKD T
CKD 3-4, etc.	Range of specific stages (e.g., both CKD 3 and CKD 4)
CKD 5D	Dialysis-dependent CKD 5
CKD 5HD	Hemodialysis-dependent CKD 5
CKD 5PD	Peritoneal dialysis-dependent CKD 5

CONVERSION FACTORS OF METRIC UNITS TO SI UNITS

Parameter	Metric units	Conversion factor	SI units
Ferritin	ng/ml	1	μg/l
Hemoglobin	g/dl	10	g/l

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Abbreviations and Acronyms

Δ	Change
AGREE	Appraisal of Guidelines for Research and Evaluation
BM	Bone marrow
CBC	Complete blood count
CERA	Continuous erythropoietin receptor activator
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CI	Confidence interval
CKD	Chronic kidney disease
CKiD	Chronic Kidney Disease in Children Prospective Cohort Study
COGS	Conference on Guideline Standardization
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta Trial
CRP	C-reactive protein
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPO	Erythropoietin
ERT	Evidence review team
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
EQ-5D	A measure of health status from the EuroQol Group
FACT-Fatigue	Functional Assessment of Cancer Therapy-Fatigue
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
Hb	Hemoglobin
Hct	Hematocrit
HCV	Hepatitis C virus
HD	Hemodialysis
HEMO Study	Kidney Disease Clinical Studies Initiative Hemodialysis Study
HLA	Human leukocyte antigen
HR	Hazard ratio
IM	Intramuscular
IU	International unit
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	Clearance expressed as a fraction of urea or body water volume
MCH	Mean corpuscular hemoglobin
NAPRTCS	North American Pediatric Renal Transplant Cooperative Study
ND	Non-dialysis
NHANES	National Health and Nutrition Examination Survey
PD	Peritoneal dialysis
PRA	Panel reactive antibody
PRCA	Pure red cell aplasia
QoL	Quality of life
RBC	Red blood cell
RCT	Randomized controlled trial
rHuEPO	Recombinant human erythropoietin
ROC	Receiver operating characteristic
RR	Relative risk
SC	Subcutaneous
SF-36	36-Item Medical Outcomes Study Short-Form Health Survey
TRALI	Transfusion-related acute lung injury
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSAT	Transferrin saturation
USRDS	United States Renal Data System
WHO	World Health Organization

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Notice

Kidney International Supplements (2012) **2**, 279; doi:10.1038/kisup.2012.37

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon systematic literature searches last conducted in October 2010, supplemented with additional evidence through March 2012. It is designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information will be printed in the final publication and are on file at the National Kidney Foundation (NKF), Managing Agent for KDIGO.

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Foreword

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It is our hope that this document will serve several useful purposes. Our primary goal is to improve patient care. We hope to accomplish this, in the short term, by helping clinicians know and better understand the evidence (or lack of evidence) that determines current practice. By providing comprehensive evidence-based recommendations, this guideline will also help define areas where evidence is lacking and research is needed. Helping to define a research agenda is an often neglected, but very important, function of clinical practice guideline development.

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to rate the strength of evidence and the strength of recommendations. In all, there were only 2 (5.4%) recommendations in this guideline for which the overall quality of evidence was graded 'A,' whereas 9 (24.3%) were graded 'B,' 14 (37.8%) were graded 'C,' and 12 (32.4%) were graded 'D.' Although there are reasons other than quality of evidence to make a grade 1 or 2 recommendation, in general, there is a correlation between the quality of overall evidence and the strength of the recommendation. Thus, there were 15 (40.5%) recommendations graded '1' and 22 (59.5%) graded '2.' There were 2 (5.4%) recommendations graded '1A,' 8 (21.6%) were '1B,' 1 (2.7%) were '1C,' and 4 (10.8%) were '1D.' There were 0 (0%) graded '2A,' 1 (2.7%) were '2B,' 13 (35.1%) were '2C,' and 8 (21.6%) were '2D.' There were 22 (37.3%) statements that were not graded.

Some argue that recommendations should not be made when evidence is weak. However, clinicians still need to make clinical decisions in their daily practice, and they often ask, 'What do the experts do in this setting?' We opted to give guidance, rather than remain silent. These recommendations are often rated with a low strength of recommendation and a low strength of evidence, or were not graded. It is important for the users of this guideline to be cognizant of this (see Notice). In every case these recommendations are meant to be a place for clinicians to start, not stop, their inquiries into specific management questions pertinent to the patients they see in daily practice.

We wish to thank the Work Group Co-Chairs, Drs John McMurray and Pat Parfrey, along with all of the Work Group members who volunteered countless hours of their time developing this guideline. We also thank the Evidence Review Team members and staff of the National Kidney Foundation who made this project possible. Finally, we owe a special debt of gratitude to the many KDIGO Board members and individuals who volunteered time reviewing the guideline, and making very helpful suggestions.

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Abstract

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The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease aims to provide guidance on diagnosis, evaluation, management and treatment for all CKD patients (non-dialysis, dialysis, kidney transplant recipients and children) at risk of or with anemia. Guideline development followed an explicit process of evidence review and appraisal. The guideline contains chapters addressing diagnosis and evaluation of anemia in CKD and the use of various therapeutic agents (iron, ESAs and other agents) and red cell transfusion as means of treatment. Treatment approaches are addressed in each chapter and guideline recommendations are based on systematic reviews of relevant trials. Appraisal of the quality of the evidence and the strength of recommendations followed the GRADE approach. Ongoing areas of controversies and limitations of the evidence are discussed and additional suggestions are also provided for future research.

Keywords: anemia in CKD; blood transfusions; clinical practice guideline; erythropoiesis-stimulating agent; KDIGO; evidence-based recommendation; iron; systematic review.

In citing this document, the following format should be used: Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney inter., Suppl.* 2012; **2**: 279–335.

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Summary of Recommendation Statements

Kidney International Supplements (2012) **2,** 283–287; doi:10.1038/kisup.2012.41

Chapter 1: Diagnosis and evaluation of anemia in CKD

TESTING FOR ANEMIA

Frequency of testing for anemia

1.1.1: For CKD patients without anemia (as defined below in Recommendation 1.2.1 for adults and Recommendation 1.2.2 for children), measure Hb concentration when clinically indicated and (*Not Graded*):
- **at least annually in patients with CKD 3**
- **at least twice per year in patients with CKD 4–5ND**
- **at least every 3 months in patients with CKD 5HD and CKD 5PD**

1.1.2: For CKD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and (*Not Graded*):
- **at least every 3 months in patients with CKD 3–5ND and CKD 5PD**
- **at least monthly in patients with CKD 5HD**
  [See Recommendations 3.12.1–3.12.3 for measurement of Hb concentration in patients being treated with ESA.]

Diagnosis of anemia

1.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (*Not Graded*)

1.2.2: Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dl (<110 g/l) in children 0.5–5 years, <11.5 g/dl (115 g/l) in children 5–12 years, and <12.0 g/dl (120 g/l) in children 12–15 years. *(Not Graded)*

Investigation of anemia

1.3: In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (*Not Graded*):
- **Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count**
- **Absolute reticulocyte count**
- **Serum ferritin level**
- **Serum transferrin saturation (TSAT)**
- **Serum vitamin B_{12} and folate levels**

Chapter 2: Use of iron to treat anemia in CKD

TREATMENT WITH IRON AGENTS

2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). *(Not Graded)*

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):
- **an increase in Hb concentration without starting ESA treatment is desired* and**
- **TSAT is $\leq 30\%$ and ferritin is ≤ 500 ng/ml (≤ 500 μg/l)**

*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.

2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):
- **an increase in Hb concentration** or a decrease in ESA dose is desired*** and**
- **TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 μg/l)**

2.1.4: For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (*Not Graded*)

2.1.5: Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (*Not Graded*)

2.1.6: For all pediatric CKD patients with anemia not on iron or ESA therapy, we recommend oral iron (or IV iron in CKD HD patients) administration when TSAT is ≤20% and ferritin is ≤100 ng/ml (≤100 μg/l). (*1D*)

2.1.7: For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, we recommend oral iron (or IV iron in CKD HD patients) administration to maintain TSAT >20% and ferritin >100 ng/ml (>100 μg/l). (*1D*)

**Consistent with Recommendations #3.4.2 and 3.4.3.
***Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

IRON STATUS EVALUATION

2.2.1: Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (*Not Graded*)

2.2.2: Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (*Not Graded*)

CAUTIONS REGARDING IRON THERAPY

2.3: When the initial dose of IV iron dextran is administered, we recommend (*1B*) and when the initial dose of IV non-dextran iron is administered, we suggest (*2C*) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

Iron during infection

2.4: Avoid administering IV iron to patients with active systemic infections. (*Not Graded*)

Chapter 3: Use of ESAs and other agents to treat anemia in CKD

ESA INITIATION

3.1: Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. (*Not Graded*)

3.2: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (*1B*)

3.3: We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(*1B*), a history of stroke (*1B*), or a history of malignancy (*2C*).

3.4.1: For adult CKD ND patients with Hb concentration $\geq$10.0 g/dl ($\geq$100 g/l), we suggest that ESA therapy not be initiated. (*2D*)

3.4.2: For adult CKD ND patients with Hb concentration $<$10.0 g/dl ($<$100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (*2C*)

3.4.3: For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l). (*2B*)

3.4.4: Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (*Not Graded*)

3.4.5: For all pediatric CKD patients, we suggest that the selection of Hb concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (*2D*)

ESA MAINTENANCE THERAPY

3.5.1: In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (*2C*)

3.5.2: Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (*Not Graded*)

3.6: In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). (*1A*)

3.7: In all pediatric CKD patients receiving ESA therapy, we suggest that the selected Hb concentration be in the range of 11.0 to 12.0 g/dl (110 to 120 g/l). (*2D*)

ESA DOSING

3.8.1: We recommend determining the initial ESA dose using the patient's Hb concentration, body weight, and clinical circumstances. (*1D*)

3.8.2: We recommend that ESA dose adjustments be made based on the patient's Hb concentration, rate of change in Hb concentration, current ESA dose and clinical circumstances. (*1B*)

3.8.3: We suggest decreasing ESA dose in preference to withholding ESA when a downward adjustment of Hb concentration is needed. (*2C*)

3.8.4: Re-evaluate ESA dose if (*Not Graded*):

- **The patient suffers an ESA-related adverse event**
- **The patient has an acute or progressive illness that may cause ESA hyporesponsiveness (See Recommendations 3.13.1–3.13.2)**

ESA ADMINISTRATION

3.9.1: For CKD 5HD patients and those on hemofiltration or hemodiafiltration therapy, we suggest either intravenous or subcutaneous administration of ESA. (*2C*)

3.9.2: For CKD ND and CKD 5PD patients, we suggest subcutaneous administration of ESA. (*2C*)

Frequency of administration

3.10: We suggest determining the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA. (*2C*)

TYPE OF ESA

3.11.1: We recommend choosing an ESA based on the balance of pharmacodynamics, safety information, clinical outcome data, costs, and availability. (*1D*)

3.11.2: We suggest using only ESAs that have been approved by an independent regulatory agency. Specifically for 'copy' versions of ESAs, true biosimilar products should be used. (*2D*)

EVALUATING AND CORRECTING PERSISTENT FAILURE TO REACH OR MAINTAIN INTENDED HEMOGLOBIN CONCENTRATION

Frequency of monitoring

3.12.1: During the initiation phase of ESA therapy, measure Hb concentration at least monthly. (*Not Graded*)
3.12.2: For CKD ND patients, during the maintenance phase of ESA therapy measure Hb concentration at least every 3 months. (*Not Graded*)
3.12.3: For CKD 5D patients, during the maintenance phase of ESA therapy measure Hb concentration at least monthly. (*Not Graded*)

Initial ESA hyporesponsiveness

3.13.1: Classify patients as having ESA hyporesponsiveness if they have no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing. (*Not Graded*)
3.13.2: In patients with ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the initial weight-based dose. (*2D*)

Subsequent ESA hyporesponsiveness

3.14.1: Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration. (*Not Graded*)
3.14.2: In patients with acquired ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable. (*2D*)

Management of poor ESA responsiveness

3.15.1: Evaluate patients with either initial or acquired ESA hyporesponsiveness and treat for specific causes of poor ESA response. (*Not Graded*)
3.15.2: For patients who remain hyporesponsive despite correcting treatable causes, we suggest individualization of therapy, accounting for relative risks and benefits of (*2D*):
- **decline in Hb concentration**
- **continuing ESA, if needed to maintain Hb concentration, with due consideration of the doses required, and**
- **blood transfusions**

ADJUVANT THERAPIES

3.16.1: We recommend not using androgens as an adjuvant to ESA treatment. (*1B*)
3.16.2: We suggest not using adjuvants to ESA treatment including vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline. (*2D*)

EVALUATION FOR PURE RED CELL APLASIA (PRCA)

3.17.1: Investigate for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 weeks develops the following (*Not Graded*):
- **Sudden rapid decrease in Hb concentration at the rate of 0.5 to 1.0 g/dl (5 to 10 g/l) per week *OR* requirement of transfusions at the rate of approximately 1 to 2 per week, *AND***
- **Normal platelet and white cell counts, *AND***
- **Absolute reticulocyte count less than 10,000/μl**

3.17.2: We recommend that ESA therapy be stopped in patients who develop antibody-mediated PRCA. (*1A*)
3.17.3: We recommend peginesatide be used to treat patients with antibody-mediated PRCA. (*1B*)

Chapter 4: Red cell transfusion to treat anemia in CKD

USE OF RED CELL TRANSFUSION IN CHRONIC ANEMIA

4.1.1: When managing chronic anemia, we recommend avoiding, when possible, red cell transfusions to minimize the general risks related to their use. (*1B*)

4.1.2: In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (*1C*)

4.1.3: When managing chronic anemia, we suggest that the benefits of red cell transfusions may outweigh the risks in patients in whom (*2C*):

- **ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance)**
- **The risks of ESA therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke)**

4.1.4: We suggest that the decision to transfuse a CKD patient with non-acute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia. (*2C*)

URGENT TREATMENT OF ANEMIA

4.2: In certain acute clinical situations, we suggest patients are transfused when the benefits of red cell transfusions outweigh the risks; these include (*2C*):

- **When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable coronary artery disease)**
- **When rapid pre-operative Hb correction is required**

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Chapter 1: Diagnosis and evaluation of anemia in CKD

Kidney International Supplements (2012) **2,** 288–291; doi:10.1038/kisup.2012.33

TESTING FOR ANEMIA

BACKGROUND

In any individual, anemia may be the initial laboratory sign of an underlying medical problem. Consequently, a complete blood count, including the hemoglobin (Hb) concentration, is routinely part of global health assessment in most adults, whether or not they have chronic kidney disease (CKD). In patients with CKD but stable kidney function, the appearance or progression of anemia may herald a new problem that is causing blood loss or is interfering with red cell production. The anemia should be evaluated independently of CKD stage in order to identify any reversible process contributing to the anemia. The causes of acquired anemia are myriad and too many to include in a guideline such as this. A comprehensive list of causes and the approach to diagnosis can be found in a standard textbook of medicine or hematology. The most commonly encountered reversible cause of chronic anemia or worsening anemia in CKD patients, other than anemia related directly to CKD, is iron deficiency anemia.

Frequency of testing for anemia

1.1.1: For CKD patients without anemia (as defined below in Recommendation 1.2.1 for adults and Recommendation 1.2.2 for children), measure Hb concentration when clinically indicated and (*Not Graded*):
- **at least annually in patients with CKD 3**
- **at least twice per year in patients with CKD 4–5ND**
- **at least every 3 months in patients with CKD 5HD and CKD 5PD**

1.1.2: For CKD patients with anemia not being treated with an ESA, measure Hb concentration when clinically indicated and (*Not Graded*):
- **at least every 3 months in patients with CKD 3–5ND and CKD 5PD**
- **at least monthly in patients with CKD 5HD**

[See Recommendations 3.12.1–3.12.3 for measurement of Hb concentration in patients being treated with ESA.]

RATIONALE

Relatively little is known about the development and progression of anemia in patients with CKD. Consequently, one cannot determine precisely the optimal frequency at which Hb levels should be monitored. The recommendation that patients with CKD be periodically evaluated for anemia rests on observations that, in the absence of use of erythropoiesis-stimulating agents (ESAs), there often is a gradual decline in Hb over time in patients with CKD as the level of glomerular filtration rate (GFR) declines,[1] suggesting the need for regular surveillance of Hb concentration. The frequency of Hb monitoring, regardless of CKD stage, should be influenced by the Hb level (i.e., more frequent monitoring may be appropriate in patients with more severe anemia) and rate of decline in Hb level. As kidney function declines and in patients with more advanced CKD stages, the incidence and prevalence of anemia increases. Thus, in order to identify CKD patients who may need intervention with iron administration, an ESA, or even require a transfusion, more frequent monitoring of the Hb concentration will be necessary at later CKD stages.

More frequent monitoring is recommended for adult CKD 5HD and CKD 5PD patients with anemia who are not receiving an ESA; at least monthly in CKD 5HD patients and at least every 3 months in CKD 5PD patients. In CKD 5HD patients, Hb monitoring is traditionally performed prior to a mid-week hemodialysis (HD) session. While this is not essential it probably does tend to minimize Hb variability due to the longer inter-dialytic interval between the last treatment of one week and the first of the next. As in all patients, Hb testing should be performed whenever clinically indicated, such as after a major surgical procedure, hospitalization, or bleeding episode.

In the pediatric population with CKD, there is no direct evidence to recommend a different frequency of monitoring for anemia than for adults. In the Chronic Kidney Disease in Children Prospective Cohort Study (CKiD), which evaluated 340 North American children with CKD using iohexol-determined GFR,[2] below a GFR threshold of 43 ml/min per 1.73 m^2, there was a linear relationship between Hb and GFR, with Hb 0.3 g/dl (3 g/l) lower per 5 ml/min per 1.73 m^2 lower GFR. Above that threshold, there was a nonsignificant association of 0.1 g/dl (1 g/l) lower Hb for every 5 ml/min per 1.73 m^2 lower GFR. Because serum creatinine-based estimated glomerular filtration rate (eGFR) using the Schwartz formula may overestimate the true GFR in the children[3] providers need to consider the potential for Hb decline and anemia even at early stages of CKD and monitor accordingly. In children with CKD 5HD and CKD 5PD, monthly monitoring for anemia is standard clinical practice.

Diagnosis of anemia

1.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (*Not Graded*)

1.2.2: Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dl (<110 g/l) in children 0.5–5 years, <11.5 g/dl (115 g/l) in children 5–12 years, and <12.0 g/dl (120 g/l) in children 12–15 years. *(Not Graded)*

RATIONALE

The Hb concentration values that define anemia and should lead to initiation of an evaluation for the cause of anemia are dependent on sex and age. The recommended Hb values for adults and children represent the World Health Organization (WHO) definition of anemia and establish a benchmark for anemia workup that has been applied across populations.[4]

An alternative source for Hb concentration values that define anemia in children between 1 and 19 years is based on US National Health and Nutrition Examination Survey III (NHANES III) data from 1988–94[5] (Table 1). For children between birth and 24 months, the data are taken from normal reference values[6] (Table 2).

These thresholds for diagnosis of anemia and evaluation for the causes of anemia should not be interpreted as being thresholds for treatment of anemia. Rather than relying on a single laboratory test value, in patients without an apparent cause for a low Hb level, the value should be confirmed to be below the threshold values for diagnosis of anemia prior to initiating a diagnostic work up.

Investigation of anemia

1.3: In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (*Not Graded*):

- **Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count**
- **Absolute reticulocyte count**
- **Serum ferritin level**
- **Serum transferrin saturation (TSAT)**
- **Serum vitamin B_{12} and folate levels**

RATIONALE

Complete blood count

The complete blood count (CBC) provides information about the severity of anemia and adequacy of bone marrow function. Severity of anemia is assessed best by measuring Hb

Table 2 | Hb levels in children between birth and 24 months for initiation of anemia workup[a]

Age	Mean Hb g/dl (g/l)	−2 SD[b] g/dl (g/l)
Term (cord blood)	16.5 (165)	13.5 (135)
1–3 d	18.5 (185)	14.5 (145)
1 wk	17.5 (175)	13.5 (135)
2 wk	16.5 (165)	12.5 (125)
1 mo	14.0 (140)	10.0 (100)
2 mo	11.5 (115)	9.0 (90)
3–6 mo	11.5 (115)	9.5 (95)
6–24 mo	12.0 (120)	10.5 (105)

d, day; Hb, hemoglobin; mo, month; SD, standard deviation; wk, week.
[a]Data taken from normal reference values. This was published in Nathan DG, Orkin SH. Appendix 11: Normal hematologic values in children. In: Nathan DG, Orkin SH, Ginsburg D *et al.* (eds). *Nathan and Oski's Hematology of Infancy and Childhood*, 6th edn. p 1841, © Elsevier, 2003.[6]
[b]Values 2 standard deviations below the mean are equivalent to <2.5th percentile.

Table 1 | Hb levels in children between 1–19 years for initiation of anemia workup[a]

All races/ethnic groups	Number of subjects	Mean Hb g/dl (g/l)	Standard deviation g/dl (g/l)	Anemia definition met if value is <5th percentile g/dl (g/l)
Boys				
1 yr and over	12,623	14.7 (147)	1.4 (14)	12.1 (121)
1–2 yr	931	12.0 (120)	0.8 (8)	10.7 (107)
3–5 yr	1,281	12.4 (124)	0.8 (8)	11.2 (112)
6–8 yr	709	12.9 (129)	0.8 (8)	11.5 (115)
9–11 yr	773	13.3 (133)	0.8 (8)	12.0 (120)
12–14 yr	540	14.1 (141)	1.1 (11)	12.4 (124)
15–19 yr	836	15.1 (151)	1.0 (10)	13.5 (135)
Girls				
1 yr and over	13,749	13.2 (132)	1.1 (11)	11.4 (114)
1–2 yr	858	12.0 (120)	0.8 (8)	10.8 (108)
3–5 yr	1,337	12.4 (124)	0.8 (8)	11.1 (111)
6–8 yr	675	12.8 (128)	0.8 (8)	11.5 (115)
9–11 yr	734	13.1 (131)	0.8 (8)	11.9 (119)
12–14 yr[b]	621	13.3 (133)	1.0 (10)	11.7 (117)
15–19 yr[b]	950	13.2 (132)	1.0 (10)	11.5 (115)

Hb, hemoglobin; yr, year.
[a]Based on NHANES III data, United States, 1988–94.[5]
[b]Menstrual losses contribute to lower mean and 5th percentile Hb values for group.

concentration rather than hematocrit. The latter measurement is a relatively unstable analyte and its measurement lacks standardization and is instrumentation dependent, since it is derived indirectly by automated analyzers.[7–9] There is no evidence to support any different recommendation for the initial evaluation of anemia for children compared to adults.

In addition to Hb concentration, other reported results of the CBC may convey important clinical information. The anemia of CKD is hypoproliferative, and in general, normochromic and normocytic. In this regard it is morphologically indistinguishable from the anemia of chronic disease.[10] Folate or vitamin B_{12} deficiencies may lead to macrocytosis, whereas iron deficiency or inherited disorders of Hb formation (e.g., α- or β-thalassemia) may produce microcytosis. Iron deficiency, especially if long-standing, is associated with hypochromia (low mean corpuscular hemoglobin [MCH]). Macrocytosis with leukopenia or thrombocytopenia suggests a generalized disorder of hematopoiesis caused by toxins (e.g., alcohol), nutritional deficit (vitamin B_{12} or folate deficiency), or myelodysplasia. When these findings are present, further diagnostic evaluation may be indicated.

The low erythropoietic activity that characterizes the anemia of CKD is consistent with insufficient erythropoietin stimulation. Erythropoietin levels are not routinely used in distinguishing erythropoietin deficiency from other causes of anemia in patients with CKD in most clinical settings and their measurement is generally not recommended.[11,12] Effective erythropoietic proliferative activity is most simply assessed by determination of the absolute reticulocyte count. Abnormalities of the white blood cell count and differential or platelet count are not typical of the anemia of CKD and should prompt investigation for other processes.

Reticulocyte count, which may be obtained with automated CBC testing, may be high in patients who have active blood loss or hemolysis, and may be low in hypoproliferative erythropoiesis with anemia.

Iron status

There are two important and distinct aspects of the assessment of iron status testing: the presence or absence of storage iron and the availability of iron to support ongoing erythropoiesis. The serum ferritin is the most commonly used test for evaluation of storage iron, for which the 'gold standard' remains examination of a bone marrow aspiration stained for iron.[13] The transferrin saturation (TSAT; serum iron $\times$ 100 divided by total iron binding capacity) is the most commonly used measure of the availability of iron to support erythropoiesis. The serum ferritin is affected by inflammation and is an 'acute phase reactant'[13] and, thus, ferritin values have to be interpreted with caution in CKD patients, especially those on dialysis in whom subclinical inflammation may be present.[14]

Serum ferritin values ≤ 30 ng/ml (≤ 30 µg/l) indicate severe iron deficiency and are highly predictive of absent iron stores in bone marrow.[15,16] Ferritin values > 30 ng/ml (> 30 µg/l), however, do not necessarily indicate the presence of normal or adequate bone marrow iron stores. Studies assessing ferritin levels above which all or nearly all patients with CKD have normal bone marrow iron stores have produced varied results but most CKD patients, including those who are on HD, will have normal bone marrow iron stores when their serum ferritin level is ≥ 300 ng/ml (≥ 300 µg/l). Even at serum ferritin levels of 100 ng/ml (100 µg/l) most CKD patients have stainable bone marrow iron stores.[16–21] As will be discussed in Chapter 2, the serum ferritin and TSAT values are often used together to assess iron status, diagnose iron deficiency, and predict an erythropoietic response to iron supplementation (Supplementary Table 1 online).

Other tests of iron status, such as percentage of hypochromic red blood cells and reticulocyte Hb content may be used instead of, or in addition to, TSAT and ferritin levels if available. Measurement of hepcidin levels has not been shown to be clinically useful or superior to more standard iron status tests in patients with CKD.[22,23]

Vitamin B_{12} and folate

Folate and vitamin B_{12} deficiency are uncommon but important causes of treatable anemia, typically associated with macrocytic red blood cell (RBC) indices. Limited data indicate a prevalence of vitamin B_{12} and folate deficiency in $\leq 10\%$ of HD patients; the prevalence in CKD patients is not known. Nonetheless, since these deficiencies are easily correctable, and in the case of vitamin B_{12} may indicate other underlying disease processes, assessment of folate and vitamin B_{12} levels are generally considered standard components of anemia evaluation, especially in the presence of macrocytosis. Folate deficiency is best detected in most patients with serum folate level testing; RBC folate levels can be measured when serum folate levels are equivocal or when there is concern that recent dietary intake may obscure underlying folate deficiency using serum levels alone.[24]

Additional tests

Other tests, in addition to those indicated above, may be appropriate in individual patients and in certain specific clinical settings. For instance measurement of high sensitivity C-reactive protein (CRP) may be indicated if occult inflammation is a concern. In certain countries and/or in patients of specific nationalities or ethnicities, testing for hemoglobinopathies, parasites, and other conditions may be appropriate.

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SUPPLEMENTARY MATERIAL

Supplemental Table 1: Association between iron status and level of anemia in multivariable analyses.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/anemia.php

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Chapter 2: Use of iron to treat anemia in CKD

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TREATMENT WITH IRON AGENTS

BACKGROUND

Correction of iron deficiency with oral or intravenous iron supplementation can reduce the severity of anemia in patients with CKD.[25,26] Untreated iron deficiency is an important cause of hyporesponsiveness to ESA treatment.[27,28] It is important to diagnose iron deficiency because treatment can readily correct the associated anemia and investigation for the cause of iron deficiency, which should follow its detection, can lead to important diagnoses. In the absence of menstrual bleeding, iron depletion and iron deficiency usually result from blood loss from the gastrointestinal tract. There are additional considerations in CKD patients with iron deficiency. For instance, hemodialysis patients are subject to repeated blood loss due to retention of blood in the dialyzer and blood lines. Other contributing causes in hemodialysis and other CKD patients include frequent blood sampling for laboratory testing, blood loss from surgical procedures (such as creation of vascular access), interference with iron absorption due to medications such as gastric acid inhibitors and phosphate binders, and reduced iron absorption due to inflammation.[29] The reader is referred to standard textbooks of medicine and pediatrics for more extensive discussions on the diagnosis and evaluation of patients with known or suspected iron deficiency.

Iron supplementation is widely used in CKD patients to treat iron deficiency, prevent its development in ESA-treated patients, raise Hb levels in the presence or absence of ESA treatment, and reduce ESA doses in patients receiving ESA treatment. Iron administration is appropriate when bone marrow iron stores are depleted or in patients who are likely to have a clinically meaningful erythropoietic response. It is prudent, however to avoid iron therapy in patients in whom it is unlikely to provide meaningful clinical benefit, i.e., avoid transfusion and reduce anemia-related symptoms, and in those in whom potential benefit is outweighed by risks of treatment.[23,30–32] There are relatively few data on the long-term clinical benefits of iron supplementation other than direct effects on the Hb concentration. There is similarly little information on the long-term adverse consequences of iron supplementation in excess of that necessary to provide adequate bone marrow iron stores.[33–35] Since bone marrow aspiration for assessment of iron stores is rarely done in clinical practice, iron supplementation is typically assessed by blood-based iron status tests without knowledge of bone marrow iron stores.[27,28,36–38]

The following statements provide recommendations for use of iron supplementation in patients with CKD.

2.1.1: When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). *(Not Graded)*

2.1.2: For adult CKD patients with anemia not on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):
- **an increase in Hb concentration without starting ESA treatment is desired* and**
- **TSAT is $\leq$30% and ferritin is $\leq$500 ng/ml ($\leq$500 μg/l)**

2.1.3: For adult CKD patients on ESA therapy who are not receiving iron supplementation, we suggest a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (*2C*):
- **an increase in Hb concentration** or a decrease in ESA dose is desired*** and**
- **TSAT is $\leq$30% and ferritin is $\leq$500 ng/ml ($\leq$500 μg/l)**

2.1.4: For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (*Not Graded*)

2.1.5: Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (*Not Graded*)

*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.

**Consistent with Recommendations #3.4.2 and 3.4.3.

***Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

2.1.6: For all pediatric CKD patients with anemia not on iron or ESA therapy, we recommend oral iron (or IV iron in CKD HD patients) administration when TSAT is ≤20% and ferritin is ≤100 ng/ml (≤100 μg/l). (*1D*)

2.1.7: For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, we recommend oral iron (or IV iron in CKD HD patients) administration to maintain TSAT >20% and ferritin >100 ng/ml (>100 μg/l). (*1D*)

RATIONALE

In patients with CKD-associated anemia, iron supplementation is intended to assure adequate iron stores for erythropoiesis, correct iron deficiency, and, in patients receiving ESA treatment, prevent iron deficiency from developing. Iron supplementation, particularly with intravenous iron, can enhance erythropoiesis and raise Hb levels in CKD patients with anemia even when TSAT and ferritin levels are not indicative of absolute iron deficiency, and even when bone marrow studies reveal adequate iron stores.[38–40] Iron treatment, particularly when administered intravenously, has also been consistently demonstrated to improve the erythropoietic response to ESA treatment.[27,28,32,36,37,41–43] For any individual patient the optimal balance of Hb level, ESA dose, and iron dose at which clinical benefit is maximized and potential risk is minimized is not known. Prescribing iron therapy for CKD patients is complicated by the relatively poor diagnostic utility of serum ferritin and TSAT tests to estimate body iron stores or for predicting a Hb response to iron supplementation.[23,30] Even examination of bone marrow iron stores, considered the 'gold standard' for assessment of iron stores, does not predict erythropoietic responsiveness to iron supplementation in patients with CKD with a high degree of accuracy.[16,23,30,40] It is important that the short- and long-term safety of oral and intravenous (IV) iron agents, when known, be carefully considered when iron therapy is prescribed, and that the potential for as yet undiscovered toxicities also be taken into account. In each patient there must be consideration of current and desired Hb level, ESA dose and trends in ESA dose over time, assessment of the Hb response to iron supplementation, ongoing blood loss, and changes in iron status tests. While observational studies have not for the most part produced strong evidence of significant toxicity of chronic IV iron administration, the clinical benefit of such treatment has also not been convincingly demonstrated, although a recent randomized controlled trial (RCT) in patients with heart failure (some of whom also had mild CKD) is encouraging.[44]

TSAT and ferritin levels

The two most widely available tests for assessing iron status are the TSAT and serum ferritin level. A very low serum ferritin (<30 ng/ml [<30 μg/l]) is indicative of iron deficiency.[16] Except in this circumstance, the TSAT and serum ferritin level have only limited sensitivity and specificity in patients with CKD for prediction of bone marrow iron stores and erythropoietic response to iron supplementation[16-21,40,45] (Figures 1 and 2). Their utility is further compromised by substantial inter-patient variability unrelated to changes in iron store status.[46]

Evidence to support a recommendation for specific TSAT and ferritin levels at which iron therapy should be initiated or as 'targets' for iron therapy is limited, with very few RCTs.[16–21] No iron intervention trials have been sufficiently powered or of long enough duration to assess long-term safety and no studies have addressed the clinical benefit, cost-effectiveness, and risk-benefit comparison of using different TSAT and ferritin levels for the diagnosis of iron deficiency or as a trigger for iron supplementation.

The Work Group sought to recommend iron targets that balance diagnostic sensitivity and specificity with assumptions regarding safety. Previous clinical practice recommendations (Kidney Diseae Outcomes Quality Initiative [KDOQI] 2006 and others), largely opinion-based, indicated that supplemental iron should be administered to maintain ferritin levels >200 ng/ml (>200 μg/l) in CKD 5HD patients and >100 ng/ml (>100 μg/l) in CKD ND and CKD 5PD with TSAT >20% in all CKD patients. These guidelines also indicated that there was insufficient evidence to recommend routine IV iron administration when the ferritin level was >500 ng/ml (>500 μg/l).

Most CKD patients with serum ferritin levels >100 ng/ml (>100 μg/l) have normal bone marrow iron stores,[16–21] yet many such patients will also have an increase in Hb concentration and/or reduction in ESA dose if supplemental iron is provided.[16,23,30,31,40,45] A substantial fraction of CKD patients with anemia and TSAT >20% respond to iron supplementation with an increase in Hb concentration and/

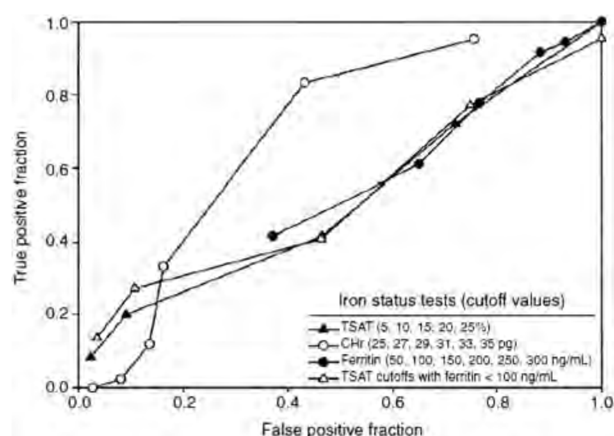

Figure 1 | Receiver operating characteristic (ROC) curves, examining the utility of iron status tests to distinguish iron deficient from nondeficient study patients. Reprinted with permission from Macmillan Publishers Ltd: *Kidney International*. Van Wyck DB, Roppolo M, Martinez CO *et al*. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005; 68: 2846–2856;[45] accessed http://www.nature.com/ki/journal/v68/n6/full/4495631a.html.

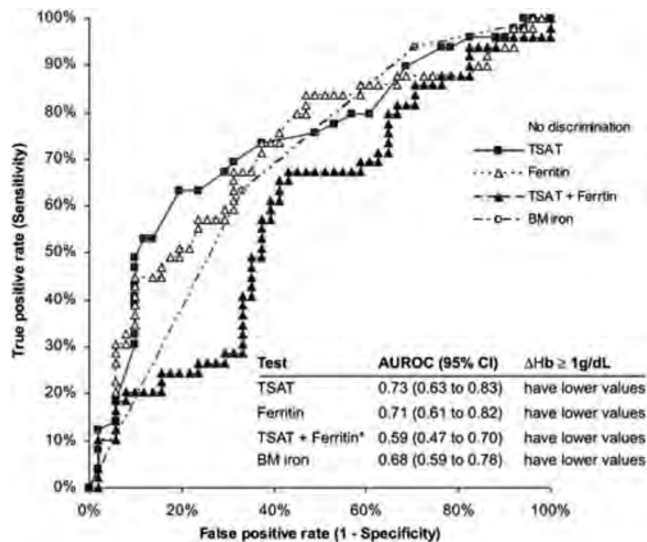

Figure 2 | Sensitivity and specificity of TSAT and serum ferritin (ferritin) and their combination (TSAT + ferritin) and bone marrow iron (BM iron) to identify correctly a positive erythropoietic response (≥1-g/dl [≥10-g/l] increase in Hb [ΔHb]) to intravenous iron in 100 nondialysis patients with CKD (areas under the ROCs). Reproduced with permission from American Society of Nephrology[40] from Stancu S, Barsan L, Stanciu A *et al*. Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? *Clin J Am Soc Nephrol* 2010; 5: 409–416; permission conveyed through Copyright Clearance Center; accessed http: http://cjasn.asnjournals.org/content/5/3/409.long

or reduction in ESA dose. Therefore, for patients who have not been receiving iron supplementation, we suggest iron administration in anemic CKD patients with TSAT <30% and serum ferritin <500 ng/ml (<500 μg/l) if an increase in Hb level is desired, particularly if intended to avoid transfusions and reduce anemia-related symptoms, and/or reduction in ESA dose, after consideration of the potential risks of iron administration. The safety of providing additional iron to intentionally maintain TSAT >30% and serum ferritin >500 ng/ml (>500 μg/l) has been studied in very few patients. We do not recommend routine use of iron supplementation in patients with TSAT >30% or serum ferritin >500 ng/ml (>500 μg/l) since, as stated above, the benefits and risks of doing so are inadequately studied. In all patients receiving iron, it is important to weigh both short-term and acute toxicities associated with iron therapy and exclude the presence of active infection (Recommendation 2.4) before embarking on a course of IV iron treatment.

There is only very limited evidence in patients with CKD that informs any decision about defining any specific upper limits for iron status targets in guiding iron treatment.[47,48] Previous guidelines, such as the 2006 KDOQI guidelines and others, have specified serum ferritin levels above which additional IV iron therapy was generally not recommended,[8,49–52] usually citing limits of 500–800 ng/ml (500–800 μg/l). However, no RCTs and few other studies have examined the efficacy and safety of providing IV iron to maintain ferritin levels >500–800 ng/ml (>500–800 μg/l). Most studies are retrospective and the few prospective studies have had small numbers of patients and short follow up, using surrogate outcomes such as Hb and ESA dose rather than more meaningful patient outcomes such as infection risk and mortality. In most patients with TSAT >30% or serum ferritin >500 ng/ml (>500 μg/l), any erythropoietic responsive to iron supplementation alone (i.e., the incremental change in Hb and/or reduction in ESA dose) will be small. In one RCT conducted in CKD 5HD patients with anemia, serum ferritin 500–1200 ng/ml (500–1200 μg/l), and TSAT<25%, patients received a 25% increase in epoetin dose and were randomly assigned to receive either no iron (control) or 1000 mg IV iron. At 6 weeks, Hb increased to a greater extent in the IV iron group.[53] This study was not considered in the choice of target levels for ferritin and TSAT in this guideline in part because it studied only a restricted group of patients, all of whom also received an increase in ESA dose. The number of patients was too small and the period of observation too short to assess either clinically important outcomes or toxicity in a meaningful way (Supplementary Tables 2–4 online).

High ferritin levels in some studies have been associated with higher death rates, but whether elevation of ferritin levels is a marker of excessive iron administration rather than a nonspecific acute phase reactant is not clear. At increasingly higher ferritin levels, there is some evidence to indicate that hepatic deposition of iron increases.[54,55] Clinical sequelae of this have not been documented although such hepatic iron deposition might be of particular concern in patients with hepatitis C virus (HCV) infection.[56] While some data are available linking ferritin levels in patients with hemochromatosis and transfusional tissue iron deposition in patients without CKD,[57] it is not clear to what extent these findings are relevant to CKD patients or should be used to guide clinical practice in CKD patients.

Rather than focusing on serum ferritin levels as a predictor of outcomes, some observational studies have examined associations between patient outcomes and amount of iron administered. One such study found no adverse association between 2-year survival when the IV iron dose over 6 months was ≤1000 mg, but a statistically significant higher mortality for iron doses >1000 mg (adjusted hazards ratio [HR] 1.09; 95% confidence interval [CI] 1.01–1.17 for > 1000 mg to 1800 mg and 1.18; 95% CI 1.09–1.27 for > 1800 mg).[33] However, after using multivariable models accounting for time-varying measures of iron administration and other parameters, there was no statistically significant association between any level of iron administration and mortality. Another retrospective study using time-dependent and multivariate adjustment for case mix found that IV iron doses up to 400 mg/month were associated with lower death rates compared to doses >400 mg/month[35] (Supplementary Table 5 online).

It is the consensus of the Work Group that additional IV iron should not routinely be administered in patients with

serum ferritin levels that are consistently >500 ng/ml (>500 μg/l). In patients with Hb below the desired level who are receiving relatively high ESA doses, or in whom discontinuation of ESA therapy is preferred (for instance a CKD patient with malignancy), a therapeutic trial of additional IV iron (i.e., a single course of up to 1000 mg over a period of several weeks which can be repeated as needed) may be undertaken in patients with serum ferritin levels >500 ng/ml (>500 μg/l) after due consideration of potential acute toxicities and long-term risks. Subsequent treatment decisions should be based on the patient's clinical status, including trends in TSAT, ferritin, and Hb level, and ESA dose and responsiveness.

Ferritin levels need to be interpreted with caution in patients who may have an underlying inflammatory condition as they may not predict iron stores or responsiveness to iron therapy in a manner similar to that when inflammation is absent. In the absence of a clinically evident infectious or inflammatory process, assessment of CRP may suggest the presence of an occult inflammatory state that may be associated with an elevated ferritin level and ESA-hyporesponsiveness (Supplementary Table 6 online).

Other iron status tests not as widely available as TSAT and ferritin such as percentage of hypochromic red cells, reticulocyte Hb content, zinc protoporphyrin, and soluble transferrin receptors may be used to assess iron status, but are less well studied.[22,23]

There is no evidence that a higher ferritin target of 200 ng/ml (200 μg/l) is the appropriate or inappropriate cutoff in CKD 5HD pediatric patients. Consequently no change has been made to the 2006 KDOQI guideline in children with CKD and anemia, which recommended a ferritin target greater than 100 ng/ml (100 μg/l) for CKD 5HD, as well as for CKD 5PD and CKD ND who are not on ESA therapy.[58]

Iron treatment

A decision to provide an individual patient with iron therapy should be based on an assessment that an increase in Hb level is desirable, that is, to avoid transfusions or reduce anemia-related symptoms, and that the potential adverse effects of iron supplementation, either oral or IV, have been considered and are appropriately outweighed by the expected treatment benefit. Such supplementation could be in the form of oral or intravenous iron. Use of intramuscular iron has largely been abandoned. Each route has its own potential advantages and disadvantages. Oral iron is inexpensive, readily available, and does not require IV access, a particular concern in CKD patients not on HD. It is also not associated with severe adverse effects but gastrointestinal side effects are common and may limit adherence. This, along with variable gastrointestinal tract absorption, limits the efficacy of oral iron. IV iron avoids concerns about medication adherence and efficacy in treating iron deficiency, but requires IV access and has been associated with infrequent but severe adverse reactions. Decisions about the preferred route of iron supplementation should take into consideration severity of anemia and iron deficiency, the response, tolerance and adherence to prior oral iron administration, costs, and ease of obtaining venous access balanced against the desire to preserve venous access sites.

In patients with CKD ND, the available evidence supports an efficacy advantage of IV compared with oral administration of iron although the effect is rather small, with a weighted mean Hb difference of 0.31 g/dl (3.1 g/l).[45,59–63] Whether the small Hb benefit of IV iron in CKD ND patients is clinically meaningful or justifies the small risk of serious adverse events and unknown long-term risks is uncertain. The consensus of the Work Group is that a clearly defined advantage or preference for IV compared to oral iron was not supported by available evidence in CKD ND patients. Therefore, in such patients, the route of iron administration can be either IV or oral. In some patients the desire to avoid venipuncture (and preserve IV access) may favor in some patients, particularly those with mild iron deficiency, an initial trial of oral iron.

Oral iron is typically prescribed to provide approximately 200 mg of elemental iron daily (for instance ferrous sulfate 325 mg three times daily; each pill provides 65 mg elemental iron). Smaller daily doses may be useful and better tolerated in some patients. Although ferrous sulfate is commonly available and inexpensive, other oral iron preparations may also be used; there is not significant evidence to suggest that other oral iron formulations are more effective or associated with fewer adverse side effects than ferrous sulfate. If the goals of iron supplementation are not met with a 1–3 month course of oral iron, it is appropriate to consider IV iron supplementation in a manner consistent with the above recommendation statements and the discussion that follows.

There is evidence supporting a preference for the IV route of iron administration in CKD 5HD patients derived from RCTs and other studies comparing IV iron with oral iron and placebo, with and without concomitant ESA treatment.[27,32,62,64,65] In most of these studies, IV iron administration led to a greater increase in Hb concentration, a lower ESA dose, or both. In CKD 5HD patients, the ready IV access and convenience of being able to administer IV iron during HD treatments further supports the preference for the IV route for iron administration in these patients.

In prior CKD anemia guidelines,[50] CKD 5PD patients were considered more similar to CKD ND than CKD 5HD in their need for and likely responsiveness to iron, as well as in their absence of ready venous access for IV iron administration. Limited studies of iron administration in CKD 5PD patients indicate that oral iron is of limited efficacy and that IV iron is superior to oral iron in terms of achieved Hb level and ESA dose. Consequently, this route is preferred in these patients, although the desire to preserve potential future venous access sites must be considered in such patients.[66–70]

IV iron may be provided as a single large dose or as repeated smaller doses depending on the specific IV iron preparation used (with the highest single dose varying by specific formulation). It is common practice to provide an initial course of IV iron amounting to approximately 1000 mg; this may be repeated if an initial dose fails to increase Hb level and/or allow a decrease in ESA dose and if the TSAT remains $\leq 30\%$ and serum ferritin remains ≤ 500 ng/ml (≤ 500 μg/l).[38]

Decisions regarding continued iron therapy should take into consideration recent patient responses to iron therapy, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA-treated patients, ongoing blood losses, trends in each parameter, and the patient's clinical status. Serum ferritin and TSAT levels should not be measured until at least one week has elapsed since the most recent prior IV iron dose. Consideration of expected iron needs and evaluation for ongoing iron losses should precede further IV iron administration. Blood loss should be minimal in CKD ND and CKD 5PD patients, while CKD 5HD patients have reported to lose between 1–2 gm of iron per year related to the HD procedure and related circumstances.[71–73] Thus, an apparent ongoing need for any iron supplementation in CKD ND and CKD 5PD patients or for more than 1–2 gm/yr in CKD 5HD patients should prompt assessment for a source of active blood loss. The need to consider trends in iron status tests are highlighted by consideration of a patient with decreasing TSAT and ferritin levels which may signify the presence of gastrointestinal bleeding or excessive dialysis-associated blood loss. As another example, an increasing TSAT and ferritin level may indicate excessive iron supplementation and a need to decrease or discontinue iron administration. Finally, an increase in ferritin level accompanied by a decrease in TSAT and Hb level suggests inflammation-mediated reticuloendothelial blockade.[14]

There are two commonly used approaches to ongoing or maintenance IV iron treatment in CKD 5HD patients: (1) periodic iron repletion, consisting of a series of IV iron doses administered episodically to replenish iron stores whenever iron status tests indicate the likelihood of iron deficiency or decrease below specific target levels; or (2) maintenance treatment, consisting of smaller doses administered at regular intervals to maintain iron status tests stable within specific limits with the intent of avoiding iron deficiency or decline of iron test parameters below specific levels. Limited evidence suggests that regular maintenance IV iron administration in CKD 5HD is associated with use of lower ESA doses and may result in lower cumulative iron doses[41,74,75] but these data are insufficient to support a recommendation favoring any particular IV iron dosing strategy in this patient population. By nature of the clinical encounters with CKD 5PD patients, IV iron supplementation is often provided at periodic (e.g., monthly) visits.

Overall, the TSAT and ferritin recommendations above are applicable to children with CKD on ESA therapy. However, there is no evidence that a higher ferritin target of 200 ng/ml (200 μg/l) is the appropriate or inappropriate cutoff in pediatric CKD HD patients. Consequently no change has been made to the 2006 KDOQI guideline in CKD in children with anemia, which recommended a ferritin target greater than 100 ng/ml (100 μg/l) for CKD 5HD, as well as for CKD 5PD and CKD ND who are on ESA therapy.[58]

IRON STATUS EVALUATION

2.2.1: Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (*Not Graded*)

2.2.2: Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (*Not Graded*)

RATIONALE

In the absence of clinical trials that specifically inform the optimal frequency for testing of iron status, and consistent with prior guidelines,[50] the consensus of the Work Group is that patients who are on ESA therapy, regardless of whether iron treatment is also being used, should have tests of iron status at least every 3 months. Falling TSAT and/or ferritin levels are likely to reflect ongoing blood loss or consumption of available iron stores, and can be used to anticipate the need for future or additional iron supplementation. In patients on oral iron treatment, iron status testing can also be used to assess adherence with iron treatment. Increasing TSAT and/or ferritin levels may indicate that iron treatment is excessive and can be stopped or reduced. Increasing ferritin levels in association with stable or declining TSAT levels may also indicate the presence of inflammation, infection, or other clinical situations inducing acute phase reactants during which time the appropriateness of continued iron administration may need to be reassessed.[14]

In some circumstances, more frequent iron status testing may be appropriate, including following initiation of ESA or iron therapy or when the ESA dose or dose frequency is increased. Iron status testing is also important in the assessment of patients who become less responsive to ESA treatment.

Despite the absence of specific data in the pediatric CKD population, this recommendation is considered applicable to children since there are no reasons to suggest a different recommendation. Since the 2006 KDOQI guideline for anemia in pediatric CKD,[58] no new evidence regarding iron therapy for children with CKD has been published. The suggestion for oral iron supplementation in children is 2–6 mg/kg/day of elemental iron in 2–3 divided doses.[76,77] An RCT of 35 iron replete pediatric CKD 5HD patients evaluated

their response to either weekly IV iron dextran dosed by weight or oral iron 6 mg/kg/day. Only the IV iron dextran produced a significant increase in the serum ferritin levels and showed a significant decrease in ESA dose required to maintain target Hb levels.[78] An international multicenter double-blind RCT investigated the safety and efficacy of two dosing regimens (1.5 mg/kg or 3 mg/kg) of ferric gluconate in iron-deficient pediatric hemodialysis patients receiving concomitant ESA therapy. Efficacy and safety profiles were comparable, with no unexpected adverse events with either dose.[79] Based on this trial, the recommendation for initial ferric gluconate therapy is 1.5 mg/kg for eight doses for iron-deficient pediatric CKD 5HD patients and 1 mg/kg per week for iron-replete pediatric CKD 5HD patients, with subsequent dose adjustments made according to TSAT and/or ferritin levels.[79,80] Iron sucrose has also been used in children with CKD[81] but, as of yet, no RCTs have been published in this population. Although it is not uncommon that pediatric CKD 5PD and CKD ND patients either do not respond to or tolerate oral iron therapy, the need for IV access for parenteral iron therapy often limits its utilization in children.

CAUTIONS REGARDING IRON THERAPY

2.3: When the initial dose of IV iron dextran is administered, we recommend (*1B*) and when the initial dose of IV non-dextran iron is administered, we suggest (*2C*) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

RATIONALE

Any form of IV iron may be associated with potentially severe acute reactions.[82–91] The symptoms of most concern are hypotension and dyspnea, which in the worst cases may be catastrophic with features of anaphylaxis. The cause of reactions has not been fully characterized, but may involve immune mechanisms and/or release of free, reactive iron into the circulation with induction of oxidative stress. The mechanisms of acute reactions may differ for different iron preparations. Certain iron dextrans in particular have been associated with reactions characteristic of anaphylaxis. The rate of such reactions is estimated to occur in 0.6–0.7% of patients treated. The serious adverse effect event rate may be lower with low molecular weight iron dextran compared to high molecular weight iron dextran.[92–96]

With non-dextran IV iron drugs, it is believed that anaphylactoid and other severe and potentially life-threatening reactions are less common, but this has not been well substantiated. Serious reactions including profound hypotension do occur, even if uncommonly, with all non-dextran IV iron preparations. Because all forms of IV iron drugs can be associated with serious immediate reactions, they should be used with vigilance. Since the rate of such reactions may be greater for iron dextran drugs we recommend that resuscitative medications and personnel trained to evaluate and treat serious adverse reactions be available when the initial dose of IV iron dextran is administered. The data to support such a recommendation for the initial dose of non-iron dextran compounds is not as strong. In the US, the Food and Drug Administration (FDA)-mandated labeling for ferumoxytol specifies that patients be observed for 60 minutes after administration. This may be reasonable advice for all IV iron drugs, including other new iron preparations such ferric carboxymaltose and iron isomaltoside. For each IV iron preparation prescribing physicians should be familiar with the drug's safety and toxicity profile and the product labeling warnings and recommendations for administration, as well as patient monitoring during and after treatment.

Iron during infection

2.4: Avoid administering IV iron to patients with active systemic infections. (*Not Graded*)

RATIONALE

Iron is essential for the growth and proliferation of most pathogens including many bacteria, viruses, fungi, parasites and helminthes, and also exerts subtle effects on immune function and host responses towards microbes.[97] There is theoretical and experimental evidence to suggest that iron administration may worsen an existing infection but clinical evidence is lacking. In animal models, iron overload results in an impaired control of infections, specifically with intracellular bacteria or fungi.[98–101] In humans, tissue iron overload has been considered as a risk factor for the acquisition of certain infections and for an unfavorable clinical course of the infection. Data in CKD patients are conflicting.[102–104] Since current evidence cannot provide a clear answer as to whether specific CKD patient groups are at increased risk for infection, or of having a poorer outcome with infection when anemia is treated with IV iron, the Work Group suggests that IV iron not be administered when patients have an active systemic infection. Clinical judgment is necessary in each individual patient to assess whether there is an immediate need for IV iron (as opposed to delaying treatment until resolution of an infection), likelihood of achieving benefit from a dose of IV iron in the setting of an active infection, and the severity of an infection.

RESEARCH RECOMMENDATIONS

Much regarding the testing of iron status and use of iron supplementation, particularly IV, in CKD patients of all stages remains unknown. There is a serious lack of large, prospective clinical trials with assessment of clinically meaningful outcomes and toxicities; rather, most have been small, short-term studies focusing primarily on surrogate outcomes such as increase in Hb level and reduction in ESA dose. Some

important questions that should be addressed in future studies might include:

- What is the comparative risk-benefit balance of various treatment strategies that include differing ratios of ESA dosing and iron supplementation to achieve a particular Hb level?
- Is there a role, and if so under what circumstances, for anemia management in CKD patients with iron alone, without ESA treatment (or with only ESA 'rescue therapy' for particularly low Hb levels)?
- Is there important long-term toxicity of IV iron supplementation and if so, under what circumstances and in what CKD patient groups?
- Is IV iron administration, with or without concomitant ESA dose increases, safe and of clinical benefit, in patients with ferritin levels >500–800 ng/ml (>500–800 μg/l)?
- What are the best laboratory tests to guide decisions regarding initiation, ongoing treatment, and discontinuation of iron supplementation?
- Is current iron and anemia management in pediatric CKD patients appropriate?

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SUPPLEMENTARY MATERIAL

Supplemental Table 2: Summary table of RCT examining the effect of IV iron + EPO vs. EPO only in patients with HD-CKD (categorical outcomes).
Supplemental Table 3: Summary table of RCT examining the effect of IV iron + EPO vs. EPO only in patients with HD-CKD (continuous outcomes).
Supplemental Table 4: Summary table of adverse events in RCT examining the effect of IV iron + EPO vs. EPO only in patients with HD-CKD (continuous outcomes).
Supplemental Table 5: Association between cumulative iron dose and clinical outcome in multivariable analyses.
Supplemental Table 6: Association between iron status and clinical outcome in multivariable analyses.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/anemia.php

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Chapter 3: Use of ESAs and other agents* to treat anemia in CKD

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ESA INITIATION

BACKGROUND

The introduction of recombinant human erythropoietin (rHuEPO) into clinical practice in the 1980 s was a major breakthrough in the treatment of the anemia of patients with CKD. The development of rHuEPO was aimed at replacing the insufficient endogenous erythropoietin (EPO) production related to CKD progression. It remains unclear whether the main cause of anemia is a loss of kidney EPO production capacity or a derangement in oxygen sensing, as proposed more recently.[105]

In the early years, rHuEPO administration was regarded by the nephrology community as a beneficial therapy for long-term dialysis patients whose Hb values fell to extremely low levels, making them transfusion-dependent. The immediate benefit of rHuEPO in CKD patients with severe anemia and anemia-related signs and symptoms was clear. In addition, the reduction in the need for regular blood transfusions was another major benefit, resulting in less frequent transmission of blood-borne viral diseases, such as hepatitis B and C, less allosensitization, predisposing to prolonged wait times or failure to receive a kidney transplant, transplant rejection, and less transfusional hemosiderosis.[106–109]

After introduction of rHuEPO into clinical practice its administration was limited to dialysis patients with the most severe forms of anemia. Progressively, its use was extended to the majority of dialysis patients with renal anemia, and subsequently also to anemic patients with CKD 4–5 in countries in which the high cost of rHuEPO did not limit the number of patients eligible for this treatment.

Hb targets also increased progressively, often into the range of normal values. The idea that anemia should be corrected completely was based on pathophysiologic considerations and the demonstration by numerous observational studies of an inverse association between Hb concentrations up into the normal range and intermediate outcomes such as left ventricular hypertrophy,[110] as well as hard patient outcomes such as cardiovascular events,[111–113] hospital admission,[114] and death.[115,116] Of note, a recent study also showed that CKD 5D patients with naturally occurring Hb concentrations greater than 12 g/dl (120 g/l) were not at increased mortality risk.[117] However, the suggestion drawn from epidemiological studies that anemia should be completely corrected in patients with CKD was not supported by the Normal Hematocrit Study in CKD 5D patients[118] and several recent randomized controlled trials (RCTs) performed in large CKD patient cohorts (Supplementary Table 7 online).

In CKD 5D patients Hb concentrations often fall below 8 g/dl (80 g/l) if anemia is untreated, whereas in CKD ND patients higher Hb concentrations are usual, unless patients are close to dialysis or have another contributing cause. The decision to prescribe ESAs should be based on evidence accrued from RCTs. However substantial heterogeneity exists in RCTs performed to evaluate ESA therapy, particularly in relation to classification of patients, research design, baseline Hb, target Hb, clinical outcome measures, and definitions of clinically meaningful improvements.

Outcomes of interest in RCTs of ESAs include mortality, cardiovascular and kidney endpoints, safety, quality of life (QoL), blood transfusions and cost. QoL outcomes are particularly important for CKD 5D patients and for some may be more important than cardiovascular events or mortality, since they have relatively short life expectancy and the symptoms attributable to anemia (e.g., low energy, fatigue, decreased physical function, and low exercise capacity) occur frequently and can be disabling.[119] However, QoL is extremely difficult to quantify as is the clinical importance of changes measured. Furthermore, unless assessed under rigorous double-blind conditions, the validity of QoL measurements is questionable. Avoidance of transfusions is important, as mentioned above.

The guidelines to treat or not to treat the anemia of CKD are also valid for CKD 4–5T patients. Of note, blood transfusions may increase the risk of alloreactivity and rejection episodes after kidney transplantation.[120] In addition a recent randomized trial has shown that early post-kidney transplant anemia correction by ESAs reduces the progression of allograft nephropathy, although its effect on hard outcomes in this patient population remains unknown.[121]

3.1: Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. (*Not Graded)*

RATIONALE

After diagnosing anemia in a patient with CKD all correctable causes should be treated before considering ESA therapy. Above all, this recommendation is based on the observation that iron supplementation given to CKD patients with

*Excluding iron which is discussed in Chapter 2.

proven iron deficiency or impaired iron availability ('functional iron deficiency') generally leads to an increase in Hb (See Chapter 2). However, the correction of other deficiency states also may ameliorate anemia. In patients with inflammatory diseases, including bacterial and viral infections, the attenuation of the inflammatory status is often followed by an improvement of Hb.

There are several reasons why correctable causes other than erythropoietin deficiency should be actively sought. As in any disease state, pathological conditions which can be cured should be corrected first. As examples, ESA treatment is unlikely to be fully effective in raising Hb concentrations until either severe systemic bacterial infections or severe secondary hyperparathyroidism are appropriately treated (Supplementary Table 8 online). When several different factors are thought to contribute to the anemia of CKD, even though the main underlying cause is impaired kidney EPO synthesis, appropriate medical care dictates treating all underlying causes.

3.2: In initiating and maintaining ESA therapy, we recommend balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). *(1B)*

RATIONALE

Treatment of severe anemia

Objective evidence to support treatment of Hb concentrations below 9 g/dl (90 g/l) is quite strong because the transfusion benefits are substantial and the QoL improvements are clinically important. However the safety of ESAs in treating severe anemia has not been evaluated in large placebo controlled trials.

The Canadian Erythropoietin Study Group reported a double-blind RCT of 118 CKD 5HD patients in 1990. ESA was utilized in patients with Hb concentrations <9 g/dl (<90 g/l), and three randomly allocated groups were followed (placebo, target Hb 9.5–11 g/dl [95–110 g/l], high target Hb >11 g/dl [>110 g/l]).[122] Baseline Hb was 7.0 g/dl (70 g/l) and the mean transfusion requirement was 7 transfusions per year. After 8 weeks, 58% (N = 23/40) in the placebo group were transfused and only 2.5% (N = 1/40) was transfused in the group with target Hb of 9.5–11g/dl (95–110 g/l) and 2.6% (N = 1/38) in the group with target Hb > 11g/dl (>110 g/l). After 6 months, significant improvements in fatigue, physical function, and 6 minute walking tests were reported for the low Hb group compared to placebo, but no improvement was observed comparing low vs high Hb group. In an open-label RCT of only 83 CKD ND patients with Hb <10 g/dl (<100 g/l), significant improvements in energy and physical function were also reported.[123]

Treatment of moderate anemia

There are several large RCTs of ESA therapy where baseline Hb is >10 g/dl (>100 g/l).[118,124–128] The intervention being tested in these trials is complete correction of anemia with ESAs, compared to partial correction with ESAs in five RCTs[118,124–126,128] and to placebo in one.[127] A double-blind design is necessary to accurately assess subjective or clinician-driven endpoints particularly QoL, starting dialysis, and giving transfusions. Notably, only 3 of the 6 trials were double-blind – the Normal Hematocrit Study reported in 1998,[118] the Canada-Europe Study reported in 2005,[126] and TREAT reported in 2009.[127] The Scandinavian Study,[125] CREATE[124] and CHOIR[128] trials were open label.

The US Normal Hematocrit Trial by Besarab *et al.*[118] was the first of a series of RCTs which cast serious doubt on the assumption that full anemia correction should be achieved in the majority of dialysis patients. A cohort of 1233 prevalent CKD 5HD patients with symptomatic heart failure or ischemic heart disease were allocated to either partial treatment of anemia or full anemia correction, using epoetin-alfa. The eventually achieved hematocrit values were 31% and 40%, respectively. In the normal hematocrit group treated with epoetin there were 183 deaths and 19 myocardial infarcts, producing 202 primary events, compared to 164 events (150 deaths, 14 myocardial infarcts) in the group in which anemia was partially corrected with epoetin. The risk ratio for the primary endpoint was 1.3 (95% CI 0.9–1.9) which did not satisfy the pre-specified criterion for statistical significance (even though the nominal p value was 0.03) after adjusting for interim analyses. The trial was stopped early in a situation where the primary hypothesis was unlikely to be proven and the intervention being tested caused harm: 39% had vascular access clotting in the intervention arm and 29% in the control arm ($P = 0.001$).

The double-blind Canada-Europe trial by Parfrey *et al.*[126] of 596 incident CKD 5HD patients without symptomatic heart disease (18% with diabetic nephropathy) examined the question whether full anemia correction by epoetin-alfa in the group randomized to a Hb target of 13.5–14.5 g/dl (135–145 g/l), as compared to partial treatment of anemia in the group randomized to a Hb target of 9.5–11.5 g/dl (95–115 g/l), had a beneficial effect on left ventricular volume and mass index. The eventually achieved Hb values were 13.1 and 10.8 g/dl (131 and 108 g/l), respectively. There was no difference in left ventricular volume index or mass index between the two groups during this 96-week study. Of note, patients in the full anemia correction group had a significantly higher stroke incidence (secondary endpoint) than patients in the partial treatment correction group. However, the absolute numbers of patients with stroke were very small. As one might expect, the high Hb group received significantly fewer transfusions than the low Hb group, but extent of the benefit was modest: although 9% in the high Hb arm received at least one transfusion compared to 19% in the low Hb arm ($P = 0.004$) during the 96-week study, the transfusions per patient per year was 0.3 in the high Hb arm and 0.7 in the low Hb arm ($P < 0.0001$).[129] In addition significant improvements in QoL were reported for the *a priori* selected domains of vitality and of fatigue.[126,130]

The goal of the CREATE study by Drueke *et al.*[124] was to show superiority of full anemia correction in terms of cardiovascular events, as compared to partial correction of anemia, when starting ESA therapy at an earlier stage than end-stage renal disease (ESRD). In this trial, 603 CKD 3–5 patients (26% with diabetes) were randomly allocated to either a Hb target of 13.0–15.0 g/dl (130–150 g/l) or a Hb target of 10.5–11.5 g/dl (105–115 g/l) using epoetin-beta. The eventually achieved Hb values were 13.5 and 11.6 g/dl (135 and 116 g/l), respectively. Dialysis was required in significantly more patients in the high Hb group than in the low Hb group. However the rate of fall of GFR in the two groups during the 3 year study was similar. Statistically significant improvements in some domains of QoL, including physical function and vitality, were observed in the high Hb group, although these must be interpreted cautiously because the study was open-label.

The US CHOIR study by Singh *et al.*[128] similarly aimed to show superiority of full anemia correction by ESA administration in terms of cardiovascular events and death, as compared to partial treatment of anemia, in patients with CKD not yet on dialysis. In this trial, 1432 CKD 3–4 patients (49% with diabetes) were randomized to Hb targets of 13.5 g/dl (135 g/l) and 11.3 g/dl (113 g/l) using epoetin-alfa. Withdrawal rate was high: 17% due to renal replacement therapy and 21% for other reasons. The study was prematurely stopped after an interim analysis with a median study duration of 16 months. The achieved Hb values were 12.6 and 11.3 g/dl (126 and 113 g/l), respectively. At this time point, 125 patients in the complete anemia correction group but only 97 patients in the standard correction group had reached the primary combined cardiovascular endpoint ($P = 0.03$). No differences in QoL were observed comparing the two groups although, again, this finding must be interpreted cautiously because the study was open-label.

Finally, the international trial of darbepoetin-alfa in type 2 diabetes and CKD (TREAT) by Pfeffer *et al.*[127] examined cardiovascular and kidney outcomes in 4038 CKD 3–4 patients. Of note, this is by far the largest ESA trial, and has the best research design, as it was placebo controlled and double-blinded. Patients received either darbepoetin-alfa to achieve a Hb target of 13.0 g/dl (130 g/l) or placebo with rescue darbepoetin-alfa when the Hb concentration was $<$9.0 g/dl ($<$90 g/l). The achieved Hb values were 12.5 and 10.6 g/dl (125 and 106 g/l), respectively. The median follow-up duration of the study was 29 months. There were no differences in the two primary endpoints, which were the composite outcomes of death or a cardiovascular event (first primary endpoint) and death or ESRD (second primary endpoint). The hazard ratio for death/composite cardiovascular event was 1.05 (95% CI 0.94–1.17), and for death or ESRD it was 1.06 (95% CI 0.96–1.19). However there was a substantial increased risk of stroke (HR 1.92; 95% CI 1.38–2.68), although the absolute risk of stroke overall was modest: 5.0% of the high Hb group had a stroke compared to 2.6% in the placebo group ($P < 0.001$). The relative increase in risk of stroke was similar in patients with and without a past history of stroke. As a result, the absolute risk of stroke was substantial in the 11% of subjects with a prior history of stroke; 12% in the darbepoetin group compared to 4% in the placebo group. Venous thrombo-embolic events occurred significantly more frequently in the high Hb arm (2.0%) compared to the placebo arm (1.1%, $P = 0.02$). A signal that normalization of Hb with darbepoetin may be harmful in patients with a history of malignancy was reported following a post-hoc analysis: 14/188 (7.4%) of those with a history of malignancy at baseline died from cancer in the darbepoetin arm compared to 1/160 (0.6%) ($P = 0.002$) in the placebo arm. A statistically significant improvement in Functional Assessment of Cancer Therapy-Fatigue (FACT-fatigue) scores was reported at week 26 favoring the darbepoetin group, but the clinical significance of this was modest, as 55% of the high Hb group had a clinically important improvement in fatigue score compared to 50% of the placebo group. Transfusions were prescribed relatively frequently, and more often in the placebo arm (25%) compared to the high Hb arm (15%). The harm:benefit trade-off in TREAT was 1 stroke for 5 transfusions prevented by the high Hb target[131] (Supplementary Tables 9–19 online). In a large subset of the TREAT patients QoL was assessed using FACT-fatigue, SF-36, and EQ-5D through 97 weeks. Compared to placebo, darbepoetin conferred a consistent, but small improvement over 97 weeks in fatigue and overall QoL, but none in energy and physical function. Interim stroke had a substantial negative impact on fatigue and physical function.[132]

Meta-analyses

Assessment of ESAs in CKD using meta-analysis is problematic because of the heterogeneity of patients entered, the different quality and research designs of the RCTs performed, and differences in definitions of endpoints. In addition abstraction of aggregate data from the reports of RCTs to populate the meta-analysis data base is also a limitation, as individual patient data would be preferable. The most recent meta-analysis[133] concluded that higher Hb concentrations in CKD increases risk for stroke (relative risk [RR] 1.51, 95% CI 1.03–2.21), hypertension (RR 1.67, 95% CI 1.31–2.12), and vascular access thrombosis (RR 1.33; 95% CI 1.16–1.53), and may perhaps increase risk for death (RR 1.09; 95% CI 0.99–1.20), serious cardiovascular events (RR 1.15, 95% CI 0.98–1.33) or ESRD (RR 1.08; 95% CI 0.97–1.20). In our opinion, because of the heterogeneity of patients and interventions across studies in the meta-analysis greater credence should be given to the results of the very large, placebo controlled, double-blind trial, TREAT, than to the meta-analyses, in areas where the results differ: TREAT found no difference between the higher Hb, darbepoetin, group and the lower Hb, placebo, group for the two primary composite outcomes (either death or a cardiovascular event, or death or a renal event).[127]

The existing meta-analyses of QoL outcomes are further complicated by inclusion of data from open label studies,

different instruments to measure QoL, differences in research design across RCTs, incomplete reporting as some trials chose (*a priori*) specific domains as trial outcomes, and differences in the definition of clinically meaningful improvement in QoL domains.[119] Results from two systematic reviews published recently[134,135] suggest that improvements in QoL are maximized in the 10–12 g/dl (100–120 g/l) range. In CKD ND patients the review focused on energy and physical function[134] and in CKD 5D patients the review focused on physical function and the meta-analysis on exercise tolerance.[135]

3.3: We recommend using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(*1B*), a history of stroke (*1B*), or a history of malignancy (*2C*).

RATIONALE

The joint guideline from the American Society of Clinical Oncology[136] and the American Society of Hematology[137] recommend using ESA therapy with great caution in patients with active malignancy, particularly when cure is the anticipated outcome. This advice is supported in CKD patients by the post-hoc analysis in TREAT which demonstrated a significantly higher death rate from cancer in the darbepoetin arm in patients with a history of a malignant condition at baseline as compared with the placebo arm.[127]

The relative risk of stroke in patients in the darbepoetin arm of TREAT was the same in those with and without a history of stroke (i.e., approximately doubled). However the absolute risk of stroke was much higher in subjects with a history of stroke (in both study arms) and the absolute risk of stroke attributable to high Hb/darbepoetin was particularly high, 8% in those with a history of stroke vs 1% in those without a history of stroke over 29 months.[138] Consequently the Work Group concluded that ESAs should be used with great caution in those with a prior history of stroke.

3.4.1: For adult CKD ND patients with Hb concentration $\geq$10.0 g/dl ($\geq$100 g/l), we suggest that ESA therapy not be initiated. (*2D*)

3.4.2: For adult CKD ND patients with Hb concentration $<$10.0 g/dl ($<$100 g/l) we suggest that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (*2C*)

3.4.3: For adult CKD 5D patients, we suggest that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l). (*2B*)

3.4.4: Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (*Not Graded*)

3.4.5: For all pediatric CKD patients, we suggest that the selection of Hb concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (*2D*)

RATIONALE

In adult CKD-ND patients TREAT demonstrated that the high Hb darbepoetin arm was associated with harm. In the patients on placebo with rescue treatment allowed when Hb fell to below 9.0 g/dl (90 g/l) the achieved median Hb value was as high as 10.6 g/dl (106 g/l), despite the majority of patients receiving no or little darbepoetin[127] (Supplementary Tables 15–19 online).

There is no convincing evidence that the active increase of Hb towards concentrations in the normal range leads to demonstrable benefit in adult patients with CKD stages 3–5. Moreover, when Hb falls below 10 g/dl (100 g/l) in these patients the Work Group were unconvinced that all patients should have an ESA initiated, particularly as the rate of Hb fall may be slow. It was suggested that the decision to initiate ESA therapy in CKD-ND when Hb is $>$9.0 and $<$10.0 g/dl ($>$90 and $<$100 g/l) should be individualized based on risk of requiring transfusions and on the presence of symptoms attributable to anemia, particularly as some patients may be at higher risk of requiring red-cell transfusions, and some patients are more prone to developing symptoms and signs associated with anemia (Supplementary Tables 15–19 online).

In adult hemodialysis patients the rate of fall of Hb is faster than in ND patients, and if untreated Hb will frequently fall below 8 g/dl (80 g/l).[122] As the risk of transfusions is high in those HD patients whose Hb falls below 9 g/dl (90 g/l) the Work Group suggested that ESA therapy should be used to prevent the Hb concentration from falling below 9.0 g/dl (90 g/l), which in practice means that the Hb concentration at which ESA should be initiated should be between 9.0 and 10.0 g/dl [90 and 100 g/l] (Supplementary Tables 9–14 online).

However, there may be subgroups of adult CKD stage 3–5 and 5D patients in whom it may not be wise to let Hb values descend below 10 g/dl (100 g/l), particularly in elderly patients who are more prone to developing symptoms and signs associated with anemia, and those who are prone to requiring red-cell transfusions.

Moreover, physical and mental performances and QoL may be seriously compromised in adult CKD patients with severe anemia. RCTs supporting registration of epoetin-alfa for the treatment of anemia in dialysis patients demonstrated that ESA treatment of subjects with a Hb of $<$ 10 g/dl ($<$100 g/l) to a Hb target of approximately 10–12 g/dl

(100–120 g/l) improved patient-reported physical functioning.[134,135] The question of the Hb value above which there is no further improvement in these parameters remains unsolved, especially for CKD-ND patients without diabetes and CKD-5D patients with or without diabetes.

In anemic children with CKD there are no RCTs examining the effects of ESA administration on hard outcomes. Therefore, any suggestion for Hb targets in this subgroup of CKD patients has to rely on results obtained in the adult CKD patient population and on clinical experience in the pediatric setting. The upper and lower Hb targets are opinion-based, in keeping with the lack of pediatric specific evidence. There are a number of factors unique to children that make exclusive reliance on evidence in adults inappropriate such as age-specific variation of normal Hb concentrations as well as QoL, growth, developmental, and psychological differences between children and adults.[58] Limited data suggest that children with CKD and a Hb less than 9.9 g/dl (99 g/l) are at increased risk for mortality,[139] left ventricular hypertrophy,[140,141] and/or decreased exercise capacity[142] compared to those with a Hb greater than 9.9 g/dl (99 g/l). When evaluated as a continuous variable, hematocrit (Hct) was linked directly to measures of improved health and physical functioning in a health based QoL questionnaire administered to a pediatric CKD population.[143]

ESA MAINTENANCE THERAPY

3.5.1: In general, we suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (*2C*)

3.5.2: Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (*Not Graded*)

RATIONALE

The suggestion to set the upper Hb target in general to values ≤11.5 g/dl (≤115 g/l) in adult CKD patients is based on the interpretation of the combined results of the recent major RCTs that there may be more harm than benefit at higher Hb concentrations. Of note, the update of the 2006 KDOQI anemia guideline in 2007 had already led to the recommendation to limit the upper Hb target to 12 g/dl (120 g/l), not to exceed 13 g/dl (130 g/l).[51] The present suggestion not to exceed in general a Hb limit of 11.5 g/dl (115 g/l) has been influenced by the fact that the upper boundary of the Hb concentration in the control group of the major ESA RCTs usually did not exceed 11.5 g/dl (115 g/l); no data exist on the benefits of Hb targets between 11.5 and 13.0 g/dl (115 and 130 g/l); and high Hb targets are associated with adverse outcomes.

The Work Group recognized that some patients experience an improvement in QoL when the Hb value is above 11.5 g/dl (115 g/l). This opinion is supported by the heterogeneity of QoL outcomes in the major RCTs: in the double-blind Canada-Europe Study and in open label CREATE study statistically significant improvements in some QoL domains that may be clinically important were reported with higher Hb values.[124,126,130] In the double-blind TREAT study the QoL benefits of higher Hb were modest[127,132] and in open label CHOIR study no benefits were observed[128] (Supplementary Tables 9–19 online).

As all CKD patients in TREAT study also had type 2 diabetes, it is possible that improvements in QoL may be more difficult to achieve in this subgroup of patients than in those not suffering from diabetes.

An increase of Hb above 11.5 g/dl (115 g/l) towards 13 g/dl (130 g/l) may also be justified in individual patients with a high bleeding tendency since this results in lower transfusion needs, as shown by 8 RCTs.[133]

Obviously, increasing Hb above 11.5 g/dl (115 g/l) up to 13 g/dl (130 g/l) has to be weighed against the probability of increased harm. This perspective needs to be clearly explained to each patient who wishes to examine the possible benefits of more complete anemia correction.

3.6: In all adult patients, we recommend that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). (*1A*)

RATIONALE

The strong recommendation not to aim for Hb increases to concentrations >13 g/dl (>130 g/l) is based on the interpretation of the combined results of the recent major RCTs showing more harm than benefit with higher Hb targets, as compared to lower Hb targets, including increased risks for stroke,[126,127] hypertension,[133] and vascular access thrombosis (in hemodialysis patients).[118] TREAT did not demonstrate significant differences for serious cardiovascular or kidney events comparing correction of anemia with darbepoetin to the placebo group.[127] Thus the increased risk of kidney events reported in CREATE[124] and of cardiovascular events reported in CHOIR[128] were not substantiated in the much larger TREAT trial.[127] However, a recent meta-analysis point estimate indicated increased mortality at higher Hb target[133] (Supplementary Tables 9–19 online).

An exception to the recommendation to avoid Hb increases to concentrations >13 g/dl (>130 g/l) might however be made for patients with comorbidities that are normally associated with elevated Hb levels (e.g., cyanotic heart disease).

3.7: In all pediatric CKD patients receiving ESA therapy, we suggest that the selected Hb concentration be in the range of 11.0 to 12.0 g/dl (110 to 120 g/l). (*2D*)

RATIONALE

As mentioned above, in children with CKD observational data associates high Hb with better survival[139] and/or increased exercise capacity.[142] Moreover, a recent North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) retrospective analysis done on pediatric CKD

patients found an increased risk of hospitalization in children with low Hb compared to those with normal Hb.[144] However, based on recent experience with the adult CKD patient population, caution is warranted with any extrapolation from observational treatment studies to conclusions on hard outcomes. This being said, direct extrapolation of the results from adult trials to pediatric patients is not appropriate given the differences in causes of CKD, contributions of age to growth and development, and impact of comorbidities on outcomes.

ESA DOSING

3.8.1: We recommend determining the initial ESA dose using the patient's Hb concentration, body weight, and clinical circumstances. (*1D*)

3.8.2: We recommend that ESA dose adjustments be made based on the patient's Hb concentration, rate of change in Hb concentration, current ESA dose and clinical circumstances. (*1B*)

3.8.3: We suggest decreasing ESA dose in preference to withholding ESA when a downward adjustment of Hb concentration is needed. (*2C*)

3.8.4: Re-evaluate ESA dose if (*Not Graded*):
- **The patient suffers an ESA-related adverse event**
- **The patient has an acute or progressive illness that may cause ESA hyporesponsiveness (see Recommendations 3.13.1–3.13.2)**

RATIONALE

The initiation of ESA therapy, ESA dose adjustments and rates of changes have remained similar to those outlined in the 2006 KDOQI Anemia Guideline.[50] In general, the objective of initial ESA therapy is a rate of increase in Hb concentrations of 1.0 to 2.0 g/dl (10 to 20 g/l) per month. This is consistent with the findings in ESA trials of CKD-associated anemia where the mean initial rates of Hb concentration increase were of 0.7 to 2.5 g/dl (7 to 25 g/l) in the first 4 weeks. However, a rise in Hb of greater than 2.0 g/dl (20 g/l) over a 4-week period should be avoided.

The rate of increase varies greatly as a function of individual ESA responsiveness. Poor responders are more likely to be female, to have a history of cardiovascular disease (CVD), to have signs of iron deficiency and inflammation, and to be overweight.[145] The response also depends on initial dose, dosing frequency, and route of administration. The dependence on dosing frequency and route of administration concerns epoetin-alfa, epoetin-beta, and darbepoetin but not CERA (continuous erythropoietin receptor activator [methoxy polyethylene glycol-epoetin-beta]). When ESAs were introduced into clinical practice over 20 years ago, hypertension was frequently noted in the first 3 months after initiating therapy in severely anemic patients, and seizures in rare instances. It is possible, although not proven, that these events were related to a too rapid rate of increase in Hb concentrations.

Epoetin-alfa or epoetin-beta dosing usually starts at 20 to 50 IU/kg body weight three times a week. Darbepoetin-alfa dosing usually starts at 0.45 μg/kg body weight once weekly by subcutaneous (SC) or IV administration, or 0.75 μg/kg body weight once every 2 weeks by SC administration. CERA dosing starts at 0.6 μg/kg body weight once every 2 weeks by SC or IV administration for CKD ND and CKD 5D patients, respectively, or 1.2 μg/kg body weight once every 4 weeks by SC administration for CKD ND patients. Higher baseline Hb concentrations require lower initial ESA doses, except for CERA for which there is no initial dose change. In patients with a history of CVD, thrombo-embolism or seizures, or in those with high blood pressure, the initial doses should be in the lower range. Epoetin-alfa or epoetin-beta dosage may subsequently be increased every 4 weeks by a weekly dose of 3×20 IU/kg if the increase of Hb is not adequate. Increases in dose should not be made more frequently than once a month. If the Hb is increasing and approaching 11.5 g/dl (115 g/l), the dose should be reduced by approximately 25%. If the Hb continues to increase, doses should be temporarily withheld until the Hb begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. Alternatively, one could simply repeat the Hb determination again in a shorter interval (e.g., weekly) and interpret any further rise, in particular in light of reticulocyte counts and their direction, before considering holding the dose. If the Hb increases by more than 1.0 g/dl (10 g/l) in any 2-week period, the dose should be decreased by approximately 25%. See Recommendations 3.13.1 to 3.15.2 regarding ESA hyporesponsiveness and loss of ESA response (Supplementary Table 20 online).

Dose adjustments may be necessary once the Hb target range has been reached. Note that in clinical practice, achieved Hb values may easily rise above or fall below the optimal Hb limits. Therefore, cautious dose adaptations are required. In general, ESA dose adjustments are made only after the first 4 weeks after ESA initiation. The frequency of ESA dose adjustment should be determined by the rate of increase in Hb concentrations during initial ESA therapy, the stability of Hb concentrations during maintenance ESA therapy, and the frequency of Hb testing. The minimum interval between ESA dose adjustments in the outpatient setting generally is 2 weeks because the effect of most dose changes will not be seen within a shorter interval. ESA doses should be decreased, but not necessarily held, when a downward adjustment of Hb concentration is needed. Withholding ESA doses, particularly for long periods, may lead to a delayed decrease in Hb concentrations to less than target range. Such a decrease may initiate periodic cycling of Hb concentrations at greater than and less than the target Hb range.[146] Hb variability has been found to be an independent predictor of mortality in a large US CKD 5HD patient population[147] although this observation could not be confirmed in a large European CKD 5HD patient cohort.[148]

Each time a patient with CKD is hospitalized the treating clinician should evaluate or reevaluate the patient's ESA

requirements. Disease states such as severe infections or post-surgery may modify the ESA responsiveness profoundly. In case of profound anemia and markedly impaired ESA response a red cell transfusion may be preferred to administering ESAs or increasing ESA dose.

ESA ADMINISTRATION

3.9.1: For CKD 5HD patients and those on hemofiltration or hemodiafiltration therapy, we suggest either intravenous or subcutaneous administration of ESA. (*2C*)

3.9.2: For CKD ND and CKD 5PD patients, we suggest subcutaneous administration of ESA. (*2C*)

RATIONALE

As outlined in the 2006 KDOQI guideline,[50] the route of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and the class of ESA used. Among CKD 5D patients undergoing intermittent hemodialysis or hemofiltration therapy, either SC or IV administration is possible. In the outpatient setting, SC administration is the only routinely feasible route of administration for patients with CKD 3–5 or on peritoneal dialysis treatment. Among short-acting ESAs, efficacy of SC administration in patients with CKD 5HD may be superior to that of IV administration, as shown by a large multicenter RCT in hemodialysis patients.[149] However, another RCT of much smaller sample size did not find an advantage of SC over IV administration in CKD 5HD patients.[150] Among long-acting ESAs, efficacy of SC compared with IV administration appears to be equivalent at examined dosing frequencies.[151–153] Furthermore, CKD 5HD patients in general prefer IV to SC administration of ESAs because SC administration may be painful (Supplementary Tables 21–24 online).

Frequency of administration

3.10: We suggest determining the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA. (*2C*)

RATIONALE

The frequency of ESA administration depends on considerations of efficacy, convenience and comfort. Maximum efficacy occurs within dosing intervals that are ESA class specific. For example, in patients on hemodialysis treatment receiving SC or IV short-acting ESA therapy, epoetin-alfa efficacy decreases when the dosing is extended from 3 times weekly to once-weekly administration,[154] and even more so when the dosing intervals are extended to every other week administration.[155] Among long-acting ESAs, darbepoetin-alfa appears to have maximum efficacy when administered every 2 weeks, and methoxy polyethylene glycol-epoetin-beta (CERA) every 4 weeks.[156] When converting short-acting ESAs to long-acting ESAs, differences in drug half-life need to be considered. For the sake of comparison, 3 times weekly administered epoetin-alfa to darbepoetin-alfa given only once monthly resulted in a decreased frequency of injections needed to maintain Hb concentrations of CKD patients within an accepted target range[157] (Supplementary Tables 25–28 online).

When converting a patient from one ESA to another the pharmacokinetic and pharmacodynamic characteristics of the new ESA need to be taken into consideration. The manufacturers have provided conversions from epoetin-alfa or epoetin-beta to darbepoetin-alfa or CERA. Note that the conversion ratios from epoetin to darbepoetin are non-linear.

When using different types of approved ESAs (biosimilars that have received approval by official regulatory bodies such as FDA and European Medicines Agency [EMA]), license information provided by companies should also be taken into account.

TYPE OF ESA

3.11.1: We recommend choosing an ESA based on the balance of pharmacodynamics, safety information, clinical outcome data, costs, and availability. (*1D*)

3.11.2: We suggest using only ESAs that have been approved by an independent regulatory agency. Specifically for 'copy' versions of ESAs, true biosimilar products should be used. (*2D*)

RATIONALE

As outlined above, the choice of short-acting or long-acting ESAs needs to take into account a number of different aspects, encompassing patient-oriented issues and country-specific considerations. At present, there is no evidence that any given ESA brand is superior to another in terms of patient outcomes, with the historical exception of the temporary increase in the incidence of antibody-mediated pure red cell aplasia (PRCA) about 10–20 years ago, which was associated with SC administration of an epoetin-alfa formulation available in Europe, but not in the United States.[158,159] It is the considered opinion of the Work Group that the likelihood of differences in clinical outcomes among ESA brands is low, although there is no robust evidence supporting this assumption (Supplementary Tables 29–32 online).

At present, a number of different types of short-acting or long-acting ESAs are available worldwide, including original formulations, biosimilars, and 'copy' ESAs which have not been exposed to the rigor of scientific evaluation as mandated by the regulatory agencies prior to approval. Their accessibility and costs vary from country to country. True biosimilars, as defined by the EMA, are not identical to the originator products, but they have undergone a minimum number of regulatory 'equivalence' or 'non-inferiority' studies to gain marketing authorization in Europe. In other countries outside Europe, some 'copy' ESA products have

been marketed that may not have undergone the same rigorous testing.[160] Since patient safety is one of the most important drug treatment issues, only biosimilars approved by an independent regulatory agency should be used.

EVALUATING AND CORRECTING PERSISTENT FAILURE TO REACH OR MAINTAIN INTENDED HEMOGLOBIN CONCENTRATION

Frequency of monitoring

3.12.1: During the initiation phase of ESA therapy, measure Hb concentration at least monthly. (*Not Graded*)

3.12.2: For CKD ND patients, during the maintenance phase of ESA therapy measure Hb concentration at least every 3 months. (*Not Graded*)

3.12.3: For CKD 5D patients, during the maintenance phase of ESA therapy measure Hb concentration at least monthly. (*Not Graded*)

RATIONALE

ESA initiation phase. The suggestion to monitor Hb values at least monthly in patients in whom ESA therapy is started is intended to provide sufficient surveillance information to assist in achieving and maintaining desired Hb concentrations safely and follows common practice.[50] The minimum interval between ESA dose adjustments is 2 weeks because the effect of most dose changes will not be seen within a shorter interval. Consideration of an ESA dose adjustment is based on the next projected Hb concentration. Because the accuracy of projection (extrapolation) increases with the number of contributing data points, the frequency of Hb monitoring is likely to be an important determinant of the accuracy of ESA dose adjustment. However, evidence to support this line of reasoning is indirect. Several RCTs have randomized CKD 5HD patients with target-range Hb concentrations to a change in frequency of ESA administration, a change in ESA class, or both. RCTs that have monitored Hb values weekly and adjusted ESA doses as frequently as every 2 weeks have achieved stable Hb concentrations early after randomization.[152,161,162] In contrast, an RCT that monitored Hb concentrations and considered ESA dose adjustment monthly required 6 to 9 months to stabilize Hb concentrations after randomization,[163] but mean Hb concentration remained within the target range for that trial.

ESA maintenance phase. Within the recommended ranges for monitoring and dose adjustment, unstable Hb concentration, inappropriate high or low Hb concentration, and hemodialysis favor shorter intervals of ESA administration, whereas stable Hb concentration, within target Hb concentration, peritoneal dialysis, CKD 3–5, and minimizing laboratory resource utilization favor longer intervals for long-acting ESAs such as darbepoetin. The frequency of ESA dose adjustment is unaffected by length of action: during an 8-week period with weekly Hb monitoring, about equal numbers of patients receiving either short-acting ESA thrice weekly or darbepoetin once weekly required dose adjustments (44% and 49%, respectively).[162]

Initial ESA hyporesponsiveness

3.13.1: Classify patients as having ESA hyporesponsiveness if they have no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing. (*Not Graded*)

3.13.2: In patients with ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the initial weight-based dose. (*2D*)

Subsequent ESA hyporesponsiveness

3.14.1: Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration. (*Not Graded*)

3.14.2: In patients with acquired ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable. (*2D*)

Management of poor ESA responsiveness

3.15.1: Evaluate patients with either initial or acquired ESA hyporesponsiveness and treat for specific causes of poor ESA response. (*Not Graded*)

3.15.2: For patients who remain hyporesponsive despite correcting treatable causes, we suggest individualization of therapy, accounting for relative risks and benefits of (*2D*):
- **decline in Hb concentration**
- **continuing ESA, if needed to maintain Hb concentration, with due consideration of the doses required, and**
- **blood transfusions**

RATIONALE

Relative resistance to the effect of ESAs is a common problem in managing the anemia of patients with CKD and remains the subject of intense interest, all the more since ESA hyporesponsiveness has been found to be among the most powerful predictors of the risk of cardiovascular events and mortality.[164] Recently a report from TREAT assessed the initial Hb response to darbepoetin after two weight-based doses at 2 weekly intervals, in 1872 patients with CKD and diabetes.[145] Patients with a poor response, (the lowest quartile, who had $<2\%$ change in Hb concentration after 1 month), had higher rates of the composite cardiovascular events (adjusted HR 1.31, 95% CI 1.09–1.59), compared to those with a better response. Although this differential effect may be related to comorbidity in hyporesponsive patients, nonetheless it is possible that the high ESA doses used in

hyporesponsive patients may be toxic. Though not empirically tested, *per se*, the definition of initial hyporesponsiveness agreed upon by the Work Group is derived from the secondary analysis of the TREAT study.[145] Since a $<2\%$ increase in the Hb concentration is likely to be within the variability range of Hb values in individual patients, this value is considered as "no increase." The definition of initial hyporesponsiveness relies on presently accepted ESA starting doses, as indicated in the Rationale under 3.8.1–3.8.4. Of note, weight-based doses for darbepoetin do not differ for IV or SC routes, but do differ for epoetin-alfa.

If lower initial dosages than those used in TREAT are chosen, the diagnosis of hyporesponsiveness must take this into account. For example, in the USA the label for darbepoetin now recommends a starting dose of 0.45 μg per kg per four weeks, much lower than the dose used in TREAT or in Europe (i.e., 0.45 μg per kg per week or 0.75 μg per kg per two weeks). If such lower starting doses are used, repeated escalations in ESA dose should be allowed to reach double the weight-based dose used in TREAT.

Although the distinction between initial ESA hyporesponsiveness and acquired partial or complete loss of ESA responsiveness in a patient with already treated, stable anemia is somewhat artificial, it is useful in our opinion for clinical practice.

In the Normal Hematocrit Study both the high Hb and the low Hb groups revealed an inverse relationship between achieved Hb and the primary outcome (death or myocardial infarction).[118] This is consistent with the idea that those patients who failed to achieve the target Hb were unable to do so because comorbid condition(s) existed that prevented achievement of this target. Thus, hyporesponsiveness may just have been a marker for adverse outcomes, although the possibility that high ESA doses used in hyporesponsive patients are toxic in themselves cannot be excluded. Dose-targeting bias has been reported by the Kidney Disease Clinical Studies Initiative Hemodialysis Study (HEMO) investigators.[165] In this RCT ESRD patients, randomly allocated to either high or low quantity of dialysis, as measured by Kt/V, demonstrated an inverse relationship between achieved Kt/V and mortality. The interpretation was that patients with comorbid conditions were unable to achieve higher Kt/V and that comorbidity predisposed these patients to earlier death.

The same principle as used with defining hyporesponsiveness to darbepoetin could be applied to the early response to other short-acting ESAs but cannot be applied to longer acting ESAs such as CERA. In that case, evaluating the Hb response after a time period of 2 months appears to be appropriate. Early ESA hyporesponsiveness or the subsequent occurrence of hyporesponsiveness in CKD patients with previously stable Hb values should lead to an intensive search for potentially correctable factors which might be causally involved. Unfortunately, besides iron deficiency, there are only few other easily reversible factors that contribute to ESA hyporesponsiveness, as shown in Table 3. If other such factors are identified they should be treated as well. Although most

Table 3 | Potentially correctable versus non correctable factors involved in the anemia of CKD, in addition to ESA deficiency

Easily correctable	Potentially correctable	Impossible to correct
Absolute iron deficiency Vitamin B_{12}/folate deficiency Hypothyroidism ACEi/ARB Non-adherence	Infection/inflammation Underdialysis Hemolysis Bleeding Hyperparathyroidism PRCA Malignancy Malnutrition	Hemoglobinopathies Bone marrow disorders

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; PRCA, pure red cell aplasia.

disorders associated with hyporesponsiveness are readily apparent, hyporesponsive patients should be evaluated for coexisting oncological or hematologic disorders. They include hematological and non-hematological malignancies as well as such diverse hematological conditions as thalassemia, sickle cell disease or the anemia associated with other chronic diseases. Myelodysplastic syndromes are a particular case. If at all ESA responsive, the anemia in patients with myelodysplastic syndrome responds more slowly. Therefore, 1 month may be too short to define hyporesponsiveness in this and several other conditions. Moreover, patients with myelodysplastic syndromes may need higher ESA doses. Finally, a rare disorder, PRCA, deserves special consideration (see 3.17.1–3.17.3). The estimation of loss of ESA response also may require a longer observation time in some patients. Note that poor ESA response, either in the initial correction phase or subsequently, is most often a transient condition. Complete loss of response is exceptional. Poor responders should periodically be re-tested for responsiveness, including after the correction of treatable causes of hyporesponsiveness.

It is important to note that the dosing requirements may differ substantially between children and adults. Registry data from NAPRTCS showed that young children require higher doses of ESA than adults, ranging from 275 U/kg/week to 350 U/kg/week for infants and 200–250 U/kg/week for older children.[166] Another retrospective analysis among patients on chronic hemodialysis found that children and adolescents required higher absolute doses of ESA than adults to maintain target hemoglobin levels, despite the lower mean body weight of the children.[167] Unfortunately, there are no RCTs that establish the appropriate dosing of ESA in children. Future research to establish pediatric ESA dosing guidelines is needed, especially for infants and younger children.

There may be toxicity from high doses of ESA, as suggested, though not proven, by recent post-hoc analyses of major ESA RCTs,[145,168] especially in conjunction with the achievement of high Hb levels.[169] Therefore, in general ESA dose escalation should be avoided. The Work Group suggestions for initial and acquired hyopresponsiveness imply that maximal doses should be no greater than four times initial weight-based appropriate doses.

Table 4 | Practical approach in presence of ESA hyporesponsiveness

Tests	Finding and action
1. Check adherence	If poor, attempt to improve (if self-injection)
2. Reticulocyte count	If >130,000/μl, look for blood loss or hemolysis: endoscopy, colonoscopy, hemolysis screen
Serum vitamin B_{12}, folate	If low, replenish
Iron status	If low, replenish iron
Serum PTH	If elevated, manage hyperparathyroidism
Serum CRP	If elevated, check for and treat infection or inflammation
Underdialysis	If underdialyzed, improve dialysis efficiency
ACEi/ARB use	If yes, consider reducing dose or discontinuing drug
3. Bone marrow biopsy	Manage condition diagnosed e.g., dyscrasia, infiltration, fibrosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CRP, C-reactive protein; PTH, parathyroid hormone.

In practice, Tables 3 and 4 can guide to diagnose and correct ESA hyporesponsiveness. In patients in whom all correctable causes have been maximally treated but who remain hyporesponsive, ESA therapy may be continued cautiously at doses up to 4 times the initial dose to prevent a further decline in Hb concentration. Red cell transfusions can be used to prevent or treat anemia-related symptoms and signs. The treatment strategy needs to take into account each patient's anemia tolerance and potential benefits and risks linked to increases in Hb values solely obtained by high ESA dosing.

Given the disproportionate burden of morbidity and mortality that the hyporesponsive patient population bears and the ESA expense that hyporesponsiveness engenders, further research is necessary on the causes and management of hyporesponsiveness.

ADJUVANT THERAPIES

3.16.1: We recommend not using androgens as an adjuvant to ESA treatment. (*1B*)

3.16.2: We suggest not using adjuvants to ESA treatment including vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline. (*2D*)

RATIONALE

Several adjuvant treatments have been proposed, either with the goal of limiting the use of more expensive ESA therapy or to improve ESA responsiveness.

Androgens. The use of androgens for treatment of anemia was suggested long before rHuEPO became available in clinical practice. Androgens were used regularly in many centers in the treatment of anemia in dialysis patients despite the need for intramuscular (IM) injection and a variety of adverse events, including acne, virilization, priapism, liver dysfunction, injection-site pain, and risk for peliosis hepatis and hepatocellular carcinoma. The three RCTs that tested androgens in combination with ESA therapy in CKD 5HD patients were all small short-term studies. Currently recommended Hb concentrations were not achieved, and in two of them the ESA doses used were lower than current practice.[170–172] The studies did not enroll patients with ESA hyporesponsiveness, so the effect of androgens on hyporesponsiveness is unknown. The risks of androgen therapy and their uncertain benefit on Hb concentration or clinical outcomes argue against their use as an ESA adjuvant.

Vitamin C. Vitamin C has been reported to increase the release of iron from ferritin and the reticuloendothelial system and increase iron utilization during heme synthesis.[173,174] A recent meta-analysis of vitamin C use in CKD 5HD[175] and a more recent small RCT[176] concluded that vitamin C may result in larger increases in Hb and may limit the use of ESAs. In seven trials, patients generally had functional iron deficiency and in three studies they had EPO hyporesponsiveness (variously defined).[176–178] However, the number of patients studied was insufficient to address the safety of this intervention. Thus the long-term safety of IV ascorbic acid in HD patients remains undefined, and whether secondary oxalosis should be a concern.

Convincing data do not exist for other potential adjuvants including vitamin D, vitamin E, folic acid, L-carnitine and pentoxifylline. Several anecdotal reports, small case series, and nonrandomized studies, primarily in CKD 5HD patients, have been published, but do not provide sufficient evidence upon which to base a recommendation. Future RCTs are clearly needed for ESA adjuvants.

EVALUATION FOR PURE RED CELL APLASIA (PRCA)

3.17.1: Investigate for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 weeks develops the following (*Not Graded*):

- **Sudden rapid decrease in Hb concentration at the rate of 0.5 to 1.0 g/dl (5 to 10 g/l) per week *OR* requirement of transfusions at the rate of approximately 1 to 2 per week, *AND***
- **Normal platelet and white cell counts, *AND***
- **Absolute reticulocyte count less than 10,000/μl**

3.17.2: We recommend that ESA therapy be stopped in patients who develop antibody-mediated PRCA. (*1A*)

3.17.3: We recommend peginesatide be used to treat patients with antibody-mediated PRCA. (*1B*)

RATIONALE

Rarely, patients undergoing ESA therapy develop antibodies that neutralize both ESA and endogenous erythropoietin. The resulting syndrome, antibody-mediated PRCA, is characterized by the sudden development of severe transfusion-dependent anemia. Rapid recognition, appropriate

evaluation, and prompt intervention can be effective in limiting the consequences of this life-threatening condition. Antibody-mediated PRCA, although rare in patients administered ESAs, received urgent attention after 1998. Between 1989 and 1998, three reports described the development of PRCA in only a small number of patients with CKD administered ESAs. Reports of PRCA increased sharply in 1998 and reached a peak in 2002.[159,179] These reports were associated with SC administration of an epoetin-alfa formulation not available in the United States. After removal of this formulation from the market, by 2004, the incidence of new antibody-mediated PRCA had decreased to pre-1998 levels. Isolated cases of PRCA have been observed in association with the use of other ESAs.[159,179,180] Outside this historical episode the incidence rate of PRCA with SC use of all other forms of SC-administered ESA is estimated to be 0.5 cases/10,000 patient-years.[158] Antibody-associated PRCA stemming from IV administration of ESAs is rare and has only been reported anecdotally.[181]

Recommendations based on expert opinions have been published to guide the workup and therapy of patients suspected to have antibody-mediated PRCA.[179,182–184] The two main distinguishing features of antibody-mediated PRCA are the associated decline in blood Hb concentration of approximately 4 g/dl (40 g/l) per month, and a decrease in the number of circulating reticulocytes to <10,000/μl of blood.[185] Bone marrow biopsy characteristically shows reduced numbers or absence of erythroblasts. The definitive diagnosis is dependent upon demonstration of the presence of neutralizing antibodies against erythropoietin. Evidence for parvovirus infection as an alternative cause of PRCA should be sought and excluded.

Following a diagnosis of antibody-mediated PRCA, patients should stop treatment with the incriminated ESA immediately and not resume treatment with the same or another EPO-derived ESA.[184] Immunosuppressive therapy may hasten the disappearance of circulating antibodies in patients with EPO-induced PRCA, and allow endogenous erythropoiesis to recover to pre-treatment levels. In a retrospective study of 47 patients who developed PRCA during EPO therapy (primarily epoetin brand 'Eprex®' in Europe), 29 of 37 patients (78%) who received immunosuppressive therapy recovered, whereas none of the nine patients who did not receive immunosuppressive therapy recovered.[185] Red cell production recovered only when patients received immunosuppressive treatment. Re-exposure to epoetins or darbepoetin-alfa can re-induce the formation of antibodies.[186] Anaphylactoid reactions after repeated injections of epoetin- or darbepoetin-alfa have been reported in a patient with pure red-cell aplasia.[187] A novel approach to the treatment of this condition using a synthetic, peptide-based erythropoietin-receptor agonist (peginesatide) has generated optimistic results,[188] and has the advantage of avoiding immunosuppressive therapy.

The recognition of antibody-mediated PRCA in patients treated with recombinant epoetins has underscored the need for full clinical documentation and post-marketing surveillance with newer ESAs and biosimilar products, as well as therapeutic recombinant proteins in general.[189]

If a decision to treat with peginesatide is taken, it can be initiated at a dose of 0.05 to 0.075 mg/kg body weight by subcutaneous injection every 4 weeks. Subsequently, the dose needs to be adjusted to reach the desired target Hb value.

RESEARCH RECOMMENDATIONS

The following research questions have arisen during the deliberations of the Work Group, and further research will be necessary to answer them.

- In cohort studies moderate anemia is associated with an increased incidence of cardiovascular events. Is anemia really a risk factor for these events or is it a marker for some other cardiovascular risk factor(s)?
- There is uncertainty about optimal Hb targets for ESA therapy. What is the risk-benefit ratio of low Hb targets <10.0 g/dl (<100 g/l) or high targets of 11.5–13.0 g/dl (115–130 g/l), compared to conventional targets of 10.0–11.5 g/dl (100–115 g/l)?
- These guidelines have stressed individualization of anemia therapy. Should the objective of anemia therapy be improvement in clinical outcomes (provided Hb concentration is <13.0 g/dl [<130 g/l]) rather than achievement of a specified Hb target range? Should these outcomes include improvements in QoL, and if so, what defines clinically important improvements?
- As the relationship between ESA responsiveness and hard patient outcomes may be the result of co-morbidity or of high ESA dose, what is the impact of high vs low dose on clinical outcomes in ESA hyporesponsive patients?
- Is the risk-benefit ratio of anemia correction similar in non-diabetic and diabetic CKD patients?
- Is there a difference in adverse clinical outcomes comparing IV and SC routes of administration?
- Are the risk-benefit ratios for biosimilars comparable to current ESAs?
- What is the pathogenesis of cerebrovascular and vascular toxicity associated with normalization of Hb using ESAs?
- Are CKD patients with cancer or a cancer history who are receiving ESA therapy at higher cardiovascular risk than non-CKD patients with cancer or a cancer history?
- What is the effect of vitamin C administration in functional iron deficiency and what is the clinical impact of increased oxalate levels?
- There appears to be differences in anemia treatment outcomes between different geographic regions. What are the reasons for this?
- What are the risks and benefits of ESA administration on outcomes in anemic children with CKD?
- What are the appropriate, weight-based, dosing regimens for the younger pediatric patients, especially those under the age of two years?

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SUPPLEMENTARY MATERIAL

Supplemental Table 7: Association between anemia severity (prior to erythropoietin use) and clinical outcome in multivariable analyses.
Supplemental Table 8: Association between hyperparathyroidism and ESA responsiveness in multivariable analyses.
Supplemental Table 9: Evidence profile of RCTs comparing higher vs. lower Hb targets/ESA doses in the HD-CKD and PD-CKD populations.
Supplemental Table 10: Summary table of RCTs comparing different Hb targets/ESA doses on key clinical outcomes in the HD-CKD and PD-CKD populations.
Supplemental Table 11: Summary table of RCTs comparing different Hb targets/ESA doses on quality of life in the HD-CKD and PD-CKD populations.
Supplemental Table 12: Summary table of RCTs comparing different Hb targets/ESA doses on Fatigue, Vitality/Energy, and Physical function in the HD-CKD and PD-CKD populations.
Supplemental Table 13: Summary table of RCTs comparing different Hb targets/ESA doses on non-CVD/mortality adverse event rates in the HD-CKD and PD-CKD populations.
Supplemental Table 14: Summary table of RCTs comparing different Hb targets/ESA doses on exercise capacity in the HD-CKD and PD-CKD populations.
Supplemental Table 15: Evidence profile of RCTs comparing different higher vs. lower Hb targets/ESA doses in the ND-CKD populations.
Supplemental Table 16: Summary table of RCTs comparing different Hb targets/ESA doses on key clinical outcomes in the ND-CKD population.
Supplemental Table 17: Summary table of RCTs comparing different Hb targets/ESA doses on quality of life in the ND-CKD population.
Supplemental Table 18: Summary table of RCTs comparing different Hb targets/ESA doses on Fatigue, Vitality/Energy, and Physical function in the ND-CKD population.
Supplemental Table 19: Summary table of RCTs comparing different Hb targets/ESA doses on non-CVD/mortality adverse event rates in the ND-CKD population.
Supplemental Table 20: ESA protocols from the major trials in CKD populations.
Supplemental Table 21: Evidence profile of RCTs examining IV vs. SC EPO in CKD patients with anemia.
Supplemental Table 22: Summary table of RCTs examining IV vs. SC ESA in CKD patients with anemia (categorical outcomes).
Supplemental Table 23: Summary table of RCTs examining IV vs. SC ESA in CKD patients with anemia (continuous outcomes).
Supplemental Table 24: Summary table of adverse events in RCTs examining IV vs. SC EPO in CKD patients with anemia.
Supplemental Table 25: Evidence profile of RCTs examining different dosing schedules in CKD patients with anemia.
Supplemental Table 26: Summary table of RCTs examining different dosing schedules in CKD patients with anemia (categorical outcomes).
Supplemental Table 27: Summary table of RCTs examining different dosing schedules in CKD patients with anemia (continuous outcomes).
Supplemental Table 28: Summary table of adverse events in RCTs examining different dosing schedules in CKD patients with anemia.
Supplemental Table 29: Evidence profile of RCTs examining ESA vs. ESA in CKD patients with anemia.
Supplemental Table 30: Summary table of RCTs examining ESA vs. ESA in CKD patients with anemia (categorical outcomes).
Supplemental Table 31: Summary table of RCTs examining ESA vs. ESA in CKD patients with anemia (continuous outcomes).
Supplemental Table 32: Summary table of adverse events in RCTs examining ESA vs. ESA in CKD patients with anemia (categorical outcomes).
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/anemia.php

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Chapter 4: Red cell transfusion to treat anemia in CKD

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USE OF RED CELL TRANSFUSION IN CHRONIC ANEMIA

Repeated transfusions or use of an erythropoiesis-stimulating agent (ESA) are treatment options for chronic anemia in CKD. The choice between these depends on their relative benefits and harms, which vary among patients. For example, patients with a previous stroke have the greatest absolute risk of ESA-related stroke,[127] whereas multiparous women have the highest risk of allosensitization with transfusion.[190,191] Although the clinical importance of allosensitization is disputed, it may delay or reduce the possibility of future kidney transplantation.

4.1.1: When managing chronic anemia, we recommend avoiding, when possible, red cell transfusions to minimize the general risks related to their use. (*1B*)

4.1.2: In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (*1C*)

4.1.3: When managing chronic anemia, we suggest that the benefits of red cell transfusions may outweigh the risks in patients in whom (*2C*):

- **ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance)**
- **The risks of ESA therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke)**

4.1.4: We suggest that the decision to transfuse a CKD patient with non-acute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia. (*2C*)

RATIONALE

As with any treatment, the use of red cell transfusions should be considered in terms of the balance of benefit and harms. The primary benefit is in maintaining sufficient oxygen-carrying capacity and improvement in anemia-related symptoms.[192] The harms are summarized in Tables 5 and 6 and discussed further below. This balance must also be considered alongside the balance between the benefits and harms of ESA therapy which is an alternative treatment for the anemia of CKD. The benefits and harms of ESA therapy are discussed in detail in Chapter 3, but, in summary, the benefits include improvement in anemia-related symptoms and reduced need for transfusion, and the most important harms are increased risk of stroke, thromboembolic events, and cancer progression or recurrence. When choosing between these two treatments for anemia in an individual, patient characteristics which influence the balance between benefits and harms for each treatment should be considered. These include history of stroke and previous or current cancer which place patients receiving ESA therapy at much higher absolute risk of these two problems. Conversely, patients potentially eligible for kidney transplantation have the greatest potential harm from transfusion, in terms of allosensitization,[191,193,194] although the clinical importance of allosensitization is disputed. Previously transplanted patients and multiparous women seem to have the greatest absolute risk of allosensitization.[190,191]

A related issue is when should the decision to treat a patient with either an ESA or a transfusion be made? This decision is subtly different for the two types of treatment as ESAs may be used to *avoid* transfusion and therefore before the need for transfusion has arisen i.e., in a *prophylactic* sense. Furthermore, the magnitude of the potential harms of transfusion (e.g., from infection) and some of the benefits from ESAs (e.g., transfusion avoidance) is dependent on the threshold for transfusion. If that threshold is high (i.e., transfusion is reserved until symptoms become severe or the Hb reaches a very low level) the risks related to transfusion will be low and the benefit of ESA therapy in avoiding transfusions will be small. Unfortunately, there is no consensus about when transfusion is indicated although we do know that the rate of transfusion increases markedly when the Hb falls below 10 g/dl (100 g/l);[122,127] whether that simply reflects practice-patterns or represents clear clinical need is uncertain. The following trials give examples of transfusion rates in CKD 5D and CKD ND patients. The trial conducted by the Canadian Erythropoietin Study Group, published in 1990, enrolled 118 CKD 5HD patients Hb <9.0 g/dl (<90 g/l), 49 (42%) of whom were described as 'transfusion-dependent'.[122] The patients averaged approximately 7 transfusions each in the previous 12 months. These patients were randomized, equally, to 6 months treatment with placebo, erythropoietin with a target Hb 9.5–11.0 g/dl (95–110 g/l), or erythropoietin with a target Hb 11.5–13.0 g/dl (115–130 g/l). After 8 weeks, 23 patients in the placebo group received a blood-transfusion, compared with one in each of the two erythropoietin groups (for a gastrointestinal hemorrhage and following surgery). More recently, in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), published in 2009, 4038 patients with diabetes, CKD ND and anemia (Hb ≤ 11.0 g/dl [≤ 110 g/l]), were randomized, equally, to darbepoetin-alfa with target Hb 13 g/dl (130 g/l) or to placebo, with 'rescue' darbepoetin-alfa when Hb fell below 9.0 g/dl (90 g/l).[127] Over a median follow-up of 29 months, 297/2012 (15%) patients randomized to

Table 5 | Estimated risk associated with blood transfusions per unit transfused

Adverse event	Estimated risk*
Immunological	
Fever/allergic reactions	1 in 100–200[a,b]
Hemolytic reaction	1 in 6000[b]
Transfusion-related acute lung injury (TRALI)	1 in 12,350[a]
Anaphylaxis	1 in 50,000[b]
Fatal hemolysis	1 in 1,250,000[a]
Graft versus host disease (GVHD)	Rare
Other	
Mistransfusion	1 in 14,000–19,000[c]

*United States data.
[a]Data from Carson JL *et al.*[212]
[b]Data from Klein.[213]
[c]Data from Klein HG *et al.*[214]

Table 6 | Estimated risk of transfusion-related infections per unit transfused

Potential transfusion-related risks	Estimated risk*
Hepatitis B	1 in 282,000–1 in 357,000[a]
West Nile virus	1 in 350,000[b]
Death from bacterial sepsis	1 in 1,000,000[b]
Hepatitis C	1 in 1,149,000[a]
Human immunodeficiency virus (HIV)	1 in 1,467,000[a]

*United States data.
[a]Data from Carson JL *et al.*[212]
[b]Data from Rawn J.[215]

darbepoetin-alfa and 496/2026 (25%) assigned to placebo received red cell transfusions (HR 0.56, 95% CI 0.49–0.65, $P<0.001$).

We suggest that the decision to transfuse in the patient with non-acute anemia related to CKD should not be based upon any arbitrary Hb threshold and should, instead, be determined by the occurrence of symptoms and signs caused by anemia. We recognize that symptoms such as dyspnea and fatigue are non-specific, and that anemia-related symptoms may occur at different Hb levels in different patients.

Risks of blood transfusion

Risks associated with blood transfusion include transfusion errors, volume overload, hyperkalemia, citrate toxicity (leading to metabolic alkalosis and hypocalcemia), hypothermia, coagulopathy, immunologically-mediated transfusion reactions, including transfusion-related acute lung injury (TRALI), and iron overload, all of which are uncommon (Table 5).[190,195–207] Transmission of infections, although rare, is a major concern and this risk varies between countries (Table 6).[208–211] These complications are reviewed extensively elsewhere. The importance of human leukocyte antigen (HLA) sensitization is disputed and discussed in more detail below.

HLA sensitization. The risk of sensitization after blood transfusion has changed over time probably, at least in part, due to changes in blood transfusion practices and the use of more precise methods to measure allosensitization.

In the early 1980s, Opelz *et al.* examined the risk of sensitization in 737 CKD 5HD patients (Figures 3A and 3B), of whom 331 were followed prospectively (Figure 3C).[190] Approximately 90% of all transfusions were given in the form of 'packed cells' and antibodies were measured by the lymphocyte cytotoxicity test. Overall, 28% of patients followed prospectively developed HLA antibodies. Of these, 18% developed reactivity to 10–50% of the panel, 7% to 50–90%, and <3% to >90% of the panel after up to 20 transfusions (Figure 3C). Among men, 90% remained 'unresponsive' (<10% antibody reactivity against the panel) and 10% developed reactivity to 10–50% of the panel (Figure 3C). In contrast, after 10 transfusions, only 60% of the women were 'unresponsive,' 11% demonstrated 10–50% reactivity, 23% 51–90% reactivity, and 6% >90% reactivity (Figure 3C). These data suggested that the main drivers of HLA sensitization following red cell transfusion are previous pregnancies and previous transplantation. The data also suggested that men have a much lower risk of HLA sensitization following transfusion than women, and women with multiple pregnancies have a much greater risk of HLA sensitization than nulliparous women. However, more recent data from the US Renal Data System (USRDS) 2010 Annual Report,[191] have challenged this assumption, suggesting that males receiving previous blood transfusions may also be at increased risk.

Studies performed in the last two decades showed that the risk of sensitization with blood transfusion is apparently lower than previously reported, with an overall response rate ranging from 2 to 21%.[216–218] A possible, albeit controversial, explanation for this lower sensitization rate is that red cell transfusions in recent years are less immunogenic because they contain fewer leukocytes due to widespread use of blood filters.

Other tentative conclusions from previous studies include the following: a) washed-red cells do not appear to be less immunogenic than non-washed red cells;[190] b) no consistent reduction in sensitization has been demonstrated with donor-specific[217] and HLA-DR matched transfusions;[219] c) higher numbers of blood transfusions have been associated with an increased risk of sensitization in some studies[220,221] but not in others.[190,222]

However, more recent data from the USRDS indicates that risk of sensitization with blood transfusions is substantial. For example, compared with patients who have never received a blood transfusion, patients who received transfusions have an odds ratio of having panel reactive antibody (PRA) >80% of 2.38.[191] Interestingly, in this analysis the risk of being highly sensitized at the time of transplantation was higher for men than for women.

Effect of leukocyte-reduced blood transfusions on sensitization. Although, leukocytes may be a contributor to, if not the cause of, a number of adverse consequences of blood transfusion, including immunologically-mediated effects,

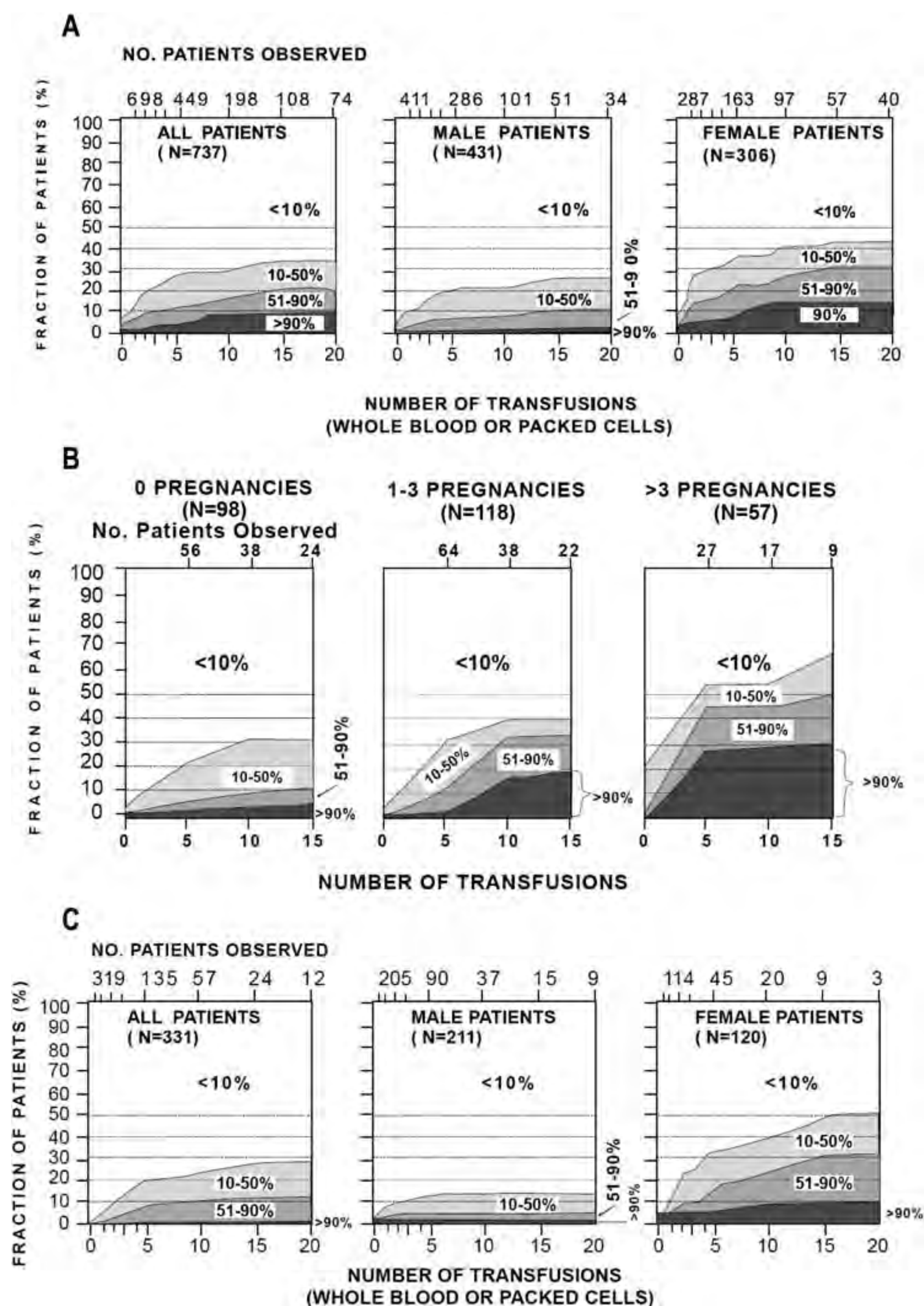

Figure 3 | Lymphocytotoxic antibody reactivity against random donor test panel in relation to the number of blood transfusions. Fractions of patients reacting against <10%, 10 to 50%, 51 to 90% and >90% of the panel donors are plotted. All 737 patients were on chronic hemodialysis, waiting for a first kidney transplant. Numbers of patients after 2, 5, 10, 15, and 20 transfusions are indicated at top of graphs. (**A**) Male and female patients. (**B**) Females patients separated by the number of previous pregnancies. (**C**) Lymphocytotoxic antibodies in patients who were studied prospectively throughout the course of treatment. Reprinted from Opelz G, Graver B, Mickey MR *et al*. Lymphocytotoxic antibody responses to transfusions in potential kidney transplant recipients. *Transplantation* 1981; 32(3): 177–183 (ref. 190) with permission from Lippincott Williams & Wilkins; accessed http://journals.lww.com/transplantjournal/Abstract/1981/09000/Lymphocytoxic_Antibody_Responses_to_Transfusions.2.aspx

infectious disease transmission, and reperfusion injury, leukoreduction of blood products does not decrease sensitization in previously transplanted or in potential future kidney transplant candidates.[223–225] One recent study reported that male patients awaiting their first organ transplant had a fourfold increased risk of developing HLA antibody if they had been previously transfused when compared with those who did not have a history of a transfusion.[226] Thus,

Table 7 | Indications for blood transfusions

Indication	Comments
When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable myocardial ischemia)	• Red cell transfusion in patients with acute hemorrhage is indicated in the following situations: a) rapid acute hemorrhage without immediate control of bleeding; b) estimated blood loss >30–40% of blood volume (1500–2000 ml) with symptoms of severe blood loss; c) estimated blood loss <25–30% blood volume with no evidence of uncontrolled hemorrhage, if signs of hypovolemia recur despite colloid/crystalloid resuscitation; d) in patients with co-morbid factors, transfusions may be necessary with lesser degrees of blood loss.[234] • Studies evaluating the importance of anemia and the role of transfusion in the setting of an acute coronary syndrome (i.e., unstable angina, myocardial infarction) have reached differing conclusions. • The American College of Cardiology/American Heart Association and American College of Chest Physicians guidelines do not make any recommendations concerning the potential benefit or risk of blood transfusion in the setting of an acute coronary syndrome.[235,236] However, in a review of clinical trials of patients with a non-ST elevation acute coronary syndrome, the risk of cardiovascular mortality, nonfatal myocardial infarction, or recurrent ischemia at 30 days was significantly higher in patients with a Hb concentration below 11 g/dl (110 g/l) than those with a Hb ≥11 g/dl (≥110 g/l).[237] • Although anemia occurs frequently in patients with heart failure, limited data are available on treatment of anemia in this population. • Correction of anemia is not an evidence-based therapy in heart failure as noted in the 2006 Heart Failure Society of America guidelines, 2012 European Society of Cardiology (ESC) guidelines, and 2009 American College of Cardiology/American Heart Association guidelines.[238–240] • Therefore, the general indications for red cell transfusion apply to patients with heart failure; however, careful attention must be paid to volume status.
When rapid pre-operative Hb correction is required	• Criteria have been proposed for perioperative transfusions.[234] These are generally not recommended when the Hb is ≥10 g/dl (≥100 g/l) in otherwise healthy subjects, but should be given when the Hb is less than 7 g/dl (70 g/l). • When Hb concentration is less than 7 g/dl (70 g/l) and the patient is otherwise stable, 2 units of red cells should be transfused and the patient's clinical status and circulating Hb should be reassessed. • High-risk patients (>65 years and/or those with cardiovascular or respiratory disease) may tolerate anemia poorly, and may be transfused when Hb concentration is less than 8 g/dl (80 g/l). • For Hb concentration between 7 and 10 g/dl (70 and 100 g/l), the correct strategy is unclear.
When symptoms and signs related to anemia are present in patients in whom ESA therapy is ineffective (e.g., bone marrow failure, hemoglobinopathies, ESA resistance)	• Patients with chronic anemia (e.g., bone marrow failure syndromes) may be dependent upon red cell replacement over a period of months or years, which can lead to iron overload. • Approximately 200 mg of iron are delivered per unit of red cells; this iron is released when Hb from the transfused red cells is metabolized after red cell death. • Given the progressive loss of red cell viability which occurs during storage, the "freshest-available" units should be selected in order to maximize post-transfusion survival. • Hemosiderosis can produce organ damage when the total iron delivered approaches 15 to 20 grams, the amount of iron in 75 to 100 units of red cells. • The issue of red cell transfusion in patients with acquired or congenital hemolytic anemia is more complex.
When symptoms and signs related to anemia are present in patients in whom the risks of ESA therapy may outweigh the benefits	• ESAs should be used with great caution, if at all, in CKD patients with active malignancy, a history of malignancy, or prior history of stroke.

CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.

transfusion in the post-leukodepletion era still continues to pose a significant risk of sensitization. A possible reason for this finding is that the number of HLA molecules contributed by the red cells is comparable to that of leukocytes.[227]

Association between sensitization and delay in organ transplantation. According to USRDS data reported in 2010, the mean wait-time to transplant for patients listed between 1991 and 2008 was an average of 2 months longer for transfused than non-transfused patients in the United States.[191] Increased PRA titers, whether due to blood transfusions or other factors, were associated with a longer wait to find a compatible donor and may have completely precluded transplantation in some patients. Non-sensitized patients (0% PRA at the time of listing) had the shortest wait-time (median of 2.5 years in 2005) while those with a PRA of 1–19% and 20–79% had median wait-times of 2.9 and 4.3 years, respectively. Highly sensitized patients (≥80% PRA) waited the longest and in these patients a median wait-time

could not be calculated for patients listed in 2005. As a result of the delay in finding compatible donors in patients with PRA $\geq$80%, the percentage of these patients increased from 7.5% at listing to 13.3% five years after listing.

Not being transplanted, or having to wait longer for transplantation, is associated with lower survival.[228,229] Receiving a transfusion while on the transplant wait list is associated with a nearly 5-fold higher risk of dying while on

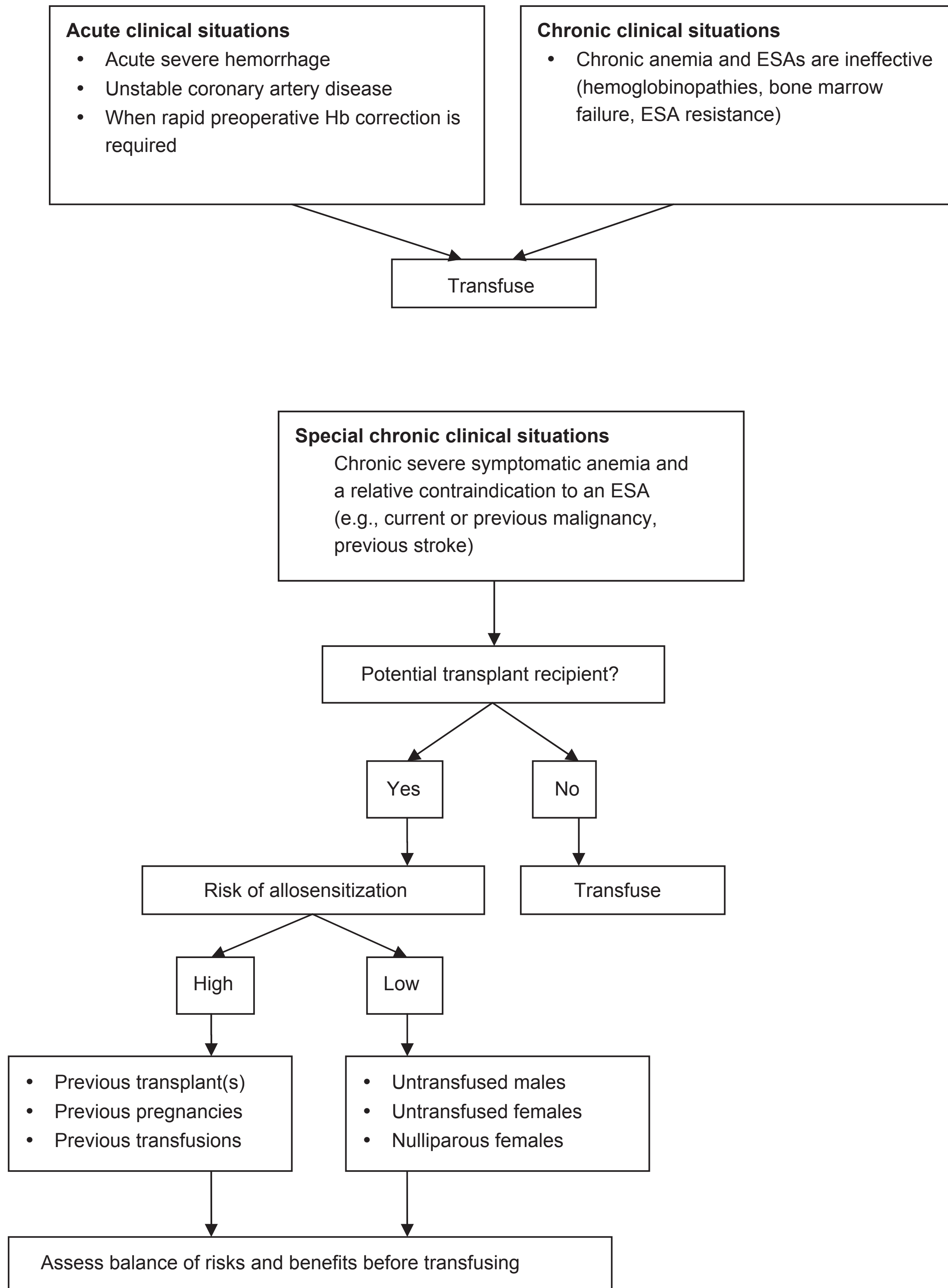

Figure 4 | Algorithms for red cell transfusion use in CKD patients. ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.

the wait list in the first five years, and an 11% reduction in the likelihood of receiving a transplant within the first five years.[191,230] In transplanted patients, the presence of preformed HLA antibodies is associated with an increased risk of early and late graft loss.[193,194,231,232] Recent data also suggest that pre-existing donor-specific HLA antibodies identified by a Luminex single-antigen assay at the time of transplantation are associated with a higher incidence of antibody-mediated rejection and inferior graft survival.[233]

URGENT TREATMENT OF ANEMIA

4.2: In certain acute clinical situations, we suggest patients are transfused when the benefits of red cell transfusions outweigh the risks; these include (*2C*):
- **When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable coronary artery disease)**
- **When rapid pre-operative Hb correction is required**

RATIONALE

In certain urgent clinical situations, red cell transfusion may be needed for the immediate correction of anemia. These include acute severe hemorrhage and other clinical problems caused by, or exacerbated by, anemia, such as acute myocardial ischemia. When urgent surgery is required, transfusion may also be given to achieve rapid preoperative correction of Hb. The Hb threshold for transfusion in this situation is uncertain but we suggest that this treatment be considered if the Hb is <7 g/dl (<70 g/l).

Table 7 and Figure 4 summarize the approaches to the use of red cell transfusions in patients with CKD.

RESEARCH RECOMMENDATIONS

There is a lack of randomized controlled trials on the use of blood transfusions as a primary intervention in patients with anemia and CKD. Given the logistical difficulties in conducting such trials, it is likely that observational data will continue to predominate in this therapeutic area.

Future research should include:
- Prospective observational data collection on the use of red cell transfusions in CKD patients, particularly dialysis patients, including the reason(s) for transfusion, intent to list for future kidney transplantation, likelihood of receiving a kidney transplant, and graft outcomes.
- Prospective observational evaluation of the impact of red cell transfusions on the level of HLA sensitization.
- Given a striking disparity in the use of blood transfusions between the US and Europe, Canada and Australia in the TREAT study, and between the US and Europe in the Phase 3 peginesatide clinical trial program, further research is needed to ascertain the 'drivers' for transfusion in CKD patients. Is this related to practice patterns or a real higher clinical need for transfusions in the US?

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Methods for guideline development

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AIM

The overall aim of the project was to develop an evidence-based clinical practice guideline for management of anemia and chronic kidney disease (CKD). The guideline consists of recommendations, rationale statements and a summary of systematically generated evidence on relevant predefined clinical topics.

OVERVIEW PROCESS

Guideline development process included the following sequential and concurrent steps:

- Appointing Work Group members and Evidence Review Team (ERT).
- Discussing process, methods, and results.
- Developing and refining topics.
- Identifying populations, interventions or predictors, and outcomes of interest.
- Selecting topics for systematic evidence review.
- Standardizing quality assessment methodology.
- Developing and implementing literature search strategies.
- Screening abstracts and retrieving full text articles based on predefined eligibility criteria.
- Creating data extraction forms.
- Data extracting and performing critical appraisal of the literature.
- Grading the methodology and outcomes in individual studies.
- Tabulating data from individual studies into summary tables.
- Grading quality of evidence for each outcome across studies, and assessing the overall quality of evidence across outcomes with the aid of evidence profiles.
- Grading the strength of recommendations based on the quality of evidence and other considerations.
- Finalizing guideline recommendations and supporting rationale statements.
- Sending the guideline draft for peer review to the KDIGO Board of Directors in June 2011, and for public review in September 2011.
- Publishing the final version of the guideline.

The Work Group, KDIGO Co-Chairs, ERT, and KDIGO support staff met for two 2-day meetings for training in the guideline development process, topic discussion, and consensus development.

Commissioning of work group and evidence review team

KDIGO Co-Chairs appointed the Work Group Co-chairs. Work Group Co-Chairs then assembled the Work Group consisting of domain experts, including individuals with expertise in internal medicine, adult and pediatric nephrology, cardiology, hematology, oncology, hypertension, pathology, pharmacology, epidemiology and endocrinology. Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA was contracted to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of physician-methodologists with expertise in nephrology, a project coordinator and manager, and a research assistant. The ERT instructed and advised Work Group members in all steps of literature review, critical literature appraisal, and guideline development. The Work Group and the ERT collaborated closely throughout the project.

Defining scope and topics

Work Group Co-Chairs first defined the overall scope and goals of the guideline. Work Group Co-Chairs then drafted a preliminary list of topics and key clinical questions. In light of new evidence, it was decided that an update of the topics presented in the 2006 and 2007 KDOQI guidelines would be the best approach. The Work Group and ERT further developed and refined each topic, specified screening criteria, literature search strategies, and data extraction forms (Table 8).

Establishing the process for guideline development

The ERT performed literature searches, organized abstract and article screening. The ERT also coordinated the methodological and analytic process of the report, defined and standardized the methodology of performing literature searches, data extraction, and summarizing the evidence. Throughout the project, the ERT offered suggestions for guideline development, led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, grading of evidence and guideline recommendations, and consensus development. The Work Group took the primary role of writing the guidelines and rationale statements and retained final responsibility for the content of the guideline statements and the accompanying narrative.

The Work Group Co-Chairs prepared the first draft of the scope of work document as a series of topics to be considered by Work Group members. The scope of work document was based primarily on the existing KDOQI guidelines on anemia. At their first two-day meeting, Work Group members revised the initial working document to include all topics of interest to the Work Group. The inclusive,

Table 8 | Systematic review topics and screening criteria

Identifying why, when and which patients to treat for anemia and iron deficiency	
Population	All CKD stages for longitudinal, cross-sectional or RCTs. Any population for systematic reviews
Intervention	RBC transfusion, Iron (all forms, routes of administration, dosages), ESA (all forms, dosages, targets, protocols, schedules, etc), pharmacological and non-pharmacological adjuvants to ESA, Hb or iron status
Comparator	Other interventions, "no" interventions, different forms, routes of administration, dosages, targets, protocols, schedules, etc.
Outcomes	All-cause mortality, Cardiovascular events, ESRD, Quality of life, Progression of kidney disease, Transfusions, Major symptoms
Study design	RCTs, Large longitudinal (prospective or retrospective) observational studies or cross sectional studies with multivariate analyses N ≥ 50 per arm
Evaluating anemia treatment, including treatment resistance	
Population	Adults and children with CKD, any stage and any comorbidity (including cancer, CVD, etc.)
Intervention	RBC transfusions; Iron (all forms, routes of administration, dosages), ESA (all forms, dosages, targets, protocols, etc), pharmacological and non-pharmacological adjuvants to ESA including L-carnitine, vitamin C, androgens, pentoxifylline; other interventions used to treat or enhance the treatment of anemia or anemia-related symptoms
Comparator	Other interventions, "no" interventions, different forms, routes of administration, dosages, targets, protocols, schedules, etc.
Outcomes	Death, Cardiac events, Stroke, CKD progression, Quality of life, Thromboembolic events, Pulmonary embolism, Symptomatic deep vein thrombosis, Loss of vascular access, Transfusion requirements, Cognitive function, Sexual function, Other similar quality of life measures, Objective physical function tests, Infections, Loss of transplant eligibility due to antibody sensitization, Antibody sensitization, New cancer or progression of existing cancer, Seizure, Other clinically important adverse events, ESA dose: for comparisons of different ESA regimens and for iron and adjuvant interventions, Achieved Hb/Hb variability for comparisons of different ESA regimens and for iron and adjuvant interventions
Study Design	RCTs N ≥ 50 per arm Minimum follow-up duration: 6 months

CKD, chronic kidney disease; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; Hb, hemoglobin; RBC, red blood cell; RCT, randomized controlled trial.

Table 9 | Hierarchy of importance of outcomes

Hierarchy[a]	Outcomes[b]
Critical importance	Mortality, Cardiovascular mortality, Cardiovascular events, ESRD
High importance	Transfusion, Quality of life
Moderate importance	Hb (categorical and continuous), ESA dose (categorical and continuous), adverse events

ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; Hb, hemoglobin.
[a]Outcomes of lesser importance are excluded from review.
[b]This categorization was the consensus of the Work Group for the purposes of this guideline only. The lists are not meant to reflect outcome ranking for other areas of kidney disease management. The Work Group acknowledges that not all clinicians, patients or families, or societies would rank all outcomes the same.

combined set of questions formed the basis for the deliberation and discussion that followed. The Work Group strove to ensure that all topics deemed clinically relevant and worthy of review were identified and addressed.

Formulating questions of interest

Questions of interest were formulated according to the PICODD (**P**opulation, **I**ntervention, **C**omparator, **O**utcome, study **D**esign and **D**uration of follow up) criteria. Details of the PICODD criteria are presented in Table 8.

Ranking of outcomes

The Work Group ranked outcomes of interest based on their importance for informing clinical decision making (Table 9). Mortality, cardiovascular mortality, cardiovascular events and ESRD outcomes were graded as 'critical,' transfusion and QoL outcomes were graded as 'high,' and all other outcomes were graded as 'moderate.'

Literature searches and article selection

The Work Group sought to build on the evidence base and topics addressed in the previous Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in 2006 as well as the KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease 2007 update of hemoglobin target. Modules were created for randomized controlled trials (RCTs), kidney disease, anemia, and erythropoietin, transfusion, iron deficiency, and adjuvant search terms. The search terms were then limited to years 2006–2010 for studies related to anemia interventions. For transfusion the literature search was conducted from 1989–2010. A separate search was run for observational studies on iron overload and hemoglobin status as predictors for clinical outcomes (See Appendix 1 online).

The searches were run in MEDLINE, Cochrane Central Register of Controlled Clinical Trials and Cochrane Database of Systematic Reviews. The initial search for RCTs was conducted in April 2010 and subsequently updated in October of 2010. The search for observational studies was later conducted in September 2010. The search yield was also supplemented by articles provided by Work Group members through March 2012. MEDLINE search results were screened by members of the ERT for relevance using pre-defined eligibility criteria.

The total yield from the search was 4,334 abstracts for RCTs and 3,717 abstracts for observational studies. Fifty-six abstracts and 53 full texts from RCTs were accepted and 97 abstracts and 21 full texts from observational studies were

Table 10 | Literature search yield of primary articles for systematic review topics

Total abstracts from updated search	Abstracts accepted	Full text accepted	Full text extracted	Articles in summary tables
4,334 RCT	56	53	53	31
3,717 Observational	97	21	21	21

RCT, randomized controlled trial.

accepted. Journal articles reporting original data, meta-analyses or systematic reviews were selected for evidence review. Editorials, letters, abstracts, unpublished reports and articles published in non-peer reviewed journals were not included. The Work Group also decided to exclude publications from journal supplements because of potential differences in the process of how they get solicited, selected, reviewed and edited compared to peer-reviewed publications. The overall search yield along with the number of abstracts identified and articles reviewed is presented in Table 10.

Data extraction

Fifty-three full text articles from RCTs were extracted by the ERT. The ERT, in consultation with the Work Group, designed forms to capture data on design, methodology, sample characteristics, interventions, comparators, outcomes, results and limitations of individual studies. Methodology and outcomes were also systematically graded (see the section on grading below) and recorded during the data extraction process.

Summary tables

Summary tables were developed for each comparison of interest. Studies included in the evidence base for the KDOQI clinical practice guidelines on Anemia in CKD and update of hemoglobin target were also incorporated if they fulfilled the inclusion criteria for the current guideline.

Summary tables contain outcomes of interest, relevant population characteristics, description of intervention and comparator, results, and quality grading for each outcome. Categorical and continuous outcomes were summarized separately. Work Group members proofed all summary table data and quality assessments. Summary tables will be available at www.kdigo.org/clinical_practice_guidelines/anemia.php.

Evidence profiles

Evidence profiles were constructed to assess and record quality grading and description of effect for each outcome across studies, and quality of overall evidence and description of net benefits or harms of intervention or comparator across all outcomes. These profiles aim to make the evidence synthesis process transparent. Decisions in the evidence profiles were based on data from the primary studies listed in corresponding summary tables, and on judgments of the ERT and the Work Group. When the body of evidence for a particular comparison of interest consisted of only one study, the summary table provided the final level of synthesis and evidence profile was not generated. Each evidence profile was initially constructed by the ERT and then reviewed, edited and approved by the Work Group.

Table 11 | Classification of study quality

Good quality	Low risk of bias and no obvious reporting errors, complete reporting of data. Must be prospective. If study of intervention, must be randomized controlled study (RCT).
Fair quality	Moderate risk of bias, but problems with study/paper are unlikely to cause major bias. If study of intervention, must be prospective.
Poor quality	High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

Grading of quality of evidence for outcomes of individual studies

Methodological quality. Methodological quality (internal validity) refers to the design, conduct, and reporting of outcomes of a clinical study. Previously devised three-level classification system for quality assessment was used to grade the overall study quality and quality for all relevant outcomes in the study (Table 11). Variations of this system have been used in most KDOQI and all KDIGO guidelines and have been recommended for the US Agency for Healthcare Research and Quality Evidence-based Practice Center program (http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf).

Each study was given an overall quality grade based on its design, methodology (randomization, allocation, blinding, definition of outcomes, appropriate use of statistical methods etc), conduct (drop-out percentage, outcome assessment methodologies, etc) and reporting (internal consistency, clarity, thoroughness/precision, etc). Each reported outcome was then evaluated and given an individual grade depending on the quality of reporting and methodological issues specific to that outcome. However, the quality grade of an individual outcome could not exceed the quality grade for the overall study.

Rating the quality of evidence and the strength of guideline recommendations

A structured approach, based on GRADE[241–243] and facilitated by the use of evidence profiles was used in order to grade the quality of the overall evidence and the strength of recommendations. For each topic, the discussion on grading of the quality of the evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Chairs. The 'strength of a recommendation' indicates the extent to which one can be

confident that adherence to the recommendation will do more good than harm. The 'quality of a body of evidence' refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.[242]

Grading the quality of evidence for each outcome

Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized based on study design. For questions of interventions, the initial quality grade was 'High' when the body of evidence consisted of randomized controlled trials; 'Low', if it consisted of observational studies; or 'Very Low', if it consisted of studies of other study designs. For questions of interventions, the Work Group decided to use only randomized controlled trials. The grade for the quality of evidence for each intervention/outcome pair was then lowered if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence including limited applicability of the findings to the population of interest, if the data were imprecise (a low event rate [0 or 1 event] in either arm or confidence interval spanning a range <0.5 to >2.0) or sparse (only 1 study or total $N<100$), or if there was thought to be a high likelihood of bias. The final grade for the quality of the evidence for an intervention/outcome pair could be one of the following four grades: 'High', 'Moderate', 'Low' or 'Very Low' (Table 12).

Grading the overall quality of evidence

The quality of the overall body of evidence was then determined based on the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were: 'A', 'B', 'C' or 'D' (Table 13).

Assessment of the net health benefit across all important clinical outcomes

The net health benefit was determined based on the anticipated balance of benefits and harms across all clinically important outcomes (Table 14). The assessment of net benefit was affected by the judgment of the Work Group and the ERT.

Grading the strength of the recommendations

The strength of a recommendation is graded as Level 1 or Level 2. Table 15 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians and policy makers. Recommendations can be for or against doing something. Table 16 shows that the strength of a recommendation is determined not just by the quality of the evidence, but also by other, often complex judgments regarding the size of the net medical benefit, values and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

Table 13 | Final grade for overall quality of evidence

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.

Table 12 | GRADE system for grading quality of evidence

Step 1: Starting grade for quality of evidence based on study design	Step 2: Reduce grade	Step 3: Raise grade	Final grade for quality of evidence and definition
Randomized trials = High	*Study quality* −1 level if serious limitations −2 levels if very serious limitations *Consistency* −1 level if important inconsistency	*Strength of association* +1 level is strong[a], no plausible confounders +2 levels if very strong[b], no major threats to validity	High = Further research is unlikely to change confidence in the estimate of the effect Moderate = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate
Observational study = Low	*Directness* −1 level if some uncertainty −2 levels if major uncertainty *Other* −1 level if sparse or imprecise data[c]	*Other* +1 level if evidence of a dose-response gradient +1 level if all residual plausible confounders would have reduced the observed effect	Low = Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate Very low = Any estimate of effect is very uncertain
Any other evidence = Very low	−1 level if high probability of reporting bias		

GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[a]Strong evidence of association is defined as 'significant relative risk of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.
[b]Very strong evidence of association is defined as 'significant relative risk of >5 (<0.2)' based on direct evidence with no major threats to validity.
[c]Sparse if there is only one study or if total N <100. Imprecise if there is a low event rate (0 or 1 event) in either arm or confidence interval spanning a range <0.5 to >2.0.
Adapted by permission from Macmillan Publishers Ltd: *Kidney International*. Uhlig K, Macleod A, Craig J *et al*. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 70: 2058–2065;[243] accessed http://www.nature.com/ki/journal/v70/n12/pdf/5001875a.pdf

Table 14 | Balance of benefits and harm

When there was evidence to determine the balance of medical benefits and harm of an intervention to a patient, conclusions were categorized as follows:

- For statistically significant benefit/harm report as 'Benefit/Harm of Drug X'.
- For non-statistically significant benefit/harm, report as 'Possible benefit/harm of Drug X'.
- In instances where studies are inconsistent, report as 'Possible benefit/harm of Drug X'.
- 'No difference' can only be reported if a study is not imprecise.
- 'Insufficient evidence' if imprecision is a factor.

Table 15 | KDIGO nomenclature and description for grading recommendations

Grade*	Implications		
	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.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
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 substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Table 16 | Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or more uncertainty in values and preferences, the more likely a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Ungraded statements

This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets the following criteria: it provides guidance based on common sense; it provides reminders of the obvious; it is not sufficiently specific to allow application of evidence to the issue and therefore it is not based on systematic evidence review. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care. We strove to minimize the use of ungraded recommendations.

This grading scheme with two levels for the strength of a recommendation together with four levels of grading the quality of the evidence, and the option of an ungraded statement for general guidance was adopted by the KDIGO Board in December 2008. The Work Group took the primary role of writing the recommendations and rationale statements and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

Format for guideline recommendations

Each chapter contains one or more specific recommendations. Within each recommendation, the strength of recommendation is indicated as level 1 or level 2 and the quality of the supporting evidence is shown as A, B, C or D. These are followed by a brief background with relevant definitions of terms and the rationale summarizing the key points of the evidence base and narrative supporting the recommendation. Where appropriate, research recommendations are suggested for future research to resolve current uncertainties.

Limitations of approach

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched. Hand searches of journals were not performed, and review articles and textbook chapters were

Table 17 | The Conference on Guideline Standardization (COGS) checklist[245] for reporting clinical practice guidelines

Topic	Description	Discussed in KDIGO Anemia Guideline
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	Abstract and Methods for Guideline Development.
2. Focus	Describe the primary disease/condition and intervention/ service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic or therapeutic interventions that were considered during development.	Management of adults and children with CKD and kidney transplant recipients at risk for or with anemia.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This clinical practice guideline is intended to assist the practitioner caring for patients with CKD and anemia and to prevent deaths, cardiovascular disease events and progression to kidney failure while optimizing patients' quality of life.
4. User/setting	Describe the intended users of the guideline (e.g. provider types, patients) and the settings in which the guideline is intended to be used.	Providers: Nephrologists (adult and pediatric), Dialysis providers (including nurses), Internists, and Pediatricians. Patients: Adult and children with CKD at risk for or with anemia. Policy Makers: Those in related health fields.
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	CKD individuals at risk for or with anemia, adult and children.
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO.
7. Funding source/ sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	KDIGO is supported by the following consortium of sponsors: Abbott, Amgen, Bayer Schering Pharma, Belo Foundation, Bristol-Myers Squibb, Chugai Pharmaceutical, Coca-Cola Company, Dole Food Company, Fresenius Medical Care, Genzyme, Hoffmann-LaRoche, JC Penney, Kyowa Hakko Kirin, NATCO—The Organization for Transplant Professionals, NKF-Board of Directors, Novartis, Pharmacosmos, PUMC Pharmaceutical, Robert and Jane Cizik Foundation, Shire, Takeda Pharmaceutical, Transwestern Commercial Services, Vifor Pharma, and Wyeth. No funding is accepted for the development or reporting of specific guidelines. All stakeholders could participate in open review. Refer to Work Group Financial Disclosures.
8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	Modules were created for randomized controlled trials (RCTs), kidney disease, anemia, and erythropoietin, transfusion, iron deficiency, and adjuvant search terms. The search terms were then limited to years 2006–2010 for studies related to anemia interventions. For transfusion the literature search was conducted from 1989–2010. A separate search was run for observational studies on iron overload and hemoglobin status as predictors for clinical outcomes. See Table 8 for screening criteria. Searches were run in MEDLINE, Cochrane Central Register of Controlled Clinical Trials and Cochrane Database of Systematic Reviews. The initial search for RCTs was conducted in April 2010 and subsequently updated in October of 2010. The search for observational studies was later conducted in September 2010. The search yield was also supplemented by articles provided by Work Group members through March 2012.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.	Quality of individual studies was graded in a three-tiered grading system (see Table 11). Quality of evidence (Table 12) was graded following the GRADE approach. Strength of the recommendation was graded in a two-level grading system which was adapted from GRADE for KDIGO with the quality of overall evidence graded on a four-tiered system (Tables 13 and 15). The Work Group could provide general guidance in ungraded statements.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.	For systematic review topics, summary tables and evidence profiles were generated. For recommendations on treatment interventions, the steps outlined by GRADE were followed.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline has undergone internal review by the KDIGO Board of Directors in June 2011 and external review in September 2011. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.

Table 17 | Continued

Topic	Description	Discussed in KDIGO Anemia Guideline
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, expiration date for this version of the guideline.	There is no date set for updating. The need for updating of the guideline will depend on the publication of new evidence that would change the quality of the evidence or the estimates for the benefits and harms. Results from registered ongoing studies and other publications will be reviewed periodically to evaluate their potential to impact on the recommendations in this guideline.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	Abbreviations and Acronyms.
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in Topic 9.	Each guideline chapter contains recommendations for management of CKD patients at risk for or with anemia. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence are provided in parenthesis within each recommendation.
15. Potential benefits and harm	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	The benefits and harm for each comparison of interventions are provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Many recommendations are Level 2 or "discretionary" which indicates a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	See Chapter 4.
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	These recommendations are global. Review criteria were not suggested because implementation with prioritization and development of review criteria have to proceed locally. Furthermore, most recommendations are discretionary, requiring substantial discussion among stakeholders before they can be adopted as review criteria. Suggestions were provided for future research.

CKD, chronic kidney disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; KDIGO, Kidney Disease: Improving Global Outcomes; RCT, randomized controlled trial.

not systematically searched. However, important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group.

Summary of the methodological review process

Several tools and checklists have been developed to assess the quality of the methodological process for systematic review and guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria,[244] the Conference on Guideline Standardization (COGS) checklist,[245] and the Institute of Medicine's recent *Standards for Systematic Reviews*[246] and *Clinical Practice Guidelines We Can Trust.*[247] Table 17 and Appendix 2 online show, respectively, the COGS criteria which correspond to the AGREE checklist and the Institute of Medicine standards, and how each one of them is addressed in this guideline.

SUPPLEMENTARY MATERIAL

Appendix 1: Online search strategies.
Appendix 2: Concurrence with Institute of Medicine standards for systematic reviews and for guidelines.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/anemia.php

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Biographic and Disclosure Information

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John J V McMurray, MD, FRCP, FESC (Work Group Co-Chair), is Professor of Medical Cardiology at BHF Glasgow Cardiovascular Research Centre and Head of Section of Academic Cardiology at University of Glasgow. Dr McMurray received his medical degree from University of Manchester and completed additional clinical training in Edinburgh, Dundee and Glasgow. He conducts clinical research in a wide span of areas including heart failure, left ventricular dysfunction, coronary heart disease, diabetes, and kidney failure. As such, Dr McMurray is a member of the Executive Committee or Steering Committee for a number of large ongoing multinational trials: ARISTOTLE, ASCEND-HF, ASPIRE, ATMOSPHERE, Dal-OUTCOMES, EMPHASIS-HF, NAVIGATOR, PARADIGM-HF, RED-HF, TREAT and VIVIDD. He is also Past President of the Heart Failure Association of the European Society of Cardiology and has authored close to 500 original publications, reviews, and book chapters. Dr McMurray is currently on a number of journal editorial boards including: *Cardiovascular Drugs and Therapy*, *Circulation: Heart Failure*, *European Heart Journal*, *European Journal of Heart Failure*, *Heart*, *Heart Failure Reviews*, *International Journal of Cardiology* and *Journal of the Renin-Angiotensin-Alderosterone System*.

Dr McMurray's employer, Glasgow University, received support from Amgen for his role as Executive Committee member of clinical trials (RED-HF; TREAT; ATOMIC-HF). Dr McMurray's salary from his employer is independent from the monies received by Glasgow University from commercial or non-commercial organizations

Patrick S Parfrey, MD, FRCPC, FRSC (Work Group Co-Chair), is a University Research Professor at Memorial University and staff nephrologist at Eastern Health, Newfoundland. Dr Parfrey received his medical degree from University College Cork, Ireland and is active in clinical epidemiology research in kidney disease, particularly as it relates to cardiovascular disease, anemia and genetic diseases. He also supervised post-graduate work of more than 50 students and has authored over 300 publications. Dr Parfrey is past Associate Editor of *CJASN*, past president of the Canadian Society of Nephrology, an Officer of the Order of Canada and Fellow of the Royal Society of Canada and has received financial support from both Amgen and Ortho Biotech, as Chair of the Data Monitoring Committee of the Normal Hematocrit Study; Co-Primary Investigator of the Canada–Europe Trial; Executive Committee Member of TREAT; and Co-Chair of the Executive Committee of EVOLVE.

Grant/Research Support: Amgen
Speaker: Amgen

John W Adamson, MD, completed his undergraduate work at the University of California, Berkeley, and received a MD degree from UCLA. Following training in Internal Medicine and Hematology at the University of Washington, he spent two years at the NIH, returning to the faculty in Seattle in 1969. He rose through the ranks to become professor and head of the Division of Hematology in 1980 and was named a Clinical Research Professor of the American Cancer Society in 1988. In 1989, he moved to New York City as President of the New York Blood Center and director of its research institute. In 1998 he moved to Milwaukee as Executive Vice President for Research at the Blood Center of Wisconsin and Director of its Blood Research Institute. Four years ago he joined the faculty at the University of California, San Diego, as Clinical Professor of Medicine in Hematology/Oncology where he serves as head of the Hematology/Oncology section at the VA Medical Center and Associate Director of the Hematology/Oncology Fellowship program at UCSD. Dr Adamson has published numerous scientific articles and reviews and has previously served as Editor-in-Chief of *Blood*; founding editor of *Current Opinion in Hematology;* President of the American Society of Hematology; and President of the International Society for Experimental Hematology. His interests lie in the areas of anemia diagnosis and management, pathophysiology of the myeloproliferative neoplasms, and the molecular biology of iron metabolism.

Advisor/Consultant: Affymax; Akebia; AMAG; Amgen; Hospira; Watson
Speaker: AMAG; Watson

Pedro Aljama, MD, PhD, received his MD from the University of Cadiz in 1971 and PhD from the University of Seville in 1975. Professor Aljama then continued his training at the Royal Victoria lnfirmary, Newcastle, United Kingdom, where he was a Medical Officier, Registrar and then Senior Registrar in Nephrology, and a Lecturer in Renal Medicine at the University of Newcastle upon Tyne (1977–1979). He returned to Spain in 1980 as a Senior Registrar at Reina Sofia Hospital, University of Cordoba, and was appointed Professor of Medicine and Nephrology in 1987. He is past President of the Spanish Society of Nephrology and presently a member of the International

Society of Nephrology, the European Society for Clinical Investigation, the British Society of Nephrology and the European Renal Association-European Dialysis and Transplant Association. Professor Aljama has authored over 250 scientific papers and 50 book chapters.

Advisor/Consultant: Amgen; Roche; Vifor
Grant/Research Support: Janssen-Cilag; Roche
Speaker: Amgen; Vifor

Jeffrey S Berns, MD, is Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania and the Penn Presbyterian Medical Center of Philadelphia, University of Pennsylvania Health System. Dr Berns is also the Associate Dean for Graduate Medical Education, Nephrology Fellowship Program Director and Associate Chief of Renal, Electrolyte and Hypertension Division at the University of Pennsylvania Health System. He obtained his medical degree from Case Western Reserve University and completed his nephrology fellowship at Yale University School of Medicine. His professional activities include his service as a long-standing Work Group member of the KDOQI Anemia guideline from 1995–2007 and currently he is the KDOQI Vice Chair for Guideline Commentaries and Updates and also a member of the National Quality Forum ESRD Steering Committee. Dr Berns has authored over 130 publications and is on the editorial board of *Clinical Nephrology*, *CJASN*, and *Seminars in Dialysis*. In recognition for his contributions, he received the Leonard Berwick Memorial Teaching Award in 2008 and the Penn Medicine Patient Advocacy Award in 2010.

Advisor/Consultant: Affymax; Amgen; Takeda

Julia Bohlius, MD, MScPH, is a physician who is trained in both hematology/oncology and public health. Dr Bohlius is Editor of the Cochrane Haematological Malignancies Group and has experience in the conduct of both literature-based and individual patient data meta-analyses. Since 2001 she is a leading systematic reviewer on ESAs in cancer patients and has worked on international health technology assessments and clinical guideline projects for ESAs and other growth factors in cancer patients. While she started her clinical and scientific career at the University of Cologne, Germany, she now works as a Senior Research Fellow at the Institute of Social and Preventive Medicine, University of Bern, Switzerland.

Dr Bohlius reported no relevant financial relationships

Tilman B Drüeke, MD, FRCP, is Emeritus Director of Research at the INSERM laboratory ERI-12, UFR de Médecine et Pharmacie, Université de Picardie Jules Verne, Amiens, France. He received his MD degree at the University of Tübingen Medical School, Germany in 1968. From 1969 through 2009, he practiced his medical and scientific activities at Necker Hospital/Necker Medical School, Université Paris V, Paris, France. Professor Drüeke's research interests focus on chronic renal failure, hemodialysis, metabolic and endocrine abnormalities, anemia, cardiovascular complications and arterial hypertension. He is a member of several scientific societies, committees and advisory boards and a former Co-Chair of the KDIGO CKD-MBD Guideline Work Group. Professor Drüeke is Editor Emeritus of *Nephrology Dialysis Transplantation*, former Associate Editor of the *CJASN*, an editorial board member of *JASN* and presently Associate Editor of *Kidney International*. He has published more than 500 original articles and reviews in peer-reviewed journals.

Advisor/Consultant: Amgen; Roche; Vifor
Speaker: Amgen; Chugai; Vifor

Fredric O Finkelstein, MD, obtained his medical degree from Columbia University and completed his nephrology fellowship at Yale University Medical School where he is also presently a Clinical Professor of Medicine. Over the span of his career, he has lectured extensively throughout the world and has held more than 30 visiting teaching positions. In addition, he is currently Chair of the International Liaison Committee of the International Society of Peritoneal Dialysis. He is also Co-Chair of the Dialysis Committee of the International Society of Nephrology and an author of over 200 publications. Dr Finkelstein has dedicated substantial research towards the understanding of quality of life and psychosocial issues for dialysis and non-dialysis patients alike. He has served on the editorial board of *Peritoneal Dialysis International* since 2004 and *Kidney International* since 2010.

Advisor/Consultant: Akebia, Amgen; Baxter
Grant/Research Support: Amgen

Steven Fishbane, MD, received his medical degree from Albert Einstein College of Medicine where he also completed his nephrology fellowship. He is currently Vice President of the North Shore-LIJ Health System in Manhasset, NY, as well as Professor of Medicine at SUNY Stony Brook School of Medicine. Dr Fishbane is the Director of Clinical Trials for the Department of Medicine of North Shore-LIJ University Hospitals. Having participated as a KDOQI Anemia Guideline Work Group member, he maintains an active research interest in this area and has written over 150 publications. In addition to serving as a reviewer for numerous journals, he currently sits on the editorial board of *CJASN* and *Kidney International*. In recognition for his commitment on enhancing healthcare delivery and assessment, Dr Fishbane was the recipient of the Physician Leadership in Quality Improvement Award from IPRO in 2002 and the Volunteerism Award of the National Kidney Foundation Serving Greater New York in 2010.

Advisor/Consultant: Affymax; Akebia; Fibrogen; Rockwell Medical Technologies

Tomas Ganz, PhD, MD, is Professor of Medicine and Pathology at the David Geffen School of Medicine at UCLA. Dr Ganz received his PhD from the California Institute of Technology in Applied Physics and MD from UCLA. He was then trained in Internal Medicine and Pulmonary/Critical Care Medicine at the UCLA Medical Center. His major focus was on research on the biological role of peptide mediators in innate immunity and iron metabolism. More recently, he has investigated the pathogenesis of anemia of inflammation and iron overload states, and worked on the development of hepcidin agonists and antagonists. Dr Ganz has served as an Associate Editor of *Blood* and a member of the Erythrocyte and Leukocyte Biology (ELB) Study Section of the National Institutes of Health. In 2005, he received the Marcel Simon Award of the International Bioiron Society for the discovery of hepcidin.

Advisor/Consultant: Alnylam; Intrinsic LifeSciences; Merganser Biotech; Ortho Biotech/Centocor; Pieris; Xenon;
Employee: Intrinsic LifeSciences; Merganser Biotech
Equity Interest: Intrinsic LifeSciences; Merganser Biotech
Grant/Research Support: Amgen; Xenon

Iain C Macdougall, BSc, MD, FRCP, is a Consultant Nephrologist and Professor of Clinical Nephrology at King's College Hospital, London, UK. He is a combined medical and science graduate of Glasgow University, Scotland, from which he was awarded a First Class Honours BSc in Pharmacology in 1980, and his medical degree in 1983. Professor Macdougall then completed his general medical and nephrology training at hospitals in Glasgow, Cardiff, and London. He developed a research interest in renal anemia while a Clinical Research Fellow in Cardiff (1988–1991) and extended this interest during his appointment at St Bartholomew's Hospital (1991–1996), where he studied the potential role of proinflammatory cytokines in mediating resistance to epoetin. He has been involved in numerous advisory boards in renal anemia management worldwide, including the Working Parties responsible for both the 1999 and the 2004 versions of the European Best Practice Guidelines, along with the Work Group that produced the latest US KDOQI Anemia Guidelines (2006; update 2007). He was a previous Board member of the KDIGO initiative, and a Council member of the European Renal Association from 2004 until 2007. He has been the UK lead on several pivotal clinical trials of anemia management in patients with chronic kidney disease, including CREATE and TREAT, and he chairs the Anaemia Clinical Study Group of the UK Kidney Research Consortium.

Advisor/Consultant: Affymax; Amgen; Ortho Biotech; Roche; Takeda; Vifor
Grant/Research Support: Affymax; Amgen; Vifor
Speaker: Amgen; Ortho Biotech; Takeda; Vifor

Ruth A McDonald, MD, is Professor of Pediatrics at University of Washington and Clinical Director of Nephrology at Children's Hospital and Regional Medical Center in Seattle, Washington. She completed her medical degree at University of Minneosta School of Medicine where she was a recipient of the Top Medical Graduate: Hewlett-Packard Award. Dr McDonald is currently involved in numerous multicenter clinical studies including a controlled trial of Anti-CD20 monoclonal antibody therapy in historically unsensitized renal transplant recipients with donor-specific antibodies; a Phase II study to determine safety and immunomodulatory functions of induction therapy with Campath 1 H, combined with mycophenolate mofetil and sirolimus; a surveillance study of viral infections in renal transplant recipients and many others. She is also a member of eight professional organizations including American Society of Pediatric Nephrology, American Society of Transplantation, International Pediatric Transplant Association and past Work Group member of the KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. Among her teaching responsibilities, she has trained over 25 fellows and has also served as Medical Student Research Mentor. Dr McDonald has authored over 60 publications and has given close to 40 invited and extra-institutional lectures in the past 10 years.

Dr McDonald reported no relevant financial relationships

Lawrence P McMahon, MBBS, MD, is Director, Department of Renal Medicine at Eastern Health Integrated Renal Services and Professor Nephrology at Monash University. Prior to his present appointments, he was Associate Professor at University of Melbourne School of Medicine; Director of Nephrology Services and Obstetric Medical Services at Western Health; and Consortium Director of Physician Training at Greater Western Consortium. Dr McMahon has participated in guideline development activities for the Australian and New Zealand Society of Nephrology and is presently the President, National Council of Society of Obstetric Medicine of Australian and New Zealand. He has written more than 50 publications and serves as a regular reviewer for more than a dozen journals, including his role as Associate Editor of *Nephrology Dialysis Transplantation*.

Grant/Research Support: Amgen; Roche

Gregorio T Obrador, MD, MPH, is Professor of Medicine and Dean at the Universidad Panamericana School of Medicine in Mexico City. He also serves as Adjunct Physician at the Tufts Medical Center's Division of Nephrology and as staff nephrologist at Dalinde Medical Center in Mexico City. He earned his medical degree from the University of Navarra, Pamplona, Spain, completed his Internal Medicine residency at the Western Pennsylvania Hospital, Pittsburgh, USA, and obtained his Nephrology training at Boston University, USA. While undertaking a clinical research fellowship at the Tufts-New England Medical Center and a Master of Public Health at Harvard University, he demonstrated that the management

of patients with CKD prior to stage 5 is suboptimal, and that this is an important factor for the high morbidity and mortality observed in these patients. He has been a member of the KDOQI's Advisory Board, the NKF/KDOQI Anemia Work Goup, and the KDIGO Transplant Guideline Work Group. Currently he is a member of the WHO's Non-Communicable diseases Network (NCDnet), Co-Chair of the Global Kidney Disease Prevention Network (KDPN), Co-Chair of the Latin American Clinical Practice Guidelines for the Prevention, Diagnosis and Treatment of CKD (Stages 1–5), and President of the Board of Directors of the Mexican Kidney Foundation. In 2009 he received the National Kidney Foundation's International Distinguished Medal. Dr Obrador is a member of the editorial board of *CJASN* and has served as reviewer for other nephrology journals. He has given more than 100 lectures in national and international forums and has several publications in the area of CKD.

Grant/Research Support: Amgen; Roche

Giovanni FM Strippoli, MD, PhD, MPH, is a nephrologist and an epidemiologist trained both in Italy and at the University of Sydney School of Public Health, Sydney, Australia where he completed a Master of Public Health and a PhD in medicine-clinical epidemiology. Dr Strippoli is an editor of the Cochrane Renal Group, and Adjunct Associate Professor of Epidemiology at the School of Public Health, and the Renal Research Coordinator at Mario Negri Sud Consortium in Italy. He also serves as scientific director of Diaverum AB. His research interests include evidence-based nephrology, with a focus on systematic reviews in the area of prognosis and treatment of renal conditions, design and conduct of randomized controlled trials in the field of prevention of chronic kidney disease and cardiovascular risk. Dr Strippoli has a substantial scientific output with independent funding in these areas. He is also the principal investigator of LIRICO, a trial on the Long Term Impact of Renin Angiotensin System Inhibitors on Cardiorenal Outcomes in people with albuminuria, and C.E. DOSE, a trial on the clinical evaluation of the Dose of Erythropoietins in people on hemodialysis.

Employee: Diaverum AB

Günter Weiss, MD, is Professor of Clinical Immunology and Infectious Diseases, Department of Internal Medicine, and Head of research laboratory for Molecular Immunology and Infectious Diseases at Medical University of Innsbruck. Dr Weiss had enrolled in Leopold Franzens University and University of Innsbruck for his medical studies and his ongoing research encompasses a wide array of topics including: anemia of chronic disease; primary and secondary iron overload; host pathogen interaction with a particular focus on the role of macrophages and natural resistance genes; and regulatory interactions between iron, immunity and infection. Dr Weiss has authored 190 original publications in peer reviewed journals including reviews on anemia of chronic disease and iron metabolism in inflammation and infection.

Grant/Research Support: Amgen
Speaker: Vifor

Andrzej Więcek, MD, PhD, FRCP, is Professor of Internal Medicine and Chief, Department of Nephrology, Endocrinology and Metabolic Diseases, at Silesian University School of Medicine, Katowice, Poland. Dr Więcek's research interests include anemia management in CKD, treatments for primary and secondary hypertension, elucidation of hormonal abnormalities in uremia, and endocrine function of adipose tissue. In addition to being a participating member of the European Renal Best Practice Anaemia Working Group, he is Past President of Polish Society of Nephrology and has served on the KDIGO Board. Dr Więcek is now a member of KDIGO Implementation Task Force Leader for Eastern Europe region and Secretary-Treasurer for the ERA-EDTA. As a prolific author with over 530 publications, he is currently Subject Editor for *Nephrology Dialysis Transplantation*.

Advisor/Consultant: Abbott; Affymax; Sandoz
Speaker: Amgen

KDIGO CHAIRS

Bertram L Kasiske, MD, is Professor of Medicine at the University of Minnesota, USA. He received his medical degree from the University of Iowa and completed his Internal Medicine residency and fellowship training in Nephrology at Hennepin County Medical Center where he is currently Director of Nephrology.

Dr Kasiske is former Deputy Director of the United States Renal Data System and former Editor-in-Chief of *The American Journal of Kidney Diseases*. He has served as Secretary/Treasurer and on the Board of Directors of the American Society of Transplantation, and on the Organ Procurement and Transplantation Network/United Network of Organ Sharing Board of Directors, and the Scientific Advisory Board of the National Kidney Foundation. He is currently serving on the Board of Councilors of the International Society of Nephrology. He is the Principal Investigator for a National Institutes of Health-sponsored, multi-center study of long term outcomes after kidney donation. He is the Director of the Scientific Registry of Transplant Recipients. He has over 160 scientific publications in major peer reviewed journals, and 230 review articles, editorials and textbook chapters. Dr Kasiske is also a recipient of the NKF's Garabed Eknoyan Award in 2003.

Advisor/Consultant: Litholink
Grant/Research Support: Bristol-Myers Squibb; Merck-Schering Plough

David C Wheeler, MD, FRCP, holds an academic position in Nephrology (Reader) at University College London, UK and is an Honorary Consultant Nephrologist at the Royal Free Hospital. His research is focused on the cardiovascular complications of chronic kidney disease and the role of vascular risk factors in progression of kidney damage. Dr Wheeler is a member of the International Steering Committee of the Study of Heart and Renal Protection (SHARP) and was UK National Coordinator for the trial. He is involved in several other randomized trials and observational studies involving patients with chronic kidney disease.

He currently serves on the executive committee of KDIGO and previously contributed as a Work Group member to the KDIGO Guideline on Chronic Kidney Disease-Mineral and Bone Disorder. He has recently received an International Distinguished Medal from the US National Kidney Foundation in recognition of his contribution to guideline development. In the UK, he has previously served on the executive committee of the Renal Association and has been elected President for the term 2012–2014.

Dr Wheeler has served on the editorial boards of the *American Journal of Kidney Diseases* and *Journal of the American Society of Nephrology* and currently acts as co-Deputy Editor for *Nephrology Dialysis Transplantation*.

Advisor/Consultant: Amgen
Honoraria: Abbott, Amgen, Fresenius, Shire
Grant/Research Support: Abbott, Genzyme

EVIDENCE REVIEW TEAM

Ethan M Balk, MD, MPH, is Director, Evidence-based Medicine at the Tufts Center for Kidney Disease Guideline Development and Implementation, in Boston, MA, USA, Associate Director of the Tufts Evidence-based Practice Center, and Assistant Professor of Medicine at Tufts University School of Medicine. Dr Balk graduated from Tufts University School of Medicine and completed a fellowship in Clinical Care Research. As Project Director, he plays a substantial role in providing methodological expertise in the guideline development process and assists in the collection, evaluation, grading, and synthesis of evidence and the revisions of the final evidence report. Dr Balk also provides methodological guidance and training of Work Group members during meetings regarding topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research interests are evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal.

Dr Balk reported no relevant financial relationships

Ashish Upadhyay, MD, is Assistant Professor, Renal Section and Associate Director, Internal Medicine Residency Program at Boston University School of Medicine, Boston, MA, USA. Dr Upadhyay was previously Assistant Professor at Tufts University School of Medicine and staff physician in the William B. Schwartz, MD, Division of Nephrology at Tufts Medical Center. He joined the ERT in July 2009 and served as the Assistant Project Director for the KDIGO Management of Blood Pressure in CKD and Anemia in CKD Guidelines. Dr Upadhyay coordinated and assisted in the collection, evaluation, grading, and synthesis of evidence, and played a critical role in the revisions of the final evidence report. He also provided methodological guidance and training of Work Group members on topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. Dr Upadhyay's past research involved studying kidney disease epidemiology in the Framingham Heart Study. He has published in areas ranging from arterial stiffness in CKD and inflammation in kidney disease to dialysis complications and epidemiology of hyponatremia.

Dr Upadhyay reported no relevant financial relationships

Dana C Miskulin, MD, MS, is Assistant Professor of Medicine at Tufts University School of Medicine, Boston, MA, USA. She completed a fellowship in Clinical Care Research and participated in the conduct of systematic reviews and critical literature appraisals for this guideline. Her primary research interests are in comparative effectiveness research in dialysis patients, blood pressure treatment in dialysis patients, and autosomal dominant polycystic kidney disease.

Dr Miskulin reported no relevant financial relationships

Amy Earley, BS, is a project coordinator at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She is key in coordinating the guideline development activities within the ERT, especially in the development of the evidence reports for all guidelines. Ms Earley also heads the actual evidence review, which includes running searches, screening, data extraction, drafting of tables and methods sections, proofing of guideline drafts and critical literature appraisals. She participates in the conduct of research projects at the Center and actively collaborates with other members of the Center on independent research topics and manuscript submissions.

Ms Earley reported no relevant financial relationships

Shana Haynes, MS, DHSc, is a research assistant at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She participates in all aspects of evidence review and guideline development. She screens abstracts and articles, extracts data, and assists in the drafting and editing of evidence tables. Dr Haynes also assists in the development of clinical practice guidelines and conducts systematic reviews and critical literature appraisals.

Dr Haynes reported no relevant financial relationships

Jenny Lamont, MS, is a project manager and medical writer at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She participates in all aspects of evidence review and guideline development, assists in the preparation of talks and manuscripts, and edits KDIGO draft guidelines currently in progress.

Ms Lamont reported no relevant financial relationships

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