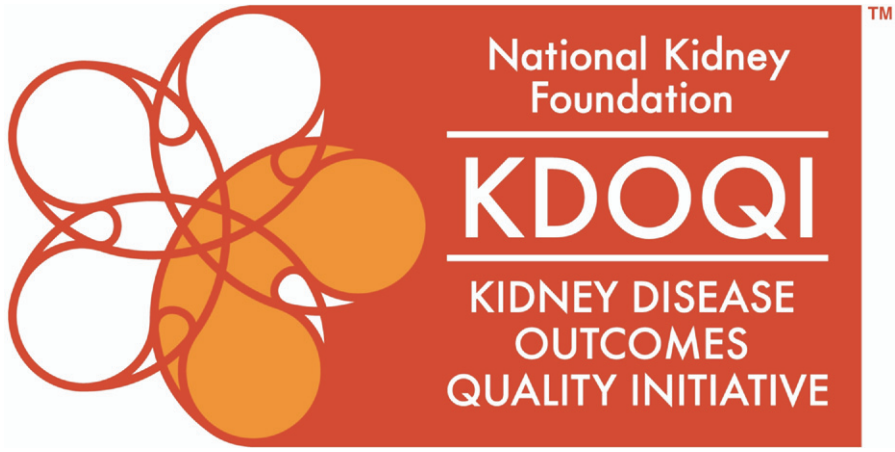

KDOQI CLINICAL PRACTICE GUIDELINE AND CLINICAL PRACTICE RECOMMENDATIONS FOR ANEMIA IN CHRONIC KIDNEY DISEASE:

2007 UPDATE OF HEMOGLOBIN TARGET

NOTICE

SECTION I: USE OF THESE CLINICAL PRACTICE GUIDELINE AND CLINICAL PRACTICE RECOMMENDATIONS

These Clinical Practice Guideline (CPG) and Clinical Practice Recommendations (CPRs) are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they 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 CPG and CPRs is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

SECTION II: DISCLOSURE

The National Kidney Foundation (NKF) makes every effort to avoid actual 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.

Based on the Foundation's conflict-of-interest policy, all members of the Work Group are required to complete, sign, and submit a Disclosure Form and Attestation Statement showing all such relationships that might be perceived as real or potential conflicts of interest. Affiliations are published in their entirety in the section of this document titled Biographical and Disclosure Information and are kept on file at the NKF.

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Work Group Membership

Work Group Co-Chairs

David B. Van Wyck, MD
University of Arizona College of Medicine
Tucson, AZ

Kai-Uwe Eckardt, MD
University of Erlangen-Nuremberg
Erlangen, Germany

Work Group

John W. Adamson, MD
Blood Center of SE Wisconsin
Blood Research Institute
Milwaukee, WI

Jeffrey S. Berns, MD
University of Pennsylvania School of Medicine
Philadelphia, PA

Steven Fishbane, MD
Winthrop University Hospital
Mineola, NY

Robert N. Foley, MD
Chronic Disease Research Group
Minneapolis, MN

Sana Ghaddar, RD, PhD
American University of Beirut
Faculty of Agriculture and Food Sciences
Beirut, Lebanon

John S. Gill, MD, MS
University of British Columbia
St. Paul's Hospital
Vancouver, Canada

Kathy Jabs, MD
Vanderbilt University Medical Center
Nashville, TN

Patricia Bargo McCarley, RN, MSN, NP
Diablo Nephrology Medical Group
Walnut Creek, CA

Allen R. Nissenson, MD
David Geffen School of Medicine at UCLA
Los Angeles, CA

Gregorio T. Obrador, MD, MPH
Universidad Panamericana School of Medicine
Mexico City, Mexico

John C. Stivelman, MD
Northwest Kidney Center
Seattle, WA

Colin T. White, MD
British Columbia Children's Hospital
Vancouver, Canada

Liaison Members

Francesco Locatelli, MD
Azienda Ospedaliera DI Lecco
Lecco, Italy

Iain C. Macdougall, MD
King's College Hospital
London, United Kingdom

Evidence Review Team

National Kidney Foundation Center for Clinical Practice Guideline Development and Implementation
at Tufts-New England Medical Center, Boston, MA

Katrin Uhlig, MD, MS, *Program Director, Nephrology*
Joseph Lau, MD, *Program Director, Evidence-Based Medicine*
Amy Earley, BS, *Research Assistant*

KDOQI™ Advisory Board Members

NKF-KDOQI™ Guideline Development Staff

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Foreword

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) was founded on the principles of structured review with data extraction of pertinent articles. Updates to the original KDOQI guidelines (1997) first appeared in 2000 and again in 2006 for Hemodialysis, Peritoneal Dialysis, Vascular Access, and Anemia. Timelines of KDOQI updates are based on criteria that include important changes in body of evidence that change the basics for specific guideline content; important changes in body of evidence that change the strength of recommendations previously published; and change in understanding of physiology or mechanisms that may impact on interpretation of previous data and/or continued variation or uncertainty, confusion, or conflict in information available such that there is overt evidence that this variation leads to compromise in clinical outcomes.

The KDOQI Chair, Vice-Chair, or Work Group Chairs can also request consideration of an update of a portion of a specific guideline when new evidence is published that may significantly impact specific CPG statements. This process was activated in November 2006 to consider possible revisions to the May 2006 CPGs and CPRs for Anemia in Chronic Kidney Disease (CKD). Discussions on possible revisions to the anemia guidelines were first held with NKF leadership, the KDOQI Chair and Vice-Chair, the NKF Evidence Review Team (ERT), and the Anemia Work Group Co-Chairs. A timetable was developed for review of new evidence since the time of the last anemia update, and the Anemia Work Group was reconvened for the 2007 Anemia Update.

A series of conference calls was held among the Anemia Work Group members and ERT in preparation for a face-to-face meeting of these individuals in Dallas, TX, on February 2–3, 2007. Additional conference calls were held after this meeting to both finalize the document and to consider possible revisions to the document based on comments received during the public review period. This publication, *KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease: 2007 Update of Hemoglobin Target,* reports the outcome of this KDOQI updating process.

This Update was developed using the usual rigorous methods of the KDOQI process, which involves a separate and independent ERT based at Tufts–New England Medical Center. This ERT evaluated and rated the available data, applying *a priori*–determined criteria about which new studies should and should not be included in the evidentiary base. Based on this review of the type and quality of data, the ERT also recommended which of the guideline statements should be considered for revision. The decision to update the 2006 Anemia Guidelines on hemoglobin (Hb) target was made in keeping with the KDOQI process, whereby new information did change the evidentiary base and thus the substance of some of the guidelines and CPRs. In contrast, the ERT and Work Group also considered an update of the iron guidelines and CPRs based on new studies. The statements on iron were not revised because the data from these studies did not meet prespecified criteria for evidence updates. The Methodology section of this document describes this process in more detail. The recommendations of the ERT for both the anemia and iron portions of the guidelines were reviewed by the Anemia Work Group, and the Work Group concurred with the ERT recommendations.

A key outcome was that the Work Group was able to clarify key aspects of a Hb target for patients receiving erythropoiesis-stimulating agent (ESA) therapy. In the new statements, the Work Group recommends what factors should be considered in selecting a Hb target and states the selected Hb target range. In addition, after reviewing the latest results from 6 new randomized controlled trials (RCTs) about anemia management in CKD (which doubled the number of patients with CKD studied), the Work Group was able to upgrade 1 of its opinion-based statements to an evidence-based guideline.

During this period, the NKF Board of Directors developed revisions to the NKF financial disclosure policy for Work Group members. Before the face-to-face meeting in Dallas, all Work Group members and the KDOQI Chair and Vice-

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Chair completed new financial disclosure statements. Based on these financial disclosure statements, the Work Group chose the KDOQI Vice-Chair to moderate the face-to-face meeting in Dallas. Complete financial disclosure statements from all Work Group members, the KDOQI Chair and Vice-Chair, and key members of the ERT are listed in the Biographical and Disclosure Information section of this document.

In a voluntary undertaking of this magnitude, many individuals make contributions to the final product now in your hands. Although it is impossible to acknowledge them individually here, we extend our sincerest appreciation to each and every one of them. This limitation notwithstanding, we heartedly thank all of you who took part in the public review process, a critical component of the KDOQI guideline development process. Finally, a special debt of gratitude is due to each member of the Anemia Work Group. It is their commitment and dedication to the KDOQI process that has made this document possible.

Adeera Levin, MD
KDOQI Chair

Michael Rocco, MD, MSCE
KDOQI Vice-Chair

CPG AND CPR 2.1 HEMOGLOBIN TARGET

The Hb target is the intended aim of ESA therapy for the individual patient with CKD. In clinical practice, achieved Hb results vary considerably from the Hb target.

2.1.1 In the opinion of the Work Group, selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events). (Clinical Practice RECOMMENDATION)

2.1.2 In the opinion of the Work Group, in dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. (Clinical Practice RECOMMENDATION)

2.1.3 In dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL. (Clinical Practice GUIDELINE - MODERATELY STRONG EVIDENCE)

BACKGROUND

KDOQI CPGs and CPRs for Anemia in CKD, published in May 2006, included recommendations for Hb targets that were based on a systematic review and structured appraisal of RCTs comparing treatment to different Hb targets. After publication of these guidelines, 5 additional RCTs were published.[1-5] An additional small trial published in 2005 was unintentionally omitted in the previous evidence review.[6] The new studies expanded the evidence on clinically important outcomes, doubled the number of all patients with CKD examined, and increased the number of nondialysis patients with CKD studied in RCTs from 575 to 3,432. In keeping with criteria for updating a systematic review and guidelines before a scheduled revision (Methods), the Work Group undertook a reexamination of the available evidence on Hb treatment targets. The reexamination included the new studies, the study not included in the previous review, and those appraised previously.

Although new evidence relevant to other topics covered in the KDOQI CPGs and CPRs for Anemia in CKD published in May 2006 is also continuously accumulating, the Work Group concluded that the evidence published since the last review and relevant to CPGs and CPRs 1.1 (Identifying Patients and Initiating Evaluation), 1.2 (Evaluation of Anemia in CKD), 3.1 (Using ESAs), 3.2 (Using Iron Agents), 3.3 (Using Pharmacological and Nonpharmacological Adjuvants to ESA Treatment in Hemodialysis-CKD, 3.4 (Transfusion Therapy), and 3.5 (Evaluating and Correcting Persistent Failure to Reach or Maintain Intended Hb) does not meet criteria for an update. For these CPRs and CPGs, for corresponding CPRs in children with anemia, and for anemia in patients after kidney transplantation, the reader is referred to the May 2006 document.[56]

The updated CPRs (2.1.1 and 2.1.2) and CPG (2.1.3) are intended to assist the practitioner caring for patients in selecting Hb targets appropriate for individual patients receiving ESA therapy or considered for ESA therapy, whether or not they are also receiving iron therapy. Recommended Hb targets apply exclusively to patients receiving ESA. Hb targets are not intended to apply to the treatment of iron deficiency in patients receiving iron therapy without the use of ESAs.

Warnings, indications, precautions, and instructions for dosing and administration of ESAs are available from national regulatory agencies, including the United States Food and Drug Administration (FDA), and product package inserts.[7-9] The Work Group directed considerable thought and attention in particular to the most recent FDA-approved prescribing information. Appendix 1 provides a detailed comparison of KDOQI CPGs and CPRs (May 2006 and update 2007) with FDA-approved prescribing information current as of March 2007.

Ongoing and future trials in patients with CKD are expected to provide more information on ESA use and Hb targets, including treatment with ESAs compared with placebo and higher compared with lower Hb targets (Table 1).

Table 1. Ongoing Randomized Controlled Trials on Hemoglobin Targets in Adult Patients with CKD Identified from Clinicaltrials.gov

Name of Study	Reference	Patient Population/Inclusion Criteria	Follow-up	N of Patients	Intervention/Treatment Targets		Outcomes	Start Date	Projected End Date
					Experimental Group	Control Group			
ND- or D-CKD Population									
TREAT: Trial to Reduce Cardiovascular Events with Aranesp Therapy PI: nd (Amgen)	*	CKD Stage 2-4 DM type 2 Hb ≤ 11.0, TSAT >15%	1.5 yrs	~4,000	Hb target 13.0 Darbepoetin alfa, Induction Phase: once every 2 weeks, Maintenance phase: once a month	Hb target ≥9.0 Placebo or Darbepoetin alfa started when Hb falls below 9 g/dL	Primary: All-cause mortality and CVD Secondary: All-cause mortality, CVD mortality, MI, CVA, CHF, KRT, eGFR decline, QoL (fatigue)		Enrollment period: 1.5 yrs Study Duration: 4 yrs
STIMULATE Study: Anemia Correction and HRQoL Outcomes in Elderly CKD Patients PI: nd (Amgen)	**	CKD Stage 3-5 (ND-CKD) age ≥70 yrs, Hb <11 g/dL, TSAT ≥15%	36 wks	260			Primary: QoL (vitality by the SF-36 vitality subscale score) Secondary: Hb ≥11 g/dL; mean Hb; QoL	8/06	1/09 (but in 8/06 not yet open for enrollment)
NEPHRODIAB2 Prospective Randomized Controlled Open-Labeled Trial Comparing Effect of Two Haemoglobin Levels PI: Villar E, Lyon France	***	CKD stage 3-4 (CG clearance 25- 60 mL/min) Type 2 DM age 18-80 yrs Hb 10-13 g/dL	2 yrs	204	Hb target 13-14.9	Hb target 11-12.9	Primary: kidney function decline Secondary: mortality; serious AEs; thrombosis; KRT; QoL	1/04	
Transplant Population									
Correction of Anemia and Progression of Renal Failure on Transplanted Patients PI: Choukroun G (Hoffmann-La Roche)	****	CKD Tx stage 3-4 (GFR 20-50 mL/min/1.73 m^2), Transplanted 1-20 yrs age 18-70 yrs Hb <11.5 g/dL, no iron deficiency	2 yrs	140	Hb target 13-15	Hb target 10.5-11.5	Primary: kidney function decline (C_{cr}) at 24 mos Secondary: iohexol GFR; SCr, QoL at 6 mos; proteinuria and albuminuria; rejection; graft and patient survival; AEs; BP; transfusions; EPO dose	4/04	12/08

References

*http://www.clinicaltrials.gov/ct/show/NCT00093015 & http://www.ikidney.com/iKidney/InfoCenter/NephrologyIncite/Archive/Treat16.htm; accessed March 2007.

ClinicalTrials.gov Identifier: NCT00093015 Phase III; accessed March 2007.

**http://clinicaltrials.gov/ct/show/NCT00364845?order=26; accessed March 2007.

***http://clinicaltrials.gov/ct/show/NCT00279084?order=32; accessed March 2007.

****http://clinicaltrials.gov/ct/show/NCT00396435?order=12; accessed March 2007.

Abbreviations: AE: Adverse event; BP: Blood pressure; C_{cr}: Creatinine clearance; CG: Cockcroft-Gault; CHF: Chronic heart failure; CVA: Cardiovascular accident; CVD: Cardiovascular disease; DM: Diabetes; eGFR: Estimated GFR; GFR: Glomerular filtration rate; Hb: Hemoglobin; KRT: Kidney replacement therapy; MI: Myocardial infarction; nd: no data; PI: Primary investigator; QoL: Quality of life; SCr: Serum creatinine; TSAT: Transferrin saturation; Tx: Transplant; wk: week; yr: year.

RATIONALE FOR CPR 2.1.1

Selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events).

The Work Group chose the wording, order, and placement of this statement to guide practitioners in selecting a Hb target for ESA therapy and a Hb level at which ESA therapy is initiated in the individual patient with CKD and anemia. The statement reflects the conclusion that improvement in quality of life and avoidance of transfusion are the most likely treatment benefits and that there is potential for harm when aiming for high Hb targets.

The statement *selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient* captures the conclusion of the Work Group that the selection of the Hb target for ESA therapy and the selection of the Hb level at which ESA therapy is initiated in the individual patient are separate but related steps in medical decision making for the individual patient. In available RCTs, treatment has generally been initiated when the baseline Hb decreases within, at, or less than the assigned Hb target.

The statement *should include consideration* reflects the limitations of our current evidence base, which does not allow precise recommendations for each individual patient (see the section **Limitations of Evidence**). The statement also acknowledges that judgments about benefits and harm may vary from patient to patient and for the same patient under different conditions. Limitations of the current evidence base, differences in individual judgments, and variable responsiveness between patients and within a patient argue for engaging the patient and for maintaining flexibility when setting Hb targets for ESA therapy.

Reference to *quality-of-life benefit* reflects the appraisal that when selecting the Hb target, an improvement in quality of life should be an expected treatment benefit. Quality of life is an outcome of direct importance to patients and should be valued accordingly.[10] Although health-related quality of life (HRQoL) is not usually quantified in a systematic fashion in clinical practice, in research studies, measurement of HRQoL is performed by using standardized instruments that have been validated in a range of target populations, including patients with CKD requiring or not requiring dialysis. Results yielded by these instruments achieve levels of reliability and precision that are comparable to those seen with other commonly used clinical tests.[11] HRQoL has been examined in several RCTs comparing lower and higher Hb targets in patients with CKD receiving ESAs for anemia. Although it is difficult to aggregate HRQoL effects across studies because different HRQoL instruments were used and some reports lacked detail, low-quality evidence suggests benefit of HRQoL (Tables 3 and 9):

- Most studies show some improvement in HRQoL in patients assigned to higher Hb targets compared with those assigned to lower Hb targets.
- However, there is inconsistency among studies because the number and class of HRQoL domains showing benefit in the higher Hb treatment group vary by instrument and by report.
- Several studies reported robust HRQoL benefits spanning multiple domains with general (36-Item Medical Outcomes Study Short-Form Health Survey)[1] and disease-specific (Kidney Diseases Questionnaire)[12,13] instruments.
- Higher Hb targets lead to improvements in both physical[1,14] and mental health domains.[1,12,13]
- The improvement in HRQoL with higher Hb targets has been seen in the earliest assessment performed, even in studies in which treatment assignment was masked to participating patients.[13,15]
- HRQoL scores deteriorate over time in dialysis patients.[15]
- HRQoL benefits of higher Hb targets diminish over time.[1,15]
- However, HRQoL effects have been seen in some domains to persist for at least 2 years.[1]
- Over the range of Hb targets tested, there is no apparent Hb threshold above which there

Table 2. Summary Table of RCTs Comparing Different Hb Targets on Key Clinical Outcomes in the HD-CKD and PD-CKD Populations

Author, Year	N	CKD Stage	Baseline[a] Hb (g/dL)	Mean Follow-up months	Applicability	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) Target (Achieved)	Clinical Outcomes (Arm 1 vs. Arm 2 vs. Arm 3)							Quality
								CVD event (%)	LVH	Mortality (%)	Hospitalizations	Dialysis Adequacy	Transfusion (%)	QoL[b]	
ESA v ESA															
Besarab, 1998 [14]	1233	HD-CKD	10.2	14 (median)	🚹🚹	ESA High ESA Low	14.0 (12.7-13.3) 10.0 (10.0)	*Non Fatal MI 3.1 vs. 2.3 NS[c, i]	—	*29.6 vs. 24.4 NS[c, i]	NS	ΔKt/V: -0.03 vs. +0.06 P<0.001	21 vs. 31 P=0.001	See QoL Table	A
Parfrey, 2005 [15]	596[l]	HD-CKD	11.0	18.5	🚹🚹	ESA High ESA Low	13.5-14.5 (13.1) 9.5-11.5 (10.8)	CVA: 4 vs. 1 P=0.045 Other CVD: NS	*NS	NS	—	ΔURR: 0 vs. +2% P<0.05	—	See QoL Table	A
Foley, 2000 [13]	146[j]	HD-CKD	10.4	12	🚹🚹	ESA High ESA Low	13–14 (13)[h] 9.5-10.5 (10.5)[h]	NS	*NS	NS	—	Kt/V LVD: 1.41 vs. 1.50 P=0.025	—	See QoL Table	A
CanEPO, 1990-1991 [39,40,44]	118	HD-CKD	7.0	6	🚹🚹	ESA High ESA Low Placebo	11.5-13 (11.7) 9.5–11 (10.2) (7.4)	—	—	NS	—	—	3 vs. 3 vs. 72 ESA vs. Placebo: P<0.05[f]	See QoL Table	A
Furuland, 2003 [12]	416[k]	4-5 PD-CKD HD-CKD[d]	10.9	12	🚹🚹	ESA High ESA Low	13.5–16.0 (13.6) 9-12 (11.3-11.7)	—	—	NS	NS	—	—	See QoL Table	C
Suzuki, 1989 [52]	179	HD-CKD	6.3	2	🚹	ESA High[e] ESA Low Placebo	<11 (8.7) (8.2) (6.1)	—	—	—	—	—	8 vs. 5 vs. 23 ESA vs. Placebo: P<0.05	—	C
Furuland, 2005 [42] Substudy of Furuland, 2003	24	HD-CKD	11.1	5.5	🚹	ESA High ESA Low	13.5–16.0 (14.3) 9-12 (10.9)	—	—	—	—	ΔKt/V: -0.1 vs. 0 nd	—	—	C
McMahon, 1999,2000 [46,47]	14	HD-CKD	8.5	1.5	🚹	ESA High[j] ESA Low	14 (14) 10 (10)	---	—	—	—	—	—	See QoL Table	C

Author, Year	N	CKD Stage	Baseline[a] Hb (g/dL)	Mean Follow-up months	Applicability	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) Target (Achieved)	Clinical Outcomes (Arm 1 vs. Arm 2 vs. Arm 3)							Quality
								CVD event (%)	LVH	Mortality (%)	Hospitali-zations	Dialysis Adequacy	Transfusion (%)	QoL[b]	
ESA v Placebo															
Nissenson, 1995 [49]	152	PD-CKD	8	6-9		ESA	10.7-12.7 (11.2)	—	—	NS	—	—	Δ U/pt/4 wk -0.21 vs. +0.42 P<0.05	—	B
						Placebo	(8.0)								
Bahlmann, 1991 [37]	129	HD-CKD	7.7	6		ESA	10-11.7 (10.6-10.9)	NS	—	NS	—	—	9 vs. 60 P<0.05	—	B
						Placebo	(7.8)								
Sikole, 1993 [51]	38	HD-CKD	6.7	12		ESA[e]	10-11.7 (11.3)	—	LVEDd (mm) 48 vs. 53 P=0.002	—	—	—	—	—	B
						Control	(8.3)[g]								
ESA v Placebo in Pediatric Patients															
Morris, 1993 [48]	11	PD-CKD HD-CKD	7.3	6		ESA	10.5 -12 (11.2)	—	—	—	—	—	—	See QoL Table	C
						Placebo	(7)								

Annotations:

∗Primary Outcome.

a. All baseline data given for arm 1, unless otherwise specified.

b. Refer to Hb Targets Quality of Life Table for details of quality of life measurements.

c. The primary outcome was a composite of non-fatal MI or death. RR 1.3, 95% CI 0.9-1.8.

d. 294 HD-CKD, 51 PD-CKD, 72 ND-CKD patients.

e. Iron co-intervention not documented.

f. Data at 8 weeks.

g. Median.

h. Estimated from graph during maintenance phase.

i. The data and safety monitoring board recommended that the study be terminated at the time of the third interim analysis because of concern about safety even though the futility boundary corresponding to an overall 5% level of significance had not been crossed.

j. 121 patients had follow-up for echocardiographic outcomes. 94 patients were evaluated for the quality of life outcome at week 48.

k. Quality of life was measured in 253 patients of whom 117 had a repeat evaluation at week 48.

l. Of the 596 patients enrolled, 324 remained in the study for 96 weeks and were evaluated for outcomes of LVH and quality of life.

Abbreviations: CABG: Coronary artery bypass graft; CVA: Cerebrovascular accident; CVD: Cardiovascular disease; LVD: Left ventricular dilation; LVEDd: Left ventricular end diastolic diameter; LVH: Left ventricular hypertrophy; MR: Mitral regurgitation; MI: Myocardial infarction; SCD: Sudden cardiac death; URR: Urea reduction ratio; U/pt/4 wk: Units per patient per 4 weeks.

Coding of Outcomes:

Mortality: all cause mortality.

CVD event: Includes CHF exacerbation, MI, arrhythmias, angina, interventional procedure such as CABG or angioplasty, sudden death, CVA.

LVH: As identified by ECHO with minimum of 6 month follow-up.

NS: Not significant.

nd: Not documented.

Table 3. Summary Table of RCTs Comparing Different Hb Targets on Quality of Life in the HD-CKD and PD-CKD Populations

Author Year	N	CKD Stage / Baseline Hb (g/dL)	Follow-up months	Applicability	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) Target (achieved)	Primary Outcome of Study	Quality of Life (Arm 1 vs. Arm 2 vs. Arm 3)				Quality
								Scale/Test	Global QoL	Vitality/Fatigue	Other Measures of QoL	
Parfrey 2005 [15]	596[k]	5 (HD) / 11.0	24	[a]	ESA High	13.5-14.5 (13.1)	Left Ventricular Volume Index	KDQOL Quality of Social Interaction subscale (at mean follow-up)			Social Interaction: NS	A
					ESA Low	9.5-11.5 (10.8)		SF-36 Vitality (at mean follow-up)		Vitality: +		
								FACIT Fatigue Scale (at mean follow-up)		Fatigue: NS		
CanEPO 1990-1991 [39, 40, 44]	118	5 (HD) / 7.0	6	[b]	ESA High	11.5-13 (11.7)	QoL and Functional Capacity[c]	KDQ (at 6 months)		Fatigue: NS	Physical Symptoms: NS Relationships: NS Depression: NS Frustration: NS	A
					ESA Low	9.5-11 (10.2)		SIP (at 6 months)	NS		Physical: NS Psychosocial: NS	
								TTO (at 6 months)			NS	
					ESA High plus ESA Low	11.5-13 (11.7) plus 9.5-11 (10.2)		KDQ (at 6 months)		Fatigue: +	Physical Symptoms: + Relationships: + Depression: + Frustration: NS	
								SIP (at 6 months)	+		Physical: + Psychosocial: NS	
					Placebo	(7.4)		TTO (at 6 months)			NS	
Besarab, 1998 [14]	1233	5 (HD) / 10.2	14		ESA High	14.0 (12.7-13.3)	Mortality and Non-fatal MI	SF-36 (at 12 months)		Vitality: NS	Physical Function: +[d] General Health: NS Bodily Pain: NS Social Function: NS Emotional Role: NS Mental Health: NS Physical Role: NS	A
					ESA Low	10.0 (10.0)						
Foley 2000 [13]	146[i]	5 (HD) / 10.1	12	[e]	ESA High	13-14 (13)	ΔLV Mass Index in individuals with concentric LVH; ΔCavity Volume Index in individuals with LVD	KDQ[f] (at 12 months)		Fatigue: +	Physical Symptoms: NS Depression: + Relationships: + Frustration: NS Physical Function: NS General Health: NS	A
					ESA Low	9.5-10.5 (10.5)		SF-36 (at 12 months)		Vitality: NS	Bodily Pain: NS Social Function: NS Emotional Role: NS Mental Health: NS Physical Role: NS	

Author Year	N	CKD Stage / Baseline Hb (g/dL)	Follow-up months	Applic-ability	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) Target (achieved)	Primary Outcome of Study	Quality of Life (Arm 1 vs. Arm 2 vs. Arm 3)				Quality
								Scale/Test	Global QoL	Vitality/Fatigue	Other Measures of QoL	
								HUI (at 12 months)			NS	
Furuland 2003 [12]	416[j]	4-5 (PD,HD) / 10.9	12		ESA High / ESA Low	13.5–16.0 (13.6) / 9-12 (11.4)	QoL and Safety	KDQ (at 12 months)		Fatigue: NS[g]	Physical Symptoms: + / Relationships: NS / Depression: + / Frustration: NS[g]	B
McMahon 1999,2000 [46,47]	14	5 (HD) / 8.3	1.5		ESA High / ESA Low	14 (~14) / 10 (~10)	Several primary outcomes, including QoL and Exercise Performance	SIP (at target Hb)	+		Physical: NS / Psychosocial: +	B
Pediatric Patients												
Morris 1993 [48]	10[l]	5 (PD,HD) / 7.0	8		ESA / Placebo	10.5 -12 (11.2) / (~6.5)	QoL, Diet, Exercise Tolerance, and PD Efficiency	25-part Parental Questionnaire[h] (after 6 months of ESA treatment)	NS		Physical Performance / General Health (includes school attendance): + / Sleep: NS / Diet: NS / School Performance: NS / Psychosocial: NS	B

Table 3 (Cont'd). Summary Table of RCTs Comparing Different Hb Targets on Quality of Life in the HD-CKD and PD-CKD Populations

Annotations:

a. No CVD or LVD.

b. All individuals had LVD or LVH at baseline, no CVD.

c. Data shown for ESA arms vs. Placebo. All statistical comparisons for ESA High vs. ESA Low were not significant.

d. Increased by 0.6 point for each percentage point increase in hematocrit.

e. Free of marked comorbidity.

f. Results given are from repeated measures analysis of variance.

g. P= 0.05.

h. 25-Part Parental Questionnaire, modified from a previously used questionnaire. [Appendix of Ref 48] Questions covered various aspects of the child's wellbeing and behavior including mood and psychological behavior, social interaction, somatic complaints and general health, sleep, diet, school functioning and physical performance.

i. Only 94 of the 146 patients were evaluated for quality of life at week 48.

j. KDQ analysis was conducted in 253 patients, 117 of which were reevaluated at week 48.

k. 324 of the 596 patients were evaluated at 96 weeks for quality of life.

l. 10 of the 11 children enrolled completed 36 weeks of the study and were evaluated for quality of life.

Abbreviations: LV: Left ventricular; LVD: Left ventricular dilation; LVH: Left ventricular hypertrophy; QoL: Quality of Life.

Coding of Outcomes: Coding of comparison of study arm 1 versus study arm 2: "+" better, "−" worse (with reference to benefit for patient). NS: Not statistically significant; nd: Not documented.

KEY to Quality of Life Measurement Scales/Tests:

36-item Medical Outcomes Study Short-Form Health Survey (SF-36) evaluates eight health-related aspects: physical function, social function, physical role, emotional role, mental health, vitality, bodily pain and general health perceptions. Each portion of the test is scored on a scale that ranges from 0 (severe limitation) to 100 (no limitation). Two summary scores can be obtained: the physical component summary score which included the following dimensions: physical functioning, role-functioning physical, bodily pain, and general health perceptions and the mental component summary score which includes the following dimensions: social functioning, role-function emotional, mental health, and vitality. Scores range from 0 to 100, a higher score indicating better QoL.

Functional Assessment of Chronic Illness Therapy (FACIT) is a 27-item compilation of general questions divided into four primary QOL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. (www.facit.org)

Health Utilities Index (HUI) provides an overall index of health, derived from scores in seven aspects: sensation, mobility, emotion, cognition, self-care, pain and fertility. This is an interval scale that can vary in theory between 0 (death) and 1 (perfect health).

Kidney Disease Quality of Life (KDQOL) is validated in dialysis patients. The Short Form (SF-36) version was used for assessment of vitality.

Kidney Diseases Questionnaire (KDQ) is validated in dialysis patients. Contains 26 questions divided into five sections: patient-specific physical symptoms, fatigue, depression, relationships and frustration. All questions are scored on a 7-point Likert scale (7=no problem, 1=severe problem).

Sickness Impact Profile (SIP) is a behavior-related questionnaire that evaluates non-disease-specific, sickness-related behavioral dysfunction. It is widely used for end-stage renal disease patients and in studies evaluating quality-of-life improvement with ESA treatment for end-stage renal disease-related anemia. The SIP includes 136 items grouped into 12 categories of activity in physical and psychologic dimensions. Scores range from 0 (no behavioral dysfunction) to 100 (100% dysfunction in a category or group). Unlike the Karnofsky performance scale (KPS) and the KDQ, lower scores for the SIP indicate better quality of life.

Time Trade-off (TTO) is a unidimensional measure of quality of life that gives a value to a patient's quality of life ranging from 1.0 (full health) to 0 (patient is indifferent between life and death). This is a utility measure using the time trade-off hypothesis.

Table 4. Summary Table of RCTs Comparing Different Hb Targets on Non-CVD/Mortality Adverse Event Rates in the HD-CKD and PD-CKD Populations

Author Year	N	Dialysis Modality	Description of Intervention	Follow-up months	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) Target (achieved)	Adverse Events (Arm 1 vs. Arm 2 vs. Arm 3)						Total D/C of Drug
							BP change or Hypertension		Access Thrombosis (%)		Seizures	Other Reported AE[a]	
							Definition	Outcome	Definition	Outcome		Description and Results	
ESA vs. ESA													
Besarab 1998 [14]	618	HD[b]	IV or SC ESA 1.5X pre-trial dose; adjusted after 2 weeks	14	ESA High	14.0 (12.7-13.3)	Mean SBP and DBP during the study[c]	NS	Both synthetic grafts and natural fistulae	39% vs. 29% (P= 0.001)	NS	—	0
	615		IV or SC ESA adjusted		ESA Low	10.0 (10.0)							0
Parfrey 2005 [15]	284	HD	IV or SC ESA for 24 wks to reach target then maintained for 72 wks	24	ESA High	13.5-14.5 (13.3)	Hypertension not specified	NS	AV fistulae, permanent catheter, non site specific embolism	23% vs. 19% (NS)	—	Overall Treatment Emergent AE in ≥10% of patients: 96% vs. 94%[d]	nd
	281				ESA Low	9.5-11.5 (10.9)							
Furuland 2003 [12]	216	HD PD[e]	SC ESA TIW	12	ESA High	13.5–16.0 (13.4-14.3)	ΔMean DBP from baseline	90 vs. 83 mmHg (P= 0.02)	Complication in synthetic graft, fistulae, catheter during study	5% vs. 2% in HD patients only (NS)	—	Individuals with at least 1 SAE NOS: 51% vs. 38.5% (NS) Thromboembolic: Event: 56 vs. 47 per arm (NS)[f]	34
	200		SC ESA TIW or no treatment		ESA Low	9-12 (11.3-11.7)							15
Suzuki 1989 [52]	59	HD	IV ESA 1500 or 3000 IU TIW	2	ESA High	<11 (8.7)	Increased dose of Anti-HTN meds	5 vs. 4 vs. 1 individuals	—	—	—	# AE NOS 6.7% vs. 8.3% vs. 1.7% per arm[g]	nd[h]
	58				ESA Low	(8.2)							
	57				Placebo	(6.1)							
Foley 2000 [13]	73	HD	SC ESA ESA high arm had a 24 wk "ramping" phase. 24 wk maintenance was similar in both arms	11	ESA High	13-14 (13)	Mean SBP, DBP, during between groups, and use of Anti-HTN meds	For LVH: significant SBP and ↑Anti-HTN For LVD: NS	AV access	8% vs. 14% (NS)[i]	—	—	nd
	73				ESA Low	9.5-10.5 (10.5)							
Abraham 1991 [36]	39	HD	IV ESA TIW after HD session 25, 100 or 200 IU/kg	2.5-4.5	ESA 200 U/kg	(11.6)	% of individuals with increases in DBP ≥10 mm Hg and/or Anti-HTN meds	56% vs. 52% vs. 45% (NS)	—	—	—	—	nd
	40				ESA 100 U/kg	(11.0)							
	42				ESA 25 U/kg	(8.8)							
CanEPO 1990 [39, 44]	38	HD	IV ESA 100 IU/kg initial dose; titrated to achieve targets	6	ESA High	11.5-13 (11.7)	Severe HTN required withdrawal[j]	5% vs. 5% vs. 0% (P=0.01)	Access clotting	# of Events: 7 vs. 4 vs. 1 (P=0.01)	0% vs. 5% vs. 2.5% (NS)	Non-Specific AEs: 63 vs. 61 vs. 65 per arm[k]	2
	40				ESA Low	9.5-11 (10.2)							2
	40				Placebo	(7.4)							0

Table 4 (Cont'd). Summary Table of RCTs Comparing Different Hb Targets on Non-CVD/Mortality Adverse Event Rates in the HD-CKD and PD-CKD Populations

Author Year	N	Dialysis Modality	Description of Intervention	Follow-up months	Arm 1 / Arm 2 / Arm 3	Mean Hb (g/dL) Target (achieved)	Adverse Events (Arm 1 vs. Arm 2 vs. Arm 3)						Total D/C of Drug
							BP change or Hypertension		Access Thrombosis (%)		Seizures	Other Reported AE[a]	
							Definition	Outcome	Definition	Outcome		Description and Results	
Berns 1999 [38]	14 14	HD	ESA to maintain target	12	ESA High ESA Low	14 (14.0) 10 (10.1)	HTN: SBP >140 mm Hg, DBP >90 mm Hg; or Δ Anti-HTN meds.	Slightly more prevalent in Low vs. High (NS)	—	—	—	—	nd
McMahon 1999 [46] 2000 [47] [Crossover]	8 6	HD	SC ESA 2x/wk if total dose <20,000 IU/wk; IV ESA TIW if total dose >20,000 IU/wk	1.5	ESA High ESA Low	14 (14.0) 10 (10)	Mean ABP for peak day and nocturnal readings taken pre and post HD	NS	—	—	—	—	0 0
ESA vs. Placebo													
Abraham 1991 [36]	151 78	HD	IV ESA TIW after HD session 100 IU/kg	2-3	ESA Placebo	12.5-13.5 (10.8) (7.5)	Correlation between BP and change in Hb or rate of Hb rise	No correlation[l] ESA arm: 1 individual withdrawn for severe high BP	—	—	3 vs. 0 individuals	—	nd
Nissenson 1995 [49] [Crossover]	78 74	PD	Self-admin. SC ESA TIW Blinded phase: 4,000 IU/mL; Maintenance phase: 2,000, 4,000, or 10,000 IU/mL	6-9	ESA Placebo	10.6-12.6 (11.2) (8.0)	Increased DBP and Anti-HTN Regimen	55% vs. 20%	—	—	—	Mild and SAE: 407 AE in 74 patients vs. 325 AE in 63 patients[m]	nd
Bahlmann 1991 [37]	53 46	HD	IV ESA each HD session Blinded Phase (4 wk): 80 IU/kg/wk to target; Maintenance phase: 40 IU/kg/wk	6	ESA Placebo	10-11.7 (10.6) (7.8)	HTN: SBP ≥ 160 mm Hg or DBP ≥ 95 mm Hg or Anti-HTN therapy initiated or intensified	28% vs. 11%	Clot of AV fistula	9% vs. 9%	0 vs. 0	Infection events: 20 vs. 10[n]	0 0

Annotations:

a. For "Other Reported AE" column, outcomes may be recorded in # or % of events per arm, or # or % of events per patient, or % given heterogeneity in reporting.

b. All individuals had evidence of congestive heart failure and ischemic heart disease.

c. Pre-study ABP had to be below 160/100 for 4 weeks prior to study. Subgroup analysis [58]: 31 patients; Mean day & nocturnal BP readings for 24 hr were NS at baseline or at follow-up.

d. Of these $P>0.05$ for all comparisons except headache was greater in the ESA high arm and skeletal pain and surgery were greater in ESA low arm.

e. Includes some pre-dialysis patients, stages 4-5.

f. Thromboembolic events were defined by WHO classification.

g. 7 of 10 continued treatment.

h. Not documented per arm. 3 individuals receiving ESA discontinued treatment.

i. Patients with ongoing access problems were specifically excluded. The event rates small and study did not have enough statistical power to detect a moderate impact on access thrombosis; the proportion using natural fistulae in the Besarab study was 23% compared to 76% in this study.

j. Diastolic BP was increased in patients on ESA compared to placebo. $P=0.001$ No statistical difference between High ESA to Low ESA.

k. Nonspecific events include: clotting of tubing in dialysis machine, flu-like symptoms, headache, red eye, epistaxis or hemorrhage, pain in chest, abnormal sense of taste, aches in bone and muscle.

l. No significant correlation but clinically important increases in BP appeared dose-related with earlier time to peak and peak BP achieved.

m. Mild and severe reactions not otherwise specified. Of 408 events such in ESA group, 37% ($N=149$) considered mild severity but possibly related to study medication, 1% ($N=5$) were considered severe or life threatening possibly or definitely related to study medication. In the placebo group 26% ($N=85$) were considered mild severity but possibly related to study medication, $<1\%$ ($N=2$) were considered severe or life threatening possibly or definitely related to study medication.

n. More infections in ESA group, but only with URTI/viral; only pneumonias seen in placebo arm.

Coding of Outcomes:

Hypertension: includes mean changes in SBP, DBP, MAP, increase in use of anti-HTN medications, difficult to control hypertension.

Access Thrombosis: synthetic grafts and fistulae.

Abbreviations: ABP: Ambulatory blood pressure; AE: Adverse events; Anti-HTN: Anti-hypertensive; BP: Blood pressure (systolic/diastolic blood pressure); D/C: Discontinuation; DBP: Diastolic blood pressure; HTN: Hypertension; LVD: Left ventricular dilation; LVH: Left ventricular hypertrophy; MAP: Mean arterial blood pressure; NOS: Not otherwise specified; SAE: Severe adverse effect; SBP: Systolic blood pressure; URTI: Upper respiratory tract infection.

Table 5. Summary Table of RCTs Comparing Different Hb Targets on Exercise Capacity in the HD-CKD and PD-CKD Populations

Author Year	N	CKD Stage / Baseline Hb (g/dL)	Follow-up months	Applic-ability	Arm1 / Arm 2 / Arm 3	Mean Hb (g/dL) Target (achieved)	Primary Outcome of Study	Quality of Life (Arm 1 vs. Arm 2 vs. Arm 3) Scale / Test	Description	Results	Quality
Parfrey 2005 [15]	324	5 (HD) / 11.0	24	[a]	ESA High	13.5-14.5 (13.1)	Left Ventricular Volume Index	6-min Walk Test	Patients are asked to cover as much distance in an enclosed corridor as they can in 6 minutes	NS	A
					ESA Low	9.5-11.5 (10.8)					
CanEPO 1990-1991 [39,40,44]	118	5 (HD) / 7.0	6	[b]	ESA High	11.5 -13 (11.7)	QoL and Functional Capacity[c]	Naughton Stress Test		NS	A
					ESA Low	9.5-11 (10.2)		6-min Walk Test	Patients are asked to cover as much distance in an enclosed corridor as they can in 6 minutes	NS	
					Placebo	(7.4)					
McMahon 1999,2000 [46,47]	14	5 (HD) / 8.3	1.5		ESA High	14 (~14)	Several primary outcomes, including QoL and Exercise Performance	Exercise Test[d]	Peak Heart Rate	NS	C
									Peak O_2 consumption	+	
					ESA Low	10 (~10)			Work Done	+	
Pediatric Patients											
Morris 1993 [48]	10	5 (PD,HD) / 7.0	8		ESA	10.5 -12 (11.2)	QoL, Diet, Exercise Tolerance, and PD Efficiency	Exercise Tolerance Test	2-min walking	NS[e]	C
					Placebo	(~6.5)			Treadmill	NS[f]	

Annotations:

a. No CVD or LVD.

b. All individuals had LVD or LVH at baseline, no CVD.

c. Data shown for ESA arms vs. Placebo. All statistical comparisons for ESA High vs. ESA Low were not significant.

d. With cycle ergometer.

e. Not a significant improvement but did improve over study time.

f. Only 3 children completed the treadmill test.

Coding of Outcomes:

Coding of comparison of study arm 1 versus study arm 2: "+" better, "−" worse (with reference to benefit for patient). NS: Not statistically significant; nd: Not documented.

Table 6. Evidence Matrix of Study Quality by Outcome for RCTs Comparing Different Hb Targets in the HD-CKD and PD-CKD Populations

Outcome	Methodological Quality								
	A			B			C		
	Author, Year	N	F/U (mo)	Author, Year	N	F/U (mo)	Author, Year	N	F/U (mo)
All Cause Mortality	Besarab, 1998	1233	14	Nissenson, 1995	152	6-9	Furuland, 2003	416	12
	Parfrey, 2005	596	24	Bahlman, 1991	129	6			
	Foley, 2000	146	11						
	CanEPO, 1990-1991	118	6						
Non-Fatal CV Events	Besarab, 1998	1233	14	Bahlman, 1991	129	6			
	Parfrey, 2005	596	24						
	Foley, 2000	146	11						
LVH	Parfrey, 2005	596	24	Sikole, 1993	38	12			
	Foley, 2000	146	11						
Hospitalizations	Besarab, 1998	1233	14				Furuland, 2003	416	12
QoL-Global Score, Generic Instrument	Parfrey, 2005	596	24				McMahon, 1999, 2000	14	1.5
	CanEPO, 1990-1991	118	6				Morris, 1993	11	8
QoL-With Kidney-Specific Instruments	Parfrey, 2005	596	24				Furuland, 2003	416	12
	CanEPO, 1990-1991	118	6						
	Foley, 2000	146	11						
Transfusion Requirement	Besarab, 1998	1233	14	Nissenson, 1995	152	6-9	Suzuki, 1989	179	2
	CanEPO, 1990-1991	118	6	Bahlman, 1991	129	6			
Access Thrombosis	Besarab, 1998	1233	14	Bahlman, 1991	129	6	Furuland, 2003	416	12
	Parfrey, 2005	596	24						
	Foley, 2000	146	11						
	CanEPO, 1990-1991	118	6						
Other Thrombotic Events							Furuland, 2003	416	12
Seizures	Besarab, 1998	1233	14	Bahlman, 1991	129	6	Abraham, 1991	229	2.5-4.5
	CanEPO, 1990-1991	118	6						
Blood Pressure Change	Besarab, 1998	1233	14	Nissenson, 1995	152	6-9	Furuland, 2003	416	12
	Parfrey, 2005	596	24	Bahlman, 1991	129	6	McMahon, 1999, 2000	14	1.5
	Foley, 2000	146	11				Suzuki, 1989	179	2
	CanEPO, 1990-1991	118	6				Berns, 1999	28	12
							Abraham, 1991 ESA vs. ESA & ESA vs. Placebo	229	2.5-4.5
Dialysis Adequacy	Besarab, 1998	1233	14				Furuland, 2005	24	5.5
	Parfrey, 2005	596	24						
	Foley, 2000	146	11						
Other Adverse Events	Parfrey, 2005	596	24	Nissenson, 1995	152	6-9	Furuland, 2003	416	12
	CanEPO, 1990-1991	118	6	Bahlman, 1991	129	6	Suzuki, 1989	179	2

Table 7. Evidence Profile of RCTs Comparing Different Hb Targets in the HD-CKD and PD-CKD Populations

Outcome	# of Studies & Study Design	Total N of Patients Randomized	Methodologic Quality of Studies[ac]	Consistency across Studies	Directness of the Evidence, including Applicability	Other Considerations	Summary of Findings		
							Quality of Evidence for Outcome	Qualitative Description of Effect (Higher versus Lower Hb Targets)	Importance of Outcome
All-Cause Mortality	7 RCTs	2790	No limitations[a]	Important inconsistencies[b]	Some uncertainty[c]	None	High for patients with CVD Moderate for others	No benefit and possible harm. The Besarab study had a composite outcome of time to death or fatal MI with 183 deaths and 19 MIs vs. 150 and 14 (Hazards ratio [95% CI] 1.3 [0.9-1.9]). Other studies (without large number of CVD patients) show no difference between arms.	High
Non-fatal CV Events	5 RCTs	2104	Some limitations[d]	No important inconsistencies	Direct	Not sparse[e]	Moderate	No benefit and possible harm. The Parfrey study reported higher CVA rates in the high Hb group, 4% vs. 1% (P=0.045), but did not show differences in other CV event rates.	High
LVH	3 RCTs	780	No limitations	Important inconsistencies[f]	Direct	None	High	No consistent or statistically significant benefit. Partial correction of anemia leads to partial regression of LVH; full correction has no incremental benefit over partial correction of anemia.	Moderate
Hospitalizations	2 RCTs	1649	Some limitations	No important inconsistencies	Major uncertainty[g]	Sparse data	Low	No benefit. The Besarab study and Furuland study showed no difference.	Moderate
QOL –Global Score, Generic Instrument	4 RCTs	739	Some limitations[h]	Important inconsistencies[i]	Direct	None	Low	Possibly some benefit, but inconsistencies. 2 of 2 studies showed improved Sickness Impact Profile with higher target. Trials using SF-36, FACIT Fatigue and Health Utilities Index showed no differences. Besarab study did not report global score but showed increase in physical function.	High
QOL – With Kidney Specific Instruments	4 RCTs	1276	Some limitations	Important inconsistencies[i]	Direct	None	Low	Possibly some benefit, but inconsistencies. All studies based on KDQ or derivative. 3 of 4 showed fatigue better (with higher Hb). 1 study approached statistical significance P=0.05. 3 of 3 showed depression better. 2 of 4 showed physical symptoms better. 2 of 3 showed relationships better. 0 of 3 showed frustration better. 1 study approached statistical significance P=0.05.	High
Transfusion Requirement	5 RCTs	1811	Some limitations[j]	No important inconsistencies	Some uncertainty[k]	None	Moderate	Benefit. Transfusion rates reduced by as little as 1/3 to essentially 0 in all studies in higher Hb arms. Differences were statistically significant.	High
Access Thrombosis	6 RCTs	2638	Some limitations[l]	No important inconsistencies	Some uncertainty[m]	None	Moderate	Harm. Increased risk of clotting with approximately 10% higher rate of thrombosis. Rates of thrombosis were 39% vs. 29% in the Besarab study, 21% vs. 12% in CanEPO. Other studies showed no significant differences.	High
Other Thrombo-embolic Events	1 RCT	416	Serious limitations[n]	N/A	Some uncertainity[o]	Sparse data	Low	No benefit. No statistically significant difference. OR of total Vascular Events was 1.24 (56 events) vs. 1.0 (47 events) (p=0.37).	Moderate or High

Outcome	# of Studies & Study Design	Total N of Patients Randomized	Methodologic Quality of Studies	Consistency across Studies	Directness of the Evidence, including Applicability	Other Considerations	Summary of Findings		
							Quality of Evidence for Outcome	Qualitative Description of Effect (Higher versus Lower Hb Targets)[2]	Importance of Outcome
Seizures	4 RCTs	1709	No limitations[p]	No important inconsistencies	Direct	Sparse data	Low	Likely no harm. No statistically significant difference in the two large studies. CanEPO provides breakdown of 3 seizures in ESA vs. 0 in Placebo arms, the Besarab study does not provide actual data, but reports NS.	Moderate
Blood Pressure Change	12 RCTs[q]	3469	Some limitations[r]	Important inconsistencies[s]	Major uncertainty[t]	No dose effect[u]	Moderate	Potential harm. In studies looking at high vs. low Hb 2 studies showed significant increase in SBP/DBP and number of antihypertensive medications. In Foley study, this was only true for subgroup with LVH, not in subgroup with LVD. 2 low quality studies suggest increase in DBP with higher ESA or Δ Hb >2.2 g/dL. In studies comparing ESA vs. Placebo (6 RCTs), the majority showed significant increases in SBP/DBP, or number of antihypertensive medications needed in patients treated with ESA.[v]	Moderate
Dialysis Adequacy	4 RCTs	1999	No limitations[w]	No important inconsistencies	Direct[x]	None	High	Potential harm. Lower Kt/V in HD-CKD patients assigned to target Hb > 13, in 4 of 4 trials.	Moderate[y]
Other Adverse Events	6 RCTs	1590	Serious limitations[z]	N/A[aa]	Major uncertainty[ab]	Sparse and imprecise data[z]	Very low	Likely no harm. There seemed to be no pattern of higher rates of additional AEs in the higher Hb arms.	N/A
Total N of Patients	14 RCTs	3205							
Balance of Benefit and Harms: **Likely some benefit for QoL at Hb ≥ 11 g/dL.** **No benefit and possible harm for mortality and cardiovascular disease.** **Uncertain trade-offs at each Hb target, but likely increasingly unfavorable risk-benefit ratio with increasing Hb targets.**							**Quality of Overall Evidence:** **Low for QoL** **Moderate for other important outcomes**		

Table 7 (Cont'd). Evidence Profile of RCTs Comparing Different Hb Targets in the HD-CKD and PD-CKD Populations

Annotations:

a. 4 Grade A, 2 Grade B and 1 Grade C trial.

b. The largest study (the Besarab study) showed significantly higher mortality in the higher Hb group. This study was composed of the highest risk patients for CVD (i.e. possible confounder). The remaining studies showed no statistically significant difference.

c. The duration of 3 of 7 trials was <1 year; unclear if this is long enough to measure mortality outcome.

d. 3 Grade A, 1 Grade B and 1 Grade C. However the 3 A studies comprise 93% of patients. Most studies were inadequately powered to study non-fatal CVD events (i.e. possible confounder). The Besarab study was adequately powered to assess CHF, but was stopped early.

e. 5/5 studies report outcomes of angina, 4/5 non-fatal MI, 3/5 pulmonary edema or heart failure.

f. Foley study shows a trend towards smaller LVMI and less progression in LV dilation in high vs. low Hb.

g. Not primary outcome; unclear if reason for admission can be solely related to the Hb level.

h. 2 Grade A and 2 Grade C studies; some studies not blinded, heterogeneity of timing and follow-up.

i. Different instruments.

j. Transfusions were not primary outcome.

k. No trial specified indications for transfusions.

l. 4 Grade A studies, 1 Grade B and 1 Grade C; the Besarab study had 76% grafts. (Other studies not powered to show difference in access clotting).

m. Most studies do not mention prior history of graft or fistula, i.e. its inherent risk of clotting.

n. Primary outcome had been physical activity, study stopped, retooled, further enrollment then another round of enrollment before recruitment complete.

o. Multiple sites across many countries. Only 1 coordinator recorded and classified events centrally and likely did not do site visits. Strength was the consistent use of scoring system from the World Health Organization.

p. 2 Grade A studies with~1300 patients and 1 Grade B study and 1 Grade C study.

q. These 12 RCTs are 11 adult, 1 Peds (n=21), 3 of the 11 are based on ABPM (n=87). Only 6 involve placebo arms, others are ESA vs. ESA.

r. 4 Grade A, 2 Grade B, 4 Grade C, and 1 grade was not documented.

s. Majority of problems are linked to the wide variation in definitions and measurements with respect to casual vs. ABPM, mean of SBP vs. DBP, different definitions of being hypertensive (being on medications vs. specific cut-off), defining worsening BP as both increase in BP and or medication amount/dose.

t. Reason: Unclear how this translates into clinical outcomes.

u. Restricted to looking at 6 studies involving high vs. low dose ESA.

v. In the Furuland study, a number of patients were not on ESA in low Hb arm but data not available to extract; and only the Abraham study, which reported on only blood pressure outcomes from 3 other multi-site trials did not show a difference in BP between ESA vs. placebo groups.

w. 3 Grade A studies and 1 Grade C study.

x. Only issue here is use of URR as 'surrogate' for Kt/V in the Foley study.

y. From the HEMO study, it is relatively clear that even a statistically significant decrease in Kt/V is unlikely to affect mortality (presume spKt/V > ~1.3 URR 66%).

z. Ascertainment of additional AEs was not consistently or prospectively performed. Reporting was not standardized. Only AEs that occurred during duration of RCTs were captured.

aa. Numbers too small.

ab. Reported events included sick leave, infection events, hyperkalemia, gastrointestinal symptoms, or were unspecified.

ac. See Evidence Matrix for quality grades of individual studies assessed for each outcome.

Abbreviations: ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure; CHF: Congestive heart failure; CV: Cardiovascular; CVA: Cerebrovascular accident; DBP: Diastolic blood pressure; LVH: Left ventricular hypertrophy; LVMI: Left ventricular mass index; LVVI: Left ventricular volume index; KDQ: Kidney disease questionnaire; MI: Myocardial infarction; OR: Odds ratio; SBP: Systolic blood pressure; SF-36: 36-item Medical Outcomes Study Short-Form Health Survey; URR: Urea reduction ratio.

Table 8. Summary Table of RCTs Comparing Different Hb Targets on Key Clinical Outcomes in the ND-CKD Population

Author, Year	N	CKD Stage	Baseline[a] Hb (g/dL)	Mean Follow-up (mo)	Applicability	Arm 1 Mean Hb (g/dL) Target (Achieved)	Arm 2 Mean Hb (g/dL) Target (Achieved)	Clinical Outcomes (Arm 1 vs. Arm 2)							Quality
								CVD event	LVH	Mortality	Kidney Disease Progression: Creat/Creat-Based Measurement or ΔCreat or ΔeGFR	Kidney Disease Progression: Events	Trans-Fusions	QoL[b]	
Singh, 2006 [2][c]	1432	3-4	10.1	16		ESA High 13.5 (12.7[d])	ESA Low 11.3 (11.4[d])	*125 vs. 97[e] HR: 1.34 (1.03:1.74) P=0.03	—	52 vs. 36 HR: 1.48 (0.97:2.27) NS	—	KRT: 155 vs. 134 HR: 1.19 (0.94:1.49) P=0.15	—	See QoL Table	A
Drueke, 2006 [1]	603	3-4	11.6	36[f]		ESA High 13-15 (13.4[d])	ESA Low 10.5-11.5 (11.6[d])	*58 vs. 47[g] HR: 1.28 (0.69:1.89) NS	ΔLVMi: NS	31 vs. 21 HR:1.51 (0.87:2.63)[v] NS	ΔeGFR: ↓6.8 ml/min vs. ↓5.0 ml/min NS	KRT: 127 vs. 111 Shorter Time to Dialysis P=0.03	26 vs. 33	See QoL Table	A
Ritz, 2007 [5]	172	1-3	11.9	15		ESA High 13-15 (13.5)	ESA Low 10.5-11.5 (12.1)	6 vs. 6[h]	*ΔLVMi: NS	nd	ΔeGFR: ↓5.5 ml/min vs. ↓3.4 ml/min	KRT: 2 vs. 3	—	See QoL Table	A
Levin, 2005 [26]	172	3-4	11.8	22.6 (median)		ESA High 12-14 (12.8)	ESA Low 9-10.5 (11.5)	1 vs. 1 NS	*ΔLVMi: NS	1 vs. 3 NS[i]	ΔeGFR: NS	KRT: 8 vs. 11 NS	—	—	A
Roger, 2004 [27]	155	3-4	11.2	24		ESA High 12-13 (12.1)	ESA Low 9-10 (10.8)	nd	*ΔLVMi: NS[i]	nd	ΔGFR:NS	nd	—	NS	A
Roth, 1994 [30] Revicki, 1995 [50]	83	4-5	8.9	11		ESA 11.7 (11.2)	Control (8.7)	0 vs. 1 NS	—	0 vs. 1 NS	*ΔeGFR: NS	KRT: 16 vs. 13	4 vs. 9	*See QoL Table	A
Gouva, 2004 [6][k]	88	3-5	10.1	22.5		ESA Early 13 (12.9[l])	ESA Late[m] 13 (10.3[l])	nd	—	3 vs. 4	—	*Composite End Point: 13 vs. 23[n] P=0.0078	—	—	B
Kuriyama, 1997 [29]	73	3-5	9	14-36		ESA 11.0-11.7 (11.8)	Control (8.4)	nd	—	1 vs. 2 NS	—	*Doubling Creatinine: 22 vs. 26 P=0.0003 KRT: 14 vs. 20 P=0.008	—	—	B

Table 8 (Cont'd). Summary Table of RCTs Comparing Different Hb Targets on Key Clinical Outcomes in the ND-CKD Population

Author, Year	N	CKD Stage	Baseline[a] Hb (g/dL)	Mean Follow-up (mo)	Applicability	Arm 1 Mean Hb (g/dL) Target (Achieved)	Arm 2 Mean Hb (g/dL) Target (Achieved)	Clinical Outcomes (Arm 1 vs. Arm 2)							Quality
								CVD event	LVH	Mortality	Kidney Disease Progression: Creat/Creat-Based Measurement or ΔCreat or ΔeGFR	Kidney Disease Progression: Events	Trans-Fusions	QoL[b]	
Kleinman, 1989 [43]	14	1-3	9.4	3	🧍	ESA 12.7-13.3 (11.9)	Placebo (9.4)	1 vs. 0	—	0	*1/creatinine: NS	—	—	—	B
Rossert, 2006 [3]	390[o]	3-4	11.6	11.8[p]	🧍🧍	ESA High 13-15[q] (14.0[d,r])	ESA Low 11-12 (12.0[d,r])	3 vs. 4	—	1 vs. 6 NS	*Rate of GFR decline: NS	—	—	See QoL Table	C
Macdougall, 2007 [4][s]	197	2-5	10.9	22[t]	🧍	ESA Early 11 (11)	ESA Late 11 (10.5)	nd	*Worst LVM: NS	1 vs. 6[u]	—	KRT: 30 vs. 63 Mean Time to Dialysis or Death: NS	—	—	C
Clyne, 1992 [41]	20	4-5	8.6	3	🧍	ESA 10.0 (11.7)	Control (9.4)	nd	—	nd	*ΔGFR: NS	nd	—	—	C
Lim,1989 [45]	14	4-5	9.1	2	🧍	ESA 150 IU/kg TIW (13.7) / ESA 100 IU/kg TIW (12.0) / ESA 50 IU/kg TIW (11.7)	Placebo (8)	nd	—	0	ΔCreatinine clearance: NS	nd	—	—	C
Watson, 1990 [53]	11	5	9.7	3	🧍	ESA 12.6 (11.7)	Placebo (8.7)	nd	—	nd	—	Accelerated renal failure: 0 vs. 2 NS	—	—	C
Abraham, 1990 [35]	8	3-5	10.0	2-3	🧍	ESA 12.3-13.3 (12.3)	Placebo (9.6)	nd	—	nd	*ΔSCr: NS	—	—	—	C

Note: Studies newly included in update are shaded.

Annotations:

*Primary outcome.

a. All baseline data given for arm 1, unless otherwise specified.

b. Global Scores, if documented, are provided here. Refer to Hb Targets Quality of Life Table for details of quality of life measurements.

c. The data and safety monitoring board recommended that the study be terminated in May 2005 at the time of the second interim analysis, even though neither the efficacy nor the futility boundaries had been crossed, because the conditional power for demonstrating a benefit for the high-Hb group by the scheduled end of study was less than 5% for all plausible values of the true effect for the remaining data. Other factors that the board considered included an examination of differences between the treatment groups in adverse events, biochemical data, and QoL data.

d. From graph. Averaged over all measurements.

e. End point was a composite of death, myocardial infarction, hospitalization for congestive heart failure (excluding kidney replacement therapy), and stroke. There was statistically significant imbalance at baseline with more individuals with CABG and HTN in higher Hb target arm. Statistical significance of the primary outcome is lost after multivariate adjustment for CHF, atrial fibrillation/flutter, serum albumin, reticulocyte count, and age [HR 1.24 (95% CI: 0.95;1.62), P=0.111].

f. Follow-up in Arm 1 was 35 months; Arm 2 was 36 months.

g. End point was a composite of a first cardiovascular event including sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease (amputation or necrosis), or cardiac arrhythmia resulting in hospitalization for 24 hours or more.

h. 6 vs. 5 patients for cardiac adverse events and 0 vs. 1 patient for ischemic stroke.

i. All adverse events leading to death were determined to be unrelated to the study drug.

j. Pre-power calculation: sample size of 75 patients/treatment arm needed to detect difference in LVMi of 15 g/m^2 at α =0.05 (2-sidedCI) with 80% power. Number actually analyzed at 2 year follow-up was less in each arm.

k. In February 2002, case series of PRCA were reported in patients receiving mainly SC EPO alpha. Although no such adverse events had been recorded in any of the enrolled patients in this study, enrollment of new patients was suspended, with 88% of the target enrollment being achieved. In November 2002, the indication of SC EPO alpha administration in chronic kidney failure patients was withdrawn because PRCA had been documented in a further number of patients receiving EPO in Europe, Australia, and Canada. At this point all study patients were informed of this modification and SC EPO alpha was discontinued.

l. Results at 12-month measurement.

m. Because no patient in the deferred arm had their Hb fall to < 9 g/dL, this group was not treated with EPO and is considered to be a control group.

n. End point was a composite of doubling of creatinine, initiation of kidney replacement therapy, or death. Adjusted analysis for baseline serum creatinine resulted in a trend toward a higher risk in patients in the ESA High group [hazard ratio of 0.37 (95% CI: 0.18-0.73, P=0.004).

o. Because of safety concerns in late 2002 related to the risk for EPO-induced pure red cell aplasia and subsequent labeling changes for SC administration of Eprex®, the study was terminated prematurely by the sponsor. Thus GFR decline over 1 year could only be assessed in 163 patients (75 in Arm 1 and 88 in Arm 2) and quality of life follow-up was assessed in 177 patients with a median duration of 5.8 months between assessments.

p. Intended 36 months, but study stopped early. Therefore, study duration was 4 months of stabilization phase and a median of 7 months in the High Hb and 8.6 months in the Low Hb group of maintenance phase.

q. Hemoglobin target was 14-15 g/dL for men and 13-14 g/dL in women.

r. In the High Hb group, the achieved Hb for men was 14.2 g/dL and for women was 13.6 g/dL. In the low Hb group, the achieved Hb for men was 12.1 g/dL and for women was 11.5 g/dL.

s. The study, which began in 1997, was stopped early (December 2002) by the sponsor due to contraindication of the SC route of administration for EPO. Patients were followed-up for reasons of safety after their discontinuation, and were subsequently continued on a different EPO preparation to maintain their well-being. The results presented here provide some of the final available trial data in CKD patients administered EPO by the SC route before discontinuation of the study.

t. Follow-up in Arm 1 was 24 months; Arm 2 was 21 months.

u. Arm 2 results include one death that occurred after dialysis started.

v. For HR inverse was taken of those reported in the article to convert to HR of higher versus lower Hb target.

Abbreviations: CABG: Coronary artery bypass graft; CV: Cardiovascular; CVD: Cardiovascular disease; eGFR: Estimated glomerular filtration rate; KRT: Kidney replacement therapy: Dialysis or Transplantation; LVH: Left ventricular hypertrophy; LVMi: Left ventricular mass index; PRCA: Pure red cell aplasia; SC: subcutaneous.

Coding of Outcomes:

NA: Not applicable.

nd: Not documented.

NS: Not significant.

Table 9. Summary Table of RCTs Comparing Different Hb Targets on Quality of Life in the ND-CKD Population

Author, Year	N	CKD Stage / Baseline Hb (g/dL)	Follow-up months	Applic-ability	Arm 1 Mean Hb (g/dL) Target (achieved)	Arm 2 Mean Hb (g/dL) Target (achieved)	Primary Outcome of Study	Quality of Life (Arm 1 vs. Arm 2)				Quality
								Scale / Test	Global QoL	Vitality/Fatigue	Other Measures of QoL	
Drueke, 2006 [1]	603	3-4	36		ESA High 13-15 (13.4)	ESA Low 10.5-11.5 (11.6)	CVD event	SF-36 (at 12 months)		Vitality: +	General health: + Mental health: + Physical function: + Physical Role: + Social function: +	A
		11.6						SF-36 (at 24 months)		Vitality: +	General Health + Other 4 Scales: NS	
Ritz, 2007 [5]	172	1-3 / 11.9	15		ESA High 13-15 (13.5)	ESA Low 10.5-11.5 (12.1)	Change in LV Mass	SF-36 (at 15 months)		Vitality: nd	General Health: +	A
Roger, 2004 [27]	155[a]	3-4	24		ESA High 12-13 (12.1)	ESA Low 9-10 (10.8)	Change in LV Mass	SF-36 (at 24 months)			Physical Health Component: NS Mental Health Component: NS	A
		11.2						RQoLP (at 24 months)	NS			
Singh, 2006 [2]	1432	3-4	16		ESA High 13.5 (12.7)	ESA Low 11.3 (11.4)	CVD event	LASA (nd when assessed)			NS	B
								KDQ (nd when assessed)		Fatigue: NS	NS	
		10.1						SF-36 (nd when assessed)		Vitality: NS	Physical Function: NS General Health: NS Bodily Pain: NS Social Functioning: NS Emotional Role: - Mental Health: NS Physical Role: NS	
Revicki,1995 [50]; Roth,1994 [30]	83	4-5	12		ESA 11.7 (11.2)	Control (9.0)	Health-Related Quality of Life[b]	Selected SIP Scales (at 12 months)			Home Management: NS Alertness Behavior: NS Social Interaction: NS	B
								Selected SF-36 Scales (at 12 months)		Vitality: +	Physical Function: + Role Function: NS Health Distress: NS	
								QoAL (at 12 months)			Life Satisfaction: NS	
		8.9						CESDS (at 12 months)			Depression: NS	
								Sexual Dysfunction Interview (at 12 months)			NS	

Author, Year	N	CKD Stage / Baseline Hb (g/dL)	Follow-up months	Applic-ability	Arm 1 Mean Hb (g/dL) Target (achieved)	Arm 2 Mean Hb (g/dL) Target (achieved)	Primary Outcome of Study	Quality of Life (Arm 1 vs. Arm 2)				Quality
								Scale / Test	Global QoL	Vitality/Fatigue	Other Measures of QoL	
Rossert, 2006 [3]	390[c]	3-4 11.6	7.8		ESA High 13-15 (14.0)	ESA Low 11-12 (12.0)	GFR decline	SF-36 (after 4 months of stabilization)		Vitality: +	Physical Function: NS General Health: NS Bodily Pain: NS Social Functioning: NS Emotional Role: NS Mental Health: NS Physical Role: NS	C

Note: Studies newly included in update are shaded.

Annotations:

a. Excluded patients with unstable or poorly controlled angina, severe congestive heart failure (grade III-IV), severe chronic respiratory disease, symptomatic peripheral vascular disease, or a created arteriovenous fistula.

b. The interview incorporated dimensions of HRQL identified to cover the expected effects ESA therapy and anemia in pre-dialysis CKD patients based on review of medical literature and discussions with nephrologists and nurses. The intent was to comprehensively measure broad areas of functioning and well-being.

c. Quality of life follow-up was assessed in 177 patients with a median duration of 5.8 months between assessments.

Abbreviations: CVD: Cardiovascular disease; GFR: Glomerular filtration rate; LV: Left ventricular

Coding of Outcomes: Coding of comparison of study arm 1 versus study arm 2: "+" better, "−" worse (with reference to benefit for patient). NS: Not statistically significant; nd: Not documented.

Key for QOL Scales

36-item Medical Outcomes Study Short-Form Health Survey (SF-36) evaluates eight health-related aspects: physical function, social function, physical role, emotional role, mental health, vitality, bodily pain and general health perceptions. Each portion of the test is scored on a scale that ranges from 0 (severe limitation) to 100 (no limitation). Two summary scores can be obtained: the physical component summary score which included the following dimensions: physical functioning, role-functioning physical, bodily pain, and general health perceptions and the mental component summary score which includes the following dimensions: social functioning, role-function emotional, mental health, and vitality. Scores range from 0 to 100, a higher score indicating better QoL.

Center for Epidemiologic Studies Depression Scale (CESDS) has been used extensively in epidemiologic studies of the general community and chronic disease populations. It is scored from 0 to 60, with higher scores indicating a greater number of depression symptoms.

Kidney Diseases Questionnaire (KDQ) is validated in dialysis patients. Contains 26 questions divided into five sections: patient-specific physical symptoms, fatigue, depression, relationships and frustration. All questions are scored on a 7-point Likert scale (7=no problem, 1=severe problem).

Linear Analogue Self-Assessment (LASA) questionnaire is a brief measurement tool consisting of 3 questions that evaluate energy level, daily activity, and overall QOL. It uses a 100-mm linear analogue scale for responses; the opposite ends represent the negative and positive extremes for each measured variable, with 0 being the lowest score and 100 being the highest (best HRQOL). This tool is easy to use and takes 1 to 2 minutes to complete. Patients draw a line on the 100-point scale to reflect their perceived QOL, with the score being measured as the number of millimeters from the zero reference point. [Coates A, et al. On the receiving end--II. Linear analogue self-assessment (LASA) in evaluation of aspects of the quality of life of cancer patients receiving therapy. European Journal of Cancer & Clinical Oncology. 1983; 19(11):1633-7].

Quality of American Life Survey (QoAL) is a life satisfaction scale from Campbell et al. The Quality of American Life. New York, NY, Russell Sage Foundation, 1976.

Renal Quality of Life Profile (RQoLP), although renal-specific, is comprehensive in its own right (the construct coming from the patients themselves). Its perspective is social psychological consisting of five dimensions, namely eating and drinking, physical activity leisure, psychosocial aspects, and treatment effects, with each representing several QOL indicators. [Salak S. Quality-of-Life Assessment in Patients on Peritoneal Dialysis. Proceedings of the ISOD '95-The VIIth Congress of the ISPD. Peritoneal Dialysis International. 1996; Vol 16: Supplement 1].

Sickness Impact Profile (SIP) established generic health status measure of disability associated with chronic illness.

definitely is or is not any quality-of-life improvement in the higher Hb treatment arms.

Reference to *avoidance of transfusions* reflects the appraisal that higher compared with lower Hb targets are associated with a decrease in red blood cell transfusion rates in hemodialysis patients (Table 2). Assignment to Hb targets greater than 13 g/dL decreases, but does not eliminate, transfusions in hemodialysis patients.[14] Transfusion-related risks are discussed in detail elsewhere (CPR 3.4[56]).

Potential harms refers to evidence from RCTs suggesting that assignment to Hb targets greater than 13.0 g/dL may increase the risk of life-threatening adverse events. This evidence is discussed in detail in the rationale to statement 2.1.3.

The distinction between *Hb targets* and *achieved Hb levels* is fundamental to the development of this guideline. In considering information available to guide selection of Hb targets, we specifically excluded evidence from Hb levels *achieved* in RCTs or reported in observational studies. Whereas higher *achieved* Hb levels in patients assigned to similar *target* Hb levels is associated with decreased risk of mortality and hospitalization,[12,14,16-20] treatment assignment to *target* Hb levels greater than 13.0 g/dL may increase the risk of life-threatening cardiovascular events.

The consensus opinion of the Work Group that potential benefits, for improvement in HRQoL and avoidance of transfusion, and potential harms must each be considered, coupled with an absence of specific quantitative information to assist the practitioner in weighing each component, renders statement 2.1.1 a CPR.

RATIONALE FOR CPR 2.1.2

In dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL.

Evidence supporting the statement that in dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL includes results from 14 RCTs in dialysis patients and 15 RCTs in nondialysis patients and is presented in detail for each trial (Tables 2 to 5 and 8 to 10) and in summary for each outcome (Tables 6, 7, 11, and 12).

The evidence considered by the Work Group to support the statement is confined to results of between-group comparisons generated by intention-to-treat trials that randomly assigned patients to distinct Hb targets, including trials that used ESAs in both treatment arms and trials that used ESAs in 1 treatment arm and either placebo or no treatment in the control arm (Fig 1).

The practitioner approaches the decision to select a Hb treatment goal with the intent to treat the individual patient and should expect that the achieved Hb level will vary considerably from the intended Hb target. To develop these guidelines and recommendations, we therefore appraised only evidence that was generated from intent-to-treat analyses of trials in patients randomly assigned to either higher or lower Hb targets.

The evidence base for the statement *the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL* includes results from trials that examined Hb targets from 6 to 16 g/dL (Tables 2 to 5 and 8 to 10; Fig 1). Early RCTs differ substantially from later RCTs in both size and Hb targets. RCTs conducted before 1998 are characterized by smaller study size, upper Hb targets in the range of 10 to 13 g/dL, and lower Hb targets that reflect assignment to placebo or no-treatment control. Trials published in 1998 and thereafter are characterized by larger study size, higher Hb targets in the range of 12 to 16 g/dL, and lower Hb targets between 9 and 12 g/dL. In more recent trials, by comparison, Hb baseline values are higher than those seen in early trials. Moreover, recent RCTs set lower targets at Hb levels well above those in earlier trials, in which patients in the control arm were assigned to placebo or no-treatment control groups. Both effects combine to render differences between Hb targets smaller in more recent trials.

In the statement *the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL,* the Work Group used the word *target* to distinguish between a Hb target and an achieved Hb level. In hemodialysis patients receiving ESA therapy with a Hb target in the range of 11.0 to 12.0 g/dL, the proportion of patients who achieve Hb levels from 11.0 to 12.0 g/dL in a

Table 10. Summary Table of RCTs Comparing Different Hb Targets on Non-CVD/Mortality Adverse Event Rates in the ND-CKD Population

Author, Year	N	CKD Stage	Description of Intervention	Follow-up (mo)	Arm 1 Mean Hb (g/dL) Target (Achieved)	Arm 2 Mean Hb (g/dL) Target (Achieved)	Adverse Events (Arm 1 vs. Arm 2)			
							BP change or Hypertension		Any non-CVD/ mortality AE[a]	
							Definition	Outcome	D/C of Drug or Withdraw (N / arm)	Reason for D/C or Withdraw
Singh, 2006 [2]	715 717	3-4	Initially received 10,000 U ESA SC weekly for 3 weeks; Subsequent ESA permitted every other week if Hb level was stable	16	ESA High 13.5 (12.7)	ESA Low 11.3 (11.4)	Mean SBP from baseline to the end of the study	↓2.3 mm Hg vs. ↓2.6 mm Hg (NS)	147 vs. 160	nd (not for KRT)
Drueke, 2006 [1]	301 302	3-4	Initial dose of ESA 2000 IU SC weekly dose. Dose adjustments to achieve target were permitted	36	ESA High 13-15 (13.4)	ESA Low 10.5-11.5 (11.6)	HTN	89 vs. 59 (30% vs. 20%) P=0.005	17 vs.10 NS	nd[b]
Ritz, 2007 [5]	88[c] 82[c]	1-3	SC ESA 2000 IU once weekly SC ESA 2000 IU once weekly if Hb <10.5 g/dL	15	ESA High 13-15 (13.5)	ESA Low 10.5-11.5 (12.1)	HTN	15 vs. 9 (17% vs. 11%)	0	---
Levin, 2005 [26]	85 87	3-4	SC ESA 2000 IU once weekly SC ESA 2000 IU once weekly if Hb <9.0 g/dL	24	ESA High 12-14 (12.8)	ESA Low 9-10.5 (11.5)	Individuals with at least 1 recorded BP > 140/90[d]	51% vs. 54%	nd	---
Roger, 2004 [27]	75 80	3-4	SC ESA SC ESA if Hb <9 g/dL	24[e]	ESA High 12-13 (12.1)	ESA Low 9-10 (10.8)	2 yr adjusted mean SBP and DBP between high and low ESA arms	Systolic: NS Diastolic: 81 vs. 78 P=0.009	0 vs. 3	nd
Roth,1994 [30]	43 40	1-3	SC ESA 50 IU/kg/wk, which could be increased by 75 IU/kg/wk; adjusted monthly Placebo	12	ESA 11.7 (11.2)	Placebo (8.7)	Reported Hypertension Not otherwise specified	26% vs. 10%	1 vs. 0	Individual with nausea, vomiting, GI bleed
Gouva, 2004 [6]	45 43	3-5	SC ESA 50 U/kg once weekly SC ESA 50 U/kg once weekly if Hb <9.0 g/dL	22.5	ESA Early 13 (12.9)	ESA Late[f] 13 (10.3)	HTN BP Change	1 vs. 1 NS	---	---
Kleinman, 1989 [43]	7 7	1-3	SC ESA 100 IU/kg TIW Placebo	3	ESA 12.7-13.3 (11.9)	Placebo (9.4)	ΔAnti-HTN medication over the 3-month & ΔMean SBP, DBP during study	NS	0	---

Table 10 (Cont'd). Summary Table of RCTs Comparing Different Hb Targets on Non-CVD/Mortality Adverse Event Rates in the ND-CKD Population

Rossert, 2006 [3]	195 195	3-4	Initial dose of ESA was 25-100 IU/kg. Therapy was given in weekly SC doses. Dose adjustments were permitted in steps of 4 weeks as needed to achieve target Hb level, with a permitted increase in weekly dose of 25 IU/kg.	36	ESA High 13-15 (13.0)	ESA Low 11-12 (11.8)	HTN	26 vs. 22 (13% vs. 11%) NS	6 vs.6	PRCA (N=2 in ESA high group), angina, pruritus
Macdougall, 2007 [4]	65 132	2-5	SC ESA 1000 U twice weekly SC ESA 2000 U thrice weekly if Hb <9.0 g/dL	36	ESA High 11 (11)	ESA Low 9-11 (10.5)	HTN	14 vs. 9 (22% vs. 7%)		
Clyne, 1992 [41]	12 8	4-5	ESA dose of 300 IU/kg maintained until Hct ↑10% of initial value or stabilized at Hct >30% Control	3	ESA 10.0 (11.7)	Control (9.4)	↑ in SBP by 10 mmHg or more or ↑ in DBP by 5 mmHg or made adjustments Anti-HTN medications	67% vs. 38%	4 vs. 0	ESA stopped until BP controlled
Lim, 1989 [45]	4 4 3 3	4-5	IV ESA 50, 100 or 150 IU/kg TIW Placebo	2	ESA 150 (13.7)	ESA 100 (12.0)	ESA 50 (11.7)	Placebo (8)	–	–	0 vs. 0 vs. 0 vs. 1	Seizure
Watson, 1990 [53]	5 6	5	SC ESA 100 IU/kg TIW Placebo	3	ESA 12.6 (11.7)		Placebo (8.7)		Mean BP during trial	No increase with ESA treatment	2 vs. 0	Patients withdrew because of suspicion of acceleration of renal failure
Abraham, 1990 [35]	4 4	3-5	IV or SC ESA 50 -150 IU/kg TIW Placebo	1.9	ESA 12.3-13.3 (12.3)		Placebo (9.6)		Increase in Anti-HTN medications	50% vs. 50%	nd	---

Note: Studies newly included in update are shaded.
Annotations:
a. Any non-CVD/mortality related adverse event that required discontinue of drug or resulted in withdrawal from study.
b. 12 of the 127 (9%) kidney replacement therapy patients in the High ESA group and 8 of the 111 (7%) kidney replacement therapy patients in the Low ESA group experienced a thrombotic event.
c. Two patients from a single center were randomly assigned, but were excluded from all analysis because the center was closed due to major violation of Good Clinical Practice guidelines.
d. Statistically significant difference in Δ DBP between arms (P = 0.027). However, baseline DBP was higher in Late ESA group. There were 4 episodes of hypertension as an adverse event. None were attributed to the study drug and all were resolved.
e. Or until KRT.
f. Because no patient in the deferred arm group had their Hb fall to <9 g/dL, they were not treated with EPO and are considered to be a control group.
Abbreviations: AE: Adverse events; Anti-HTN: Anti-hypertensive; BP: Blood pressure; D/C: Discontinuation; DBP: Diastolic blood pressure; GI: Gastrointestinal; HTN: Hypertension; KRT: Kidney replacement therapy; MAP: Mean arterial blood pressure; PRCA: Pure red cell aplasia; SBP: Systolic blood pressure.
Coding of Outcomes:
NA: Not applicable; nd: Not documented; NS: Not significant.

single month may be 30% or less.[21,22] Moreover, achievement of a Hb level within the 11.0- to 12.0-g/dL target in hemodialysis patients is transitory. More than 90% of patients experience cyclical Hb excursions averaging 10.3 weeks in duration and 2.5 g/dL in amplitude.[23] In part because of these fluctuations, approximately 50% of patients who achieve a Hb level in a 11.0- to 12.0-g/dL target range in 1 month will show Hb results greater or less than that range in the subsequent month.[21,22] Given the variability in Hb levels observed in clinical practice, the width of a Hb interval that would encompass 95% of Hb results in a population of dialysis patients undergoing ESA therapy could be as high as 5.6 g/dL.[24] Accordingly, to ensure that no more than 2.5% of patients exceed a Hb target of 12.0 g/dL, a target range designed to include 95% of patients would have a lower Hb limit of 6.4 (that is, 12.0 minus 5.6) g/dL.

In the statement *the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL,* the word *generally* emphasizes the need to maintain flexibility in medical decision making given the breadth of variability between patients' individual needs, values, functional status, disease burden, prognosis, and responsiveness to ESA therapy (Rationale for CPR 2.1.1).

In the statement *the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL,* the 2 specific values *11.0 g/dL* and *12.0 g/dL* define inclusively either a single Hb target range (11.0 to 12.0 g/dL) or a range of possible single-point Hb targets between 11.0 and 12.0 g/dL; entail unavoidable subjectivity in selecting Hb cutoff values; explicitly exclude reference to *achieved* Hb levels; and together reflect the efforts of the Work Group to balance the potential quality-of-life benefits and avoidance of transfusion gained by ESA therapy against the potential harm suffered by patients with Hb targets greater than 13 g/dL.

Available RCTs illustrate the distinction between a Hb target range[1,3,5,26,27] and a discrete Hb target (Fig 1).[2,14]

The lack of information to support specific Hb cutoff values in defining an optimum Hb target renders statement 2.1.2 a CPR.

Table 11. Evidence Matrix of Study Quality by Outcome for RCTs Comparing Different Hb Targets in the ND-CKD Population

Outcome	Methodological Quality								
	A			B			C		
	Author, Year	N	F/U (mo)	Author, Year	N	F/U (mo)	Author, Year	N	F/U (mo)
All Cause Mortality	Singh, 2006	1432	16	Gouva, 2004	88	22.5	Rossert, 2006	390	7.8
	Drueke, 2006	603	36	Kuriyama, 1997	73	14-36	Macdougall, 2007	197	22
	Levin, 2005	172	24	Kleinman, 1989	14	3	Lim, 1989	14	2
	Roth, 1994; Revicki, 1995	83	11						
Non-Fatal CV Events	Singh, 2006	1432	16	Kleinman, 1989	14	3	Rossert, 2006	390	7.8
	Drueke, 2006	603	36						
	Ritz, 2007	172	15						
	Levin, 2005	172	24						
	Roth, 1994; Revicki, 1995	83	11						
LVH	Drueke, 2006	603	36				Macdougall, 2007	197	22
	Ritz, 2007	172	15						
	Levin, 2005	172	24						
	Roger, 2004	155	24						
QoL	Drueke, 2006	603	36	Singh, 2006	1432	16	Rossert, 2006	390	7.8
	Ritz, 2007	172	15	Roth, 1994; Revicki, 1995	83	11			
	Roger, 2004	155	24						
Transfusion Requirement				Drueke, 2006	603	36			
				Roth, 1994; Revicki, 1995	83	11			
Kidney Disease Progression	Singh, 2006	1432	16	Gouva, 2004	88	22.5	Rossert, 2006	390	7.8
	Drueke, 2006	603	36	Kuriyama, 1997	73	14-36	Macdougall, 2007	197	22
	Ritz, 2007	172	15	Kleinman, 1989	14	3	Clyne, 1992	20	3
	Levin, 2005	172	24				Lim, 1989	14	2
	Roger, 2004	155	24				Watson, 1990	11	3
	Roth 1994; Revicki, 1995	83	11				Abraham, 1990	8	2-3
Seizures							Lim, 1989	14	2
							Watson, 1990	11	3
Blood Pressure Change	Singh, 2006	1432	16	Gouva, 2004	88	22.5	Rossert, 2004	390	7.8
	Drueke, 2006	603	36	Kleinman, 1989	14	3	Macdougall, 2007	197	22
	Ritz, 2007	172	15				Clyne, 1992	20	3
	Levin, 2005	172	24				Watson, 1990	11	3
	Roger, 2004	155	24				Abraham, 1990	8	2-3
	Roth, 1994; Revicki, 1995	83	11						

Note: Studies newly included in update are shaded.

Table 12. Evidence Profile of RCTs Comparing Different Hb Targets in the ND-CKD Population

Outcome	# of Studies & Study Design	Total N of Patients Randomized	Methodologic Quality of Studies[a]	Consistency across Studies	Directness of the Evidence including Applicability	Other Considerations	Summary of Findings: Quality of Evidence for Outcome	Summary of Findings: Qualitative Description of Effect Size (Higher versus Lower Hb Targets)	Summary of Findings: Importance of Outcome
All Cause Mortality	10 RCTs	3066	No limitations	No important inconsistencies	No major uncertainty	None	High	No benefit.	High
					Some uncertainty[c]		Moderate	Harm: Singh HR: 1.48 (0.97;2.27), Drueke HR: 1.51 (0.87;2.63)	
CVD (including Mortality)	7 RCTs	2866	No limitations	No important inconsistencies	No major uncertainty	None	High	No benefit.	High
					Some uncertainty[d]		Moderate	Harm: Singh HR: 1.34 (1.03;1.74), Drueke HR:1.28 (0.69;1.89)	
LVH	5 RCTs	1299	No limitations	No important inconsistencies	No major uncertainty	None	High	No benefit.	Moderate
QoL	6 RCTS	2835	No limitations	Some inconsistency[e]	Some uncertainty[f]	None	Low	Potential benefit, but inconsistent findings with four studies showing some benefit for QoL and two showing no benefit. There was inconsistency across studies regarding which subscales showed statistically significant benefit. In one study that showed benefit for QoL in 6/6 subscales at 1 year, 4 subscales lost statistical significance at 2 years. Three out of four studies showing some benefit for QoL tested vitality and found benefit in this subscale. In contrast, one of the two studies which showed no benefit for any QoL scale also assessed vitality.	High
Transfusion Requirement	2 RCTs	686	Some limitations[b]	No important inconsistencies	Some uncertainty[g]	None	Low	Potential benefit.	Moderate
Kidney Disease Progression	15 RCTs	3432	No limitations	No important inconsistencies among large high quality studies	Some uncertainty[h]	None	Moderate	No benefit, based on large high quality studies.	High
Seizures	2 RCTs	25	Major limitations	N/A	Some uncertainty[i]	Sparse data	Very low	No harm; potential benefit. 0 vs. 2 individuals.	Moderate
Blood Pressure Change (Hypertension)	13 RCTs	3345	No limitations	No important inconsistencies	Some uncertainty[j]	None	Moderate	Potential harm requiring increased intensity of monitoring and treatment.	Moderate
Total N of Patients	15 RCTs	3432							

Balance of Benefit and Harm:
Likely benefit for QoL, in particular vitality, with higher Hb targets.
Harm for mortality and cardiovascular disease with Hb targets > 13 compared to < 11.5 g/dL.
Uncertain trade-offs at each Hb target, but likely increasingly unfavorable risk-benefit-ratio with increasing Hb targets.

Quality of Overall Evidence:
Low for QoL
Moderate for other important outcomes

Table 12 (Cont'd). Evidence Profile of RCTs Comparing Different Hb Targets in the ND-CKD Population
Abbreviations: BP: Blood pressure; LVH: Left ventricular hypertrophy; QoL: Quality of Life.
Annotations:
a. See Evidence Matrix for quality grades of individual studies assessed for each outcome.
b. Quality for the evidence for this particular outcome is lower than the quality of the studies for their primary outcome.
c. Outcome not statistically significant in primary studies.
d. In Singh study, statistical significance of the primary outcome is lost after multivariate adjustment for CHF, atrial fibrillation/flutter, serum albumin, reticulocyte count, and age [HR 1.24 (95% CI: 0.95;1.62), P=0.111].
e. See qualitative description of effect size.
f. Unable to assess the comparability of baseline QoL or compare the magnitude of the changes across different studies because of incomplete reporting.
g. Indications for transfusions were not per protocol.
h. Different degrees of blood pressure control and dietary modifications as concomitant therapies.
i. Seizures were not primary or secondary outcomes of the studies.
j. Inconsistent reporting and use of different definitions for HTN. Some uncertainty about clinical relevance of reported changes in BP.

RATIONALE FOR CPG 2.1.3

In dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL.

The conclusion that *the Hb target should not be greater than 13.0 g/dL* is based on analysis of all-cause mortality and adverse cardiovascular events in patients with CKD assigned to Hb targets greater than 13.0 g/dL compared with lower Hb targets for ESA therapy (Tables 2, 4, 6 to 8, and 10 to 12). These trials evaluated whether a Hb target greater than 13.0 g/dL would prevent adverse cardiovascular events or mortality, testing the specific hypothesis that rates of fatal and nonfatal cardiovascular events or all-cause mortality in patients assigned to Hb targets greater than 13 g/dL differed from those in patients assigned to lower targets. None of the trials showed a benefit of higher Hb targets for these outcomes. Similarly, there is no evidence from the trials performed to date that higher Hb targets have a beneficial effect on left ventricular dimensions. With the exception of 1 small trial,[6] RCTs also failed to show a benefit of higher Hb targets in terms of reducing the progression of kidney disease.

In developing the statement that *in dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL,* the Work Group considered a meta-analysis performed by the ERT. The meta-analysis included published trials that reported results of all-cause mortality and adverse cardiovascular events in patients assigned to higher compared with lower Hb targets.

In patients with nondialysis CKD (predominantly stages 3 and 4), combining mortality outcomes from 8 studies with 3,038 individuals yields a risk ratio (RR) of 1.01 (95% confidence interval [CI], 0.63 to 1.61; Fig 2, left panel). Most deaths derive from the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)[2] and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)[1] studies, which together contribute 87% of the weight. Ordering studies chronologically in cumulative meta-analysis (Fig 2, right panel) shows that an earlier (1994 to 2005) nonsignificant trend favoring higher Hb targets

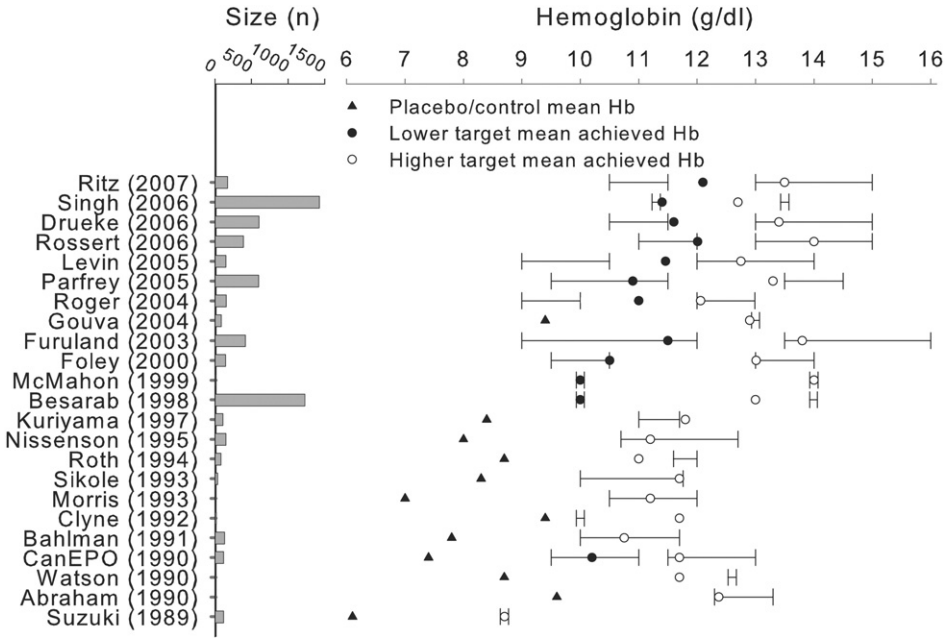

Figure 1. Randomized controlled trials comparing lower with higher hemoglobin (Hb) target levels. Data are represented as target Hb (whiskers), achieved mean Hb for patients assigned to lower (closed circles) or upper (open circles) Hb targets, and placebo or untreated control (filled triangles). Study size (N) is indicated by the bars on the left. In several large trials published since 1998, achieved mean Hb levels were not within the intended target.

resolves to a point estimate of 1 after addition of the 2 later largest studies.

In patients with nondialysis CKD (predominantly stages 3 to 4), combining adverse cardiovascular events from 6 studies in 2,850 individuals yields an RR of 1.24 (95% CI, 1.02 to 1.51; Fig 3; left panel). Again, most events derive from the primary composite outcomes of the CHOIR[2]

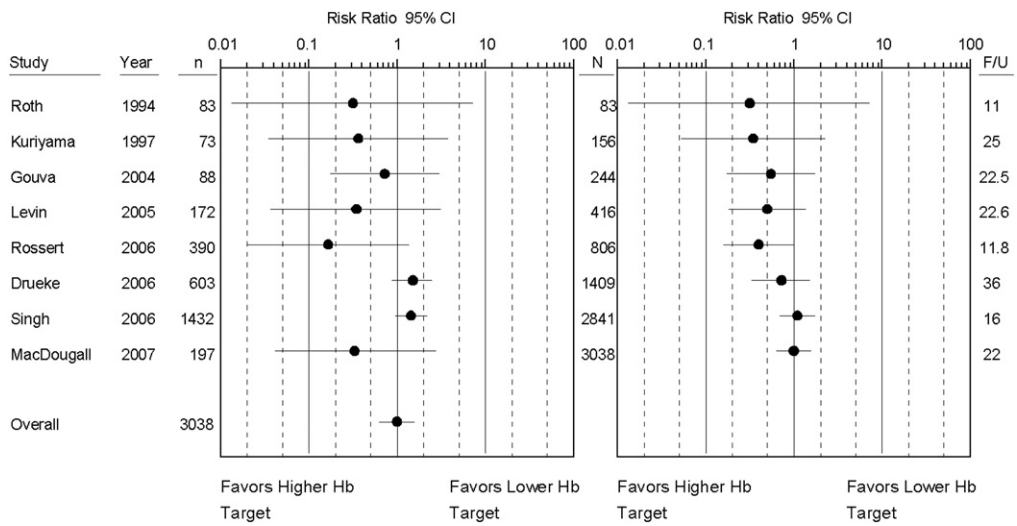

Figure 2. Relative mortality risk for assignment to higher hemoglobin (Hb) treatment targets in patients with nondialysis chronic kidney disease. Point estimate, 1.01 (95% confidence interval [CI], 0.63 to 1.61), standard (left) and cumulative (right) meta-analysis plots according to random-effects model. Abbreviations: n, number of patients in each study; N, number of patients in cumulative meta-analysis; F/U, mean follow-up duration of study in months.

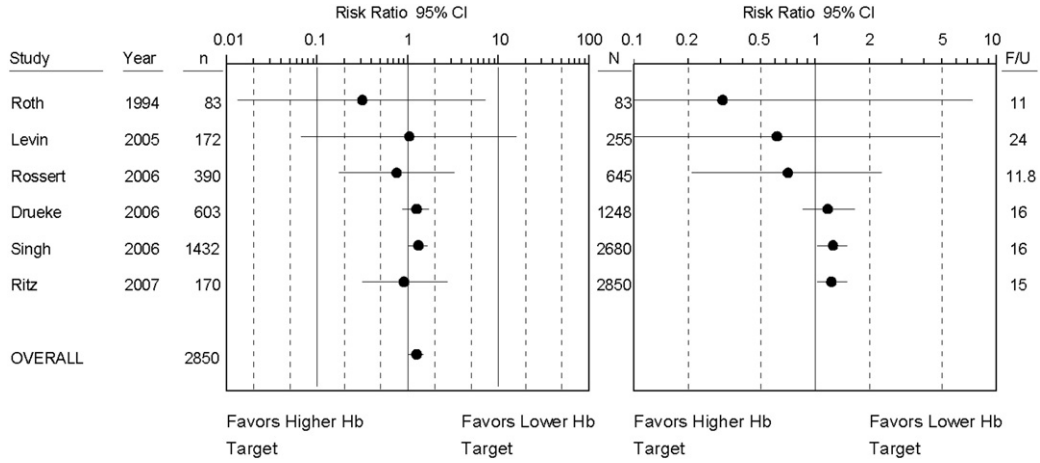

Figure 3. Relative risk of adverse cardiovascular events for assignment to higher hemoglobin (Hb) treatment target in patients with nondialysis chronic kidney disease. Point estimate, 1.24 (95% confidence interval [CI], 1.02 to 1.51), standard (left) and cumulative (right) meta-analysis plots according to random-effects model. Abbreviations: n, number of patients in each study; N, number of patients in cumulative meta-analysis; F/U, mean follow-up duration of study in months.

and CREATE[1] studies, which include deaths from any cause as a first event. Together, these 2 studies contribute 94% of the weight in this meta-analysis. The cumulative meta-analysis (Fig 3; right panel) shows that with the addition of these 2 studies, the point estimate moves from favoring higher Hb targets to favoring control treatment, a finding that becomes statistically significant.

In dialysis patients with CKD, combining mortality outcomes from 4 studies with 2,391 individuals yields an RR of 1.12 (95% CI, 0.91 to 1.37; Fig 4; left panel). Most deaths derive from the study by Besarab et al,[14] which contributes 81% of the weight.

In dialysis patients with CKD, combining adverse cardiovascular events from 3 studies in 1,975 individuals yields an RR of 1.14 (95% CI, 0.79 to 1.64; Fig 5; left panel). Again, most events derive from the study by Besarab et al,[14] which contributes 88% of the weight.

We compared both our methods and our results with those reported in another recent meta-analysis.[28] We included RCTs with 6 months or longer follow-up without restriction on study size, whereas the previous meta-

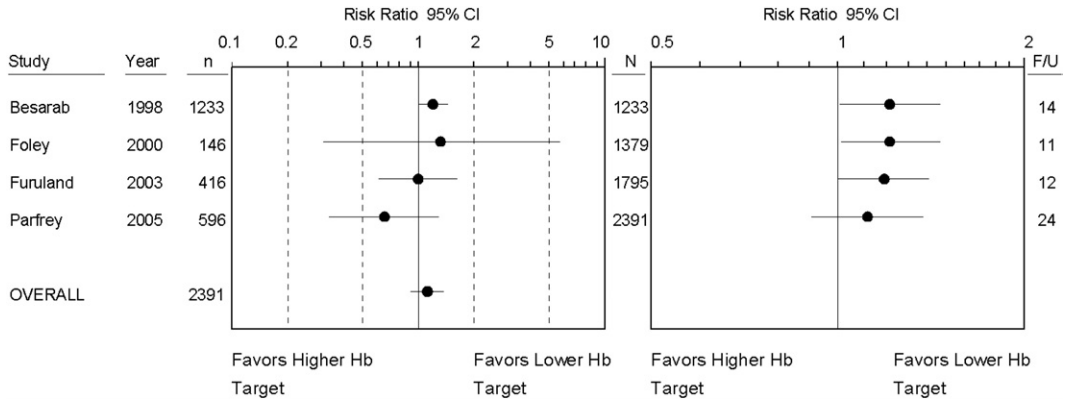

Figure 4. Relative mortality risk for assignment to higher hemoglobin (Hb) treatment target in patients with chronic kidney disease undergoing dialysis. Point estimate, 1.12 (95% confidence interval [CI], 0.91 to 1.37), standard (left) and cumulative (right) meta-analysis plots according to random-effects model. Abbreviations: n, number of patients in each study; N, number of patients in cumulative meta-analysis; F/U, mean follow-up duration of study in months.

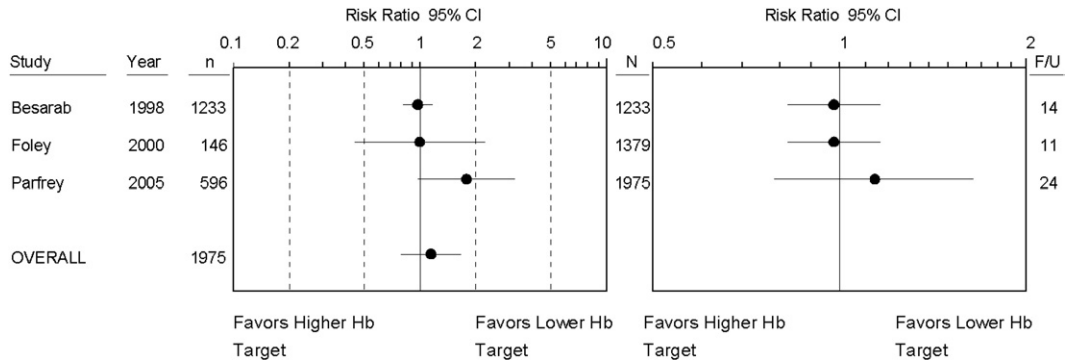

Figure 5. Relative risk of adverse cardiovascular events for assignment to higher hemoglobin (Hb) treatment target in patients with chronic kidney disease undergoing dialysis. Point estimate, 1.14 (95% confidence interval [CI], 0.79 to 1.64), standard (left) and cumulative (right) meta-analysis plots according to random-effects model. Abbreviations: n, number of patients in each study; N, number of patients in cumulative meta-analysis; F/U, mean follow-up duration of study in months.

analysis included RCTs with 12 weeks or longer follow-up and greater than 100 subjects; our statistical model was more conservative (random-effects model always versus fixed-effects model if no statistical heterogeneity), and unlike the previous report, we did not pool studies in dialysis patients with those from nondialysis patients given the dissimilarities between these 2 target populations in ESA administration, Hb monitoring, and the presence or absence of dialysis. Finally, for cardiovascular outcomes, the previous meta-analysis included only myocardial infarctions, whereas we combined all cardiovascular disease events, including all events from the primary composite outcome in both CHOIR and CREATE. Thus, our definition of cardiovascular disease as an outcome was less precise, but more inclusive, than that of the other meta-analysis.

For mortality, our meta-analysis, like the recently published meta-analysis, showed no statistically significant difference for assignment to higher versus lower Hb level in either subgroup of dialysis or nondialysis patients. In nondialysis patients with CKD, we showed a RR closer to 1.0 and a wider CI (RR, 1.01; CI, 0.63 to 1.61 versus 1.33; CI, 0.98 to 1.81) than that previously reported because our analysis included results from 4 studies[4,6,29,30] not included in the other meta-analysis. These 4 studies added 441 patients and 18 deaths (5 in the upper Hb arms and 13 in the lower Hb arms). In patients with CKD on dialysis, the 2 meta-analyses included the same studies and yielded essentially identical results (RR, 1.12; CI, 0.91 to 1.37 versus 1.11; CI, 0.94 to 1.31, current versus previous meta-analysis).

In appraising the overall evidence, the Work Group considered mortality, cardiovascular events, and HRQoL as outcomes of high importance. The Work Group rated the evidence showing a trend toward greater cardiovascular events in dialysis and nondialysis patients assigned to Hb targets greater than 13.0 g/dL to be of moderately high quality for showing harm and of high quality for showing lack of benefit. The Work Group considered the HRQoL benefits in patients assigned to higher Hb targets as low-quality evidence based on the limitations of reported HRQoL evidence (see the following section, Limitations of Evidence). The conclusion that *in dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL* reflects the Work Group's judgment that the possibility to cause harm weighs more heavily than the potential to improve quality of life and to decrease transfusions.

The appraisal of the Work Group that the evidence for harm is moderately high renders statement 2.1.3 a moderately strong evidence-based CPG. As discussed in more detail elsewhere (Methods), the designation *moderately strong* acknowledges the possibility that further research may alter either the appraisal of the quality of the evidence or the estimate of the effect size and thus result in a change in the guideline. The designation *moderately strong* therefore does not impede continued investigation.

LIMITATIONS OF EVIDENCE

Patient Outcomes

Most reports provide incomplete information with respect to HRQoL findings. Complete reporting should include point estimates and assessments of dispersion of HRQoL scores for each domain at each interval measured, by Hb target assignment.

Meta-analysis of cardiovascular events in dialysis patients is dominated by the results of the study by Besarab et al[14] (1998), and in nondialysis patients with CKD, by the results of the study by Singh et al[2] (2006). Although all RCTs have limitations, major limitations of those trials dominating meta-analysis results are of particular importance. In both Besarab et al[14] (1998) and Singh et al[2] (2006), the decision to prematurely stop the trial was made before the efficacy or futility boundaries were crossed. In Singh et al[2] (2006), compared with the group assigned to the lower Hb treatment target, the group assigned to the higher Hb target showed at baseline a statistically greater proportion of patients with a history of hypertension and coronary artery bypass graft. A report posted by the study sponsor (PROCRIT®: Clinical Study Report PR00-06-014 (CHOIR) SYNOPSIS, 12 September 2006; available at: www.clinicaltrials.gov, last accessed January 12, 2007) indicates that patients assigned to the higher Hb treatment arm also had a significantly greater severity of congestive heart failure (CHF) at baseline. The results of a multivariate analysis, included in this report, indicate that after adjustment for baseline conditions (CHF by National Health and Nutrition Examination Survey CHF score, atrial fibrillation/flutter, serum albumin level, reticulocyte count, and age), the relationship between treatment assignment and primary composite outcome events is no longer statistically significant (hazard ratio, 1.24; 95% CI, 0.95 to 1.62; $P = 0.11$ compared with the unadjusted hazard ratio of 1.34; 95% CI, 1.03 to 1.74; $P = 0.03$ reported in the publication[2]). Thus, although a trend toward greater risk of events in the higher Hb arm remains after adjustment for baseline imbalances, the finding of statistical significance is not robust and the change in the point estimate and CI with adjustment casts doubt on the success of randomization. Quality of the CHOIR study is further limited by censoring at the initiation of dialysis and by lack of information on when HRQoL was measured. One of the limitations of the CREATE trial is that the event rate was much lower than predicted; thus, the power to detect a difference in event rates was decreased.

Several studies are characterized by a failure to achieve the higher Hb target in the majority of patients at any time (Fig 1), and no study provided description of the Hb cycling around the achieved mean for either the higher or lower target treatment. In addition, several studies using subcutaneous (SC) epoetin alfa were prematurely terminated when reports of pure red cell aplasia emerged.

A further limitation of the currently available evidence is that important CKD subgroups have not been specifically studied or are not well represented in the existing studies, including children and young adults and patients with ischemic vascular disease or chronic lung disease.

Finally, trials published to date have not been designed to distinguish between the potential effects of Hb targets, ESA doses, and concomitant anemia therapy, including iron.

Implementation Issues

In clinical practice, medical decision making in the management of anemia at the level of the individual patient requires selection of the starting Hb level; choice of the initial dose, route, and frequency of ESA therapy; determination of Hb monitoring frequency; the aspiration to reach a threshold Hb or target Hb level; determination of the frequency and size of sequential ESA dose adjustments in relationship to a threshold Hb or target Hb level; and an interpretation of previous therapeutic trends and responsiveness to ESA therapy. Although available RCTs used either a *range* or a *discrete value* to represent the aspirational *target Hb* (Fig 1), published reports include little additional information to assist medical decision making. Specifically, information is lacking about how ESA and iron therapy were actually adjusted based on achieved Hb levels and how closely actual adjustments adhered to study protocol. Comparative information is similarly lacking to determine optimum frequency for monitoring Hb, the number of Hb results needed to reliably measure clinical performance,

or the expected day-to-day within-patient variability in Hb levels in different patient populations (nondialysis CKD, hemodialysis CKD, and peritoneal dialysis CKD).

Aiming for a Hb target within narrow boundaries in ESA-treated patients requires frequent dose adjustments in many patients. More than 60% of patients receiving ESA therapy with Hb targets between 11.0 and 12.0 g/dL require between 6 and 9 dose changes per year.[23] No comparative information is available to support evidence-based guidelines for the dosing and administration of ESA therapy to achieve a target Hb. However, descriptive information from quality improvement interventions and RCT treatment protocols may be helpful to practitioners in weighing options that may best fit patient needs and practice settings.

In a 24-month study examining the effectiveness of a computer-assisted decision support algorithm for anemia management in hemodialysis patients, epoetin therapy (administered SC thrice weekly) was adjusted monthly in response to monthly Hb determinations by using stepwise ESA dosing adjustments, a lower Hb threshold below which ESA doses were increased, and an upper Hb threshold above which ESA downward adjustments were made.[31] Epoetin doses were adjusted upward by 1,000 U/dose to achieve threshold Hb levels greater than 11.0 g/dL and downward by 1,000 U/dose once a month when Hb results exceeded predetermined ceilings (12.0, 13.0, and then 12.0 g/dL at intervals during the study) or by 50% if the Hb level exceeded 15.5 g/dL. In patients receiving epoetin doses near the mean for the study population (ranging from 9,800 to 6,400 IU/wk during the course of the study), a stepwise increase or decrease of 1,000 IU/dose represented on average a 10% to 16% change in epoetin dose. Although the ceiling Hb level alternated in 3 time periods between 12.0 and 13.0 g/dL, median achieved Hb remained stable, as did Hb variability around the median, with approximately 50% of achieved Hb results within 1.0 g/dL greater and less than the median at each monthly interval.[31] A similar algorithm was used to adjust epoetin and darbepoetin doses given SC weekly.[32]

In hemodialysis patients, withholding ESA doses for a Hb level greater than target range is associated with subsequent downward Hb excursions,[23] often less than target range, consistent with the biology of erythropoietin as a cell-salvage agent.[56] The time between holding ESA doses and return of Hb to target range is variable and unpredictable. In hemodialysis patients with Hb values greater than 14.0 g/dL, the median time for Hb to return to 12.0 g/dL or less after holding of a SC-administered ESA is 7 weeks for long-acting ESAs (range, 2 to 13 weeks) and 9 weeks for short-acting ESAs (range, 6 to 13 weeks); the difference between long and short-acting ESAs is not significant.[33]

The effect of initiating a fixed monthly downward epoetin dose adjustment in response to achieved Hb levels greater than 13.0 g/dL was recently examined using the database of a large US dialysis provider.[22] At baseline, approximately 35% of 95,000 patients receiving epoetin therapy showed average 3-month Hb results within the target range of 11 to 12 g/dL, and 15% showed average 3-month Hb results greater than 13.0 g/dL. When a computer-mandated 25% monthly dose decrease was initiated for end-of-month Hb results greater than 13.0 g/dL, percentages of patients with Hb values less than 11.0 and greater than 13.0 g/dL both increased. However, mean Hb level did not change.

The necessary ESA dose adjustment frequency may differ between initiation and maintenance of ESA therapy. In a randomized double-blind trial comparing a short-acting ESA with a long-acting ESA in hemodialysis patients previously receiving epoetin alfa, dose adjustments were made in 25% increments or decrements of the baseline dose, aiming to maintain individual Hb concentrations within -1.0 and $+1.5$ g/dL of their baseline values and within a range of 9.0 to 13.0 g/dL.[34] Approximately 70% of patients required dose adjustment in the 20-week titration period, and 50% required dose adjustment during the 8-week maintenance period. Both dose increases and dose decreases were required. No between-group differences were seen in frequency or direction of ESA dose change.

Taken together, these reports suggest that when the target Hb level is 11.0 to 12.0 g/dL, variability of achieved Hb levels around the target is high, the fraction of prevalent patients with achieved Hb levels within the target range is low, ESA dose titration is required frequently during maintenance therapy, and either 25% ESA dose

changes[34] or 10% to 16% dose changes can be an effective maintenance dose-titration strategy.[32] Clinical evidence is lacking about how to respond to achieved Hb levels greater than target range. Holding ESA doses may lead to steep downward Hb excursions and high amplitude Hb cycling.[23] On the other hand, flexibility in determining the size of the dose adjustment may be needed. Imposing a fixed 25% dose decrease in response to greater-than-target Hb levels appears to promote greater Hb variability and more greater-than-target Hb values in patients undergoing maintenance therapy.[22]

In practice, when the target Hb is 11 g/dL or greater or 11.0 to 12.0 g/dL, achievement of Hb levels greater than the 11.0-g/dL threshold or greater than the 11.0- to 12.0-g/dL range is associated with lower mortality and less frequent hospitalization rates compared with achievement of lower Hb levels, an observation that is consistent in prospective longitudinal cohort studies[16,18] and cross-sectional studies of large medical databases.[17,19,20] In patients treated in facilities with the same *target* Hb, associated mortality and hospitalization rates are 10% to 12% lower for every 1.0-g/dL greater facility mean *achieved* Hb level.[16] The same inverse relationship between achieved Hb and mortality and hospitalization also was seen in RCTs within assigned treatment arms (including arms with targets ≥ 13 g/dL).[12,14] Failure to show between-group benefits in mortality, hospitalization, and left ventricular hypertrophy in patients assigned to higher compared with lower Hb targets in RCTs (Tables 2 and 8) confirms that the relationship between higher achieved Hb and lower risk is not causal. However, the results are consistent with the conclusion that when the *target* Hb is greater than 11.0 g/dL or 11.0 to 12.0 g/dL, *achieved* Hb levels greater than the 11.0-g/dL threshold or greater than the 11.0- to 12.0-g/dL range, whether facility specific or patient specific, do not constitute increased risk to patients. In general, higher facility-specific and country-specific *achieved* mean Hb levels and a lower percentage of patients with achieved Hb less than target range are associated with increased ESA use.[16,25] However, adjustment for dose of ESA administered does not diminish the relationship between baseline Hb and mortality or hospitalization risk.[16]

Additional practical information on the use of ESA therapy to manage anemia in patients with CKD is provided in Section 3.1 of the KDOQI CPGs and CPRs for Anemia in CKD, published in May 2006.[56]

Measuring Performance

In general, a Hb target *range* suggests that ESA dose adjustment decisions are made by comparing the patient's achieved Hb with the selected Hb target. Although performance in managing to a Hb target can be expressed as the proportion of patients with Hb levels within the target range, in practice, only 30% of patients at any 1 time have an actual Hb level in the Hb target range of 11.0 and 12.0 g/dL when targeted to that range. The result of a single sampling in a single patient cannot be expected to lie within a narrow Hb target range (eg, Hb of 11.0 to 12.0 g/dL) or to equal a discrete point Hb target (eg, Hb of either 11.0, 11.5, or 12.0 g/dL). However, mean or median Hb levels of a group of patients or mean Hb levels of a single patient repeated over time would be expected to lie within a Hb target range or to approximate a discrete Hb target. In short, measures of clinical performance, to be clinically useful, must account for a high degree of within-patient and between-patient variability.

CPR FOR PEDIATRICS 2.1 HEMOGLOBIN TARGET

The Hb target is the intended aim of ESA therapy for the individual patient with CKD. In clinical practice, achieved Hb results vary considerably from the Hb target.

2.1.1 (FULLY APPLICABLE TO CHILDREN) In the opinion of the Work Group, selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual pediatric patient should include consideration of potential benefits (including improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events). (Clinical Practice RECOMMENDATION)

2.1.2 (FULLY APPLICABLE TO CHILDREN) In the opinion of the Work Group, in pediatric dialysis and nondialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. (Clinical Practice RECOMMENDATION)

2.1.3 (APPLICABLE TO CHILDREN, BUT NEEDS MODIFICATION) In dialysis and nondialysis patients with CKD receiving ESA therapy, the Hb target should not be greater than 13.0 g/dL. (Clinical Practice RECOMMENDATION)

BACKGROUND

We refer the reader to the prior rationale outlining the Work Group's understanding of the unique factors to be considered in the selection of the Hb target in the pediatric CKD population (reference 56, page S90). There continues to be a lack of evidence to support the assignment of benefits and harms to any given level of Hb for an individual child. This difficulty is compounded by age and sex variation in Hb values in children and the need to address metabolic, growth, and developmental issues in children that are not part of the adult data sets.

Furthermore, and as previously stated by the Work Group, we affirm the comments made regarding the choice of Hb target; in particular, that it should remain an opinion-based CPR and that any individual patient target should be chosen with consideration made for uniquely pediatric factors, including, but not restricted to, age- and sex-specific Hb distribution, neurocognitive development, school attendance, exercise capacity, and family support.

With respect to adult data regarding the safety of targeting Hb levels greater than 13.0 g/dL; although the Work Group acknowledges similar concerns might exist in children, there are currently no studies to support an increased risk at Hb levels at or greater than 13.0 g/dL in this group. However, given the evidence that is available in relation to increased risk of cardiovascular death and coronary artery calcification in older children/young adults with CKD, it would seem prudent to carefully weigh the individual child's likely benefit of an incremental increase in quality of life, school performance, or exercise tolerance from a Hb level greater than 13.0 g/dL, to their uncertain, but potentially devastating, risk of a myocardial event, stroke, or loss of venous access.

ANEMIA UPDATE METHODS

Criteria for Updating a Guideline and Updating a Systematic Review

An **update of a systematic review** of a guideline topic denotes an event with the aim to search for and identify new evidence to incorporate into a previously completed systematic review.[54] **Changes to guidelines** can be undertaken for correction of typographical or content errors. Such changes do not constitute an update because they do not allow for the possibility of new evidence being identified.[54]

In general, guidelines and the systematic reviews they are based on should be updated as scheduled. An earlier update of the systematic review on a particular guideline topic can be prompted if all of the following conditions are met:

- There is new evidence on important clinical outcomes.
- The evidence is from a study or studies that was or were adequately powered for the clinical outcome(s).
- The new evidence has the potential to change the grade for the quality of the evidence or change the assessment of the balance of benefits and harms.

Evidence from surrogate end point trials can prompt an update of a systematic review for a guideline if the criteria outlined by the "Users' Guide for a Surrogate End Point Trial" are met (see Table 13).[55] As an example, the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study[59] did not initiate an update of the systematic review for Guideline 3.2 on Iron Targets because the study examined a surrogate outcome (change in Hb) after short follow-up duration (6 weeks).

Methods Used for this Guideline Update

Process

For this guideline update, the Evidence Review Team (ERT) at Tufts-New England Medical Center in Boston, MA and the Work Group updated the systematic review of RCTs that compared the effect of targeting different Hb levels with ESA treatment. A detailed description of the methods can be found in the methods chapter of the 2006 Anemia guidelines.[56] The inclusion criteria were: RCTs in patients with CKD stages 1 to 5, with a minimum of 2-month follow-up duration. Outcomes of interest were all-cause mortality; cardiovascular, cerebrovascular, and peripheral vascular disease; left ventricular hypertrophy; quality of life; hospitalizations; progression of kidney disease; dialysis adequacy; hypertension; transfusions; and seizures.

An updated search conducted on December 7, 2006, with the previously used key words of KIDNEY and ANEMIA identified 639 citations of English-language studies indexed in MEDLINE after November 2004. Furthermore, the ERT searched the clinicaltrials.gov registration website to identify additional studies that might be completed. The search update resulted in the addition of 6 RCTs to the systematic review on this topic.[1-6] All were in patients not on dialysis therapy, mostly with CKD stages 3 to 4. The ERT also updated Table 1 of "ongoing studies" to show what trials will be completed in the future.

The new studies were critically appraised by the ERT. The ERT extracted the data from these studies and added them to the summary tables published in the KDOQI 2006 Anemia in CKD guidelines. Each study was graded with regard to its method quality. The Work Group experts reviewed and confirmed data and quality grades in the summary tables. The ERT and the Work Group members updated the evidence profiles for nondialysis patients following the modified Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach.[57, 60] The ERT tabulated an evidence matrix that provides an overview of the quality of the reviewed evidence. It tabulates all studies included in the review by type of outcome and quality.

A meeting of the original 2006 KDOQI Anemia guidelines Work Group members, the ERT, and NKF support staff was held in Dallas, TX, on February 2 and 3, 2007. Before the face-to-face meeting in Dallas, all Work Group members and the KDOQI Chair and Vice-Chair completed new financial disclosure statements. Based on these financial disclosure statements, the Work Group chose the KDOQI Vice-Chair to moderate the face-to-face meeting in Dallas. The Work Group reviewed the summary tables; evidence profiles; a FDA-approved prescribing information for ESAs current as of March 2005 (Appendix 1); and the table of ongoing studies (Table 1).

Table 13. Consideration for Appraisal of Surrogate Outcome Trials

Are the results valid?
• Necessary, but not sufficient: is there a strong, independent, consistent association between the surrogate end point and the clinical end point?
• Is there evidence from randomized trials in other drug classes that improvement in the surrogate end point has consistently led to improvement in the target outcome?*
• Is there evidence from randomized trials in the same drug class that improvement in the surrogate end point has consistently led to improvement in the target outcome?*
What were the results?
• How large, precise, and lasting was the treatment effect? Effect should be large, precise, and lasting to consider a surrogate trial as possible basis for offering patients the intervention.
Will the results help me in caring for my patients?
• Are the likely treatment benefits worth the potential harms and costs? Offer intervention on basis of surrogate data only if patient's risk of the target outcome is high, patient places a high value on avoiding the target outcome, and if there are no satisfactory alternative therapies.
*Answers to one or both of these questions should be "yes" for surrogate trial to be an adequate guide for clinical action.

It then deliberated on what guideline recommendation the expanded evidence base would support. The Work Group then drafted recommendations and graded the strength of the recommendations. The strength of a guideline recommendation is shown in parentheses after the guideline statement as "strong" or "moderately strong." A "Clinical Practice Recommendation" is followed by "CPR" in parentheses. Issues considered in the grading of the quality of the evidence and the strength of the recommendations were detailed in the rationale section corresponding to each statement.

The draft of the updated guidelines underwent refinement and internal review by the Work Group by using emails and conference calls, subsequent review by the KDOQI Advisory Board and the public in April 2007, followed by further revisions by the Work Group.

Grading of the quality of a study

A detailed description can be found in the methods section of the 2006 KDOQI Anemia guidelines.[56] Each study was graded with regard to its method quality mainly for its primary outcome and also for the quality-of-life outcome, if this was reported and was not the primary outcome. Table 14 shows the grading scheme for study quality.

Grading of the quality of evidence

The evidence profile recorded the assessment of the quality of evidence, the summary of the effect for each outcome, the judgment about the overall quality of the evidence, and a summary assessment of the balance of benefits and harms.[57]

The quality of a body of evidence pertaining to a particular outcome of interest was initially categorized based on study design (Table 15). For questions of interventions, the initial quality grade is "high" if the body of evidence consists of RCTs, "low" if it consists of observational studies, or "very low" if it consists of studies of other study designs. The grade for the quality of evidence for each intervention/outcome pair was then decreased if there were limitations to the method quality of the aggregate of studies, if

Table 14. Grading of Study Quality

A	Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; clear description of the population and setting; clear description of an appropriate reference standard; proper measurement techniques; appropriate statistical and analytic methods; no reporting errors; and no obvious bias. Not retrospective studies or case series.
B	Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in category above. It has some deficiencies but none likely to cause major bias.
C	Significant bias that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

Table 15. 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***	***Strength of association***	**High** = Further research is unlikely to change confidence in the estimate of the effect
	-1 level if serious limitations	+1 level if strong*; no plausible confounders	
	-2 levels if very serious limitations	+2 levels if very strong **; no major threats to validity	**Moderate** = Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
	Consistency	+1 level if evidence of a dose response gradient	
	-1 level if important inconsistency	+1 level if all residual plausible confounders would have reduced the observed effect	
Observational studies = **Low**	***Directness***		**Low** = Further research is very likely to have an important impact on confidence in the estimate and may change the estimate
	-1 level if some uncertainty		
	-2 levels if major uncertainty		
Any other evidence = **Very Low**	***Other Considerations***		**Very Low** = Any estimate of effect is very uncertain
	-1 level if sparse or imprecise data		
	-1 level if high probability of reporting bias		

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*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.

**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.

GRADE, Grades of Recommendation Assessment, Development, and Evaluation

Table 16. Strength of Guideline Recommendations, Consensus-Based Statements, and Linkage to Quality of Evidence

Recommendation or statement	Description in GRADE approach	Prerequisite	Assumption	Implication
Strong guideline recommendation	We recommend (should)	The quality of the evidence is 'high' and other considerations support a strong recommendation	Most well-informed individuals will make the same choice	The expectation is that the recommendation will be followed, unless there are compelling reasons to deviate from the recommendation in an individual. A strong recommendation may form the basis for a clininal performance measure
Weak guideline recommendation[1]	We suggest (might)	The quality of the evidence is 'high' or 'moderate', but additional considerations support a 'weak' recommendation	A majority of well-informed individuals will make this choice, but a substantial minority may not	The expectation is that consideration should be given to follow the recommendation
Consensus-based statement[2]	Not applicable	The quality of the evidence is 'low', 'very low', or absent. This is a consensus based on expert opinion, supported in the public review of the statement		The expectation is that consideration should be given to follow the statement

Reprinted with permission.[57] Modified from reference[60].
GRADE, Grades of Recommendation Assessment, Development, and Evaluation. [1] Anemia workgroup chose to designate as "Moderately strong"; [2] Anemia workgroup chose to denote as Clinical Practice Recommendation.

there were 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 or sparse, or if there was thought to be a high likelihood of reporting bias (Table 15). The final grade for the quality of the evidence for an intervention/outcome pair could be one of the following 4 grades: "high," "moderate," "low," or "very low" (Table 15).

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 of the outcomes. To judge the balance between benefits and harms, the summaries for the actual results for each outcome were reviewed. Four grades for the quality of overall evidence were used, as defined in Table 15.

Grading of guideline recommendations

Overall, the strength of a guideline was based on the extent to which the Work Group could be confident that adherence will do more good than harm. The strength of a recommendation was based on the quality of the overall supporting evidence, as well as additional considerations (Table 16). The strength of a guideline recommendation could be rated as either "strong" or "moderately strong." A "strong" guideline requires support by evidence of "high" quality. A "moderately strong" guideline requires support by evidence of at least "moderate" quality. Incorporation of additional considerations can modify the linkage between quality of evidence and strength of a guideline, usually resulting in a lower strength of the recommendation, than would be supportable based on the quality of evidence alone.

A "strong" rating indicates the expectation that the guideline recommendation will be followed unless there are compelling reasons to deviate from the recommendation in an individual. This is based on "high"-quality evidence that the practice results in net medical benefit to the patient and the assumption that most well-informed individuals will make the same choice. A "moderately strong" rating indicates the expectation that consideration will be given to follow the guideline recommendation. This is based on at least "moderate"-quality evidence that the practice results in net medical benefit to the patient and the assumption that a majority of well-informed individuals will make this choice, but a substantial minority may not.

Clinical practice recommendations

In the absence of "high"- or "moderate"-quality evidence or when additional considerations did not support "strong" or "moderately strong" evidence-based guideline recommendations, the Work Group was able to draft "CPRs" based on overall consensus of the opinions of the Work Group members (Table 16). As such, the Work Group recommends that clinicians give consideration to following these "CPRs" for eligible patients.

Meta-analyses

Meta-analyses were performed on a subset of RCTs in our systematic review that had 6 or more months of mean follow-up. RRs with 95% CIs were calculated for each study for mortality and for cardiovascular disease. For the cardiovascular disease end point, we combined events for coronary, cerebrovascular, and peripheral vascular disease and heart failure as defined in each study. For CHOIR[2] and CREATE,[1] we included all events from the primary composite outcomes, even though they also included deaths from any cause or from cardiac arrhythmias. We grouped studies according to whether they were conducted in nondialysis patients or dialysis patients. We included the study by Furuland et al[12] with the dialysis studies, even though it contained a subgroup of nondialysis patients.

Calculations were performed using Meta-Analyst (version 0.99 1997; Joseph Lau, Tufts–New England Medical Center, Boston, MA). Because of the clinical heterogeneity of the studies in terms of populations, interventional protocols, durations of follow-up, and outcome definitions, we used a random-effects model according to DerSimonian and Laird for dichotomous outcomes. The random-effects model incorporates both within-study and between-studies variability in assigning weights to each study. It gives a wider CI when heterogeneity is present and thus is more conservative compared with a fixed-effect model.

Appendix 1. Comparison of FDA-Approved Prescribing Information for Epoetin Alfa and KDOQI Anemia Guidelines

Epogen® & Procrit® Prescribing Information (March 2007 product labeling)		**KDOQI Anemia Guidelines** (May 2006 CPRs and CPGs & update 2007)
Section	**Recommendation**	
Black Box Warning		
1. Goal of Treatment	Avoid transfusion or Hb > 12	CPR 2.1.1: Selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events) CPR 2.1.2: The selected Hb target should generally be in the range of 11.0 to 12.0 g/dL CPG 2.1.3: Hb target should not be above 13.0 g/dL CPR 3.4: No single Hb concentration justifies or requires transfusion. The target Hb should not serve as a transfusion trigger.
Indications and Usage		
2. Indications	Elevate Hb, decrease transfusion need	CPR 2.1.1 Rationale: Identifies both HRQoL improvement and lower transfusion need as potential benefits of ESA therapy, describes relationship of benefit to Hb target and achieved Hb in RCTs by target population.
3. Starting Hb in CKD	Hb < 10 g/dL	CPR 2.1.1 Rationale: Selection of Hb target and selection of Hb level to initiate therapy are separate but related steps in medical decision-making. Makes no specific recommendation but notes that target Hb assignment and threshold for initiation of therapy have generally been the same in available RCTs
4. Starting Hb in HD	*no specific recommendation*	CPR 2.1.1 Rationale: As above
5. Iron status	TSAT > 20%, Ferritin > 100 ng/mL prior to Epogen	CPR 3.2.3.1: TSAT > 20% or CHr > 29 pg/cell and ferritin > 200 ng/mL in HD-CKD CPR 3.2.3.2: TSAT > 20% and ferritin > 100 ng/mL in ND-CKD, PD-CKD CPR 3.2.4: Upper level of ferritin: insufficient evidence to recommend IV iron if ferritin > 500 ng/mL
6. Physicians Role	Under guidance of physician	Executive Summary: Guidelines are intended to assist practitioners caring for individual patients with CKD. Refer to disclaimer.
Contraindications		
7. Hypertension Hypersensitivity	Uncontrolled hypertension, Hypersensitivity to mammalian cell-derived products and albumin	CPR 3.1.2.5: Hypertension is not a contraindication to ESA therapy. Rationale: If hypertension arises in the course of anemia treatment, it should be treated appropriately with antihypertensive measures
Warnings		
8. Target Hb	When administered to target a Hb > 12 g/dL	CPR 2.1.2: The selected Hb target should generally be in the range of 11.0 to 12.0 g/dL
9. Rate of Hb Rise	A Hb rate of rise > 1 g/dL over 2 weeks	CPR 3.1.2.1: The initial ESA dose and dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level, and clinical circumstances Rationale 3.1: In general, the objective of initial ESA therapy is a rate of Hb increase of 1.0 to 2.0 g/dL per month.
10. Achieved Hb	The Hb concentration should not exceed 12 g/dL	CPR 2.1, Background, Statements, & Rationale: Distinguishes achieved Hb from target Hb. Achieved Hb varies considerably from target Hb. To avoid achieved Hb > 12 g/dL would require a Hb target as low as 9.2 g/dL.

11. Rate of Hb Rise	The Hb rate of rise should not exceed 1 g/dL in any 2 week period	CPR 3.1 Rationale: In general, the objective of initial ESA therapy is a rate of Hb increase of 1.0 to 2.0 g/dL per month.
12. Hypertension	If hypertension is difficult to control by appropriate measures, decrease epoetin dose	CPR 3.1.2.5: Hypertension is not a contraindication to ESA therapy. Rationale: If hypertension arises in the course of anemia treatment, it should be treated appropriately with antihypertensive measures.
13. Cardiovascular Disease	Patients with pre-existing cardiovascular disease should be monitored closely	Guideline statements do not distinguish between patients with and without cardiovascular disease.
Precautions		
14. Lack or Loss of Response	Consider iron deficiency and 8 other categories of conditions.	CPR 3.2: Gives explicit guidance on evaluating and maintaining optimum iron status. CPR 3.5: Gives specific information on evaluating and correcting persistent failure to reach or maintain intended Hb, defines hyporesponse features, lists associated disorders. Specifies when to consider and how to evaluate PRCA.
15. Iron Evaluation	TSAT should be > 20% and ferritin > 100 ng/mL before starting epoetin.	CPRs specify recommended iron status for patients undergoing ESA therapy, including ferritin upper limit. CPR 3.2.3.1: TSAT > 20% or CHr > 29 pg/cell and ferritin > 200 ng/mL in HD-CKD CPR 3.2.3.2: TSAT > 20% and ferritin > 100 ng/mL in ND-CKD, PD-CKD CPR 3.2.4: Upper level of ferritin: insufficient evidence to recommend IV iron if ferritin > 500 ng/mL
	Monitor TSAT and ferritin regularly, provide iron	CPR 3.2.1: Specifies frequency of iron status tests as monthly during initial ESA treatment, at least every 3 months during stable ESA treatment
16. Informing Patients	Patients should be informed of increased risks when epoetin used in off-label dose regimens or populations	Guidelines do not apply to either non-renal population or off-label use. Guidelines recommend to involve patient in decision making related to Hb target.
17. Hematology and Laboratory Monitoring	Monitor Hb twice weekly for 2-6 weeks, adjust dose no more frequently than 2 week intervals; CBC with platelets and differential should be performed regularly; chemistries (list) should be performed regularly; diet may need to be adjusted; hyperkalemia should be monitored; dialysis prescription may need to be adjusted; no change in renal function expected in ND-CKD	CPR 1.2.1: Recommends CBC with platelets, differential WBC, absolute reticulocyte count, and iron status tests *on first evaluation of anemia in CKD.* CPR 3.1.1: Specifies frequency of Hb monitoring as at least monthly in patients treated with ESA therapy. Rationale reviews published experience, describes twice-monthly and monthly Hb determination, no reports of twice-weekly Hb monitoring in CKD. No specific recommendations for monitoring non-hematological laboratory tests or monitoring non-Hb elements of CBC. Table 2 includes evidence that dialysis adequacy is statistically lower in patients higher compared to lower Hb target, but difference is small. No evidence from Hb target trials that diet modification or potassium monitoring should be included in anemia management. Table 8 presents evidence from 10 Hb target trials in ND-CKD showing no between-group effect (benefit or harm) on renal function.
Dosing & Administration:		
18. Starting Dose	50-100 u/kg/tiw	CPR 3.1.2.1: The initial ESA dose and dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level, and clinical circumstances CPR 3.1.2.1 Rationale: In general, the objective of initial ESA therapy is a rate of Hb increase of 1.0 to 2.0 g/dL per month.
19. Route	IV recommended in HD	CPR 3.1.3.1: Route of administration should be determined by the CKD stage, treatment setting, efficacy, safety and class of ESA used. CPR 3.1.3.2: Convenience favors SC administration in non-HD-CKD patients. CPR 3.1.3.3: Convenience favors IV administration in HD-CKD patients.
20. Reduce Dose When	Hb approaches 12 g/dL, or Hb rise exceeds 1 g/dL over 2 weeks	CPR 2.1 Rationale: Review of literature on dose adjustment options and dose titration in response to Hb above and below Hb target. CPR 3.1 Rationale: In general, the objective of initial ESA therapy is a rate of Hb increase of 1.0 to 2.0 g/dL per month.

21. Increase Dose If	Hb does not increase by 2 g/dL over 8 weeks of therapy and Hb remains at a level not sufficient to avoid the need for transfusion	CPR 2.1, 3.1: No specific recommendations on timing of 1st dose adjustment after ESA initiating therapy.
22. Maintenance Dose	Individually titrate to achieve and maintain the lowest Hb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dl	CPR 2.1.2: Specifies that the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL, on basis of balance of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events) at Hb targets > 13 g/dL.
23. Individualize Dose	Doses must be individualized to ensure that Hb is maintained at an appropriate level for each patient	CPR 2.1.1: Selection of the Hb target and selection of the Hb level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events)
24. Dose Adjustment ***Frequency***	Increases should not be made more often than once a month	No specific recommendations on frequency of dose adjustment. CPR 2.1.2 Rationale includes literature review of approaches to dose adjustment.
25. Dose Adjustment ***Hb level***	Hb increasing and approaching 12 g/dL	No specific recommendations on the level of Hb that requires dose adjustment in relation to Hb 12 g/dL or lower Hb targets. CPR 2.1.2 Rationale includes literature review of approaches to dose adjustment.
26. Dose Adjustment ***% Dose Decrease For Hb Level***	1st dose decrease: 25% If Hb continues to increase and approaches 12 g/dL, doses should be temporarily held until the Hb begins to decrease, at which point therapy should be reintroduced at a dose approximately 25% below the previous dose.	No specific recommendations on the level of Hb that requires dose adjustment in relation to Hb 12 g/dL or lower Hb targets. CPR 2.1.2 Rationale includes literature review of approaches to dose adjustment. Review includes evidence that holding ESA doses is associated with Hb cycling above and below the Hb target range. Report of impact of fixed 25% dose adjustment for Hb > 13 g/dL is reviewed in "implementation issues."
27. Dose Adjustment ***Slow Hb Rise***	If the increase in Hb is < 1 g/dL over 4 weeks and iron stores are adequate, dose of Epogen may be increased by 25% of the previous dose. Further increases may be made at 4-week intervals until the specified Hb is obtained.	No specific recommendations on the rate of Hb increase that requires dose adjustment in relation to Hb 12 g/dL or lower Hb targets. No specific recommendations on frequency of dose adjustment. CPR 2.1.2 Rationale: No specific recommendations on percent dose increments or decrements, but literature on available information is reviewed.
28. Dose Adjustment ***Maintenance Iron Status***	If TSAT is > 20%, dose may be increased	CPRs specify recommended iron status for patients undergoing ESA therapy, including ferritin upper limit. CPR 3.2.3.1: TSAT > 20% or CHr > 29 pg/cell and ferritin > 200 ng/mL in HD-CKD CPR 3.2.3.2: TSAT > 20% and ferritin > 100 ng/mL in ND-CKD, PD-CKD CPR 3.2.4: Upper level of ferritin: insufficient evidence to recommend IV iron if ferritin > 500 ng/mL
29. Dose Adjustment ***Maintenance Hb Monitoring***	Hb should be monitored twice weekly for 2 to 6 weeks following dose increases	CPR 3.1.1.1: Recommends Hb monitoring no less frequently than monthly.
30. Lack or Loss of Response	If TSAT is < 20%, supplemental iron should be administered	Specifies that iron should be given to maintain TSAT > 20% but adds caution that safety of IV iron administration when ferritin > 500 ng/mL has not been established. CPR 3.2.4: Upper level of ferritin: insufficient evidence to recommend IV iron if ferritin > 500 ng/mL.

BIOGRAPHICAL AND DISCLOSURE INFORMATION

Work Group

John W. Adamson, MD, has served as Executive Vice President for Research and Director of the Blood Research Institute of the Blood Center of Southeastern Wisconsin in Milwaukee since 1998. He holds the position of Professor of Medicine (Hematology) at the Medical College of Wisconsin. Before moving to Milwaukee, he was Director of the Lindsley F. Kimball Research Institute of the New York Blood Center since 1989 and President of the Center from 1989 to 1997. Dr Adamson received his MD from the University of California, Los Angeles, after which he trained at the University of Washington in Seattle and the National Institutes of Health (NIH) in Bethesda, MD, in the fields of internal medicine and hematology. Before assuming his position in New York, Dr Adamson was professor of medicine and head of the Division of Hematology at the University of Washington. Dr Adamson is a past President of the American Society of Hematology and past Chairman of its committees on scientific affairs and transfusion medicine. Dr Adamson served as a member of the Advisory Council of the National Institute of Diabetes, Digestive and Kidney Diseases of the NIH. In 1988, he was designated clinical research professor by the American Cancer Society and elected a Fellow of the American Association for the Advancement of Science. Dr Adamson is past editor-in-chief of *Blood*, past editor of the *Journal of Cellular Physiology*, and founding editor of *Current Opinion in Hematology*. Altogether, he has authored or co-authored more than 400 scientific publications.

Consultant: Affymax; Fibrogen; Watson

Speaker: Watson

Grant/Research Support (no personal income): N/A

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Jeffrey S. Berns, MD, earned his MD at Case Western Reserve University, then completed his internship and residency in Internal Medicine at University Hospitals of Cleveland. He completed a fellowship in Nephrology and was an Associate Research Scientist in the Department of Physiology at Yale University. Dr Berns was recently promoted to Professor of Medicine at the University of Pennsylvania School of Medicine, where he is Director of Clinical Nephrology and Director of the Renal Fellowship Program for the Renal, Electrolyte and Hypertension Division. He has published and lectured on topics related to CKD, anemia management in patients with CKD, and other areas in clinical nephrology. He is co-editor of *Drug Prescribing in Renal Failure-Dosing Guidelines for Adults*. He also serves on the editorial board of *Seminars in Dialysis*, *American Journal of Kidney Diseases*, and *Clinical Journal of the American Society of Nephrology*. He is an active investigator in clinical trials related to anemia treatment in patients with CKD.

Consultant: Amgen; Neose

Speaker: N/A

Grant/Research Support (no personal income): Advanced Magnetics; Hoffman LaRoche

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Kai-Uwe Eckardt, MD *(Work Group Co-Chair)*, is Professor of Medicine and Chief of Nephrology and Hypertension at the University of Erlangen–Nuremberg, Germany. He received his MD from the Westfälische Wilhelms-Universität Münster, Germany. In 1993, following postgraduate training in internal medicine, pathology, and physiology, he was appointed Assistant Professor of Physiology at the University of Regensburg, Germany. Subsequently, he continued his training in internal medicine and nephrology at the Charité, Humboldt University in Berlin, where he was appointed Associate Professor of Nephrology in 2000. His major scientific interests are in the molecular mechanisms and physiological/pathophysiological relevance of oxygen sensing and the management of anemia. Professor Eckardt is Subject Editor of *Nephrology, Dialysis and Transplantation* and serves on the editorial board of several other journals. He contributed to the development of the European

Best Practice Guidelines for Anemia. Management and is a member of the executive committee of Kidney Disease: Improving Global Outcomes (KDIGO). Dr Eckardt is associated with the CREATE and TREAT studies.

Consultant: Affymax; Amgen; Hoffman LaRoche; Ortho Biotech/Johnson & Johnson

Speaker: Amgen; Hoffman LaRoche; Ortho Biotech/Johnson & Johnson

Grant/Research Support (no personal income): Hoffman LaRoche; Ortho Biotech/Johnson & Johnson

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Steven Fishbane, MD, currently is Chief of Nephrology and Associate Chair of the Department of Medicine at Winthrop-University Hospital (WUH) in Mineola, NY, as well as Professor of Medicine at SUNY Stony Brook School of Medicine. He is the Medical Director of WUH Dialysis Network, which includes 4 outpatient dialysis units and 3 hospital units. Dr Fishbane serves as the Chairman of the Long Island Health Network Quality Council; Chairman of the Department of Medicine Quality Improvement Program, WUH; Chairman of Clinical Guidelines Committee, WUH; Co-Chairman of WUH Patient Care Committee; and Associate Chairman of the Department of Medicine, WUH. Dr Fishbane is a member of the Network 2 Medical Review Board.

Consultant: Abbott; Affymax; Amgen; Genzyme; Hoffman LaRoche; Renal Management Strategies; Watson

Speaker: Abbott; Genzyme; Ortho Biotech; Watson

Grant/Research Support (no personal income): Abbott; Amgen; Genentech; Genzyme; Hoffman LaRoche; Ortho Biotech; Shire; Speedel; Watson

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Robert N. Foley, MD, was born in Ireland and received his undergraduate MD from University College Cork. He completed Internal Medicine training in Cork, later moving to Saint John's, Newfoundland, Canada, where he completed a residency in nephrology, as well as a Masters in Clinical Epidemiology. From 1999 to 2002, Dr Foley worked at Hope Hospital, Salford, UK, and has been Director of the Chronic Disease Research Group since September of 2002. Dr Foley was also a Co-Editor of the *American Journal of Kidney Diseases*. His major interest is in outcomes research, especially the interplay of cardiovascular and renal disease. Dr Foley is active in anemia correction trials, as well as in the US Renal Data System Cardiovascular Special Study Center.

Consultant: Amgen; Genzyme; Hoffman LaRoche; Ortho Biotech

Speaker: Amgen; Hoffman LaRoche; Ortho Biotech

Grant/Research Support (no personal income): Amgen; Hoffman LaRoche; Ortho Biotech

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Sana Ghaddar, PhD, RD, is an Assistant professor at the American University of Beirut, Lebanon. She has more than 10 years of experience in the renal and clinical dietetics field. She was a renal dietitian and researcher at Peninsula Nephrology Inc in San Mateo, currently a division of Satellite Healthcare. She has served as a principal investigator for anemia management studies that examined the response of heme-iron polypeptide to ESAs in patients with CKD, in addition to other studies that examined patient perceptions, beliefs, and compliance with hemodialysis and nutritional therapy. She has presented her studies at national conferences, including the NKF, American Dietetic Association, and Gerontological Society of America.

Dr. Ghaddar reported no relevant financial relationships.

John S. Gill, MD, MS, obtained his MD from the University of British Columbia (UBC) in 1995. He completed his internal medicine training at the University of Western Ontario in 1998 and his nephrology training in 2000 at UBC. He then completed his transplantation training at Tufts–New England Medical Center in Boston, MA, and obtained a Masters in Clinical Care Research from Tufts in 2002. Dr Gill currently is assistant professor of medicine in the Division of

Nephrology at UBC and has a cross appointment at Tufts–New England Medical Center. Dr Gill's research interests focus on clinical outcomes in kidney transplant recipients. He is the principal investigator and co-investigator on current Canadian Institutes of Health Research, Kidney Foundation, and Michael Smith funded studies. Dr Gill is Chair of the Canadian Society of Transplantation Work Group for Pan-Canadian database development, member of the Canadian Organ Replacement Register Advisory Board, and member of a number of NKF Committees.

Consultant: Hoffman LaRoche

Speaker: N/A

Grant/Research Support (no personal income): N/A

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Kathy Jabs, MD, is a Pediatric Nephrologist who was trained at Babies Hospital, NY, and Children's Hospital, Boston, MA. She was a faculty member at Children's Hospital in Boston (1988 to 1996) and served as Director of Dialysis and Renal Transplantation at Children's Hospital of Philadelphia (1996 to 2000). She currently is the Director of Pediatric Nephrology at Vanderbilt Children's Hospital and an Associate Professor of Pediatrics at Vanderbilt University School of Medicine, Nashville, TN. Dr Jabs has had a long-standing interest in the care of children with chronic kidney disease. Dr Jabs is associated with the CKid and FSGS studies sponsored by the NIH.

Dr Jabs reported no relevant financial relationships.

Francesco Locatelli, MD, FRCP, is Head of the Department of Nephrology and Dialysis at A. Manzoni Hospital, Lecco, Italy, and postgraduate Professor of Nephrology at the Universities of Brescia and Milan. He is Past President of the European Renal Association–European Dialysis and Transplant Association, the International Society of Blood Purification, and the Italian Society of Nephrology. He is an Honorary Member of the Czech, Hungarian, Polish, Romanian, and Turkish Societies of Nephrology and an International Distinguished Medalist and recipient of the Garabed Eknoyan Award of the NKF, United States (2006). He is also an honorary fellow of the Royal College of Physicians of London, UK (FRCP). He has been Chairman of the Lombardy Regional Dialysis and Transplantation Registry since 1982. He also serves as Chairman of the board of European Best Practice Guidelines and is on the board of the NKF-Dialysis Outcomes Quality Initiative and the executive board of directors of KDIGO. Dr Locatelli is President-Elect of the World Congress of Nephrology (2009), Subject Editor of *Nephrology Dialysis Transplantation,* Associate Editor of the *Journal of Nephrology*, member of the Editorial Board of *Journal of the American Society of Nephrology*, past Associate Editor of the *American Journal of Kidney Diseases* (2001 to 2004), and serves as reviewer for a number of journals (including the *New England Journal of Medicine* and *The Lancet*). He has authored more than 600 papers in the fields of hypertension, nutrition, and CKD progression; adequacy in dialysis; sodium and other electrolyte balance, immunoglobulin A nephropathy, and anemia.

Consultant: Amgen; Dompé Biotec; Hoffman LaRoche; Shire

Speaker: Abbott; Amgen; Bayer; Bellco; Bristol-Myers Squibb; Dompé Biotec; Fresenius; Gambro-Hospal; Hoffman LaRoche; Merck Sharp & Dohme; Novartis; Pfizer; Sanofi-Aventis; Shire

Grant/Research Support (no personal income): N/A

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Iain C. Macdougall, MD, 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. For the last 11 years, he has been Consultant Nephrologist and Honorary Senior Lecturer at King's College Hospital in London, UK. He developed both a clinical and a basic science research interest in factors affecting responsiveness to ESAs. He has served on the Working Parties responsible for both the 1999 and the 2004 versions of the European Best Practice Guidelines on Renal Anaemia Management, as well as the KDOQI Anemia Guidelines Work

Group. He is a current Council member of the European Renal Association and a past member of the KDIGO Board of Directors. He has co-authored the section on renal anemia for the last 2 editions of the *Oxford Textbook of Clinical Nephrology* and the current edition of *Comprehensive Clinical Nephrology* and is a Subject Editor of *Nephrology Dialysis Transplantation*.

Consultant: Affymax; Amgen; Hoffman La-Roche; Ortho Biotech; Shire

Speaker: Amgen; Hoffman LaRoche; Ortho Biotech; Shire

Grant/Research Support (no personal income): Affymax; Amgen; Hoffman LaRoche; Ortho Biotech; Shire

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Patricia Bargo McCarley, RN, MSN, NP, is a nephrology nurse practitioner at Diablo Nephrology Medical Group in Walnut Creek, CA. Ms McCarley received her BSN and MSN from Vanderbilt University. She is active in the American Nephrology Nurses Association (ANNA), having served on local, regional, and national committees. She is currently a member of the Nephrology Nursing Journal Board. Ms McCarley has authored many publications, including most recently chapters in the 2005 ANNA Nephrology Nursing Standards of Practice and Guidelines for Care and the Contemporary Nephrology Nursing: Principles and Practice (2nd edition).

Consultant: N/A

Speaker: Amgen

Grant/Research Support (no personal income): N/A

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Allen R. Nissenson, MD, FACP, is Professor of Medicine and Director of the Dialysis Program at the David Geffen School of Medicine at University of California at Los Angeles (UCLA), where he has developed a comprehensive dialysis program. He is President of the National Anemia Action Council and recently chaired a Chancellor's committee at UCLA on Financial Conflicts of Interest in Clinical Research. He is currently serving on a University of California Task Force on Institutional Conflicts of Interest in Research. Dr Nissenson is Chair of the Faculty Executive Council for the David Geffen School of Medicine at UCLA. He has served as Chair of the Southern California End-Stage Renal Disease (ESRD) Network during its organizational years in the early 1980s and is its recent President-Elect. He is Chair of the Medical Review Board. Dr Nissenson served as a Robert Wood Johnson Health Policy Fellow of the Institute of Medicine from 1994 to 1995. He is Immediate Past President of the Renal Physicians Association and has served as a member of the Advisory Group overseeing the entire NKF-Dialysis Outcomes Quality Initiative. Dr Nissenson's major research interests focus on the quality of care for patients with CKD. His research has included extensive clinical trials of new devices and drugs related to renal disease. Dr Nissenson is co-principal investigator on a recently obtained NIH Center Grant looking at issues of disparities in health care delivery for patients with CKD. He is the author of 2 dialysis textbooks, both in their fourth editions, and was the founding Editor-in-Chief of *Advances in Renal Replacement Therapy* (currently, *Advances in Chronic Kidney Disease*), an official journal of the NKF. He currently is Editor-in-Chief of *Hemodialysis International*, the official journal of the International Society for Hemodialysis. He has more than 340 publications in the field of nephrology, dialysis, anemia management, and health care delivery and policy. Among his numerous honors is the President's Award of the NKF.

Consultant: Advanced Magnetics; Affymax; Amgen; DaVita; Fibrogen; Hoffman LaRoche; Medgenics; Ortho Biotech; Prometic

Speaker: Watson

Grant/Research Support (no personal income): Amgen; Hoffman LaRoche; Ortho Biotech

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: Advanced Magnetics

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 Staff at the Division of Nephrology of the Tufts–New En-

gland Medical Center and Assistant Professor of Medicine at the Tufts University School of Medicine in Boston, MA. While doing a clinical research fellowship at the Tufts–New England Medical Center and a Master of Public Health at Harvard University, he began a line of investigation in the area of CKD. Through several publications, he and others showed that the pre-ESRD management of patients with CKD is suboptimal, and that this is an important factor for the high morbidity and mortality observed in these patients. A particular area of interest has been anemia management before the initiation of dialysis therapy. By using population registry data, he and his colleagues have reported trends in anemia and iron management. Dr Obrador has served as reviewer for several journals, including *Kidney International*, the *Journal of the American Society of Nephrology*, and the *American Journal of Kidney Diseases*. He also has been a member of the Advisory Board of the NKF-KDOQI.

Dr Obrador reported no relevant financial relationships.

John C. Stivelman, MD, is Chief Medical Officer of the Northwest Kidney Centers and Associate Professor of Medicine in the Division of Nephrology, Department of Medicine, at the University of Washington School of Medicine in Seattle. Dr Stivelman obtained his MD from the University of Pennsylvania, completed his residency in Internal Medicine at Harbor-UCLA Medical Center, and nephrology training at Brigham and Women's Hospital. Dr Stivelman has been involved in investigative efforts to optimize hematopoietic therapy for dialysis patients since the phase III recombinant erythropoietin trials in 1986. His major interests and literature contributions center on iron utilization, mechanisms of resistance of erythropoietin therapy, improved dialytic survival in disadvantaged populations, and the interaction of regulatory issues with optimization of care. Dr Stivelman has served as the Chair of the Network 6 Medical Review Board and a member of the Forum of ESRD Networks Board of Directors. He currently serves as medical director of one of Northwest Kidney Centers' free-standing facilities and as a member of the Boards of Directors of the Renal Physicians' Association and the Northwest Renal Network (Network 16).

Consultant: Watson

Speaker: Watson

Grant/Research Support (no personal income): Amgen; Auxilium; Watson

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

David B. Van Wyck, MD *(Work Group Co-Chair)*, is Professor of Medicine and Surgery at the University of Arizona College of Medicine in Tucson. After completing his undergraduate studies at Washington University, St Louis, Dr Van Wyck earned his MD at the University of Arizona College of Medicine. There, he undertook a research fellowship in Surgical Biology and completed his residency in Internal Medicine and fellowship in Nephrology. Dr Van Wyck has written or contributed to books, book chapters, articles, and abstracts on basic iron metabolism and reticuloendothelial function and on clinical aspects of iron and anemia in patients with CKD. On the subject of anemia and kidney disease, he pursues research, provides consultation to industry including American Regent, Amgen, and DaVita, Inc, and reviews manuscripts for the major nephrology journals. Dr Van Wyck served on the original KDOQI Anemia Work Group and assumed Co-Chair responsibilities in 2002. Frequently invited to speak, Dr Van Wyck has lectured on the molecular and cellular control of erythropoiesis and iron homeostasis, diagnostic and treatment issues in anemia and iron management, protocol development in the treatment of dialysis-associated anemia, and new approaches to iron and erythropoietin replacement therapy.

Consultant: Affymax; American Regent; Amgen; DaVita; Ortho Biotech/Johnson & Johnson; Vifor

Speaker: American Regent; Amgen; DaVita; Ortho Biotech/Johnson & Johnson; Vifor

Grant/Research Support (no personal income): N/A

Grant/Research Support (includes personal income): American Regent

Part-Time Employee: DaVita

Shares:N/A

Colin T. White, MD, is a pediatric nephrologist at British Columbia (BC) Children's Hospital in Vancouver and clinical assistant professor at the University of BC in Canada. He completed medical school in Ottawa and Pediatrics in London, Ontario. There, he finished 3 years of pediatric nephrology training before moving to Vancouver to complete 3 more years. He has been on staff as a Pediatric Nephrologist since 2003 and is currently the Director of Dialysis at BC Children's Hospital. He has a number of research interests, including medical education, optimizing dialysis care in children, estimation of glomerular filtration rate, and CKD and its complications. Dr White's interest in anemia management is geared towards children. He is presently completing a Masters degree in Medical Education. Dr White is associated with the CKid study and various NAPRTC protocols.

Consultant: Hoffman LaRoche

Speaker: N/A

Grant/Research Support (no personal income): Genzyme Canada

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

KDOQI Chair, Vice-Chair and ERT

Adeera Levin, MD, FACP, is Professor of Medicine and the Co-Chair of the Clinical Investigator Program at the University of British Columbia (UBC). She received her medical degree from McMaster University and nephrology training at the University of Toronto. Dr Levin currently serves as the Director of the Kidney Function Clinic at St Paul's Hospital in Vancouver, Executive Director of the British Columbia Provincial Renal Agency, Curriculum Chair of the Kidney Research Scientist Core Education and National Training program, and KDOQI Chair at the NKF. In addition, she is a member of the KDIGO Executive Committee, International Society of Nephrology Council, and ROFAR Board of Trustees. Her research interests include early kidney disease, anemia, mineral metabolism disorders, cardiovascular diseases, and CKD progression and health outcomes. Dr. Levin is also the recipient of the UBC Martin Hoffman Award for research excellence and the Dean Whitlaw Award for Outstanding Grand Rounds. She is presently on the editorial board of the *American Journal of Kidney Diseases* and *Nephrology Dialysis and Transplantation*.

Consultant: Hoffman LaRoche

Speaker: Abbott; Amgen; Hoffman LaRoche; Merck Frosst; Ortho Biotech

Grant/Research Support (no personal income): Abbott; Genzyme; Merck Frosst; Ortho Biotech; Shire

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A

Shares: N/A

Michael V. Rocco, MD, MSCE, is Professor of Medicine at Wake Forest University in Winston-Salem, NC. He received his MD degree from Vanderbilt University in Nashville, TN, and also served his Internal Medicine residency at Vanderbilt. He completed a nephrology fellowship at the University of Pennsylvania in Philadelphia, PA, and received a master's degree in epidemiology at Wake Forest University. He has been on the faculty of the Wake Forest University School of Medicine since 1991 and currently holds the Vardaman M. Buckalew Jr Chair in Nephrology. He has more than 100 manuscripts and book chapters in the areas of hemodialysis, peritoneal dialysis, nutrition, chronic renal failure, and epidemiology. He has served as the clinical center Principal Investigator at Wake Forest for several NIH trials, including the HEMO Study, the Acute Renal Failure Trial Network, the Dialysis Access Consortium, and the Frequent Hemodialysis Network. Dr. Rocco has served as the Vice-Chair for KDOQI since 2003 and was the Vice-Chair for the NKF-KDOQI Hypertension Work Group. He was also a workgroup member of the Centers for Medicare & Medicaid Services (CMS) ESRD Clinical Performance Measures Quality Improvement Committee and served as the Chair of the peritoneal dialysis subcommittee.

Consultant: Amgen; DaVita; Hoffman LaRoche; Renaissance Health Care

Speaker: N/A

Grant/Research Support (no personal income): N/A

Grant/Research Support (includes personal income): N/A

Part-Time Employee: N/A
Shares: N/A

Joseph Lau, MD, is a Professor of Medicine at Tufts University and Program Director, Evidence-based Medicine, NKF Center for CPG Development and Implementation at Tufts New England Medical Center in Boston, MA. Dr Lau completed a fellowship in Clinical Decision Making and Medical Computer Science and he holds a joint appointment as Physician and Clinical Investigator at Tufts. He is also a recipient of the Tufts School of Medicine Distinguished Faculty Award (2003) and an Agency for Healthcare Research and Quality Evidence-Based Practice Center contract. His primary research focus is evidence-based medicine and meta-analyses.

Dr Lau reported no relevant financial relationships.

Katrin Uhlig, MD, MS, is an Assistant Professor of Medicine at Tufts University and Program Director, Nephrology, NKF Center for CPG Development and Implementation at Tufts-New England Medical Center in Boston, MA. She completed a rheumatology fellowship at Policlinic, Munich University in Germany and a nephrology fellowship at Tufts, where she is currently a Staff Physician, Division of Nephrology. She is Co-Editor of the *American Journal of Kidney Diseases*. She is a recipient of the German National Merit Foundation scholarship. Her research interests include developing evidence-based CPGs, conducting systematic reviews, performing critical literature appraisal, and teaching evidence-based medicine.

Dr Uhlig reported no relevant financial relationships.

Amy Earley, BS, is a Research Assistant at the NKF Center for CPG Development and Implementation at Tufts–New England Medical Center in Boston, MA. She assists in the development of evidence-based clinical guidelines and conducts systematic reviews and critical literature appraisals.

Ms Earley reported no relevant financial relationships.

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