

K'atching Up with KDOQI:
Clinical Practice Guidelines &
Clinical Practice Recommendations for
Anemia of Chronic Kidney Disease
2006

Why *new* guidelines?

Rationale for KDOQI Anemia 2006

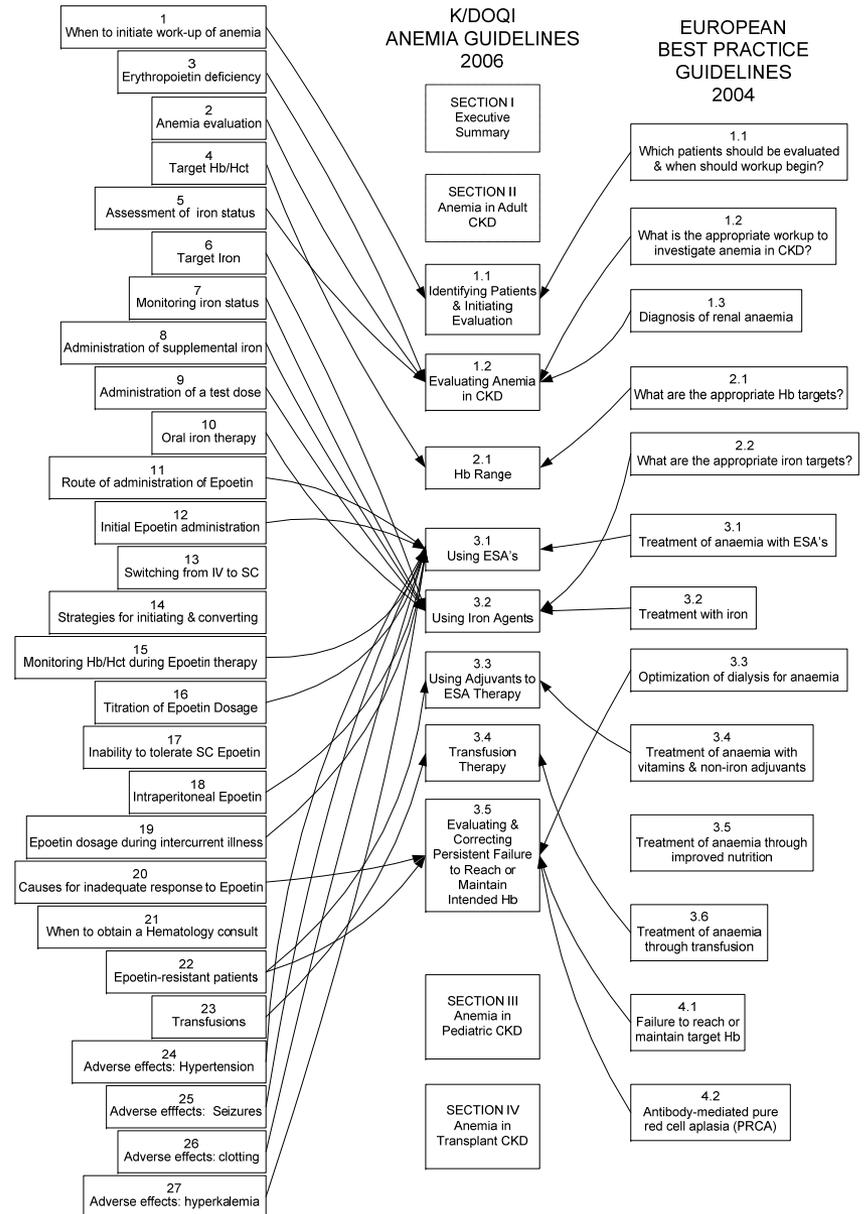
- Expand scope to all patients with CKD, Stages 1-5
 - Hemodialysis, peritoneal dialysis, transplant CKD
- Broaden intended readership
 - Practitioners in North America
- Reflect a global perspective
 - Coordinated with other guidelines
 - Membership of work group includes Latin America, Canada, Europe
- Provide foundation for KDIGO

Members of the Anemia Work Group

- David Van Wyck, MD
 - Co-chair
- John Adamson, MD
- George Bailie, PharmD, PhD
- Jeffrey Berns, MD
- Steven Fishbane, MD
- Robert Foley, MD
- Sana Ghaddar, RD, PhD
- John Gill, MD
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- Gregorio Obrador, MD
- John Stivelman, MD
- Colin White, MD
- Consultants
 - Iain Macdougall, MD
 - Francesco Locatelli, MD

Relationship between New KDOQI Guidelines And Previous Guidelines: Structure and organization

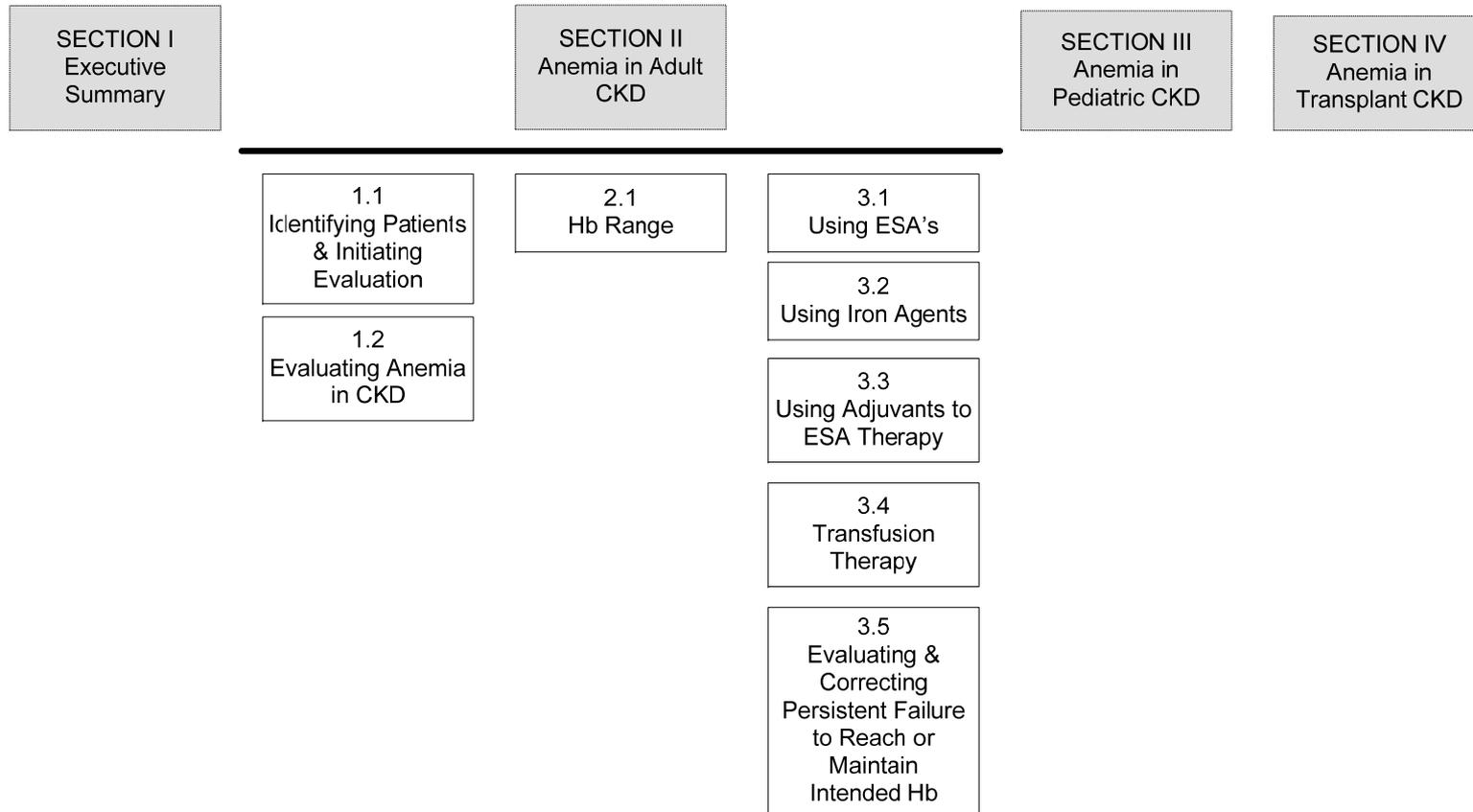
K/DOQI ANEMIA GUIDELINES UPDATE 2000



Key differences between KDOQI 2006 and previous anemia guidelines

- Definition of Anemia
- Definition of Iron Deficiency
- Hb “target” or intended treatment range
- Ferritin upper limit
- Pediatric recommendations
- Transplant CKD review

Structure and Organization



Evidence-based Guideline vs Clinical Practice Recommendation (CPR)

- Quality of evidence distinguishes two approaches
 - If high or moderately high: *Guideline statement*
 - If low, very low, or missing: *CPR (opinion)*
- High or moderately high evidence
 - Randomized, controlled trials (RCTs)
 - Method without significant limitations
 - Results consistent among available trials
 - Applicable to target patient population
 - Evidence of harm

Examples of sources of evidence *not suitable* for Evidence-Based Guidelines

- Longitudinal cohort trials
 - Prospective or retrospective
- Observational (cross-sectional) trials (e.g. NHANES)
- Non-randomized interventional trials
- Uncontrolled interventional trials
- RCTs (or groups of RCTs) lacking safety information
- RCTs in non-CKD patients

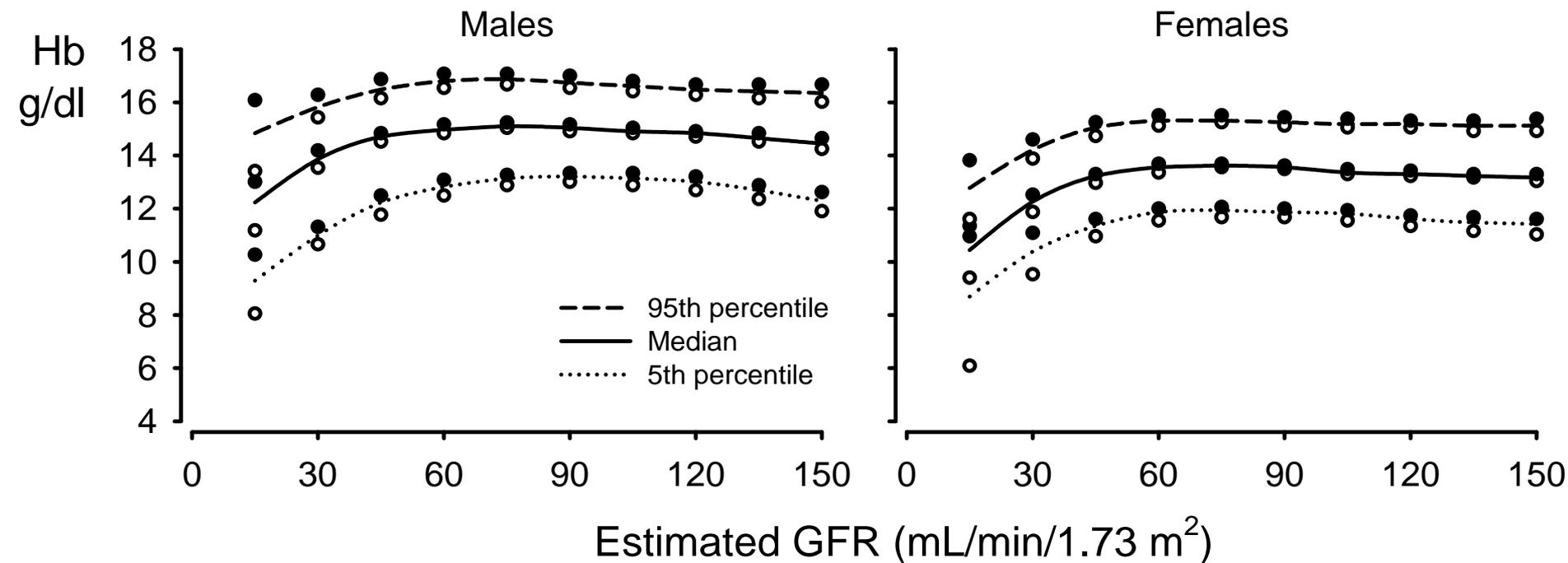
Guideline and Clinical Practice Recommendations 1.1

Identifying Patients and Initiating Evaluation

Identifying Patients and Initiating Evaluation

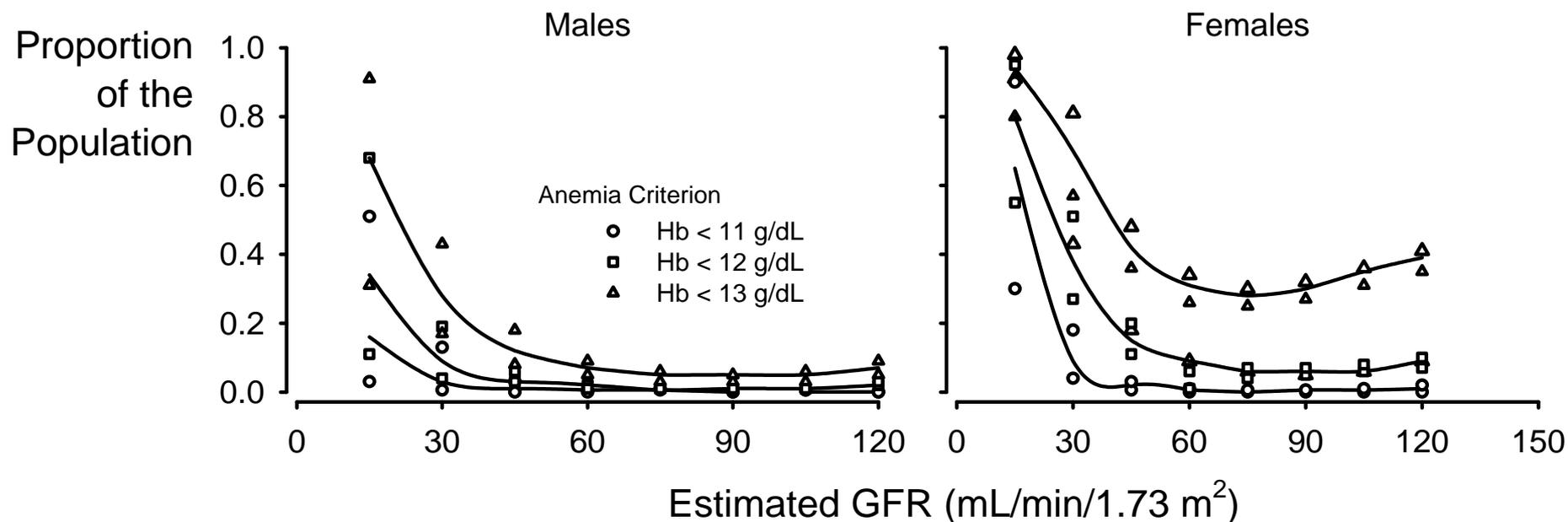
- 1.1.1 Stage and etiology of CKD:
In the opinion of the Work Group, Hb testing should be carried out in all patients with CKD, regardless of stage or etiology.
- 1.1.2 Frequency of testing for anemia:
In the opinion of the Work Group, Hb levels should be measured at least annually.
- 1.1.3 Diagnosis of anemia:
In the opinion of the Work Group, diagnosis of anemia should be made and further evaluation should be undertaken at the following Hb concentrations:
 - <13.5 g/dL in adult males**
 - <12.0 g/dL in adult females**

In the general population, anemia in CKD occurs at GFR < 60 mL/min



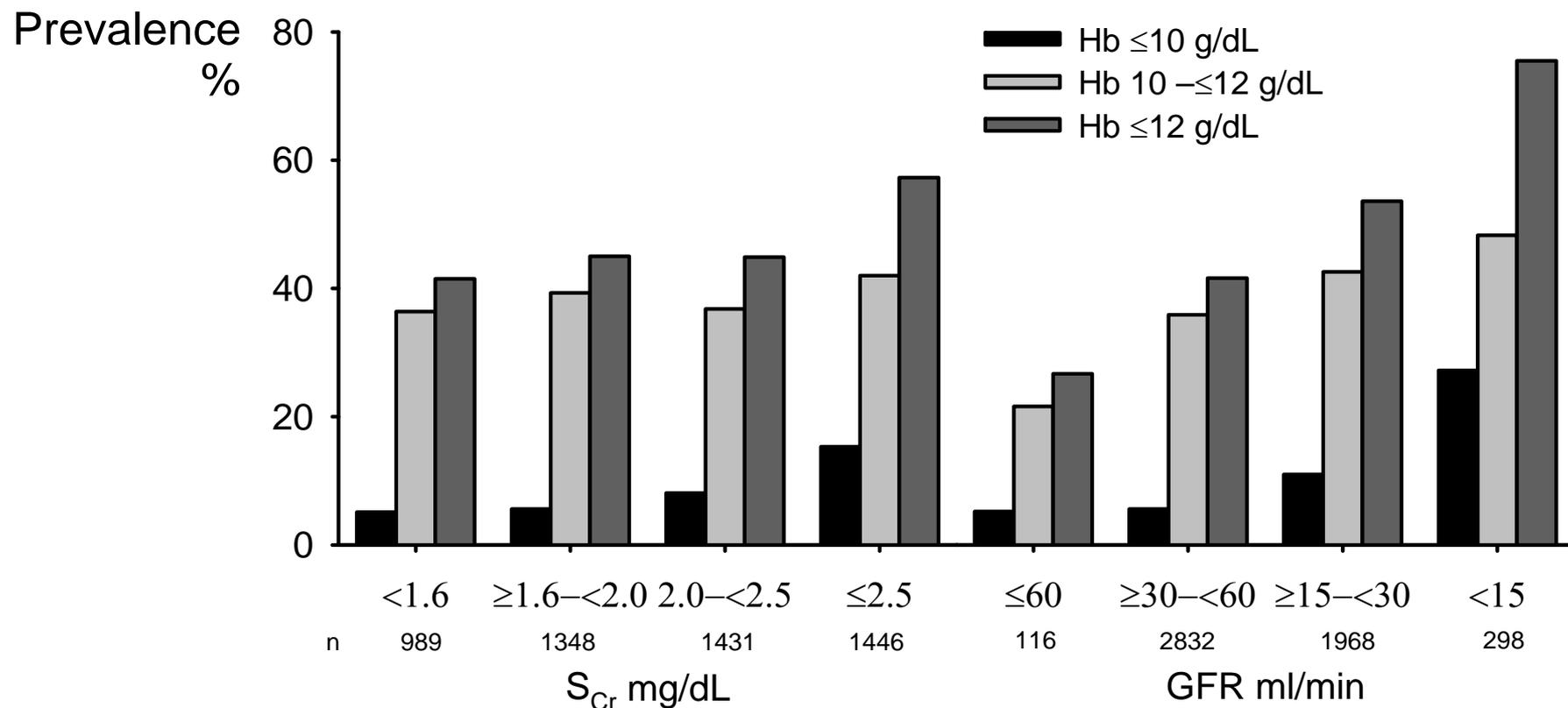
Source: Astor BC et al. *Arch Intern Med* 162:1401-1408, 2002
NHANES III

Prevalence in general population depends on definition of anemia

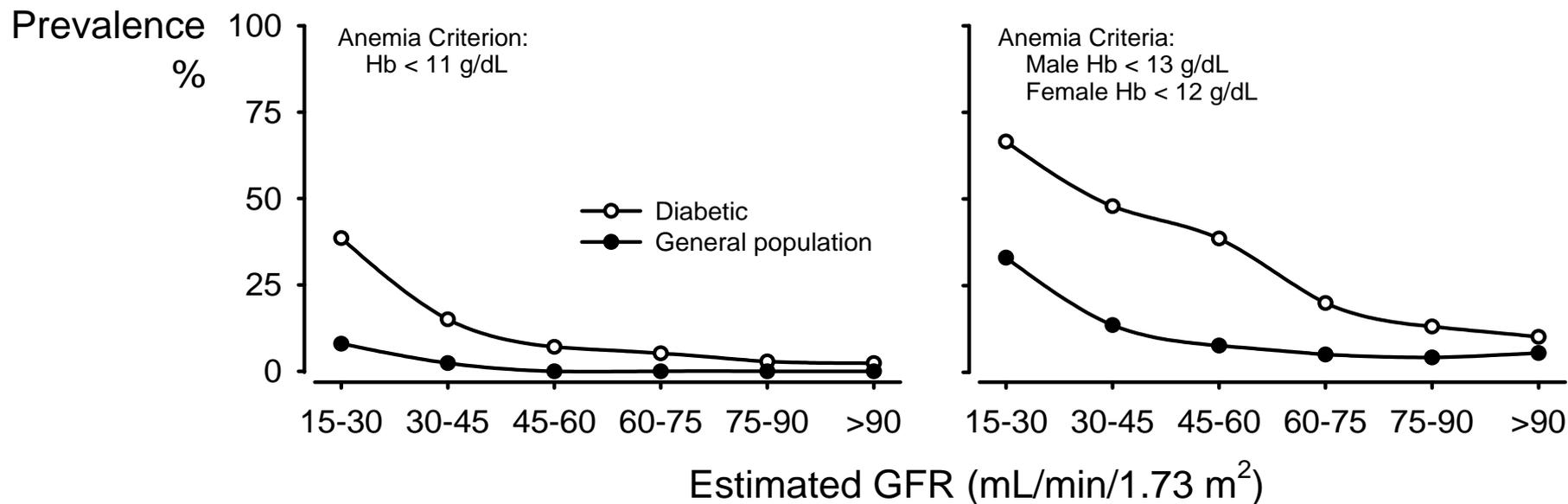


Source: Astor BC et al. *Arch Intern Med* 162:1401-1408, 2002
NHANES III

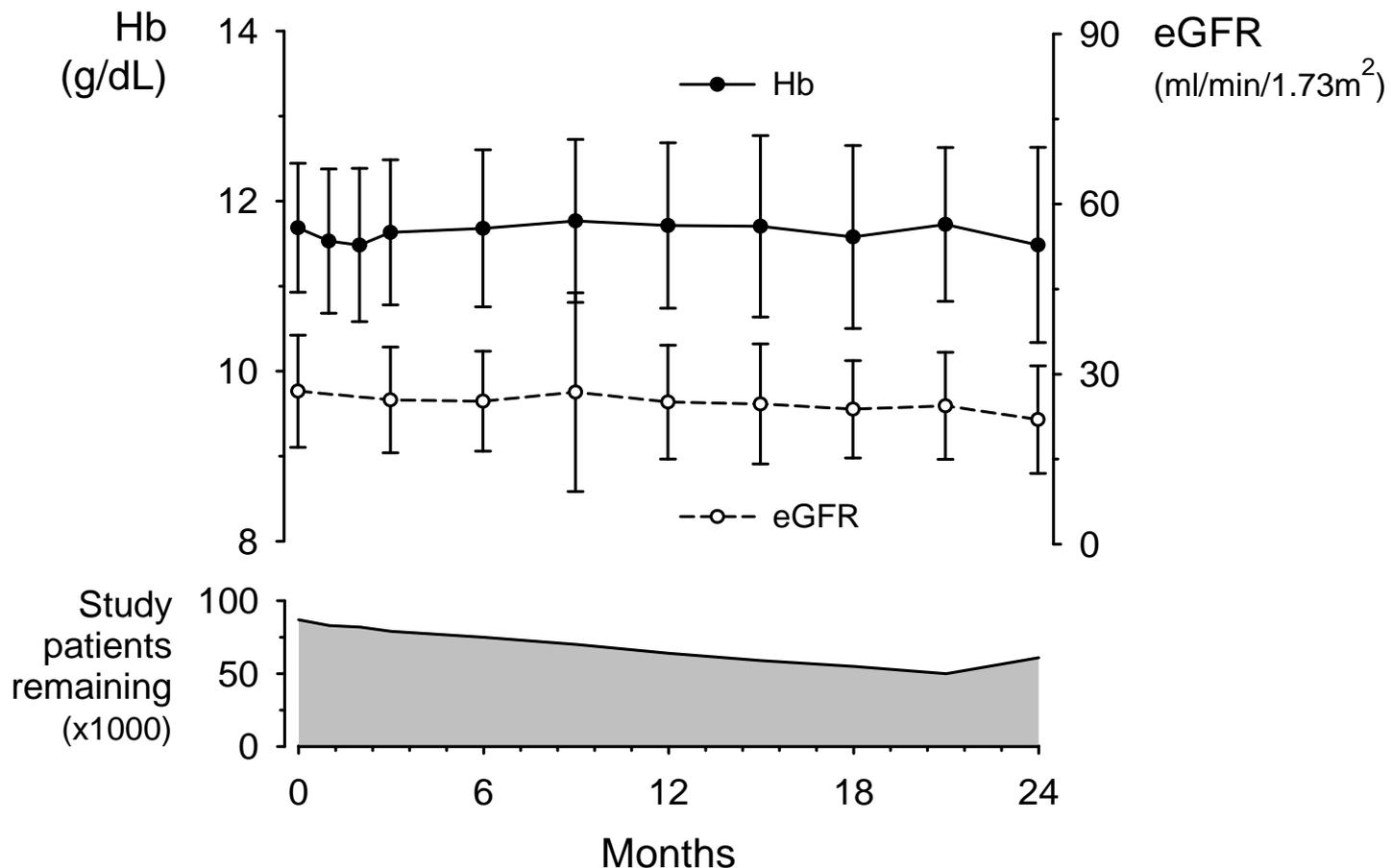
In *patients*, anemia is prevalent at all CKD Stages. Prevalence varies by Hb cutoff



Prevalence of anemia is especially high in *diabetic* patients

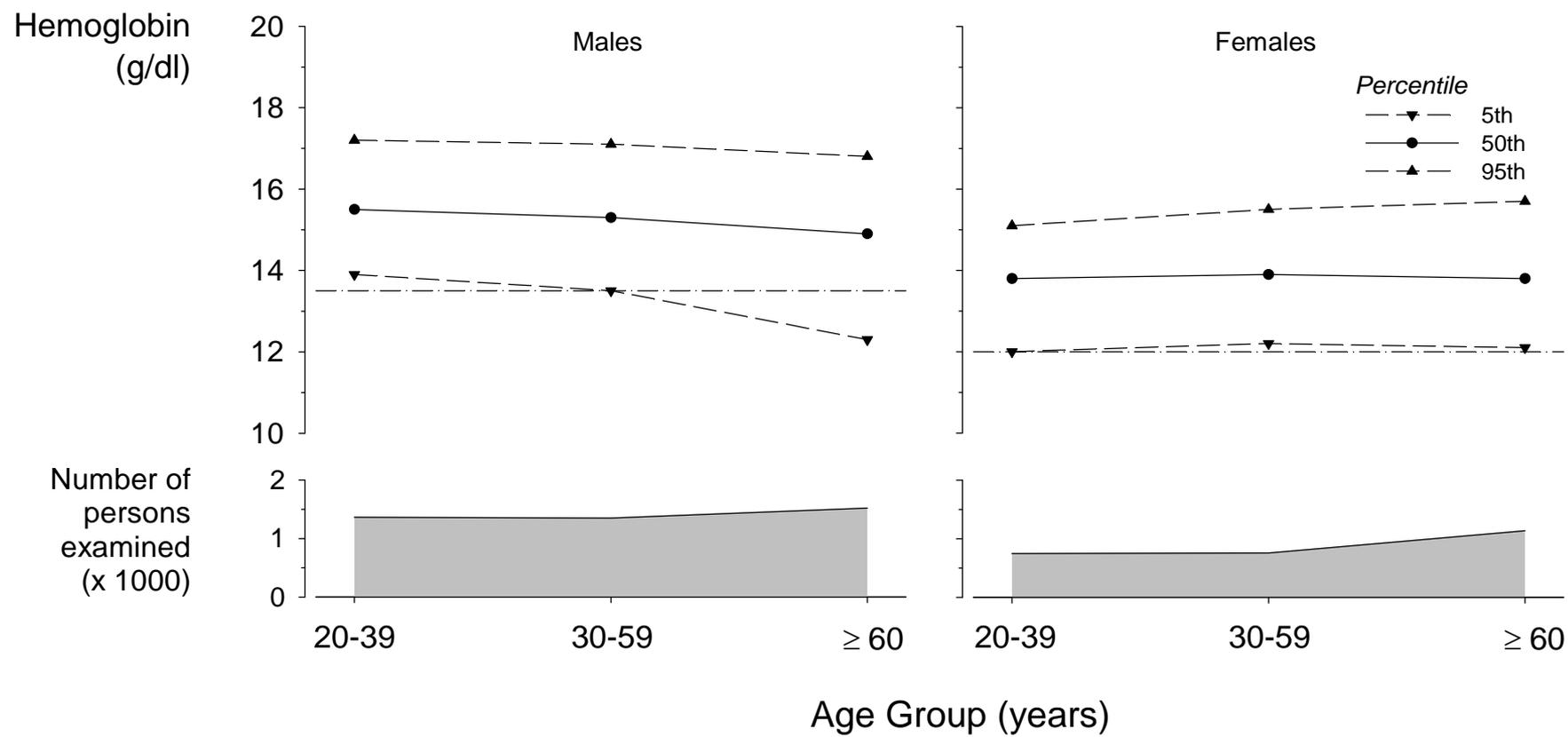


Prospective trials show Hb is fairly stable in untreated anemia of CKD



Source: Levin A et al. *Am J Kidney Dis* 46:799-811, 2005

Anemia definition is population-based: Lowest 5th Percentile of general population



Source: Hollowell JG et al. *Vital Health Stat* 11 (247):1-156, 2005
NHANES III

Limitations of current evidence

- Trials have been cross-sectional and not longitudinal in design.
- Described patients entered into clinical trials or seen by nephrologists are not a truly representative sample of patients with CKD.
- Includes small numbers of patients with CKD Stage 4, 5.
- Inconsistent measures of renal
- MDRD estimated GFR is not very precise at higher levels of kidney function.
- Detailed information on the presence or absence of disorders potentially responsible for low Hb is not available.



Guideline and Clinical Practice Recommendations 1.2

Evaluation of Anemia in CKD

Evaluation of Anemia in CKD

- **1.2.1 In the opinion of the Work Group, initial assessment of anemia should include the following hematological tests and tests of iron status:**
- **1.2.1.1 A complete blood count (CBC) including—in addition to the Hb concentration—red cell indices (mean corpuscular hemoglobin [MCH], mean corpuscular volume [MCV], mean corpuscular hemoglobin concentration [MCHC]), white blood cell count and differential, platelet count**
 - **1.2.1.2 Absolute reticulocyte count,**
 - **1.2.1.3 Serum ferritin to assess iron stores,**
 - **1.2.1.4 Serum transferrin saturation (TSAT), *or* content of Hb in reticulocytes (CHr) to assess adequacy of iron for erythropoiesis.**

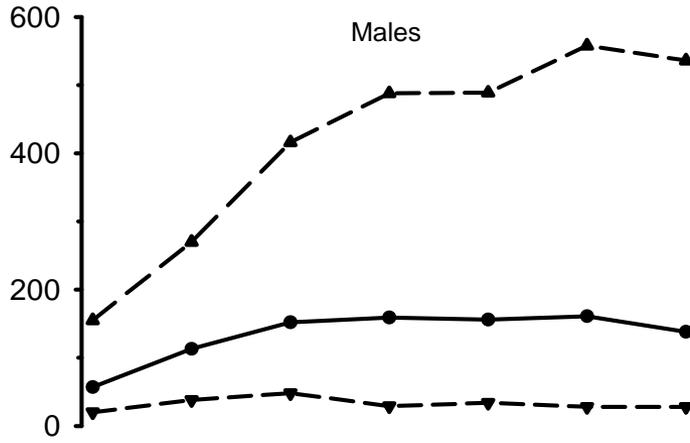
Initial Assessment Laboratory List

- CBC
 - Hb
 - MCV, MCH, MCHC
 - White cell count & differential
 - Platelet count
- Absolute reticulocyte count
- Iron status tests
 - Ferritin
 - Transferrin saturation (TSAT) or CHr

Iron test thresholds for iron deficiency: Lowest 5th percentile of population (males)

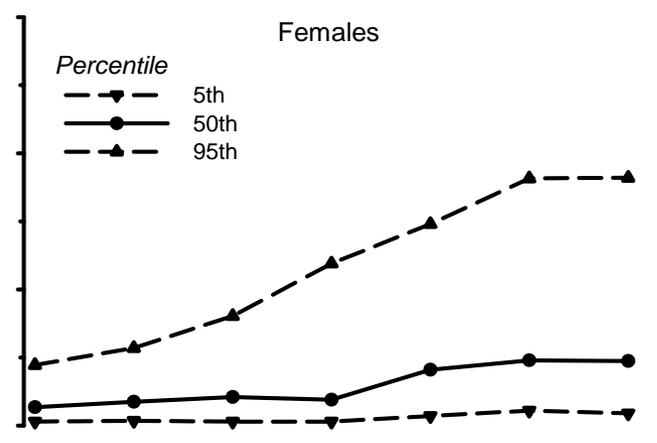
- Ferritin
 - < 25 ng/mL
- TSAT
 - $< 16\%$
- These were *not* CPRs or guidelines

Ferritin
(ng/ml)

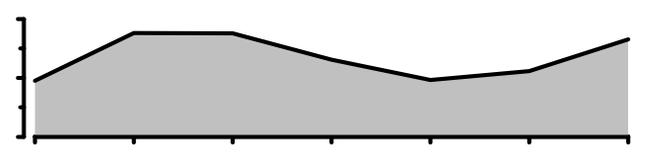
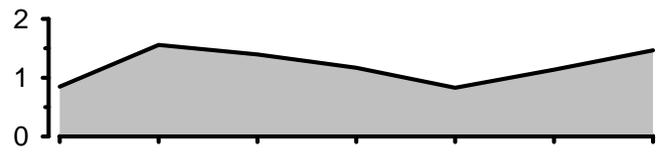


Females

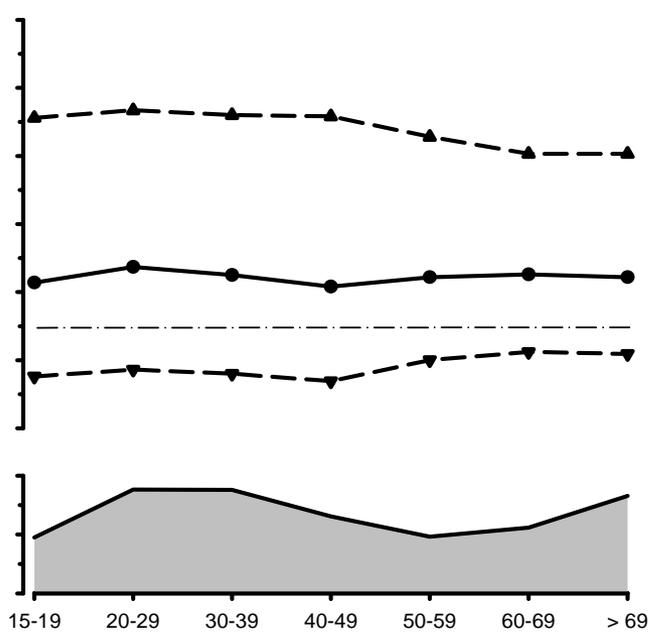
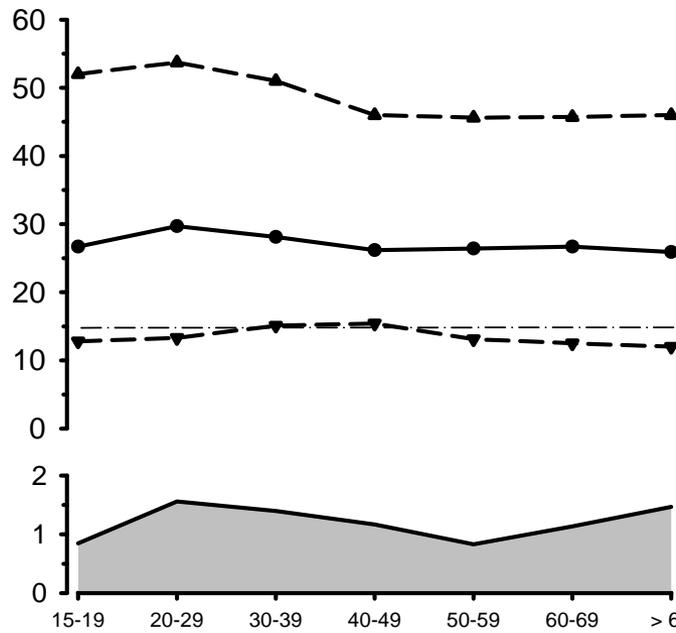
Percentile
5th
50th
95th



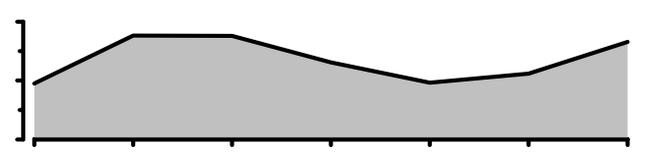
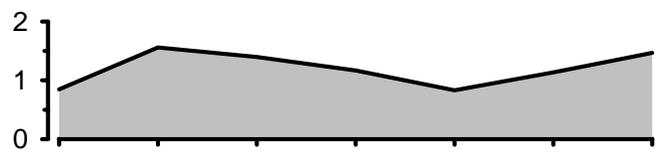
Number of
persons
examined
(x 1000)



Transferrin
Saturation
(%)

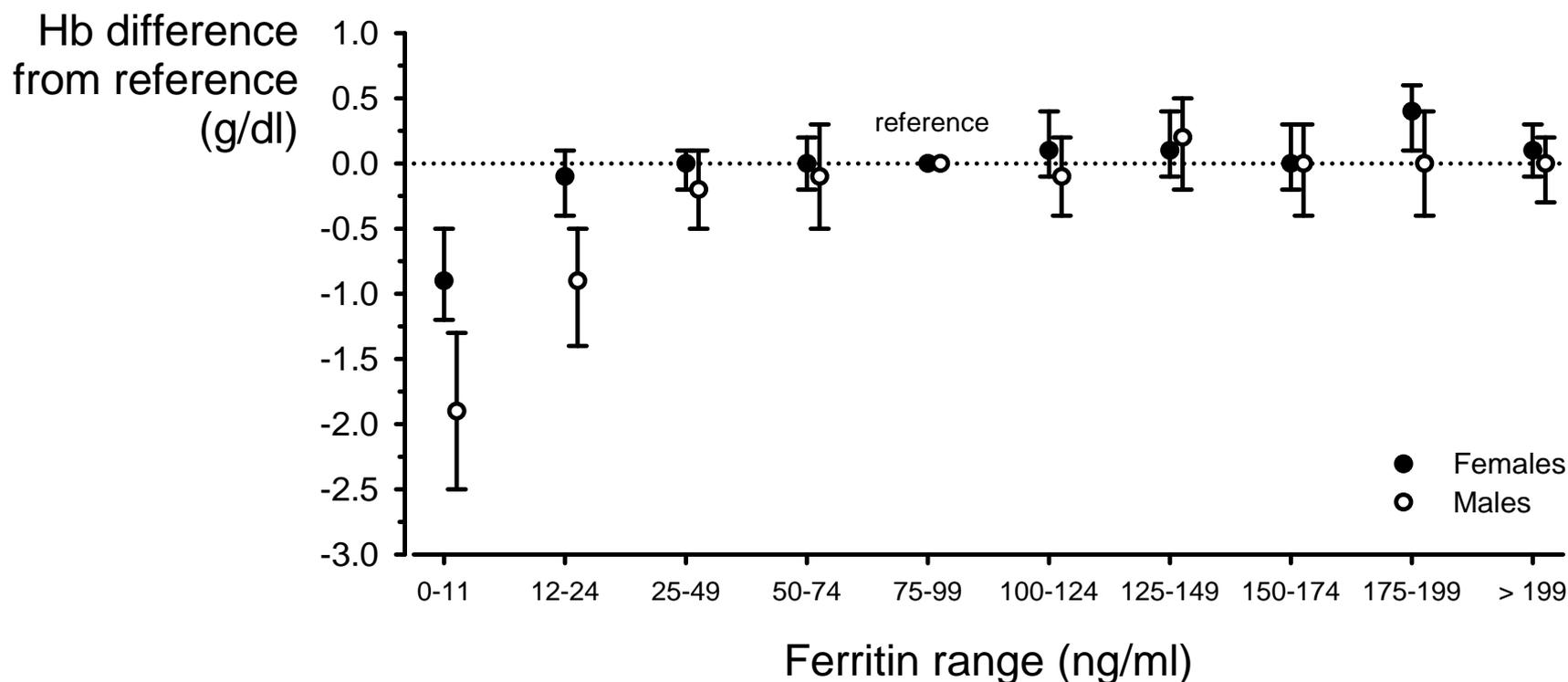


Number of
persons
examined
(x 1000)



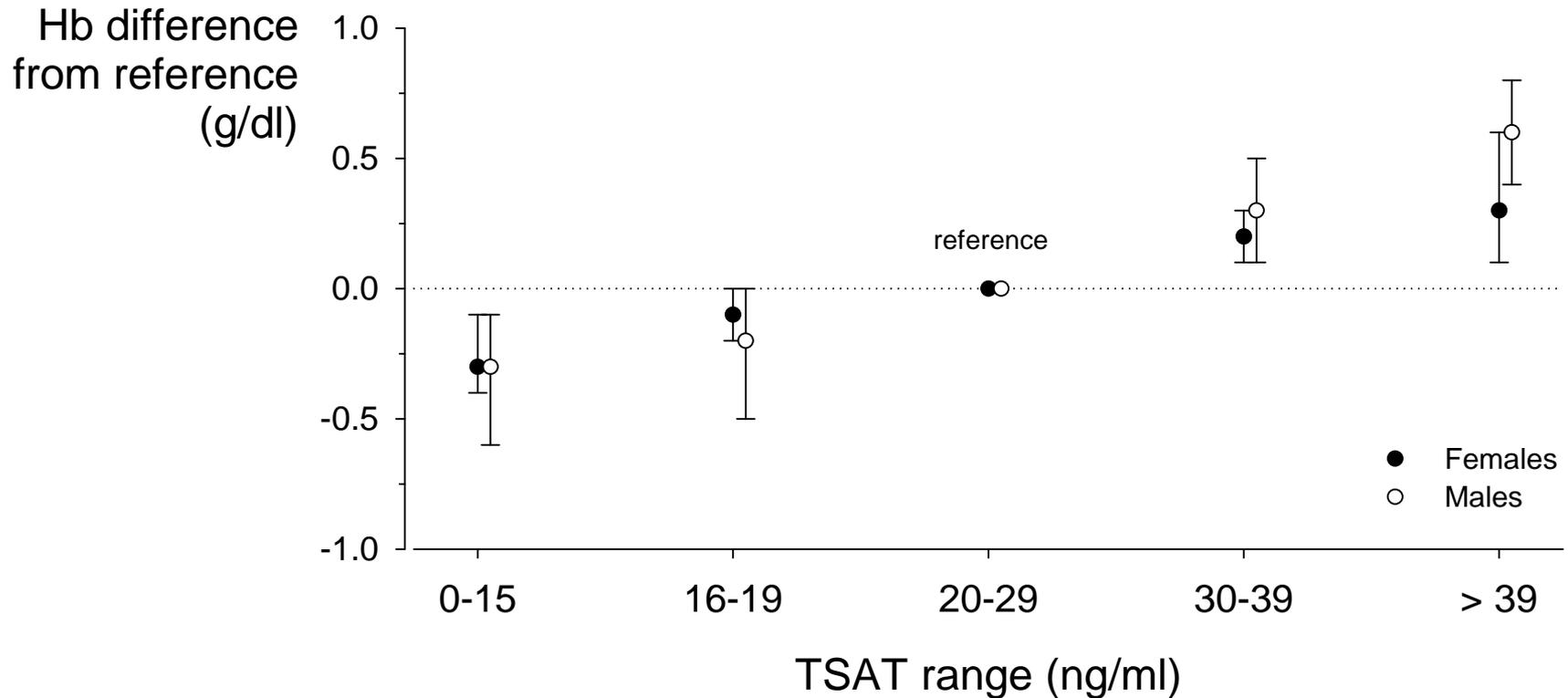
Age group in years

In CKD patients, ferritin levels < 25 ng/mL are likely to contribute to low Hb



Source: Hsu CY et al. *J Am Soc Nephrol* 13:504-510, 2002
NHANES III

In CKD patients, TSAT levels are linearly related to Hb throughout range



Source: Hsu CY et al. *J Am Soc Nephrol* 13:504-510, 2002
NHANES III



Guideline and Clinical Practice Recommendations 2.1

Intended-Treatment Range for Hemoglobin

Hemoglobin Intended-Treatment Range

- **2.1.1 Lower limit of Hb:**
In patients with CKD, the Hb should be ≥ 11.0 g/dL
(*MODERATELY STRONG RECOMMENDATION*)
- **2.1.2 Upper limit of Hb:**
In the opinion of the Work Group, there is insufficient evidence to recommend routinely maintaining Hb levels ≥ 13.0 g/dL in ESA-treated patients

Step 1: Summarize RCTs by Outcomes

Table 12. RCTs

Author, Year
ESA vs. ESA
Besarab, 1998 ¹⁰⁶
Parfrey, 2005 ¹⁰⁹
Foley, 2000 ¹¹⁰
CanEPO, 1990-1991 ^{49, 117}
Furuland, 2003 ¹¹⁸
Suzuki, 1989 ¹¹⁹
Furuland, 2005 ¹²⁰ Substudy of Furuland, 2003
McMahon, 1999, 2000 ^{121, 122}

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Furuland, 2005 ¹²⁰ Substudy of Furuland, 2003
McMahon, 1999, 2000 ^{121, 122}

Applicability	Distinct Hb Targets/Levels on Key Clinical Outcomes in the					
	Arm 1	Mean Hb (g/dL) Target (Achieved)	Clinical Outcomes (All)			
	Arm 2		CVD Events (%)	LVH	Mortality (%)	Hospitalization
	Arm 3					
↑↑	ESA High	14.0 (12.7-13.3)	*Nonfatal MI 3.1 vs. 2.3 NS ^c	—	*29.6 vs. 24.4 NS ^c	NS
	ESA Low	10.0 (10.0)				
↑↑	ESA High	13.5-14.5 (13.3)	CVA: 4 vs. 1 P = 0.045	*NS	NS	—
	ESA Low	9.5-11.5 (10.9)	Other CVD: NS			
↑↑	ESA High	13-14 (13)				—
	ESA Low	9.5-10.5 (10.5)	NS	*NS	NS	—
↑↑	ESA High	11.5-13 (11.7)				—
	ESA Low	9.5-11 (10.2)	—	—	NS	—
	Placebo	(7.4)				—
↑↑	ESA High	13.5-16.0 (3.6)	—	—	NS	NS
	ESA Low	9-12 (11.3-11.7)				
↑	ESA High*	<11 (8.7)				—
	ESA Low	(8.2)				
	Placebo	(6.1)				—
↑	ESA High	13.5-16.0 (14.3)	—	—	—	—
	ESA Low	9-12 (10.9)				
↑	ESA High*	14 (14)	—	—	—	—
	ESA Low	10 (10)				

Mortality (%)	D-CKD Populations		
*29.6 vs. 24.4 NS ^c	3)		
NS	Transfusion (%)	QOL ^b	Quality
NS	21 vs. 31 P = 0.001	See QOL Table	●
NS	—	See QOL Table	●
NS	—	See QOL Table	●
NS	3 vs. 3 vs. 72 ESA vs. Placebo: P < 0.05 ^f	*High vs. Low: NS ESA vs. Placebo: P = 0.024	●
NS	—	*See QOL Table	○
—	8 vs. 5 vs. 23 ESA vs. Placebo: P < 0.05	See QOL Table	○
—	—	—	○
—	—	P < 0.02	○
—			

Step 2: Profile Evidence for Each Outcome

Author, Year	Study Title	Follow-up (mo)	Arm 1	Arm 2	Arm 3	Mean Hb (g/dL) Target (achieved)	BP Change or Hypertension	AEs (Arm)	Other Reported AE ^a	Description and Results	Total D/C of Drug
Besarab, 1998 ¹⁰⁴	ESAs versus ESAs in RCTs Examining Distinct Hb Targets/Levels in HD-CKD		ESA High	ESA Low		14.0 (12.7-13.3)	Mean SBP and DBP during the study ^c	Both AV graft AV fistula	—	—	0
Parfrey, 2005 ¹⁰⁹	ESAs versus ESAs in RCTs Examining Distinct Hb Targets/Levels in HD-CKD	14	ESA High	ESA Low		14.0 (12.7-13.3)	Mean SBP and DBP during the study ^c	Both AV graft AV fistula	Overall treatment emergent AE in ≥10% of patients: 96% vs. 94% ^d	—	0
Parfrey, 2005 ¹⁰⁹	ESAs versus ESAs in RCTs Examining Distinct Hb Targets/Levels in HD-CKD	24	ESA High	ESA Low		13.5-14.5 (13.3)	Hypertension not specified	AV fistula permanent catheter, not specific embol	Individuals with at least 1 SAE NOS: 51% vs. 38.5% (NS)	Overall treatment emergent AE in ≥10% of patients: 96% vs. 94% ^e	nd
Furuland, 2003 ¹¹⁸	ESAs versus ESAs in RCTs Examining Distinct Hb Targets/Levels in HD-CKD	12	ESA High	ESA Low		13.5-16.0 (13.4-14.3)	Δ mean DBP from baseline	Complication AV graft, fistulae or cath during stud	Thromboembolic: Event: 56 vs. 47 per arm (NS) ^f	Individuals with at least 1 SAE NOS: 51% vs. 38.5% (NS)	34
Furuland, 2003 ¹¹⁸	ESAs versus ESAs in RCTs Examining Distinct Hb Targets/Levels in HD-CKD	12	ESA High	ESA Low		9-12 (11.3-11.7)	Δ mean DBP from baseline	Complication AV graft, fistulae or cath during stud	Thromboembolic: Event: 56 vs. 47 per arm (NS) ^f	Individuals with at least 1 SAE NOS: 51% vs. 38.5% (NS)	15
Suzuki, 1989 ¹¹⁶	ESAs versus ESAs in RCTs Examining Distinct Hb Targets/Levels in HD-CKD	2	ESA High	ESA Low	Placebo	<11 (8.7)	Increased dose of anti-HTN meds	5 vs. 4 vs. 1 individuals	No. of AE NOS 6.7% vs. 8.3% vs. 1.7% per arm ^g	No. of AE NOS 6.7% vs. 8.3% vs. 1.7% per arm ^h	nd ^h
Foley, 2000 ¹¹⁶	ESAs versus ESAs in RCTs Examining Distinct Hb Targets/Levels in HD-CKD	11	ESA High	ESA Low		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	—	—	nd
Abraham, 1991 ¹²⁷	ESAs versus ESAs in RCTs Examining Distinct Hb Targets/Levels in HD-CKD	2.5-4.5	ESA 200 U/kg	ESA 100 U/kg	ESA 25 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
Abraham, 1991 ¹²⁷	ESAs versus ESAs in RCTs Examining Distinct Hb Targets/Levels in HD-CKD		ESA 200 U/kg	ESA 100 U/kg	ESA 25 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

Step 3: Grade Evidence for Each Key Outcome Category

Table 20. Target Hb Levels in the HD-CKD and PD-CKD Populations

Outcome	No. of Studies & Study Design	Total N of Patients	Methodological 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 of High vs. Low Hb Target	Importance of Outcome
All-Cause Mortality	7 RCTs	2,790	No limitations ^a	Important inconsistencies ^b	Some uncertainty ^c	None	High for patients with CVD Moderately high 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 (Hazard ratio [95% CI] 1.3 [0.9-1.9]). Other studies (without large number of CVD patients) show no difference between arms.	High
Nonfatal CV Events	4 RCTs	2,104	Some limitations ^d	No important inconsistencies	Direct	Not sparse ^e	Moderately high	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

No consistent or statistically significant benefit. Partial

Nonfatal CV Events

4 RCTs

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.

Score, General Instrument

4 RCTs

400

Some limitations ^h

Important inconsistencies ⁱ

Direct

None

high

showed no differences. Besarab study did not report global score but showed increase in physical function.

High

QOL-With Kidney-Specific Instruments

4 RCTs

1,113

Some limitations

Important inconsistencies ⁱ

Direct

None

Moderately high

Likely some benefit. 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

High

Balance of Benefit and Harm:

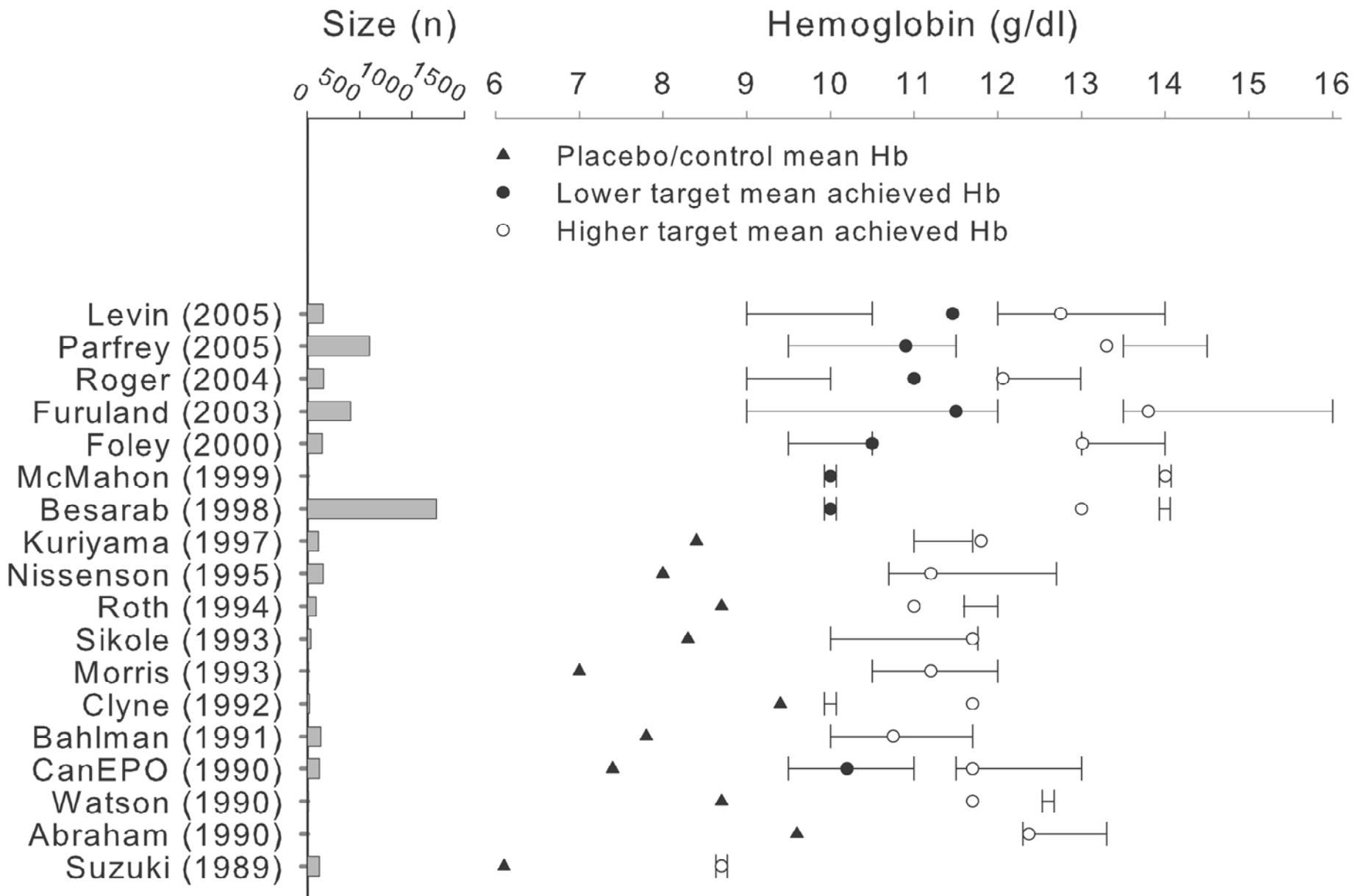
Net Benefit at Hb ≥11 g/dL based on QOL; Uncertain Trade Off with Increasing Hb Levels, QOL

Benefit may be offset by potential for harm

better.
= 0.05.
as 1/3
rms,
High

Quality of Overall Evidence:
Moderately High

RCTs with Upper & Lower Hb Targets



Hb Treatment Range: Key findings

- 22 RCTs available
 - Dating from first clinical trials with epoetin alfa
- Early RCTs differ from those after 1997
 - Early are small, show low baseline Hb (6-9 g/dL), midrange upper target (10 – 13 g/dL)
 - Recent trials are larger, baseline is mid-range, higher target arm is ≥ 13 g/dL

Efficacy and Safety Across the Spectrum of Anemia Treatment

- Range of Hb studied: 6 to 16 g/dL
- Efficacy:
 - *Improved Quality of Life (QOL)*
 - QOL increases with increase in Hb
 - *Fewer transfusions*
 - Transfusion frequency decreases as Hb increases
 - No improvement in mortality, LVH, CV events
- Safety issues are present in upper Hb arm
 - RCTs with Hb treatment arm ≥ 13 g/dL

Assessing safety of higher Hb treatment arms

- Of 22 available RCTs, only 1 had adequate power to examine safety; showed potential harm
 - Besarab 1998 (Normal Hct Heart Trial)
 - Terminated early for safety concerns
- An additional RCT also showed safety risk
 - Parfrey 2005 (Canada-Europe)
 - Increased stroke in higher target (13.5 -14.5 g/dL) compared to lower target (9.5 to 11.5 g/dL)
- Unpublished: CREATE, [CHOIR](#), ACCORD, TREAT



Clinical Practice Recommendations 3.1

Using Erythropoiesis- Stimulating Agents (ESAs)

Using ESAs: Frequency of Hb monitoring

- 3.1.1 Frequency of Hb monitoring:
 - **3.1.1.1 In the opinion of the Work Group, the frequency of Hb monitoring in patients treated with ESAs should be at least monthly.**

Using ESAs: Dosing

- 3.1.2 ESA dosing:
 - **3.1.2.1 In the opinion of the Work Group, the initial ESA dose and ESA dose adjustments should be determined by the patient's Hb level, the target Hb level, the observed rate of rise of the Hb level, and clinical circumstances.**
 - **3.1.2.2 In the opinion of the Work Group, ESA doses should be decreased but not necessarily withheld when a downward adjustment of Hb is needed.**
 - **3.1.2.3 In the opinion of the Work Group, scheduled ESA doses that have been missed should be replaced at the earliest possible opportunity.**
 - **3.1.2.4 In the opinion of the Work Group, ESA administration in ESA-dependent patients should continue during hospitalization.**

Using ESAs: Dosing (*continued*)

- **3.1.2.5 In the opinion of the Work Group, hypertension, vascular access occlusion, inadequate dialysis, history of seizures or compromised nutritional status are not contraindications to ESA therapy.**

Using ESAs: Route of Administration

- 3.1.3 Route of administration:
 - **3.1.3.1 In the opinion of the Work Group, the route of ESA administration should be determined by the CKD stage, treatment setting, efficacy, safety, and the class of ESA used.**
 - **3.1.3.2 In the opinion of the Work Group, convenience favors subcutaneous (SC) administration in non-HD-CKD patients.**
 - **3.1.3.3 In the opinion of the Work Group, convenience favors IV administration in HD-CKD patients.**

Using ESAs: Frequency of administration

- 3.1.4 Frequency of administration
 - **3.1.4.1 In the opinion of the Work Group, frequency of administration should be determined by the CKD stage, treatment setting, efficacy considerations, and the class of ESA.**
 - **3.1.4.2 In the opinion of the Work Group, convenience favors less frequent administration, particularly in non-HD-CKD patients.**

Using ESAs: Key Statements

- Measure Hb at least monthly after initiating ESA therapy
- Initial ESA dose – use clinical judgment
- Decrease but don't hold ESA dose for high Hb
- Don't hold ESA during hospitalization
- Replace missing ESA doses
- Consider convenience in choosing IV vs SC



Guideline and Clinical Practice Recommendations 3.2

Using Iron Agents

Using Iron Agents: Frequency of monitoring iron status tests

- 3.2.1 Frequency of iron status tests:

In the opinion of the Work Group, iron status tests should be performed as follows:

- **3.2.1.1 Every month during initial ESA treatment;**
- **3.2.1.2 At least every 3 months during stable ESA treatment or in HD-CKD patients not treated with an ESA**

Using Iron Agents: Interpretation of iron status tests

- 3.2.2 Interpretation of iron status tests:

In the opinion of the Work Group, results of iron status tests, Hb, and ESA dose should be interpreted together to guide iron therapy.

Using Iron Agents: Targets of iron therapy

- 3.2.3 Targets of iron therapy:

In the opinion of the Work Group, sufficient iron should be administered to generally maintain the following indices of iron status during ESA treatment:

- 3.2.3.1 HD-CKD:

- Serum ferritin >200 ng/mL, *and*
- TSAT >20%, or CHr >29 pg/cell

- 3.2.3.2 ND-CKD and PD-CKD:

- Serum ferritin >100 ng/mL *and*
- TSAT >20%

- 3.2.4 Upper level of ferritin:

- **In the opinion of the Work Group, there is insufficient evidence to recommend routine administration of IV iron if serum ferritin is > 500 ng/mL. When ferritin is > 500 ng/mL, decisions regarding IV iron administration should weigh ESA responsiveness, Hb level, TSAT, and the patient's clinical status.**

Using Iron Agents: Route of administration

- 3.2.5 Route of administration
 - 3.2.5.1 The preferred route of administration is IV in HD-CKD patients. (***STRONG RECOMMENDATION***)
 - 3.2.5.2. In the opinion of the Work Group, the route of iron administration can be either IV or oral in ND-CKD and PD-CKD patients.

Using Iron Agents: Hypersensitivity reactions

- 3.2.6 Hypersensitivity reactions:

In the opinion of the Work Group, resuscitative medication and personnel trained to evaluate and resuscitate anaphylaxis should be available whenever a dose of iron dextran is administered.

Ferritin upper limits: Key findings

- No RCTs have compared the safety and efficacy of ferritin targets above 500 ng/mL to safety and efficacy of lower targets
- Few studies have examined efficacy of IV iron at ferritin levels above 500 ng/mL
- No study has examined either efficacy or safety beyond surrogate outcomes
- No information from interventional trials is available about the safety of ferritin targets > 500 ng/mL
- Sufficient evidence exists to suggest that tissue iron stores in patients with ferritin levels > 500 ng/mL are normal to above normal.



Guideline and Clinical Practice Recommendations 3.3

Using Pharmacologic and Non-Pharmacologic Adjuvants to ESA Therapy

Using Adjuvants to ESA Treatment in HD-CKD

- **3.3.1 L-carnitine:**
In the opinion of the Work Group, there is insufficient information to recommend use of L-carnitine in the management of anemia in CKD patients.
- **3.3.2 Vitamin C:**
In the opinion of the Work Group, there is insufficient information to recommend use of vitamin C (ascorbate) in the management of anemia in CKD patients.
- **3.3.3 Androgens:**
Androgens should not be used as an adjuvant to ESA treatment in anemic CKD patients. (*STRONG RECOMMENDATION*)

Other Potential Adjuvants to ESA Treatment in HD: Insufficient evidence

- Statins
- Pentoxifylline
- Vitamins other than vitamin C
- $Kt/V > 1.2$
- Biocompatible dialyzer membrane
- High flux dialyzers
- Ultrapure dialysate
- Hemodiafiltration
- Daily and nocturnal HD
- PD



Clinical Practice Recommendations 3.4

Transfusion Therapy

Transfusion Therapy

- **3.4.1 In the opinion of the Work Group, no single Hb concentration justifies or requires transfusion. In particular, the recommended lower limit of Hb for ESA treatment (see Guideline 2.1) *should not serve as a trigger for transfusion.***



Guideline and Clinical Practice Recommendations 3.5

*Evaluating and Correcting
Persistent Failure To Reach or
Maintain Lower Limit of Hb*

Evaluating and Correcting Persistent Failure To Reach or Maintain Hb \geq 11.0 g/dL

- 3.5.1 Hyporesponse to ESA and iron therapy:

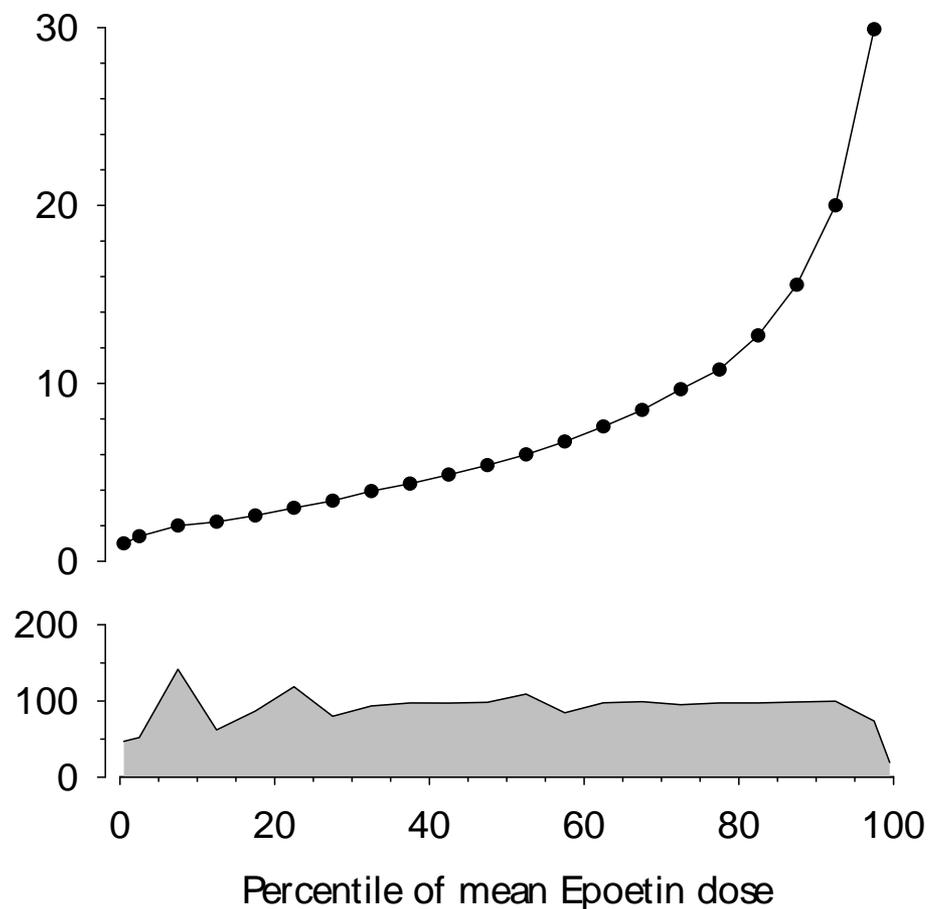
In the opinion of the Work Group, the patient with anemia and CKD should undergo evaluation for specific causes of hyporesponse whenever the Hb level is inappropriately low for the ESA dose administered. Such conditions include, but are not limited to: :

- **A significant increase of the ESA dose requirement to maintain a certain Hb level or a significant drop in Hb at a constant ESA dose.**
- **A failure to increase the Hb above 11 g/dL, despite an ESA dose equivalent to epoetin >500 IU/kg/week**

Hypo-response to ESA: Doses at the 95th percentile or greater

Mean epoetin dose
per administration
(IU x 1000)

Number of
administrations
per percentile range
(x 1000)



Evaluation for Pure Red Cell Aplasia (PRCA)

- 3.5.2 Evaluation for PRCA:

In the opinion of the Work Group, evaluation for antibody-mediated PRCA should be undertaken when a patient receiving ESA therapy for more than 4 weeks develops each of the following:

- **Sudden, rapid decline of Hb at the rate of 0.5-1.0 g/dL/week, *or* requirement of red blood cell transfusions at the rate of approximately 1-2 per week *AND***
- **Normal platelet and white blood cell counts *AND***
- **Absolute reticulocyte count $<10,000/\mu\text{L}$**