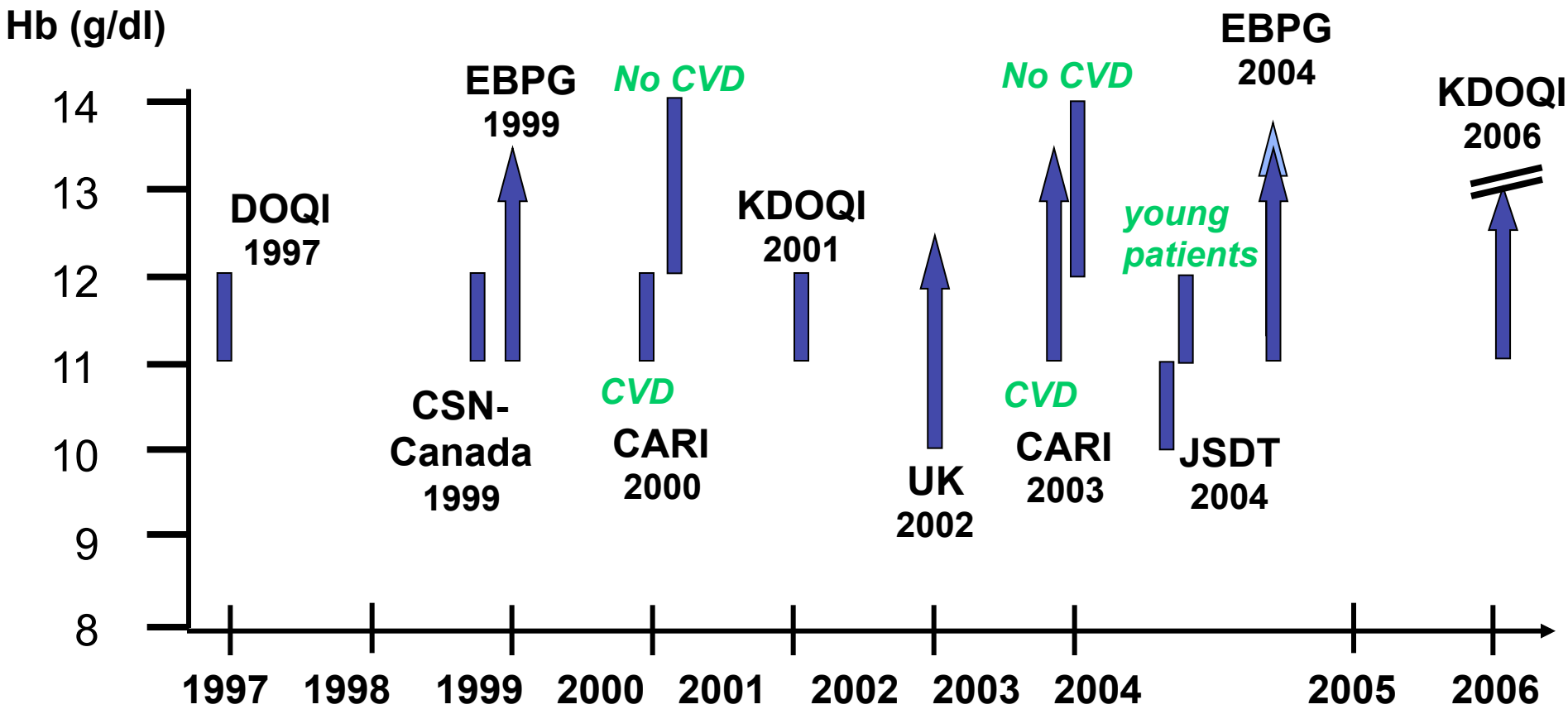
KDOQI 2007 Update on hemoglobin target:

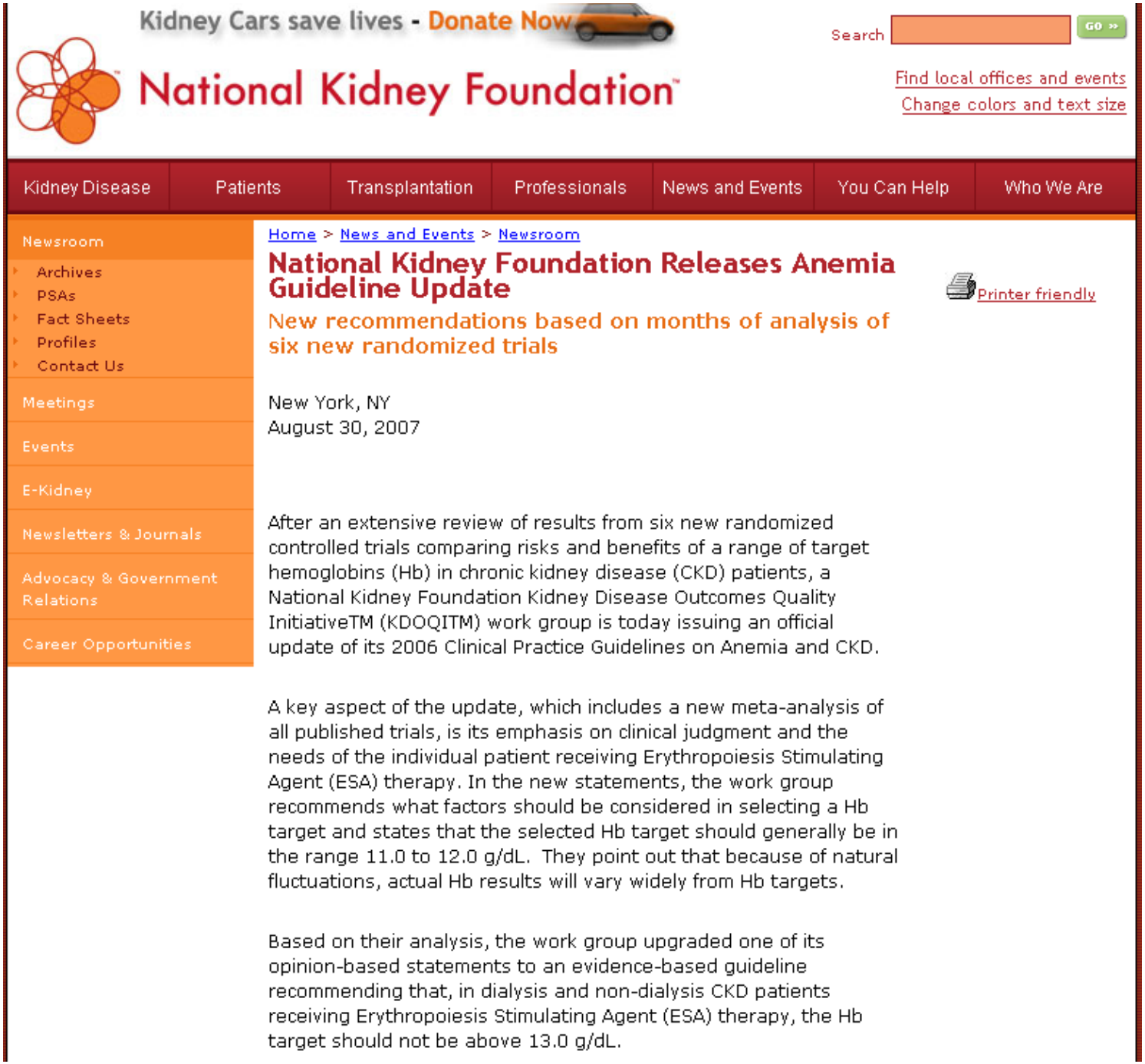
Recommendation and evidence base

Kai-Uwe Eckardt & David van Wyck

Target Hb values in international guidelines



Locatelli et al. *Nephrol Dial Transplant* 2004;19(Suppl 2):1-43
NKF-KDOQI. *AJKD* 2001;37(Suppl 1):S182-238; NKF-KDOQI. *AJKD* 2006;47(Suppl 3):S11-145
CARI. www.cari.org.au/dialysis_bht_updating.php, 2005
Renal Association. www.renal.org/Standards/Renal STandards_2002b.pdf, 2002
CSN. http://csnscn.ca/local/files/guidelines/CSN-Guidelines-1999.pdf, 1999



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National Kidney Foundation Releases Anemia Guideline Update

Printer friendly

New recommendations based on months of analysis of six new randomized trials

New York, NY
August 30, 2007

After an extensive review of results from six new randomized controlled trials comparing risks and benefits of a range of target hemoglobins (Hb) in chronic kidney disease (CKD) patients, a National Kidney Foundation Kidney Disease Outcomes Quality InitiativeTM (KDOQITM) work group is today issuing an official update of its 2006 Clinical Practice Guidelines on Anemia and CKD.

A key aspect of the update, which includes a new meta-analysis of all published trials, is its emphasis on clinical judgment and the needs of the individual patient 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 that the selected Hb target should generally be in the range 11.0 to 12.0 g/dL. They point out that because of natural fluctuations, actual Hb results will vary widely from Hb targets.

Based on their analysis, the work group upgraded one of its opinion-based statements to an evidence-based guideline recommending that, in dialysis and non-dialysis CKD patients receiving Erythropoiesis Stimulating Agent (ESA) therapy, the Hb target should not be above 13.0 g/dL.

Workgroup

D. Van Wyck (Co-chair)
K.-U. Eckardt (Co-chair)

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S. Fishbane
R.N. Foley
S. Ghaddar
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A.R. Nissenson
G.T. Obrador
J.C. Stivelman
C.T. White

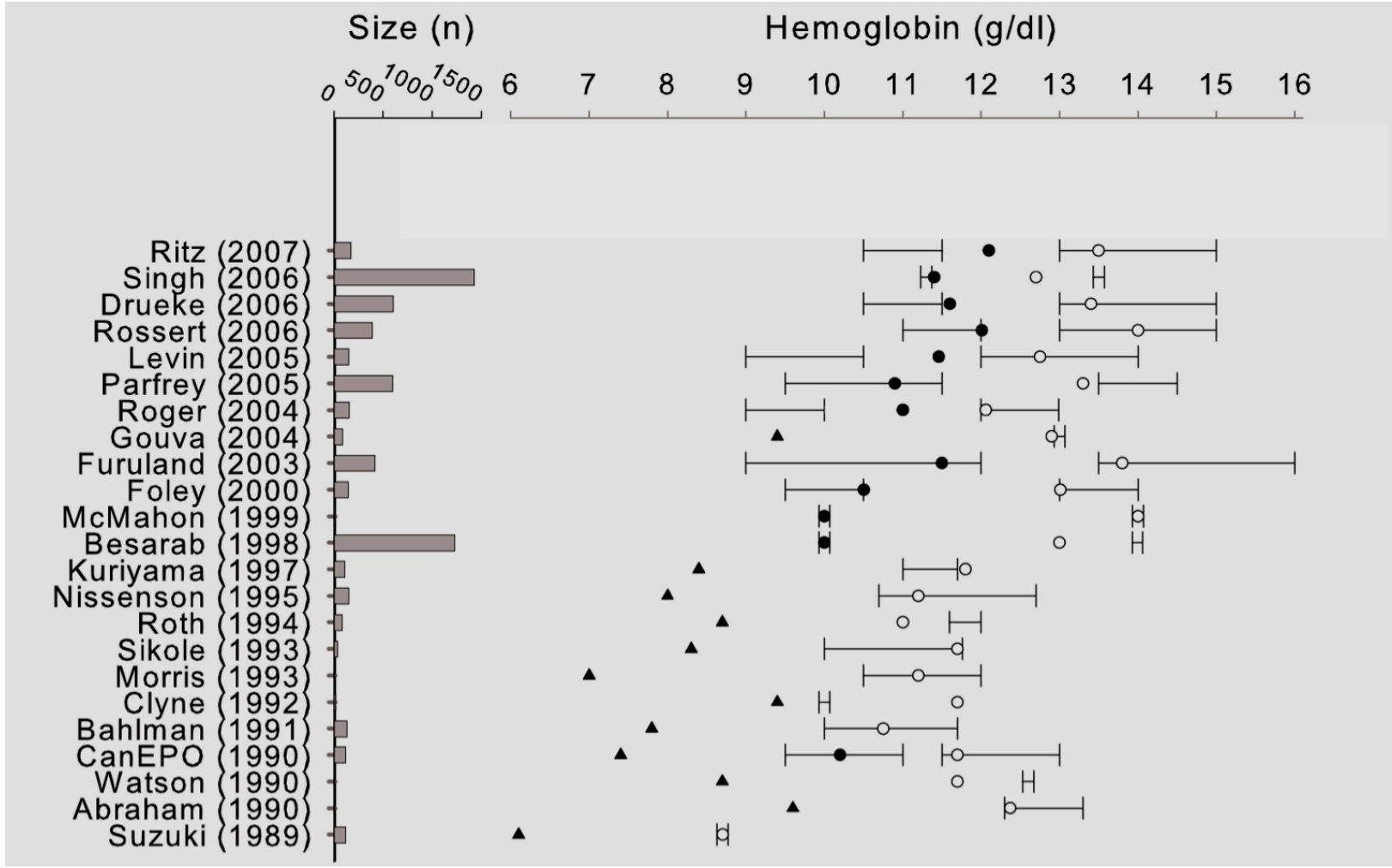
Liason members
I. Macdougall
F.Locatelli

KDOQI anemia guidelines - target Hb update

- Interdisciplinary, international work-group
- ERT: New England Medical Center, Boston
    - Systematic review and analysis of published data, including 5 trials published since 2006, which doubled the number of CKD patients studied and increased the number of nondialysis CKD patients studied from 575 to 3432
    - Metaanalysis
- Leading principle:

  Evidence is not limited to RCTs, but RCTs usually provide the strongest evidence.

RCTs assigning CKD patients to different target Hb levels



Adapted from NKF-K/DOQI. *AJKD* 2007

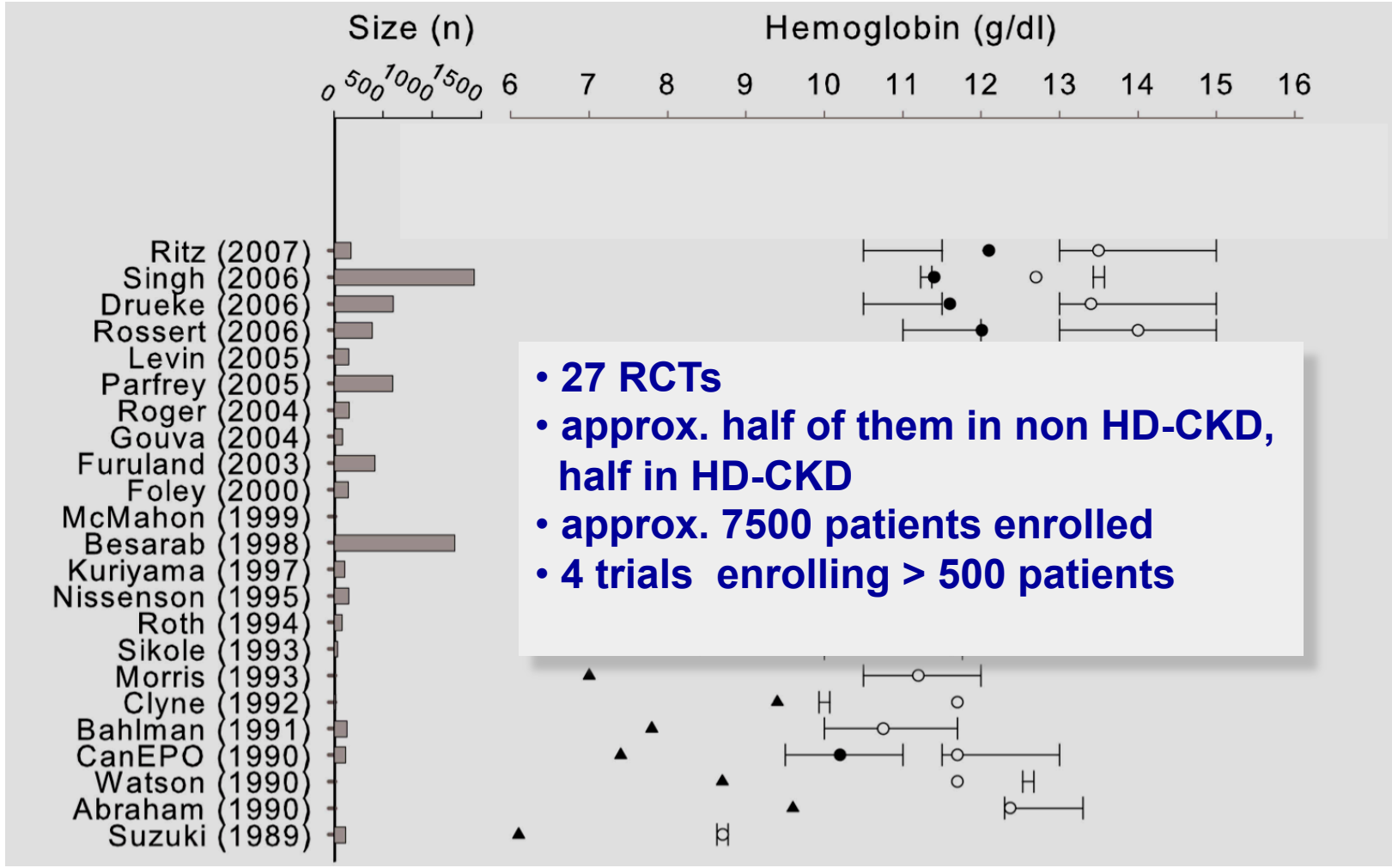
▲ **Placebo/control mean Hb**

● **Lower Hb arm: mean achieved Hb**

○ **Higher Hb arm: mean achieved Hb**

Target range

RCTs assigning CKD patients to different target Hb levels



- 27 RCTs
- approx. half of them in non HD-CKD, half in HD-CKD
- approx. 7500 patients enrolled
- 4 trials enrolling > 500 patients

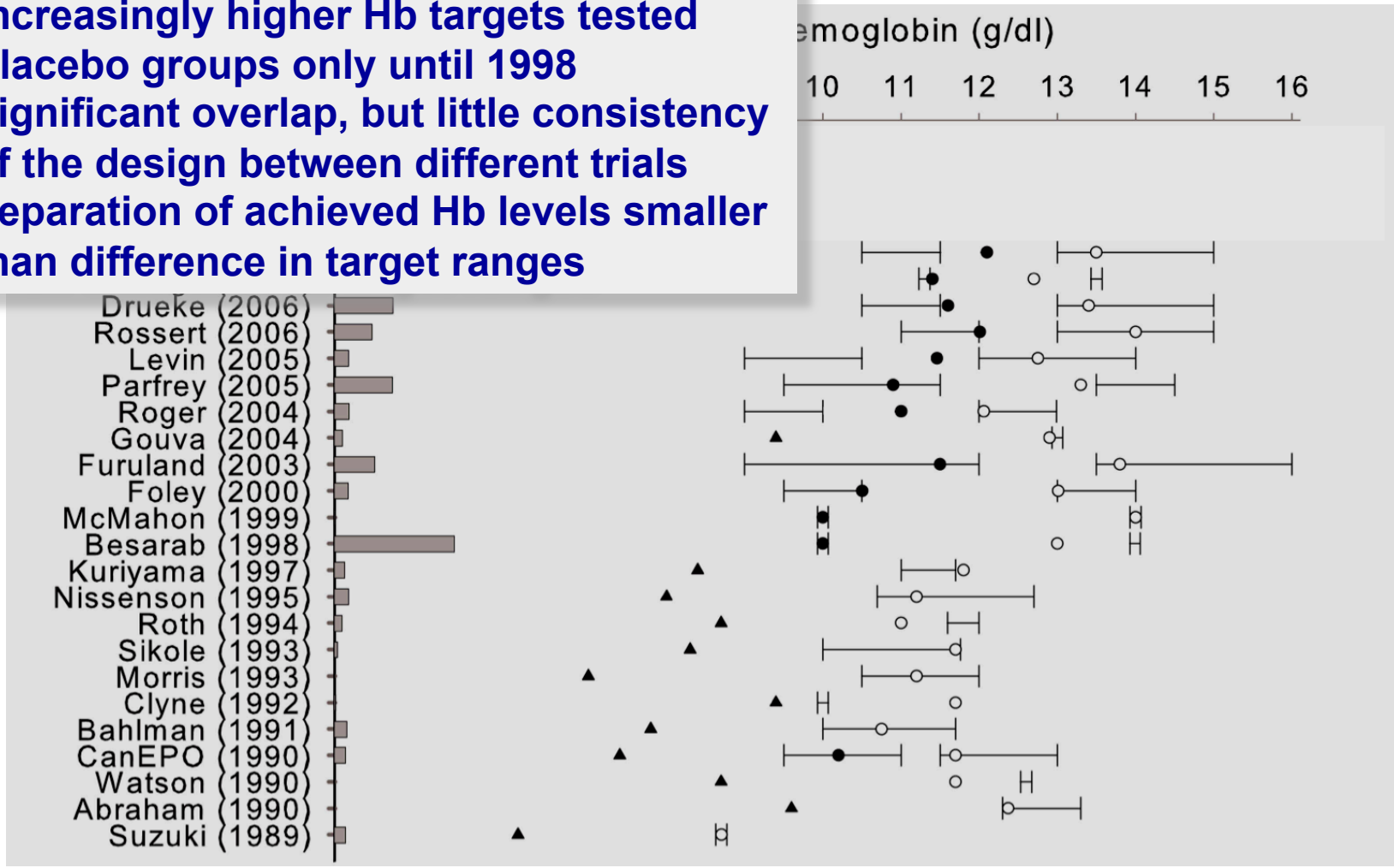
Adapted from NKF-K/DOQI. *AJKD* 2007

▲ Placebo/control mean Hb
● Lower Hb arm: mean achieved Hb
○ Higher Hb arm: mean achieved Hb

Target range

RCTs assigning CKD patients to different target Hb levels

- overall Hb range between 6 and 16 g/dl
- increasingly higher Hb targets tested
- placebo groups only until 1998
- significant overlap, but little consistency of the design between different trials
- separation of achieved Hb levels smaller than difference in target ranges



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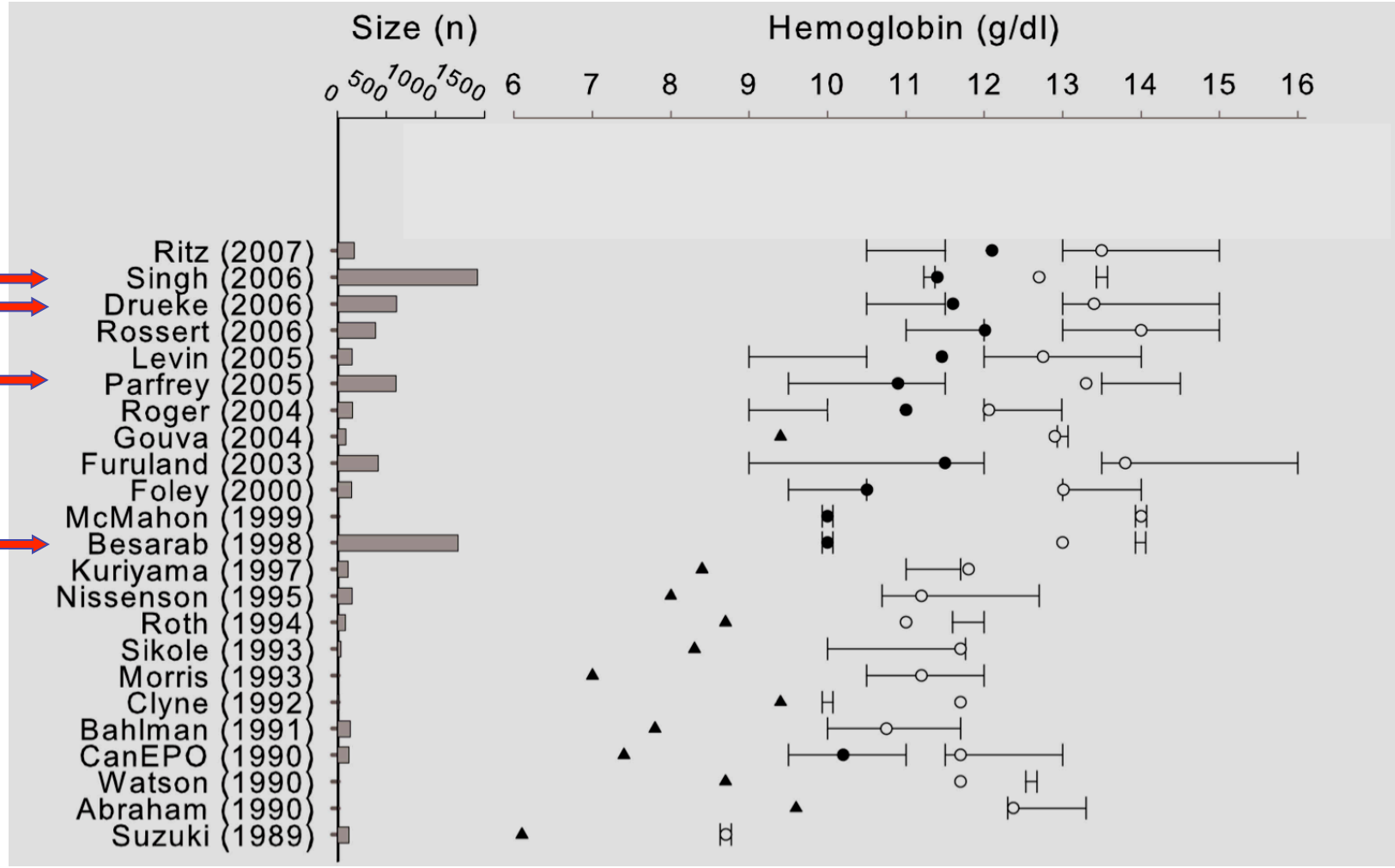
Target range

RCTs assigning CKD patients to different target Hb levels



Adapted from NKF-K/DOQI. *AJKD* 2007

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○ **Higher Hb arm: mean achieved Hb**

Target range

The New England Journal of Medicine August 27, 1998

THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT VALUES IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMODIALYSIS AND EPOETIN

ANATOLE BESARAB, M.D., W. KLINE BOLTON, M.D., JEFFREY K. BROWNE, PH.D., JOAN C. EGRIE, PH.D., ALLEN R. NISSENSON, M.D., DOUGLAS M. OKAMOTO, PH.D., STEVE J. SCHWAB, M.D., AND DAVID A. GOODKIN, M.D.

Patients:	1233, HD, clinical evidence of CHF or IHD, hct 27-33 %	
Design:	iv / sc Epoetin alfa	High arm: target hct 42 ± 3 % (= Hb 14)
		Low arm: target hct 30 ± 3 % (= Hb 10)
Primary EP:	composite of death and 1st non-fatal MI (time to first event)	

Main results:
- study terminated early (futility, safety concerns)
- more patients in the higher arm reached the endpoint (n.s.)
- physical function score increased with hct
- incidence of vascular access thrombosis higher in higher arm (243 vs 176; p=0.001)

Besarab A et al N Engl J Med 1998;339:584-590

Double-Blind Comparison of Full and Partial Anemia Correction in Incident Hemodialysis Patients without Symptomatic Heart Disease

2005

Patrick S. Parfrey,* Robert N. Foley,† Barbara H. Wittreich,‡ Daniel J. Sullivan,§ Martin J. Zagari,‡ and Dieter Frei;‡ for the Canadian European Study Group

Memorial University of Newfoundland, St. John's, Newfoundland, Canada; †Chronic Disease Research Group, Minneapolis, Minnesota; ‡Ortho Biotech, Bridgewater, New Jersey; and §Johnson and Johnson, Pharmaceutical Research, LLC, Raritan, New Jersey

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Patients:	596, recent HD initiation, no symptomatic heart disease, no left ventricular dilatation
Design:	iv / sc Epoetin alfa double-blind High arm: target Hb 13.5 – 14.5 Low arm: target Hb 9.5 – 11.5
Primary EP:	left ventricular volume index (LVVI)
Secondary EP:	LVMI, de novo CHF, QOL, 6-min walking test
Main results:	- changes in LVVI similar - only difference in secondary outcomes: improved SF-36 vitality score in the higher vs lower arm - adverse events similar, except rates of skeletal pain, surgery, and dizziness higher in lower arm; headache and cerebrovascular events higher in higher arm

Parfrey PS et al J Am Soc Nephrol 2005;16:2180-2189

The NEW ENGLAND JOURNAL of MEDICINE November 16, 2006

Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia

Tilman B. Drüeke, M.D., Francesco Locatelli, M.D., Naomi Clyne, M.D., Kai-Uwe Eckardt, M.D., Iain C. Macdougall, M.D., Dimitrios Tsakiris, M.D., Hans-Ulrich Burger, Ph.D., and Armin Scherhag, M.D., for the CREATE Investigators*

Patients:	603, eGFR 15-35, Hb 11-12.5
Design:	sc Epoetin beta High arm: target 13.0 – 15.0
	Low arm: when Hb < 10.5 → target 10.5 – 11.5
Primary EP:	composite of 8 CV events (time to first event)
Secondary EP:	change in LVMI, QOL, progression of CKD and others

Main results:
- no difference in primary endpoint
- improvement in QOL
- time to dialysis shorter in higher arm

Drüeke TB et al N Engl J Med 2006;355:2071-84

The NEW ENGLAND JOURNAL of MEDICINE November 16, 2006

Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease

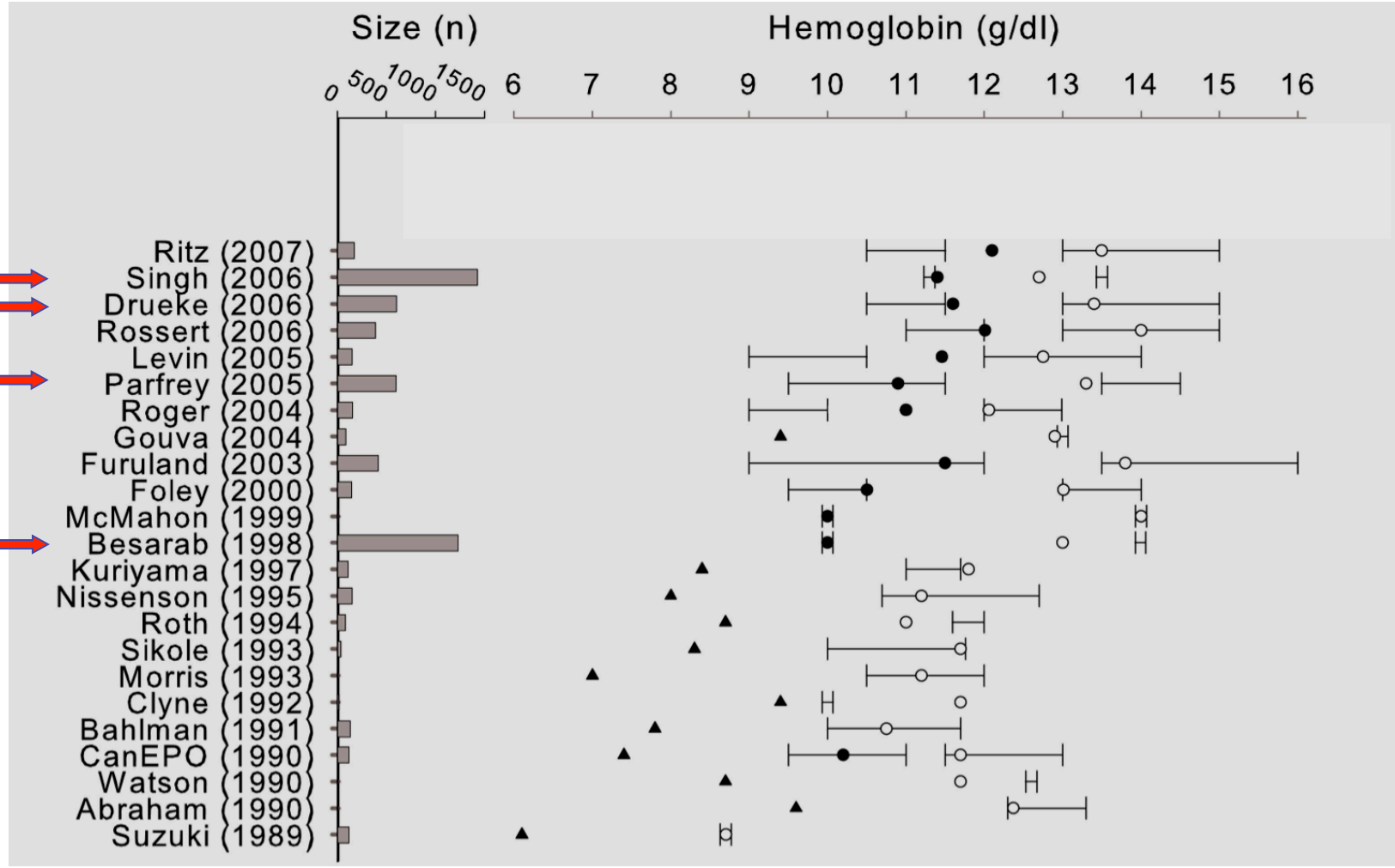
Ajay K. Singh, M.B., B.S., Lynda Szczech, M.D., Kezhen L. Tang, Ph.D., Huiman Barnhart, Ph.D., Shelly Sapp, M.S., Marsha Wolfson, M.D., and Donal Reddan, M.B., B.S., for the CHOIR Investigators*

Patients:	1432, eGFR 15-50, Hb < 11
Design:	sc Epoetin alfa High arm: target 13.5
	Low arm: target 11.3
Primary EP:	composite of 4 CV events (time to first event)
Secondary EP:	change in QOL, RRT and others

Main results:
- study terminated early (futility, safety ?)
- more patients in the higher arm had at least one CV event
- no improvement in QOL
- trend towards a higher rate of progression to RRT

Singh AK et al N Engl J Med 2006;355:2085-98

RCTs assigning CKD patients to different target Hb levels



Adapted from NKF-K/DOQI. *AJKD* 2007

▲ **Placebo/control mean Hb**

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○ **Higher Hb arm: mean achieved Hb**

Target range

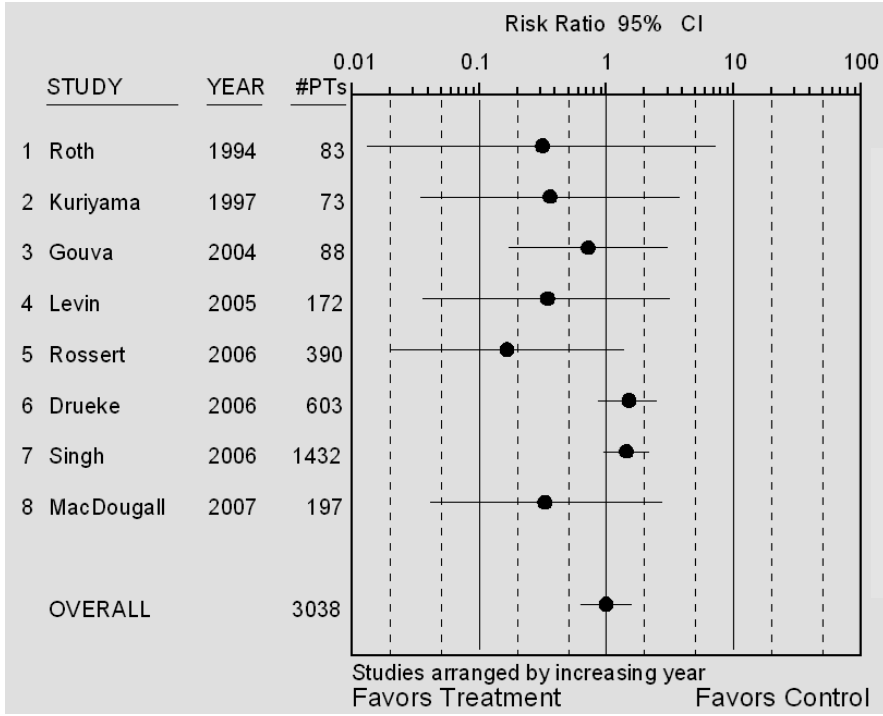
Meta-analysis

	KDOQI - ERT	Phrommintikul A, *Lancet 369, 2007*
Follow-up	6 months or longer	12 weeks or longer
Study size	all	> 100 subjects
HD-CKD / non HD-CKD	analysed separately	pooled
CV events	all	MI

Meta-analysis

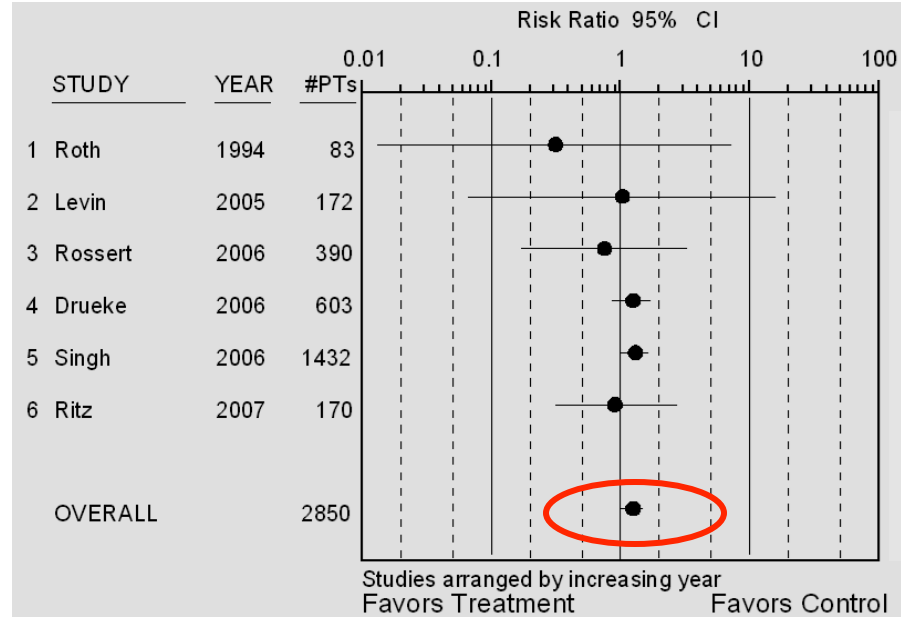
Non-dialysis CKD patients

rel. mortality risk



Z = 0.04; 2p = 0.97

rel. risk of adverse CV events



Z = 2.19; 2p = 0.029

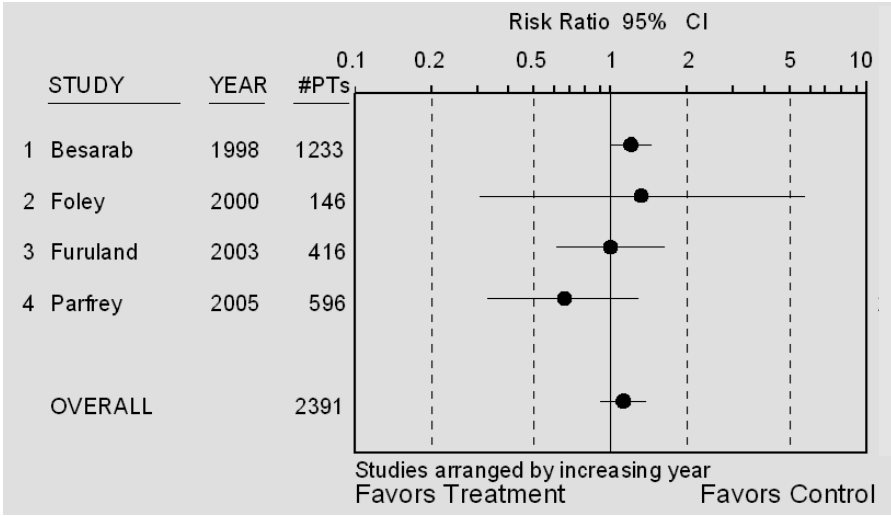
for assignment to higher Hb target

Adapted from NKF-K/DOQI Update of Hb target, 2007

Meta-analysis

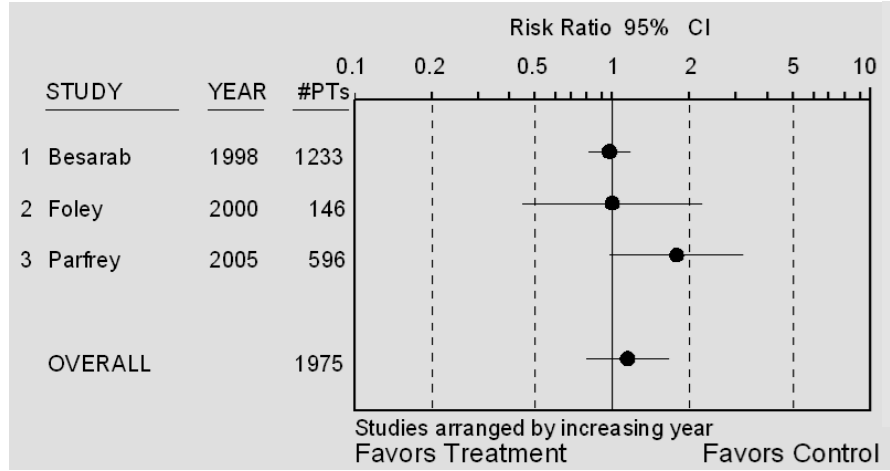
Dialysis CKD patients

rel. mortality risk



Z = 1.04; 2p = 0.30

rel. risk of adverse CV events

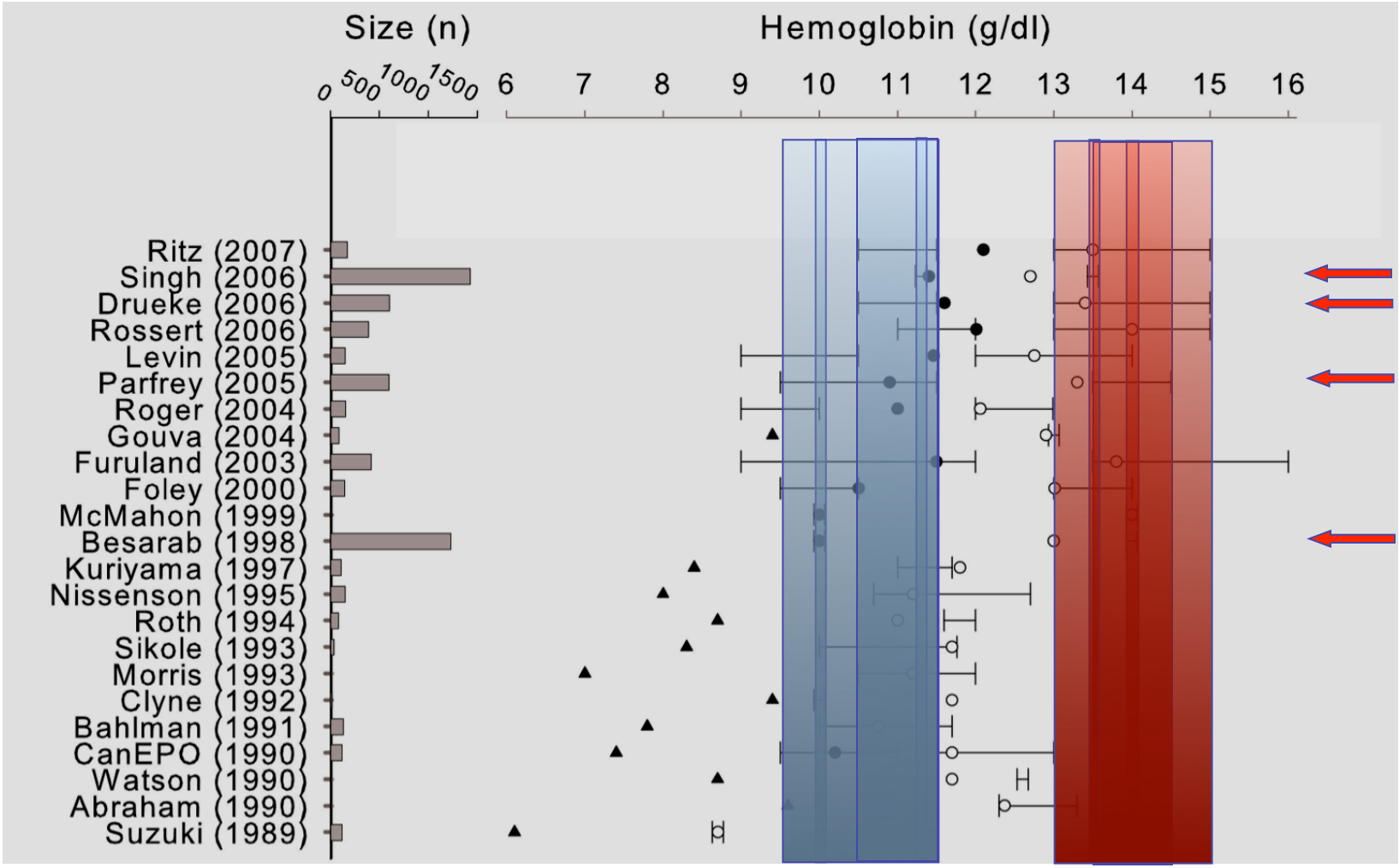


Z = 0.69; 2p = 0.49

for assignment to higher Hb target

Adapted from NKF-K/DOQI Update of Hb target, 2007

What is the optimal target Hb ?



Adapted from NKF-K/DOQI. *AJKD* 2007

▲ **Placebo/control mean Hb**

● **Lower Hb arm: mean achieved Hb**

○ **Higher Hb arm: mean achieved Hb**

Target range

KDOQI anemia guidelines - target Hb update

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

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. **In the opinion of the work group, in dialysis and non-dialysis CKD patients receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL.**
   (Clinical Practice RECOMMENDATION)
3. **In dialysis and non-dialysis CKD patients receiving ESA therapy, the Hb target should not be above 13.0 g/dL.**
   (Clinical Practice GUIDELINE - MODERATELY STRONG EVIDENCE)

Target Hb update – Introductory statement

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

Rationale

- **"Hb target"** is the aim of ESA therapy
- **"achieved Hb"** is the result of ESA therapy
- distinction between "**Hb targets**" and "**achieved Hb levels**" is fundamental for the development of the guideline
- higher achieved Hb levels in patients assigned to similar targets are associated with decreased risk of mortality and hospitalization

Target Hb update – CPR 2.1.1

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)

Rationale

- **"selection of the Hb target"** and of the "**Hb level at which ESA therapy is initiated"** are separate, but related steps in decision making
- **"should include consideration"** reflects limitations of evidence
- **HrQoL** is an outcome of direct importance to patients and should be valued accordingly; despite limitations (low-quality) evidence suggests benefit of HrQOL
- **avoidance of transfusions** is a relevant outcome; higher compared with lower targets are associated with a decrease in RBC transfusion rates
- **Potential harms** refers to outcomes from RTCs with assignment to > 13 g/dl

Target Hb update – CPR 2.1.2

2. **In the opinion of the work group, in dialysis and non-dialysis CKD patients receiving ESA therapy, the selected Hb target should generally be in the range of 11.0 to 12.0 g/dL.**
   (Clinical Practice RECOMMENDATION)

Rationale

- based on the results of 29 RCTs
- **"selected Hb target"** used to distinguish between Hb target and achieved Hb level
- **"generally"** emphasizes need to maintain flexibility
- **"Hb target … in the range 11.0 to 12.0 g/dl"** defines either a target range or a range of possible single-point targets; entails unavoidable subjectivity; reflects work-group efforts to balance potential benefits against the potential harm with Hb targets > 13 g/dl

Target Hb update – CPR 2.1.3

3. **In dialysis and non-dialysis CKD patients receiving ESA therapy, the Hb target should not be above 13.0 g/dL.**
   (Clinical Practice GUIDELINE - MODERATELY STRONG EVIDENCE)

Rationale

- largely based on the results of metaanalysis including trials reporting all-cause mortality and adverse CV events
- **"not be above 13.0 g/dL"** reflects that in patients ass. to Hb targets > 13 g/dl:
  - trend toward greater CV events in dialysis and nondialysis patients (moderately high quality evidence),
  - lack of benefit (high quality evidence)
- possibility to cause harm weighs more heavily than the potential to improve QoI and to decrease transfusions
- "**MODERATELY STRONG EVIDENCE**" acknowledges the possibility that further research may alter appraisal and does not impede continued investigation.

KDOQI anemia guidelines - target Hb update

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

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).**
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