15th Budapest Nephrology School

August 26-31, 2008
Semmelweis University, Budapest, Hungary

Renal Anaemia
(Target Hb and novel options in renal anaemia)

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Prevalence of anaemia by degree of renal function at baseline

Causes of anaemia secondary to chronic renal failure

1. Decreased red cell survival
   - External blood loss
   - Decreased red cell survival within the circulation

2. Decreased bone marrow stimulation
   - Decreased erythropoietin production by failure kidneys

3. Decreased bone marrow response
## Erythropoiesis Stimulating Agents (ESA)
### Half-life (h, mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>i.v.</th>
<th>s.c.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERA¹</td>
<td>133 ± 9.83</td>
<td>137 ± 21.9</td>
</tr>
<tr>
<td>Darbepoetin alfa²</td>
<td>25.3 ± 2.2</td>
<td>48.4 ± 5.2</td>
</tr>
<tr>
<td>Epoetin beta³</td>
<td>8.8 ± 0.5</td>
<td>24.2 ± 2.6</td>
</tr>
<tr>
<td>Epoetin alfa³</td>
<td>6.8 ± 0.6</td>
<td>19.4 ± 2.5</td>
</tr>
</tbody>
</table>

¹ from multiple dose studies
² Macdougall et al. *JASN* 1999
Treatment of renal anaemia remains suboptimal despite revised European Best Practice Guidelines (EBPG)

Francesco Locatelli, Adrian Covic, Iain C Macdougall and Andrzej Wiecek, on behalf of the ORAMA study group
Treatment of renal anaemia: Comparison between Eastern and Western Europe with respect to the European Best Practice Guidelines (EBPG)

Andrzej Wiecek¹, Adrian Covic², Francesco Locatelli³, Iain C Macdougall⁴, on behalf of the ORAMA study group

Wiecek A et al., Renal Failure, 2008
Treatment of renal anaemia: Comparison between Eastern and Western Europe with respect to the European Best Practice Guidelines (EBPG)

Andrzej Wiecek¹, Adrian Covic², Francesco Locatelli³, Iain C Macdougall⁴, on behalf of the ORAMA study group

Wiecek A et al., Renal Failure, 2008
Evidence in favor of a normal target hemoglobin

- Left ventricular hypertrophy
- Cognitive function
- Physical function
- Quality of life
- Mortality and morbidity
Target Hb values in international guidelines

Normal range of Hb with normal renal function

Hb distribution in women: 13.3 ± 0.9 g/dL
Hb distribution in men: 15.2 ± 0.9 g/dL

N=40,000 (NHANES III, 1988-1994)

Target Hb in CKD patients versus normal Hb distribution

Hb distribution in women: 13.3 ± 0.9 g/dL
Hb distribution in men: 15.2 ± 0.9 g/dL

N=40,000 (NHANES III, 1988-1994)

Optimal target Hb – a public debate

Lancet, 2007,369

Strippoli GF, Tognoni G, Navanethan SD, Nicolucci A, Craig JC. 
Lancet, 2007,369

Haemoglobin targets: we were wrong, time to move on

On the basis of the existing published trials, summarised by Phrommintikul and colleagues, we contend that more trials of haemoglobin target concentrations in patients with chronic kidney disease are no longer required, should be stopped, or at least it should be made fully and publicly explicit what reasons grant their continuation. We say this because of the rights of patients, and the credibility of the scientific nephrological community, after such a long history of contradictions. The question has been answered: higher haemoglobin target concentrations increase mortality via cardiovascular endpoints. Part rather than complete correction of anaemia is appropriate,
Risk of all-cause mortality in the higher haemoglobin group compared with the lower haemoglobin group

Risk of myocardial infarction in the higher haemoglobin group compared with the lower haemoglobin group

Risk of poorly controlled blood pressure in the higher haemoglobin group compared with the lower haemoglobin group

Figure 4: Risk of poorly controlled blood pressure in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

Risk of arterio-venous access thrombosis in the higher haemoglobin target group compared with the lower haemoglobin target group

Effect of different haemoglobin target concentrations on serious cardiovascular events

<table>
<thead>
<tr>
<th></th>
<th>High haemoglobin (n/N)</th>
<th>Low haemoglobin (n/N)</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOIR⁶</td>
<td>125/715</td>
<td>97/717</td>
<td>1.29 (1.01-1.64)</td>
<td>31.46</td>
</tr>
<tr>
<td>CREATE⁷</td>
<td>58/301</td>
<td>47/302</td>
<td>1.24 (0.87-1.76)</td>
<td>15.22</td>
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<tr>
<td>Besarab et al⁸</td>
<td>202/618</td>
<td>164/615</td>
<td>1.23 (1.03-1.46)</td>
<td>53.32</td>
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<tr>
<td>Overall</td>
<td>385/1634</td>
<td>308/1632</td>
<td>1.25 (1.09-1.42)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=0.11$, df=2 (p=0.95), $I^2=0\%$
Test for overall effect: $Z=3.30$ (p=0.0010)

**Figure:** Effects of different haemoglobin target concentrations on serious cardiovascular events
RR=relative risk.

Association between Hb values and prognosis

Fresenius Medical Care, North America (N=44,550)


<table>
<thead>
<tr>
<th>Hb range</th>
<th>% of patients surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb ≥ 13.0</td>
<td>100</td>
</tr>
<tr>
<td>12.0 ≤ Hb &lt; 13.0</td>
<td>90</td>
</tr>
<tr>
<td>11.0 ≤ Hb &lt; 12.0</td>
<td>80</td>
</tr>
<tr>
<td>10.0 ≤ Hb &lt; 11.0</td>
<td>70</td>
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<tr>
<td>9.0 ≤ Hb &lt; 10.0</td>
<td>60</td>
</tr>
<tr>
<td>Hb &lt; 9.0</td>
<td>50</td>
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</table>

Follow-up time, days

Relative risks (RR) of death (□) and hospitalization (□) from all causes [with 95% confidence intervals (CI)]. Hct. hematocrit.

Relative risks (RR) of death (□) and hospitalization (□) from cardiac causes (with 95% CI). Hct, hematocrit.

Uremic cardiomiopathy: an inadequate LVH

Hematocrit and LV cavity diameter


N = 57
r = - 0.62
P < 0.001
ESRD PATIENT RISK FACTORS
Anaemia and hospitalisation risk

US Observational Study

Hospitalization risk and Hct in HD patients

Xia et al., J. Am. Soc. Nephrol., 1999:10; 1309 - 1316
US Observational Study

Mortality risk and hematocrit in HD patients

Relative risk

< 27 %  27 – 30 %  30 – 33 %  33 – 36 %  Hct

N = 75 000

Relative Risk of Death

RR, overall = 0.95 per 1 g/dl higher Hgb (p = 0.03)

<table>
<thead>
<tr>
<th>Haemoglobin (g/dl) at study entry</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>1.22</td>
<td>0.06</td>
</tr>
<tr>
<td>10-10.9</td>
<td>1.02</td>
<td>0.86</td>
</tr>
<tr>
<td>11-11.9</td>
<td>1</td>
<td>0.49</td>
</tr>
<tr>
<td>≥12</td>
<td>0.91</td>
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</tbody>
</table>

Relative Risk of Hospitalisation

RR, overall = 0.96 per 1 g/dl higher Hgb (p = 0.02)

<table>
<thead>
<tr>
<th>Haemoglobin (g/dl) at study entry</th>
<th>RR</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>1.29</td>
<td>&lt;0.001</td>
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<tr>
<td>10-10.9</td>
<td>1.09</td>
<td>0.14</td>
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<tr>
<td>11-11.9</td>
<td>1</td>
<td></td>
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<tr>
<td>≥12</td>
<td>1.07</td>
<td>0.44</td>
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</table>

Observational trials: consistency, but limitations

**Consistency:** higher Hb values – better patient outcomes in many studies relationship extends into normal range

**Plausibility:** reduction in Hb $\rightarrow$ compensatory increase in CO, tissue ischemia

**Limitations:** Hb values can be influenced by many factors, including
- inflammation,
- comorbid conditions,
- general quality and intensity of care,
- progression of kidney disease

$\rightarrow$ observational trials can **not** assess whether
- relationship between Hb and prognosis is causal
- increasing the Hb levels improves outcomes
Randomised clinical trials in anemia management

Adapted and updated from NKF-K/DOQI. AJKD 2006; 47 (5 Suppl 3)
Randomised clinical trials in anemia management

Adapted and updated from NKF-K/DOQI. AJKD 2006; 47 (5 Suppl 3)
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)

Normal versus low haematocrit

Probability of death or first non-fatal myocardial infarction

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

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

Patients: 596, recent HD initiation, no symptomatic heart disease, no left ventricular dilatation

Design: iv / sc Epoetin alfa High arm: target Hb 13.5 – 14.5 double-blind 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

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

CREATE trial

- Hb difference 1.9 / 1.7 / 1.5 g/dl
- starting dose 2000 IU/week
  mean weekly EPO dose: 2000 vs 5000 IU

- no difference in CV events

CREATE trial

No significant impact on renal function with Hb correction to 13-15 g/dL

CREATE trial

Significant QoL improvements with complete Hb correction

Target Hb
- 13.4 g/dL
- 11.5 g/dL

<table>
<thead>
<tr>
<th>Index</th>
<th>Mean change from baseline</th>
<th>p-value</th>
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<tbody>
<tr>
<td>General health</td>
<td>4.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Physical function</td>
<td>-2.0</td>
<td>0.0004</td>
</tr>
<tr>
<td>Vitality index</td>
<td>-3.0</td>
<td>0.0009</td>
</tr>
<tr>
<td>Mental health index</td>
<td>-2.0</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

CREATE trial
CREATE: Outcomes

- No differences in primary outcomes (CV events): 58 events (high Hb) vs 47 events (low Hb), p=0.2
- No difference in LVMI change
- No difference in GFR and decline in GFR
- More patients started dialysis in high Hb group
- Improvement in QOL in high Hb group

CREATE: Issues

- Primary outcomes:
  "Ultimately underpowered to demonstrate a difference between the groups" due to lower than expected event rate (6% vs 15%)

- New on dialysis:
  "This finding should not be over-interpreted":
  ◦ Non-protocolized nature of dialysis start
  ◦ No difference in rate of decline of GFR or actual GFR at time of dialysis
  ◦ Delayed dialysis start in lower Hb group due to open-label?

• Patients in the higher target hemoglobin group (13 to 15 g/dL) were NOT found to have a statistically significant higher risk of the composite primary endpoint.

• The results of the CREATE study were strongly influenced by an overall low CV event rate (6% vs 15% anticipated).
CREATE: Conclusion

- “The CREATE study was ultimately underpowered to demonstrate a difference between the two groups, but did not describe harm to patients who were randomized to the higher Hb target arm.”

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

- Hb difference approx. 1.5 g/dl

- starting dose 10,000 IU/week
mean weekly EPO dose:
6,276 vs 11,215 IU

CHOIR: Increased Risk with Hb Correction to 13.5 g/dL in Non-Dialysis CKD Patients

1,432 non-dialysis CKD patients from 130 US centres; comparing impact of Hb correction to 13.5 g/dL with correction to 11.3 g/dL on composite endpoint events (mortality, stroke, heart attack, hospitalisation) in patients on epoetin alfa therapy

CHOIR trial

125 vs 97 events; p < 0.03
CHOIR: Outcomes

- Significant difference in primary end point (composite of death, MI, hospitalization for CHF, stroke):
  125 events (high Hb) vs 97 events (low Hb), p=0.03
- No difference in QOL

“While the findings of CHOIR are indeed ‘true’, they may not be applicable to the population to whom the authors believe they should be applied; i.e. all patients with CKD”

**CHOIR: Issues**

- Baseline imbalance (CABG and hypertension) may have impact on primary outcome measures
- “Of the original 1400 cohort, over half were lost”
- Against “recent trends in reporting RCTs”, not all randomized patients were included in the analysis
- No demographic information regarding the 700 patients who completed the study
- Representation of the most unwell of all CKD patients and not representative of the majority? (<50% with iron use, 38% withdrawal rate, not able to reach target Hb values)
- “Lack of adherence to RCT convention” by stopping the trial not according to any usual stopping rule or suggestion of harm, but rather the suggestion of harm
- “Rigorous methodologists would suggest that p values of 0.03 are not significant when more than one analysis is planned”

Levin, NDT 2007
Cox proportional hazards models for the primary composite endpoint of death, coronary heart failure hospitalization, stroke, or MI - CHOIR - Secondary analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Four-month landmark analysis N=1260</th>
<th></th>
<th>Nine-month landmark analysis N=1057</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>HR, 95% CI</td>
<td>P-value</td>
<td>HR, 95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
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<tr>
<td>Target arm (high vs low)</td>
<td>1.44, 1.05 1.97</td>
<td>0.02</td>
<td>1.62, 1.09 2.40</td>
<td>0.02</td>
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<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target arm (high vs low)</td>
<td>1.26, 0.89 1.78</td>
<td>0.20</td>
<td>1.44, 0.95 2.18</td>
<td>0.09</td>
</tr>
<tr>
<td>Not achieving hemoglobin target</td>
<td>1.46, 1.00 2.13</td>
<td>0.05</td>
<td>1.99, 1.12 3.55</td>
<td>0.02</td>
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<tr>
<td><strong>Model 3</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Target arm (high vs low)</td>
<td>1.26, 0.90 1.75</td>
<td>0.18</td>
<td>1.37, 0.89 2.11</td>
<td>0.15</td>
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<tr>
<td>High-dose ESA</td>
<td>1.71, 1.20 2.43</td>
<td>0.003</td>
<td>1.54, 1.00 2.35</td>
<td>0.05</td>
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<tr>
<td><strong>Model 4</strong></td>
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<td></td>
</tr>
<tr>
<td>Target arm (high vs low)</td>
<td>1.21, 0.85 1.71</td>
<td>0.29</td>
<td>1.28, 0.82 2.00</td>
<td>0.27</td>
</tr>
<tr>
<td>Not achieving hemoglobin target</td>
<td>1.17, 0.76 1.79</td>
<td>0.47</td>
<td>1.76, 0.97 3.20</td>
<td>0.06</td>
</tr>
<tr>
<td>High-dose ESA</td>
<td>1.60, 1.08 2.38</td>
<td>0.02</td>
<td>1.40, 0.90 2.19</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Model 5</strong></td>
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<tr>
<td>Target arm (high vs low)</td>
<td>1.17, 0.81 1.68</td>
<td>0.41</td>
<td>1.25, 0.80 1.97</td>
<td>0.33</td>
</tr>
<tr>
<td>Not achieving hemoglobin target</td>
<td>1.21, 0.78 1.89</td>
<td>0.39</td>
<td>1.80, 0.97 3.34</td>
<td>0.06</td>
</tr>
<tr>
<td>High-dose ESA</td>
<td>1.57, 1.04 2.36</td>
<td>0.03</td>
<td>1.48, 0.94 2.32</td>
<td>0.09</td>
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<tr>
<td>Self-reported hypertension</td>
<td>0.94, 0.48 1.85</td>
<td>0.86</td>
<td>0.66, 0.32 1.37</td>
<td>0.27</td>
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<tr>
<td>Previous CABG</td>
<td>2.44, 1.70 3.49</td>
<td>&lt;0.01</td>
<td>1.75, 1.08 2.86</td>
<td>0.02</td>
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<td>Use of IV iron</td>
<td>0.47, 0.12 1.90</td>
<td>0.29</td>
<td>0.36, 0.05 2.63</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Szczech L., Kidney Int, advance online publication, 2 July 2008
Cox proportional hazards models for the primary composite endpoint of death, coronary heart failure hospitalization, stroke, or MI - CHOIR - Secondary analysis

Szczech L et al. Kidney Int. 2008
Definition of an inadequate response to epoetin treatment

An arbitrary definition of resistance to epoetin in either failure to attain the target Hb concentration while receiving more than 300 IU/kg/week (ca. 20000 IU/week) of epoetin subcutaneously or a continued need for such dosage to maintain the target
## Factors influencing anemia treatment and impacting EPO Dose in HD patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact on EPO dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis adequacy</td>
<td>up to 100%</td>
</tr>
<tr>
<td>Hemodialysis quality / quantity</td>
<td>up to 30%</td>
</tr>
<tr>
<td>Iron</td>
<td>20–70%</td>
</tr>
<tr>
<td>Inflammation</td>
<td>30–70%</td>
</tr>
<tr>
<td>Infection</td>
<td>30–70%</td>
</tr>
</tbody>
</table>

Secondary analysis of the CHOIR trial epoetin-a dose and achieved hemoglobin outcomes

- Our study demonstrates that patients achieving their target had better outcomes than those who did not; and among subjects who achieved their randomized target, no increased risk associated with the higher hemoglobin goal was detected

Szczech L et al. Kidney Int. 2008
The Optimal Hemoglobin in Dialysis Patients—A Critical Review

Ajay K. Singh* and Steven Fishbane†
*Renal Division, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, and †Division of Nephrology, Winthrop-University Hospital, Mineola, New York

The ideal study to define the hemoglobin target would be a large RCT with multiple treatment targets, perhaps hemoglobin levels of 9, 10, 11, 12, and 13 g/dl. Only such a study could fully elucidate the tradeoff of QoL benefit against risks at a meaningful spectrum of hemoglobin levels. However, very large sample sizes will be required in order to obtain adequate power. Lacking such a study, the current literature does not support an evidence-based guideline for specific upper or lower target hemoglobin levels.

ACORD study: Methods

- Study design:
  - Randomized controlled trial
  - Target Hb: 13–15 g/dL (group 1) vs 10.5–11.5 g/dL (group 2)

- Inclusion criteria:
  - Diabetes mellitus type 1 or 2
  - Mild to moderate anemia
  - Chronic kidney disease stage 1 to 3

- Endpoints:
  - 1\textdegree: Change in left ventricular mass index (LVMI)
  - 2\textdegree: Echocardiographic variables, renal function, QOL, safety

ACORD study: Results

- Hb: 13.5 g/dL (group 1) vs 12.1 g/dL (group 2), p<0.001
- LVMI: 112.3 g/m² vs 116.5 g/m², ns
- Change in LVMI: greater numerical decrease in group 1, ns
- Change in CrCl: -5.5 mL/min vs -3.4 mL/min, ns
- Change in QOL (SF36): +5.33 vs -0.033, p=0.04
- Safety: No relevant differences

ACORD study: Results

Figure 4. LVMI (mean ± SD) by treatment group.

Figure 5. LVMI (mean ± SD) over time by degree of LHV at baseline. Abbreviation: BL, baseline.

ACORD study: Conclusion

- Correction to an Hb target level of 13 to 15 g/dL does not decrease LVMI
- Normalization of Hb level prevented an additional increase in LVH, was safe and improved QOL

**Meta-analysis**

**Non-dialysis** CKD patients

rel. mortality risk  
rel. risk of adverse CV events

*for assignment to higher Hb target*

<table>
<thead>
<tr>
<th>STUDY</th>
<th>YEAR</th>
<th>#PTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth</td>
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<td>83</td>
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<td>Kuriyama</td>
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<td>Levin</td>
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<td>MacDougall</td>
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<td><strong>OVERALL</strong></td>
<td><strong>2007</strong></td>
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<table>
<thead>
<tr>
<th>STUDY</th>
<th>YEAR</th>
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<tbody>
<tr>
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<td>Levin</td>
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<tr>
<td>Rossert</td>
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<td>Drueke</td>
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<td>Singh</td>
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<td>1432</td>
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<td>Ritz</td>
<td>2007</td>
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<tr>
<td><strong>OVERALL</strong></td>
<td><strong>2007</strong></td>
<td><strong>2850</strong></td>
</tr>
</tbody>
</table>

Studies arranged by increasing year  
Favors Treatment  
Favors Control

\[ Z = 0.04; \ 2p = 0.97 \]

\[ Z = 2.19; \ 2p = 0.029 \]

**Adapted and from NKF-K/DOQI “Target Hb” 2007 update**
Meta-analysis

Dialysis CKD patients

rel. mortality risk  rel. risk of adverse CV events

for assignment to higher Hb target

Z = 1.04; 2p = 0.30

Z = 0.69; 2p = 0.49

Adapted and from NKF-K/DOQI “Target Hb” 2007 update
What is the optimal target Hb?

Target > 13 g/dl:
- risk for harm
- uncertain QoL benefit

Adapted and updated from NKF-K/DOQI. AJKD 2006; 47 (5 Suppl 3)

Francesco Locatelli¹, Allen R. Nissenson², Brendan J. Barrett³, Rowan G. Walker⁴, David C. Wheeler⁵, Kai U. Eckardt⁶, Norbert H. Lameire⁷ and Garabed Eknoyan⁸

The current evidence, based on mortality data, for hemoglobin target levels intentionally aimed with ESA treatment in CKD patients treated indicates that: (1)

- levels of >13 g per 100 ml can be associated with harm
- levels of 9.5–11.5 g per 100 ml are associated with better outcomes compared with >13 g per 100 ml
- for levels between 11.5 and 13 g per 100 ml, there is no evidence at this time for harm or benefit compared with higher or lower levels.

Locatelli F et al. Kidney Int advance online publication, 2 July 2008
The relationship of the dose of ESA used and outcomes has not been examined adequately. Associations between the need for higher doses of ESA and poor outcomes could be surrogates for underlying comorbidities or toxicity.

Outcome studies of ESAs have heretofore based their interventional strategies on hemoglobin levels only, wherein the levels of hemoglobin achieved is equated with efficacy. There is a need to broaden the primary end points of clinical trials. Studies examining a given dose of ESA, as opposed to, or in combination with, that of an achieved hemoglobin target, are needed to evaluate resistance, nonresponsiveness, and ESA toxicity.

Locatelli F et al. Kidney Int advance online publication, 2 July 2008
The mechanisms of resistance to anemia correction remain poorly defined. A consistent definition of ESA resistance is crucial for future research.

Based on anticipated results from key on-going studies, it is reasonable to plan for a start-up date no earlier than 2009, with an anticipated completion date of 2011.

Locatelli F et al. Kidney Int advance online publication, 2 July 2008
Potential mechanisms of increased cardiovascular risk with targeting of higher Hb levels with ESAs

Fishbane S and Nissenson AR., Kidney Int. 2007; 49: 806-813
## Ongoing Aranesp Studies Evaluating Hb Targets and Outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Target Hb</th>
<th>Planned patient number</th>
<th>Design</th>
<th>Aranesp Dose</th>
</tr>
</thead>
</table>
| TREAT<sup>42</sup> Amgen Global | • CKD pts not yet on dialysis  
• Diabetes                             | • Aranesp: 13 g/dL  
• Placebo: rescue if Hb < 9.0 g/dL | 4000                        | RCT, double-blind, placebo-controlled | 0.75 mcg/kg/Q2W  
Double dose when stable and go to QM |
| RED-HF Trial<sup>43</sup> Amgen Global | • HF (NYHA II to IV)  
• LVEF ≤ 35%  
• Hb 9 – 12 g/dL | • Aranesp: 13 g/dL, not to exceed 14.5 g/dL | 3400                        | RCT, double-blind, placebo-controlled | 0.75 mcg/kg/Q2W  
Double dose when stable and go to QM |
# TREAT in the context of CHOIR and CREATE studies

<table>
<thead>
<tr>
<th></th>
<th>CREATE¹ (N = 603)</th>
<th>CHOIR² (N = 1432)</th>
<th>TREAT (N = 4000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Randomized, open-label</td>
<td>Randomized, open-label</td>
<td>Randomized, double-blind, placebo controlled</td>
</tr>
<tr>
<td><strong>Sponsor / Agent</strong></td>
<td>Roche / NeoRecormon® (epoetin beta)</td>
<td>J&amp;J / Procrit® (epoetin alfa)</td>
<td>Amgen / Aranesp® (darbepoetin alfa)</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>2,000 QW</td>
<td>Initiate 10,000 QW When stable go to Q2W</td>
<td>0.75 mcg/kg/Q2W Double dose when stable and go to QM</td>
</tr>
<tr>
<td><strong>Dosing Frequency</strong></td>
<td>De novo to QW</td>
<td>De novo to QW to Q2W</td>
<td>De novo to Q2W to QM</td>
</tr>
<tr>
<td><strong>Hb Target(s), g/dL</strong></td>
<td>Arm 1 13.0-15.0</td>
<td>13.5</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>Arm 2 10.5-11.5*</td>
<td>11.3</td>
<td>Placebo (Rescue for Hb &lt;9.0)</td>
</tr>
<tr>
<td><strong>Regions/Countries</strong></td>
<td>EU, Mexico, China, Taiwan, Thailand, Russia, Turkey, Greece</td>
<td>US</td>
<td>US, EU, CAN, AU, LA, RUS</td>
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<tr>
<td><strong># Centers</strong></td>
<td>94</td>
<td>130</td>
<td>~700</td>
</tr>
<tr>
<td><strong>Censor at RRT</strong></td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Treatment starts when Hb <10.5 g/dL
TREAT in context of CREATE and CHOIR studies

- Placebo-controlled double-blind study
- Event driven
- 4000 participants (vs. 605 CREATE, 1432 CHOIR)
- Type 2 diabetes with nephropathy
- TREAT has already enrolled and had more CV endpoints than CHOIR
- Data Safety and Monitoring Committee recommends continuation of TREAT
Strategies for treating renal anemia

- Prevention
- Earlier start
- Dialysis
- Higher target

Haemoglobin (g/dl) vs. Time or creatinine
New options and the future of anaemia management in uraemic patients

- Polyglycated erythropoietins
- NESP (Novel Erythropoiesis Stimulating Peptides)
- CERA (Continuous Erythropoietin Receptor Activator)
- EPO-mimetics
- Inhibitors of prolyl hydroxylase (participating in HIF degradation) – FG-2216
- Gene therapy
Comparison of rHuEPO and NESP

rHuEPO

- Four carbohydrate chains
- Up to 14 sialic acid residues
- 30,400 daltons
- 40% carbohydrate

NESP

- Six carbohydrate chains
- Up to 22 sialic acid residues (eight additional residues)
- 37,100 daltons
- 51% carbohydrate

Creation of two additional glycosylation sites

Macdougall IC. *Semin Nephrol.* 2000;20:375-381
The efficacy of intravenous darbepoetin alfa administered once every 2 weeks in chronic kidney disease patients on haemodialysis

Carrera F. et al. Nephrol Dial Transplant 2006, 21, 2846-2850
The efficacy of intravenous darbepoetin alfa administered once every 2 weeks in chronic kidney disease patients on haemodialysis

Mean (±SD) weekly dose of darbepoetin alfa (μg/kg/week).

Carrera F. et al. Nephrol Dial Transplant 2006, 21, 2846-2850
CERA

Continuous Erythropoietin Receptor Activator
Comparison of EPO with CERA
Mean dose over time 40 µg/wk (95% CI: 30, 50)

Mean (± SE) dose changes 2 ± 0.4 per patient per year

Mean Hb over time 11.2 g/dL (95% CI: 10.9, 11.4)

Locatelli et al 2005
Fusion proteins
EPO–EPO fusion protein (EPO dimer, 17 amino acid linker)

- 3 x higher specific activity *in vitro* than rhEPO
- Greater haematopoietic activity in mice than rhEPO
- Remains in plasma longer than rhEPO

*In vivo efficacy of equal doses of EPO–EPO compared with rhEPO (300 IU/kg in mice)*

Sytkowski et al. 1999 (Harvard)
Fusion proteins
GM-CSF–EPO fusion protein

- Burst forming unit-E requires at least one other factor (IL-3, IL-4, GM-CSF or *kit* ligand) + EPO
- GM-CSF upmodulates EPO receptors on progenitors: increases sensitivity to EPO
- Hybrid protein more efficient at inducing erythroid differentiation than mixture of GM-CSF and EPO

Stimulation of BFU-E + CFU-GM colonies by fusion protein and equimolar mixture of GM-CSF and EPO

Coscarella et al 1997 (Menarini Ricerche SpA)
A novel drug delivery platform has been developed that utilizes a naturally occurring receptor known as the neonatal Fc receptor (FcRn). The receptor is specific for the Fc fragment of IgG and is expressed in epithelial cells where it functions to transport immunoglobulins across these cell barriers. It has been shown that FcRn is expressed in both the upper and central airways in non-human primates as well as in humans.
Pulmonary delivery of an erythropoietin-Fc fusion molecule (EpoFc) was previously demonstrated in non-human primates using this FcRn pathway. We have now conducted a phase I clinical study to test whether the FcRn pathway functioned similarly in man using human erythropoietin (Epo) fused to the Fc portion of human IgG1. The design was a three leg, non-randomized study conducted in healthy male volunteers with rising doses (3, 10, and 30 microg/kg) of the fusion protein targeted to the central lung regions. Using a target range of 10-30% vital capacity and 15 breaths per minute, approximately 70% of the lung-deposited dose of aerosolized EpoFc was delivered safely and effectively to the central lung regions.
CONCLUSIONS

We showed dose-dependent concentrations of the fusion protein in the serum and an increase in circulating reticulocytes was evident in the highest dose group, thus demonstrating that large therapeutic molecules can be delivered to humans via the lung, with retention of biological activity, using the FcRn-mediated transport pathway.
Anemia

Vascular occlusion
Vasoconstriction
Reduced microvascular density

\[ \downarrow \]

\[ O_2 \downarrow \]

\[ \rightarrow \]

Improved \( O_2 \) supply
Reduced \( O_2 \) consumption

\[ HIF \uparrow \]

Energy deprivation
Functional impairment
Maladaptation
Structural damage

Expression of hypoxia-inducible genes
- Erythropoiesis (EPO)
- Angiogenesis (VEGF)
- Anaerobic metabolism (GLUT, glycolytic enzymes)
- Collagen metabolism (coll., collagenase, TIMP)

Inflammation

Hypoxia-inducible Factor (HIF)

- Regulates body’s protective responses to low oxygen tension
  - e.g., erythropoiesis in response to anemia
- Transcription factor necessary for expression of erythropoietin (EPO)
  - Several HIF isoforms with tissue-specific distributions and different target genes
- Function and stability regulated by unique post-translational modification involving hydroxylation of proline amino acid residues
  - Mediated by enzyme family of specific HIF-prolyl hydroxylases (HIF-PH)
- Pharmacological inhibition of HIF-PH activates HIF, leading to HIF-dependent EPO expression
Cellular Oxygen Sensing Mechanism

FG-2216: Novel HIF-PH Inhibitor that Stimulates Erythropoiesis for the Treatment of Anemia

- Orally bioavailable, small molecule inhibitor of hypoxia-inducible factor-prolyl hydroxylase (HIF-PH), FibroGen Inc., South San Francisco
- Coordinately regulates transcription of erythropoietin (EPO) gene, mobilization of iron and overcomes suppression of anti-erythropoietic cytokine effects
  - Improves iron absorption, transport, and bioavailability for heme synthesis, including reducing the expression of hepcidin to relieve block on iron bioavailability
  - Increases endogenous EPO and enhances sensitivity to EPO
  - Overcomes suppression of EPO production by TNF-α and IL-1b
- Corrects anemia in preclinical models of anemia including those with reduced renal function and mass, chemotherapy-induced anemia, and anemia of chronic disease

Więcek A et al.: XLII ERA-EDTA Annual Congress June 2005, Istambul, Turkey
FG-2216: Clinical Development

- **Summary of Phase 1 clinical results in healthy subjects**
  - Dose-dependent induction of EPO after single, oral dose of FG-2216
  - Provides first human proof of concept for inducing endogenous EPO and increasing hemoglobin (Hb) by a specific, orally active HIF-PHI inhibitor
  - No serious adverse events (SAEs) up to 30 mg/kg administered for up to 4 weeks

- **Ongoing Phase 2a dose-escalation studies in predialysis CKD patients**
  - Anemic predialysis patients with advanced stage chronic kidney disease (CKD)
    - Patients with no previous exposure to rHuEPO ("rHuEPO-naïve")
    - Patients receiving continuous rHuEPO therapy for at least eight weeks prior to switching to dosing with FG-2216 ("rHuEPO-treated")

Więcek A et al.: XLII ERA-EDTA Annual Congress June 2005, Istambul, Turkey
FG-2216 Dose-Related Induction of Endogenous Serum EPO
No Desensitization in EPO Response Following repeated Dosing with FG-2216
**Phase 2a (rHuEPO-naïve): Individual Hemoglobin Response to FG-2216 vs. Placebo – Change from Baseline**

6 mg/kg group (first cohort, rHuEPO-naïve, predialysis patients)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Mean Baseline Hb (g/dL)</th>
<th>Mean change from Baseline Hb (g/dL) Day 42* (or last value carried forward)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG-2216 (n=5)</td>
<td>9.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Placebo (n=3)</td>
<td>9.8</td>
<td>-0.35</td>
</tr>
</tbody>
</table>

*Difference between treatment and placebo group is statistically significant (Mann – Whitney rank sum test), p = 0.036

Więcek A et al.: XLII ERA-EDTA Annual Congress June 2005, Istambul, Turkey
Phase 2a (rHuEPO-treated): Individual
Hemoglobin Response to FG-2216 vs Placebo
– Change from Baseline

6 mg/kg group (first cohort, rHuEPO-treated, predialysis patients)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Mean Baseline Hb (g/dL)</th>
<th>Mean change from Baseline Hb (g/dL) Day 42* (or last value carried forward)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG-2216 (n=6)</td>
<td>11.7</td>
<td>-0.9</td>
</tr>
<tr>
<td>Placebo (n=3)</td>
<td>11.5</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

Więcek A et al.: XLII ERA-EDTA Annual Congress June 2005, Istanbul, Turkey
**FG-2216: Summary of Safety Results**

- **Phase 1 Studies: Normal Subjects**
  - n=72 treated with FG-2216
  - No SAEs
  - All AEs reported on FG-2216 treated subjects were mild and transient

- **Phase 2a Dose-Escalation Studies: CKD Patients**
  - n=14 treated with FG-2216
  - No Drug-Related SAEs
  - All AEs reported on FG-2216 treated patients have been mild and transient

Więcek A et al.: XLII ERA-EDTA Annual Congress June 2005, Istambul, Turkey
Conclusions

• The magnitude and rate of hemoglobin increases observed in patients treated with FG-2216 are likely to provide clinical benefit in treating anemia associated with chronic kidney disease.

• FG-2216’s novel mechanism of action – HIF stabilization - could provide in the future a convenient and cost-effective therapy for anemia than protein - based therapeutics.

• Larger and long - term clinical trials are needed in order to document the safety profile and final clinical benefits of this new compound.

Więcek A et al.: XLII ERA-EDTA Annual Congress June 2005, Istambul, Turkey
EPO mimetics
Rationale and strategy

• Both chains of the EPO receptor are needed

• Conformation of the EPO receptor in the dimer complex is flexible
  - suggests that a variety of molecules capable of dimerising the receptor may be able to act as EPO mimetics
AF37702 (Hematide™) Pegylated Peptide-Based Erythropoiesis-Stimulating Agent (ESA)

- AF37702 (Hematide™) is a synthetic dimeric peptide that is linked to polyethylene glycol (PEG)
- AF37702 (Hematide™) is an erythropoiesis agent (ESA) being developed by Affymax for the treatment of anemia associated with CKD or cancer
- The aminoacid sequence of AF37702 (Hematide™) is unrelated to that of EPO
- It is anticipated that AF37702 (Hematide™) may have several potential advantages over currently available EPO products

Hematide™

- Novel synthetic PEGylated peptide
- Binds to and activates the erythropoietin receptor
- Currently in Phase II clinical trials in anaemia of chronic kidney disease (CKD) and cancer

Study Design

- Multi-centre, open-label, sequential dose-finding

Objective

- To evaluate the safety and pharmacodynamics of multiple doses of once-monthly (Q4W) subcutaneous (SC) Hematide

Andrzej Wiecek et al. Abstract # SP419 43rd ERA-EDTA Congress, July 15-18, 2006, Glasgow,
Study Methods

- Total of 60 erythropoiesis-stimulating-agent-naïve, pre-dialysis, CKD patients with anaemia (Hgb 9.0–10.9 g/dL)
- Enrolled into three dose cohorts
- Patients received up to six once-monthly SC doses
- Starting Hematide doses:
  - 0.025 mg/kg (n=15)
  - 0.050 mg/kg (n=30)
  - 0.075 mg/kg (n=15)
- Dose titration allowed after the first dose, based on haemoglobin (Hgb) levels
- *This study remains ongoing; further cohorts are being recruited*

Andrzej Wiecek et al. Abstract # SP419 43rd ERA-EDTA Congress, July 15-18, 2006, Glasgow,
Hematide Mean Reticulocyte Change from Baseline (0–12 Weeks)

Andrzej Wiecek et al. Abstract # SP419 43rd ERA-EDTA Congress, July 15-18, 2006, Glasgow,
Safety Results

Adverse Events & Serious Adverse Events

► As of 26 Apr 2006, eleven (18%) patients reported 36 adverse events; all were assessed as not related to study drug
► No adverse event resulted in study withdrawal
► No injection site reaction was reported
► Eight serious adverse events were reported:

<table>
<thead>
<tr>
<th>Adverse Event</th>
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</thead>
<tbody>
<tr>
<td>H. pylori gastritis</td>
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<tr>
<td>Ischaemic heart disease</td>
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<tr>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematoma</td>
</tr>
<tr>
<td>Progression of CKD</td>
</tr>
<tr>
<td>Peritonitis</td>
</tr>
<tr>
<td>Ankle fracture</td>
</tr>
</tbody>
</table>

► All serious adverse events were assessed as not related to study drug

Andrzej Wiecek et al. Abstract # SP419 43rd ERA-EDTA Congress, July 15-18, 2006, Glasgow,
Conclusions

► Multiple monthly SC Hematide injections are well-tolerated

► Monthly Hematide 0.050 and 0.075 mg/kg dosing achieves correction of anaemia in 93% and 100% of patients by Week 8, respectively

► Hematide results in a sustained increase in Hgb (up to Week 22) when dosed monthly in patients with CKD

► Phase III Hematide studies are planned

Andrzej Wiecek et al. Abstract # SP419 43rd ERA-EDTA Congress, July 15-18, 2006, Glasgow,
Conclusions

• Renal anemia management is currently in a state of rapid development.
• New strategies for treating the anemia have emerged, particularly the concept of treating the condition earlier.
• We look forward to the results of pre-dialysis clinical trials.
• We can expect other erythropoietic substances to be available for therapeutic use.
Thank You for your attention!

A. Więcek

Katowice
Poland
Relative risks (RR) of death (□) and hospitalization (□) from infectious causes (with 95% CI). Hct, hematocrit.

Primary results of the anemia correction in diabetes (ACORD) study

Ritz E et al.

TREAT: Status and Implications

- Ongoing double-blind, placebo-controlled trial
- Continuing after CREATE and CHOIR publication and DSMB review

“This should give confidence that the potential harm as described by the CHOIR authors has not been seen”

Levin, NDT 2007
Rationale to continue RED-HF™ Trial

- The treatment of anemia in heart failure is investigative and the optimal Hb concentration for patients with heart failure has not yet been determined.

- The RED-HF trial is fundamentally different from CHOIR and CREATE because of the study rationale, hypothesis, design, endpoints and patient population.

- The design of the RED-HF Trial was based on results from Amgen’s phase 2 studies:
  - In these studies evaluating the treatment of anemia with darbepoetin alfa in heart failure patients, treatment to a target Hb of 14.0 ± 1.0 g/dL appeared to be well tolerated.
  - The incidence of adverse events, including deaths, serious adverse events, and adverse events of special interest (cardiovascular and/or thrombotic events) was similar between the treatment arms.
  - A pre-specified pooled analysis of the 2 largest phase 2 studies showed a trend towards reduced risk of all-cause mortality and heart failure hospitalization for treatment of anemia with darbepoetin alfa compared with placebo.

- The RED-HF Trial has been designed and powered to determine whether treatment of anemia with darbepoetin alfa improves clinical outcomes in patients with heart failure and anemia.
TREAT trial - ongoing

Patients: 4000, diabetic nephropathy (type 2 DM), eGFR 20-60, Hb < 11
Design: Double blinded, placebo controlled RCT

High arm: darbepoetin, target Hb 13 g/dl
Low arm: placebo, “rescue therapy“ with darbepoetin, when Hb < 9 g/dl

Primary EP: all cause mortality and non-fatal CV events

Individual physicians and national nephrological societies considered the trial as “unethical“ because of the placebo arm!


Haemoglobin targets: we were wrong, time to move on

On the basis of the existing published trials, summarised by Phrommintikul and colleagues, we contend that more trials of haemoglobin target concentrations in patients with chronic kidney disease are no longer required, should be stopped, or at least it should be made fully and publicly explicit what reasons grant their continuation. We say this because of the rights of patients, and the credibility of the scientific nephrological community, after such a long history of contradictions. The question has been answered: higher haemoglobin target concentrations increase mortality via cardiovascular endpoints. Part rather than complete correction of anaemia is appropriate.
RCTs

Adapted and updated from NKF-K/DOQI. AJKD 2006; 47 (5 Suppl 3)
ESRD PATIENT RISK FACTORS

Anaemia and hospitalisation risk

Hematocrit

<table>
<thead>
<tr>
<th>Hematocrit (%)</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 27</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>27 - 32</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 32</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

US Observational Study

Hospitalization risk and Hct in HD patients

Relative risk

Xia et al, J Am Soc Nephrol 1999:10; 1309 - 16
Cause of death:

Crude mortality (%)

- all causes
- cardio-vascular
- cerebro-vascular

Hematocrit [%]

< 27
27-32
> 32

Age 18-65 years

RR, overall = 0.96 per 1 g/dl higher Hgb (p=0.24)

RR of death

<table>
<thead>
<tr>
<th>Haemoglobin (g/dl) at study entry</th>
<th>&lt;10</th>
<th>10-10.9</th>
<th>11-11.9</th>
<th>≥12</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
<td>(909)</td>
<td>(479)</td>
<td>(414)</td>
<td>(400)</td>
</tr>
<tr>
<td>p=0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>p=0.39</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ref</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1.51</td>
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<td></td>
</tr>
<tr>
<td>p=0.42</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Age >65 years

RR, overall = 0.93 per 1 g/dl higher Hgb (p=0.01)

<table>
<thead>
<tr>
<th>Haemoglobin (g/dl) at study entry</th>
<th>&lt;10</th>
<th>10-10.9</th>
<th>11-11.9</th>
<th>≥12</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
<td>(716)</td>
<td>(473)</td>
<td>(346)</td>
<td>(282)</td>
</tr>
<tr>
<td>p=0.46</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>p=0.84</td>
<td></td>
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<tr>
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<tr>
<td>1.11</td>
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<tr>
<td>p=0.77</td>
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<tr>
<td>0.97</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1.0</td>
<td></td>
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</tr>
</tbody>
</table>

Survival curve for good vs poor responders to epoetin.

*P<0.05 vs good responders

US Observational Study

Mortality risk and hematocrit in HD patients

Relative risk

N = 75,000

Higher Hgb and Survival in HD pts

Ofsthun, et al. KI, 2003 63 (1908-1914)
## Lowest Mortality Risk With Hb Maintained at 12-13 g/dL

<table>
<thead>
<tr>
<th>Hb level</th>
<th>Hazard ratio for mortality over previous</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
</tr>
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<tbody>
<tr>
<td>g/dL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;9</td>
<td></td>
<td>1.69</td>
<td>1.62</td>
<td>1.59</td>
</tr>
<tr>
<td>9 - &lt;10</td>
<td></td>
<td>1.46</td>
<td>1.21</td>
<td>1.27</td>
</tr>
<tr>
<td>10 - &lt;11</td>
<td></td>
<td>1.23</td>
<td>1.28</td>
<td>1.21</td>
</tr>
<tr>
<td>11 - &lt;12</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>12 - &lt;13</td>
<td></td>
<td>0.97</td>
<td>0.90</td>
<td>0.80</td>
</tr>
<tr>
<td>≥13</td>
<td></td>
<td>1.1</td>
<td>1.04</td>
<td>0.79</td>
</tr>
<tr>
<td><em>p value</em></td>
<td></td>
<td>0.02</td>
<td>0.03</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

One-year adjusted survival curves after initiation of dialysis in patients grouped according to level of epoetin use during the 2-year pre-dialysis period.

Importance of hemoglobin level in HD patients

Recommended target hemoglobin of ≥ 11 g/dl leads to

- Decreased risk of mortality (5% lower for every 1 g/dl)
- Decreased risk of hospitalization (4% lower for every 1 g/dl)
- Decreased risk of infections
- Increased quality of life

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*
Probability of death or first non-fatal myocardial infarction

Normal versus low haematocrit

CREATE trial

- Hb difference 1.9 / 1.7 / 1.5 g/dl
- starting dose 2000 IU/week
  mean weekly EPO dose:
  2000 vs 5000 IU

- no difference in CV events

Significant QoL Improvements with Complete Hb Correction

Mean change from baseline

Target Hb
- 13.4 g/dL
- 11.5 g/dL

General health
Physical function
Vitality index
Mental health index

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

CHOIR trial

- Hb difference approx. 1.5 g/dl

- starting dose 10,000 IU/week
mean weekly EPO dose:
6,276 vs 11,215 IU

CHOIR trial


125 vs 97 events;
p < 0.03
ACORD study: Methods

- **Study design:**
  - Randomized controlled trial
  - Target Hb: 13–15 g/dL (group 1) vs 10.5–11.5 g/dL (group 2)

- **Inclusion criteria:**
  - Diabetes mellitus type 1 or 2
  - Mild to moderate anemia
  - Chronic kidney disease stage 1 to 3

- **Endpoints:**
  - 1°: Change in left ventricular mass index (LVMI)
  - 2°: Echocardiographic variables, renal function, QOL, safety
ACORD study: Results

- Hb: 13.5 g/dL (group 1) vs 12.1 g/dL (group 2), p<0.001
- LVMI: 112.3 g/m² vs 116.5 g/m², ns
- Change in LVMI: greater numerical decrease in group 1, ns
- Change in CrCl: -5.5 mL/min vs -3.4 mL/min, ns
- Change in QOL (SF36): +5.33 vs -0.033, p=0.04
- Safety: No relevant differences
ACORD study: Results

Figure 4. LVMI (mean ± SD) by treatment group.

Figure 5. LVMI (mean ± SD) over time by degree of LHI at baseline. Abbreviation: BL, baseline.
Risk of all-cause mortality in the higher haemoglobin group compared with the lower haemoglobin group

Figure 2: Risk of all-cause mortality in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

The Roger et al trial is not reported because there were no deaths in either group.
Risk of myocardial infarction in the higher haemoglobin group compared with the lower haemoglobin group

Figure 3: Risk of myocardial infarction in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

Risk of poorly controlled blood pressure in the higher haemoglobin group compared with the lower haemoglobin group

Figure 4: Risk of poorly controlled blood pressure in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

Risk of arterio-venous access thrombosis in the higher haemoglobin target group compared with the lower haemoglobin target group

Figure 5: Risk of arteriovenous access thrombosis in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

Optimal target Hb – a public debate


Haemoglobin targets: we were wrong, time to move on

On the basis of the existing published trials, summarised by Phrommintikul and colleagues, we contend that more trials of haemoglobin target concentrations in patients with chronic kidney disease are no longer required, should be stopped, or at least it should be made fully and publicly explicit what reasons grant their continuation. We say this because of the rights of patients, and the credibility of the scientific nephrological community, after such a long history of contradictions. The question has been answered: higher haemoglobin target concentrations increase mortality via cardiovascular endpoints. Part rather than complete correction of anaemia is appropriate.
Effect of different haemoglobin target concentrations on serious cardiovascular events


**Figure:** Effects of different haemoglobin target concentrations on serious cardiovascular events

RR=relative risk.
Factors influencing anemia treatment

AT = Adjuvant therapy
Hematocrit (%)

0 10 20 30 40 45

Normal-hematocrit group

Low-hematocrit group

Epoetin (U/kg/wk)

0 100 200 300 400 500 600 700

Normal-hematocrit group

Low-hematocrit group

Vascular events (a) and time to first vascular event (b) in diabetic patients on peritoneal dialysis not receiving EPO or receiving EPO therapy.

Treatment initiation and target Hb levels for epoetin beta therapy in the CREATE trial

- Early intervention: TARGET Hb: 13-15 g/dl
- Late intervention: TARGET Hb: 10.5-11.5

Inclusion:
- Hb 11-12.5 g/dl
- CrCl 15-35 ml/min

Negative Impact on Renal Function with Hb Correction to 13-15 g/dL

Group 1: Hb target 13-15 g/dL
Group 2: Hb target 10.5-11.5 g/dL

Negative Impact on Mortality with Hb Correction to 13-15 g/dL

**Graph:**
- **Survival** vs. **Study month**
- **Events:** 31 vs 21
- **Log rank test:** p=0.20

**N at risk**
- **Group 1:** 301 → 283 → 271 → 235 → 187 → 128 → 75 → 2
- **Group 2:** 302 → 290 → 280 → 253 → 201 → 140 → 78 → 4

**Prepare**

**Reference:**
Increased Risk with Hb Correction to 13.5 g/dL in Non-Dialysis CKD Patients

**CHOIR:** 1,432 non-dialysis CKD patients from 130 US centres; comparing impact of Hb correction to 13.5 g/dL with correction to 11.3 g/dL on composite endpoint events (mortality, stroke, heart attack, hospitalisation) in patients on epoetin alfa therapy

---

Evidence Behind Target Hb >11 g/dL  
EBPG 2004

- Improvement in QoL  
  Abundant evidence  
  (retrospective & prospective studies)

- Reduction in CV event rates  
  Some evidence based on small randomised controlled trials in ESRD patients

- Reduction in mortality  
  Correlation based on retrospective studies and registry data

- Slower CKD progression  
  No clear benefit based on randomised controlled trials

Evidence Behind Target Hb >11 g/dL
K/DOQI 2006

- Improvement in QoL: Direct supporting evidence for benefit in dialysis patients; some benefit likely in non-dialysis patients.
- Reduction in CV event rates: Direct evidence for no benefit, or possible harm in dialysis patients; uncertainty in non-dialysis patients.
- Reduction in mortality: High quality supporting evidence for no benefit or possible harm in dialysis patients particularly with CVD; uncertainty in non-dialysis patients.
- Slower CKD progression: Low quality evidence suggesting no benefit, potential harm.

NKF-K/DOQI AJKD 2006; 47(Suppl3): S11-145
Evidence for Defining an Upper Hb Limit

Hb correction to 13-15 g/dL

QoL: Strong evidence for improvement
CV morbidity: Conflicting evidence
Mortality: Neutral to date
CKD progression: No evidence of effect

CURRENTLY INCONCLUSIVE EVIDENCE FOR A SPECIFIC UPPER HAEMOGLOBIN LIMIT
Causes of an inadequate response to epoetin treatment

The most common cause of an incomplete response to epoetin is absolute or functional iron deficiency
Absolute and functional iron deficiency

- **Absolute iron deficiency**
  
  Deficit of total body iron store
  
  Ferritin < 100 µg/l

- **Functional iron deficiency**
  
  Failure of iron to reach proliferating erythroblasts despite sufficient iron stores
  
  Ferritin > 100 µg/l
  
  TSF < 20%
## Target levels of iron parameters in HD patients

### Recommendations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Optimal</th>
<th>Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin [µg/l]</td>
<td>200–500</td>
<td>100–800</td>
</tr>
<tr>
<td>Transferrin saturation [%]</td>
<td>30–40</td>
<td>20–50</td>
</tr>
<tr>
<td>Proportion of hypochromic red blood cells [%]</td>
<td>&lt; 2.5</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>
Iron Substitution

Recommendations

- Intravenous iron substitution is mandatory due to the unavoidable blood losses in hemodialysis patients (1–4 l blood/year).

- HD patients should receive at least one i.v. iron administration every two weeks.

- Continuous high dose i.v. iron therapy (Ferritin > 1000 µg/L) could result in neutrophil inhibition.

- The higher the administered i.v. iron dose the slower the administration rate.
Infection and Iron Sucrose
North American Clinical Trial and USRDS

Hospitalization for Infection
per 1,000 Patient Years

USRDS: 442
Iron Sucrose: 226

Relative Risk = 226/442
0.54, p<0.001

Hemodialysis quality / quantity

Impact of dialysis fluid on EPO dose


31% difference in EPO dose

Group I: Ultrapure dialysis fluid

Group II: Standard dialysis fluid

P<0.05

EPO dose [IU/kg/week]
30–50% of CKD patients have serological evidence of an activated inflammatory response (CRP > 8–10 mg/l).

Influence of CRP concentration on EPO dose

Group I: CRP ≥ 10 mg/l

Group II: CRP < 10 mg/l

34% difference in EPO dose

P<0.01

Correlation between inflammatory response (IL-6) and epoetin alfa dose

\[ Y = 32.603 + 1.93X; r^2 = 0.675 \]
Effect of uraemia and inflammation on erythropoiesis.

Allen DA. Et al. J Invest Med. 1999, 47: 204-211
Infection

Recommendations

- Iron supplementation should be stopped during documented infection since intravenous iron may also enhance bacterial growth.

- Patients with CRP > 20 mg/l should be screened for silent infection of hemodialysis access grafts (visual control), paradontal disease or any low grade infection (diabetic foot ulcer).

- Elderly patients should be screened for urinary tract infection when Epoetin requirements increase.
Correlation between dialysis adequacy (Kt/V) and epoetin alfa dose

PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BÉATRICE VIRON, M.D., AMIR KOLTA, M.D., JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D., VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

ABSTRACT

**Background** Within a period of three years, we identified 13 patients in whom pure red-cell aplasia developed during treatment with recombinant human erythropoietin (epoetin). We investigated whether there was an immunologic basis for the anemia in these patients.

**Methods** Serum samples from the 13 patients with pure red-cell aplasia were tested for neutralizing antibodies that could inhibit erythroid-colony formation by normal bone marrow cells in vitro. The presence of antierythropoietin antibodies was identified by means of binding assays with the use of radiolabeled intact, deglycosylated, or denatured epoetin.

level of erythropoiesis, as evidenced by the presence of erythroblasts in the bone marrow and reticulocytes in the blood.

The gene for human erythropoietin was cloned in 1985, and recombinant human erythropoietin (epoetin) was approved for marketing in France in 1988 for the treatment of anemia in patients undergoing dialysis for chronic renal failure. Endogenous erythropoietin is a heavily glycosylated protein, and glycosylation is essential for its biologic activity. Endogenous erythropoietin and epoetin have different patterns of glycosylation, which involve primarily the sialic acid composition of oligosaccharide groups.

Epoetin alfa
Cumulative incidence of suspected and confirmed PRCA cases associated with epoetin administration
## Incidence of antibody-mediated PRCA in patients with renal anaemia

The wording, number of cases, routes of administration and distribution information are as provided by the companies.

<table>
<thead>
<tr>
<th>Company</th>
<th>No. of cases</th>
<th>Route</th>
<th>Patient experience years with product (highest possible incidence per 10,000 patient years)</th>
<th>Number of cases per country</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sole use</td>
<td>Not sole use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortho Biotech Eprex®</td>
<td>106 (+ 67 under investigation)</td>
<td>15</td>
<td>s.c.</td>
<td>Not available</td>
</tr>
<tr>
<td>Roche Neorecormon®</td>
<td>5</td>
<td>3 – association cannot be ruled out</td>
<td>s.c</td>
<td>England: 3, France: 1, Germany: 2, Spain: 1, Switzerland: 1</td>
</tr>
<tr>
<td>Amgen Epogen®</td>
<td>4</td>
<td>0</td>
<td>s.c.: 1 i.v.: 2 both: 1</td>
<td>USA: 4</td>
</tr>
<tr>
<td>Amgen Aranesp®</td>
<td>0</td>
<td>3 – unlikely to be associated</td>
<td>s.c.: 1 both: 2</td>
<td>Germany: 1, Italy: 1, Netherlands: 1</td>
</tr>
</tbody>
</table>

*Locatelli F. et al.: Nephrol Dial Transplant, 2004*
**Concomitant Therapy**

**Drugs possibly affecting Hb levels in HD patients**

<table>
<thead>
<tr>
<th>Decrease Hb</th>
<th>Increase Hb</th>
</tr>
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<tbody>
<tr>
<td>Azathioprine</td>
<td>Anti-TNF-alpha</td>
</tr>
<tr>
<td>MMF</td>
<td>Anticytokine Therapy</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Talidomide</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
</tr>
</tbody>
</table>

*No conclusive studies up to now*

- ACE-Inhibitors
- Angiotensin-II blockers
- Statins
## Summary

<table>
<thead>
<tr>
<th>Approach</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene therapy</td>
<td>• Increased EPO and haematocrit levels in recipient mice</td>
</tr>
<tr>
<td></td>
<td>• High variability</td>
</tr>
<tr>
<td>Peptide EPO mimetics</td>
<td>• Agonist peptide family</td>
</tr>
<tr>
<td></td>
<td>• Inferior activity to epoetin</td>
</tr>
<tr>
<td></td>
<td>• Large molecular size</td>
</tr>
<tr>
<td>Non-peptide EPO mimetics</td>
<td>• Small molecular size</td>
</tr>
<tr>
<td></td>
<td>• Low activity</td>
</tr>
<tr>
<td>Modulators of receptor activity</td>
<td>• Inhibitors of haematopoietic cell phosphatase</td>
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</table>
## Summary

<table>
<thead>
<tr>
<th>Approach</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic Erythropoiesis Protein (SEP)</td>
<td>• Synthetic protein–polymer construct</td>
</tr>
<tr>
<td></td>
<td>• Longer half-life than epoetin</td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>• Hyperglycosylated molecule</td>
</tr>
<tr>
<td></td>
<td>• Amino acid sequence of epoetin alfa altered to create carbohydrate attachment sites</td>
</tr>
<tr>
<td></td>
<td>• Longer half-life than epoetin</td>
</tr>
</tbody>
</table>

And then . . .

<table>
<thead>
<tr>
<th>Continuous Erythropoiesis Receptor Activator (CERA)</th>
<th>• Innovative erythropoietic agent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Unique receptor binding characteristics</td>
</tr>
<tr>
<td></td>
<td>• Longer half-life than epoetin</td>
</tr>
</tbody>
</table>
Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

Guideline I.1: Which patients should be evaluated and when should work-up begin?

Recommendation

I. All patients with chronic anaemia associated with chronic kidney disease (CKD) should be investigated for possible treatment, irrespective of the stage of kidney disease and requirement for renal replacement therapy.

A work-up for a diagnosis of anaemia should be considered in patients with CKD when haemoglobin (Hb) concentration falls below the mean $-2\,\text{SD}$ (i.e. $<95\%$) Hb level of the normal population, adjusted for age and sex:

- $<11.5\,\text{g/dl}$ in adult female patients
- $<13.5\,\text{g/dl}$ in adult male patients
- $<12.0\,\text{g/dl}$ in adult male patients aged $>70$ years.

(Evidence level B)
Decreased bone marrow response to EPO stimulation in dialysis patients

- uraemic inhibitors ("middle molecules", polyamines, PTH, ribonuclease)
- iron deficiency
- inflammatory iron block (sepsis, inflammatory diseases, surgery and trauma - proinflammatory cytokines, hepcidine)
- aluminium excess/intoxication
- folate deficiency
- severe secondary hyperparathyroidism (osteitis fibrosa leads to decrease mass of erythropoietic marrow or myelofibrosis)
- physical inactivity
Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

Guideline I.2: What is the appropriate work-up to investigate anaemia in chronic kidney disease?

Recommendation

I. An initial clinical and laboratory evaluation should be completed prior to considering the commencement of treatment with an erythropoiesis-stimulating agent (ESA) in patients with chronic kidney disease (CKD), to evaluate possible causes of anaemia superimposed on relative erythropoietin deficiency. *(Evidence level C)*

Assessment of anaemia should involve laboratory measurement of the following parameters:

- haemoglobin (Hb) concentration—to assess the degree of anaemia
- red blood cell indices [mean corpuscular volume (MCV) and mean corpuscular Hb (MCH)]—to assess the type of anaemia
Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

- absolute reticulocyte count—to assess erythropoietic activity
- plasma/serum ferritin concentration—to assess iron stores
- functional iron available for erythropoiesis by the measurement of either:
  - percentage of hypochromic red blood cells (HRC)
  - plasma/serum transferrin saturation (TSAT)
  - reticulocyte Hb content (CHr)

- plasma/serum C-reactive protein (CRP)—to assess inflammation.
  (Evidence level B)

In patients on dialysis, the frequency and the received dose of dialysis should also be evaluated.
  (Evidence level C)
Initial epoetin administration in dialysis patients

The starting dose of ESA to correct renal anaemia may depend on several factors such as the degree and underlying cause of the anaemia.

- In the correction phase, the starting dose for ESA – naive patients should normally be 20-30% higher than the maintenance dose.
Route of epoetin administration

- Epoetin should normally be administered subcutaneously in predialysis and peritoneal dialysis patients – it is almost always more convenient, especially if self-administration is practiced.
Median rHuEpo dose = 91 units/kg/week
Mean rHuEpo dose = 109 units/kg/week

### Table 2. Subgroup Meta-Analysis of Parallel Studies Comparing SC and IV Epoetin

<table>
<thead>
<tr>
<th>Study</th>
<th>SC (n)</th>
<th>Mean (SD)</th>
<th>IV (n)</th>
<th>Mean (SD)</th>
<th>WMD (95% CI random)</th>
<th>Weight (%)</th>
<th>WMD (95% CI random)</th>
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<tbody>
<tr>
<td><strong>Comparison: weekly dose SC versus IV. Outcome: parallel studies (IU/kg/wk)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Parallel studies with reported means and SD</td>
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<td></td>
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</tr>
<tr>
<td>Boran et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>18</td>
<td>86.00 (29.70)</td>
<td>18</td>
<td>172.00 (29.70)</td>
<td>11.9 (-86.00 - 105.40)</td>
<td>11.9</td>
<td>-86.00 (105.40 - -66.60)</td>
</tr>
<tr>
<td>Canaud et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>16</td>
<td>110.70 (91.20)</td>
<td>18</td>
<td>129.60 (85.40)</td>
<td>7.9 (-18.90 - 78.51)</td>
<td>7.9</td>
<td>-18.90 (78.51 - 40.71)</td>
</tr>
<tr>
<td>Castro et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>8</td>
<td>186.50 (24.33)</td>
<td>6</td>
<td>189.58 (20.75)</td>
<td>11.5 (-3.08 - 26.74)</td>
<td>11.5</td>
<td>-3.08 (26.74 - 20.58)</td>
</tr>
<tr>
<td>De Schoenmaker et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>7</td>
<td>118.80 (21.00)</td>
<td>11</td>
<td>138.20 (14.10)</td>
<td>12.0 (-17.40 - 35.05)</td>
<td>12.0</td>
<td>-17.40 (35.05 - -0.25)</td>
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<tr>
<td>Kaufman et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>107</td>
<td>95.10 (75.00)</td>
<td>101</td>
<td>140.30 (88.50)</td>
<td>11.6 (-45.20 - 67.56)</td>
<td>11.6</td>
<td>-45.20 (67.56 - -22.84)</td>
</tr>
<tr>
<td>Morsli et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>10</td>
<td>104.00 (82.00)</td>
<td>10</td>
<td>156.00 (112.00)</td>
<td>5.6 (-52.00 - 138.03)</td>
<td>5.6</td>
<td>-52.00 (138.03 - 34.03)</td>
</tr>
<tr>
<td>Muirhead et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>45</td>
<td>147.10 (113.50)</td>
<td>36</td>
<td>183.90 (129.40)</td>
<td>8.5 (-38.80 - 90.53)</td>
<td>8.5</td>
<td>-38.80 (90.53 - 16.93)</td>
</tr>
<tr>
<td>Parker et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>27</td>
<td>33.00 (25.98)</td>
<td>27</td>
<td>132.00 (25.98)</td>
<td>12.2 (-99.00 - 112.86)</td>
<td>12.2</td>
<td>-99.00 (112.86 - -85.14)</td>
</tr>
<tr>
<td>Pelegri et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>16</td>
<td>97.20 (51.30)</td>
<td>19</td>
<td>144.00 (79.50)</td>
<td>9.5 (-46.80 - 90.50)</td>
<td>9.5</td>
<td>-46.80 (90.50 - -3.10)</td>
</tr>
<tr>
<td>Virut et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>24</td>
<td>84.00 (82.00)</td>
<td>25</td>
<td>112.00 (95.00)</td>
<td>9.4 (-28.00 - 72.74)</td>
<td>9.4</td>
<td>-28.00 (72.74 - -18.74)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>278</td>
<td>271</td>
<td></td>
<td></td>
<td>100.0 (-44.57 - -71.76)</td>
<td>100.0</td>
<td>-44.57 (-71.76 - 17.37)</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square = 88.15, df = 9, P < 0.00001
Test for overall effect, z = 3.21, P = 0.001

Total (95% CI) 278 271 100.0 -44.57 (-71.76 - 17.37)
Test for heterogeneity chi-square = 88.15, df = 9, P < 0.00001
Test for overall effect, z = 3.21, P = 0.001

<table>
<thead>
<tr>
<th>-100</th>
<th>-50</th>
<th>0</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favors SC</td>
<td>Favors IV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Heterogeneity null hypothesis: there are no differences in treatment effect between trials.
Abbreviations: WMD, weekly mean dose; CI, confidence interval; df, degrees of freedom.
ESAM II

8696 patients
4560 (52%) i.v.
4136 (48%) s.c.

TSAT > 20%

The effect of the route of administration (i.v. versus s.c.) on epoetin dose and hemoglobin concentration in hemodialysis patients


Figure 1. Mean monthly epoetin dosage (IU/kg/week) with 95% confidence intervals

Figure 2. Mean monthly hemoglobin concentrations (g/dL) with 95% confidence intervals

Difference 4-6%
September 2002 – change of EPO route (from s.c. to i.v.)
Plasma ferritin: 200-500 ng/ml
% Hypochromic erythrocytes: <2.5%

Dose difference after 3 months 5-6%
Erythropoietin: subcutaneous or intravenous dosing?

Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure

Recommendation

III. The frequency of administration of ESA is influenced by several factors including dose, route, treatment phase, type of ESA used and patient group being treated.

- In HD patients receiving i.v. epoetin alfa or epoetin beta, the drug should be given three times per week during both correction and maintenance phases. Evidence does not support the use of i.v. epoetin alfa or epoetin beta once weekly. However, the dosing frequency of epoetin beta may be reduced to once or twice weekly when administered s.c. in some HD patients. 
  (Evidence level A)

- In CKD, PD and transplant patients, epoetin beta can be given s.c. three times per week during the correction phase and once per week during the maintenance phase of treatment. 
  (Evidence level C)

- During the correction phase, darbepoetin alfa should be given once per week either i.v. or s.c. in HD patients, and once per week s.c. in CKD, PD and transplant patients. 
  (Evidence level A)

- During the maintenance phase, darbepoetin alfa can also be given less often (e.g. every 2–4 weeks) either s.c. or i.v. in selected patients. 
  (Evidence level C)

- Darbepoetin alfa can be given once every 2 weeks either s.c. or i.v. to patients previously given s.c. epoetin alfa or beta once weekly. 
  (Evidence level B)

Note: A table summarizing the information in this recommendation is provided at the end of this guideline.
Patient allocation

Randomised patients
n = 173

1 x weekly
n = 84

3 x weekly
n = 89

Treatment allocation

ITT population
81
69

Per-protocol population
82
65

Mean (SD) change over time: haematocrit per protocol analysis

Mean (SD) change over time: epoetin beta dose per protocol analysis

• Once weekly SC epoetin beta is therapeutically equivalent to 3 times weekly treatment in maintaining a stable haematocrit
• No statistically significant dose increases required
• Once weekly epoetin beta has a similar tolerability profile to the 3 times weekly regimen
• Different dosing regimens (1x, 2x, 3x) provide the opportunity to individualise epoetin beta therapy according to specific needs

Possible adverse effects of epoetin treatment

- hypertension
- vascular access thrombosis

Other possible adverse effects of epoetin treatment

- seizures
- increase heparin dosage
- loss of dialyser clearance and hyperkalaemia
- antibodies direct against epoetin
Increased blood viscosity
Loss of hypoxic vasodilatation
Activation of neurohumoral systems

EPO induced hypertension

↑ cell Ca$^{2+}$ uptake
↑ ET-1 release

Direct vascular effect

Mitogenic effect
Platelet-dependent mechanism
CERA: Ferritin and TSAT Levels
1x/4wk SC schedule, extension period

Median ferritin (25th, 75th percentile; ng/mL)

Median TSAT (25th, 75th percentile; %)

Locatelli et al 2005
The Normal Hematocrit Trial

Limitations and criticisms of the study

- Entry criteria required “high – risk cardiac patients”
- Increased mortality not due to the higher Hct *per se*
- Hct measured prior to HD session
- Hct less accurate marker of red cell mass than Hb
- Increased mortality not due to CV causes

Macdougall IC and Ritz E, Nephrol Dial Transplant 1998; 13: 3030
Metabolic adjuvants to epoetin therapy

- iv iron
- Folic acid
- Vit. B\textsubscript{12}
- Vit. B\textsubscript{6}
- Ascorbic acid (vit. C)
- Vit. D
- L-carnitine
- IGF-1 / IL-3
- Androgens
# Iron dose and frequency of administration in HD patients

## Recommendations

- **Absolute iron deficiency**
  - 30–50 mg Fe / HD
  - or 1000 mg Fe in 6–10 weeks

- **Maintenance phase**
  - 10–25 mg Fe Sucrose / HD
  - or 1–3 x 20 mg Fe gluconate / week
  - or 1 x 62.5 mg Fe gluconate / week
  - or 1 x 100 mg Fe sucrose / 1–2 weeks
  - or 1 x 100 mg Fe dextran* /1–2 weeks

- **Hb correction phase**
  - 150 mg of iron/Hb increase of 1 g/dl

* low molecular weight dextran
Assessing and optimising iron stores

To achieve and maintain target Hb concentration (11 g/dl = haematocrit 33 %) sufficient iron should be administered to obtain the following in all patients:

- serum ferritin \( \geq 100 \ \mu g/l \)
- hypochromic red cells < 10% (or TSAT > 20-30% or CHr > 29 pg/ml)

In practice, to achieve the minimum criteria for Hb concentration it is necessary to have:

- serum ferritin 200-500 \( \mu g/l \)
- hypochromic red cells < 2.5% (or TSAT of 30-40% or CHr \( \approx \) 35%)
Cardiac Failure in ESRD

- Consistently associated with poor survival

- Already present in 40% patients at the start of dialysis therapy
Iron and Infection

Since:
- IV iron agents release catalytically active iron (2 -6%)
- Iron is required for bacterial growth
- Iron may inhibit phagocytosis
- Iron excess in promotes infection

Then:
Does IV iron therapy promote infection?
Iron and Infection

Risk of infection related to:
- Central venous catheters
- History of bacteraemia
- AV grafts
- Immunosuppression
- Not to ferritin levels
- Not to total dose of iv iron

Safety of Parenteral Iron Life-Threatening Adverse Reactions

- Iron Dextran: 0.61%
- Sodium Ferric Gluconate: 0.04%
- Iron Sucrose: 0.00%

Causes of an inadequate response to epoetin treatment

- Chronic blood loss (gut, uterus)
- Infection/inflammation (access infections, surgical inflammation, tuberculosis, systemic lupus erythematosus, chronically rejecting allografts, AIDS)
- Hyperparathyroidism/osteitis fibrosa
- Aluminium toxicity
- Haemoglobinopathies (e.g. alpha and beta thalassaemias, sickle cell anaemia)
Inflammation

Recommendations II

- In the presence of both, a high Ca x PO$_4$ product and high serum CRP level, patients should be screened and treated for calciphylaxis.

- Patients coming back from transplantation should be monitored carefully since rejected grafts may be a source of inflammation.

- In patients with failed renal allograft still in place or in patients with intravenous catheters a higher dose of Epoetin may be needed to correct anemia.
Recommendations I

- CRP should be evaluated at least every 3 months.
- In patients with elevated CRP (> 5 mg/l) biocompatibility of dialyzer membrane and hemodialysis fluid quality should be checked.
- If chronic inflammation persists, optimization of the dialysis protocol and dialysis dose should be aimed for.
- In patients with continuous rise in CRP and a past history of systemic disease causing renal failure, recurrence of the disease should be excluded.
Causes of an inadequate response to epoetin treatment

- Folate or vitamin B$_{12}$ deficiency
- Multiple myeloma, myelofibrosis
- Other malignancy
- Malnutrition
- Haemolysis
- Drug intake (e.g. high dose ACE inhibitor or AT$_1$ receptor antagonist therapy, immunosuppressive drugs)
- Inadequate dialysis
- Antierythropoietin antibodies
Modulators of receptor activity

- Haematopoietic cell phosphatase (HCP) is a negative regulator of the EPO signalling cascade.
- It binds to phosphorylated EPO receptor and dephosphorylates JAK2, terminating signalling.
- Inhibitors of HCP will restore signalling and may enhance response to EPO.

Barbone et al 1999 (RW Johnson), Ghaffari et al 2003 (Whitehead, Mount Sinai & MIT)
AF37702 (Hematide™)
Pegylated Peptide-Based Erythropoiesis-Stimulating Agent (ESA)

- Preclinical evaluation of pegylated peptide-based ESA
  - No detectable sequence identity to human erythropoietin (EPO)
  - Equal potency to natural EPO
  - Antibodies do not crossreact with recombinant human EPO

- Pharmacokinetic data from rats, dogs, and monkeys
  - Extended plasma half-life
    - Elimination half-life in monkey with 1.35-mg/kg dose, 58.4 hrs
      - Clearance rate, 0.96 mL/hr/kg

- Erythropoietic activity detected in several models
  - Efficacy equal in in vitro and in vivo models

- This novel agent is a potent EPO receptor agonist with prolonged half-life and slow clearance
  - Clinical trials forthcoming

According to patient characteristics and preference, epoetin can be administered either subcutaneously or intravenously in patients on regular haemodialysis. Subcutaneous route will usually lead to lower doses of epoetin and in general this route is preferable.

Eprex (Erypo) - only i.v.
The average SC dose was 113 ± 43 IU/kg/wk, and mean IV dose was 161 ± 46 IU/kg/wk.

Erythropoiesis

CD-34

Stem Cell Pool

Progenitors Cells
BFU-E CFU-E

Precursors Cells Erythroblasts

Mature cells

apoptosis

EPO

GM-CSF IL-3 IGF-1 SCF

Receptors

5 days

EPO 9-11 days

Neocytolysis (RES/spleen)
Debate on the ‘epidemic’ of chronic kidney disease
The Reply
Chronic kidney disease is common: What do we do next?
Josef Coresh, Lesley A. Stevens and Andrew S. Levey

- eGFR is a useful first step in CKD detection, evaluation and management, but not the last step.
- New equations should aim to decrease the bias in GFR estimation \( >60 \text{ ml/min/1.73 m}^2 \) but estimation in this range is difficult. The MDRD study equation has been expressed in terms of standardized creatinine and its performance shown to improve after creatinine calibration compared to unstandardized creatinine. Major manufacturers have set 2008 as a target for calibrating their assays to isotope dilution mass spectrometry reference methods.
The disparity between the prevalence of earlier stages of CKD and incidence of treated kidney failure across race and sex should not be taken as conclusive evidence for inaccuracies of the GFR estimating equations or inadequacy of the current GFR cutoff value.

- Prevalence is not incidence and prevalence over-represents cases of longer duration and slower progression
- Women may have a higher prevalence at earlier stages of CKD because they progress more slowly and have a lower mortality rate

Defining ‘healthy’ in older individuals is problematic. The main rationale appears to be avoiding classification of a large number of elderly people as having CKD with limited treatments options. But inadequate treatment for common diseases should be a challenge for future research rather than a reason for changing the definition of what is normal. Defining it as normal because it is common threatens to dismiss the urgent need for research in this topic.

Josef Coresh, Lesley A. Stevens and Andrew S. Levey
Estimated glomerular filtration rate at baseline and changes of eGFR – ONTARGET study

<table>
<thead>
<tr>
<th></th>
<th>Ramipril</th>
<th>Telmisartan</th>
<th>Ramipril + telmisartan</th>
<th>Telmisartan vs ramipril p</th>
<th>Ramipril + telmisartan vs ramipril p</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR, baseline</td>
<td>73.7 (19.3)</td>
<td>73.6 (19.9)</td>
<td>73.4 (19.5)</td>
<td>0.915</td>
<td>0.388</td>
</tr>
<tr>
<td>eGFR change baseline to 6 weeks</td>
<td>-2.14 (12.9)</td>
<td>-2.51 (13.2)</td>
<td>-4.01 (13.3)</td>
<td>0.070</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR change baseline to 2 years</td>
<td>-1.96 (15.1)</td>
<td>-3.05 (15.1)</td>
<td>-5.12 (15.7)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR change 6 baseline to final</td>
<td>-2.82 (17.2)</td>
<td>-4.12 (17.4)</td>
<td>-6.11 (17.9)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR change 6 weeks to final</td>
<td>-1.17 (17.1)</td>
<td>-2.06 (17.1)</td>
<td>-2.49 (17.4)</td>
<td>0.0032</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

eGFR=estimated glomerular filtration rate (mL/min/1.73 m² [SD]). Number of participants with measurements=25 551 at baseline, 24 970 at 6 weeks, 22 573 at 2 years, 19 601 at study end.

JF Mann et al. Lancet 2008; 372: 547–53
Incidence of primary and secondary renal outcomes and of its components - ONTARGET study

<table>
<thead>
<tr>
<th></th>
<th>Ramipril n (%)</th>
<th>Telmisartan n (%)</th>
<th>Ramipril vs Telmisartan n (%)</th>
<th>Telmisartan vs Ramipril HR (95% CI)</th>
<th>Ramipril vs Telmisartan HR (95% CI)</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All dialysis,</td>
<td>1150 (13.4)</td>
<td>1147 (13.4)</td>
<td>1233 (14.5)</td>
<td>1.00 (0.92-1.09)</td>
<td>0.968</td>
<td>1.09</td>
<td>0.037</td>
</tr>
<tr>
<td>doubling, death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All dialysis</td>
<td>174 (2.03)</td>
<td>189 (2.21)</td>
<td>212 (2.49)</td>
<td>1.09 (0.89-1.34)</td>
<td>0.420</td>
<td>1.24</td>
<td>0.038</td>
</tr>
<tr>
<td>and doubling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All dialysis</td>
<td>48 (0.56)</td>
<td>51 (0.60)</td>
<td>53 (0.74)</td>
<td>1.07 (0.72-1.58)</td>
<td>0.747</td>
<td>1.33</td>
<td>0.133</td>
</tr>
<tr>
<td>and death</td>
<td>1014 (11.8)</td>
<td>989 (11.6)</td>
<td>1065 (12.5)</td>
<td>0.98 (0.90-1.07)</td>
<td>0.641</td>
<td>1.07</td>
<td>0.144</td>
</tr>
<tr>
<td>Doubling</td>
<td>140 (1.63)</td>
<td>155 (1.81)</td>
<td>166 (1.95)</td>
<td>1.11 (0.88-1.39)</td>
<td>0.378</td>
<td>1.20</td>
<td>0.110</td>
</tr>
<tr>
<td>Acute</td>
<td>13 (0.15)</td>
<td>20 (0.23)</td>
<td>28 (0.33)</td>
<td>1.55 (0.77-3.11)</td>
<td>0.221</td>
<td>2.19</td>
<td>0.020</td>
</tr>
<tr>
<td>dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>33 (0.39)</td>
<td>31 (0.36)</td>
<td>34 (0.40)</td>
<td>0.94 (0.58-1.54)</td>
<td>0.817</td>
<td>1.05</td>
<td>0.854</td>
</tr>
<tr>
<td>dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dialysis: at least one dialysis. Chronic dialysis: more than 2 months. Acute dialysis: 2 months or less. Doubling: doubling of serum creatinine from baseline values. HR: hazard ratio. Reasons for acute dialysis were reported as severe infection (n=22), volume depletion (n=9), post-surgery (n=17), drugs (n=5), specific renal diseases (n=5), and other reasons (n=23). In three of 165 originally reported cases of dialysis, a detailed analysis revealed that no dialysis took place. In three of the 162 cases of dialysis, we got no information on duration of dialysis. Investigators could report several reasons for acute dialysis.

JF Mann et al. Lancet 2008; 372: 547–53
COOPERATE –
Combined therapy ARB i ACEI in non-diabetic nephropathy

The COOPERATE trial: a letter of concern

In the context of a meta-analysis, we had reason to take an in-depth look at a study by Naoyuki Nakao and colleagues published in *The Lancet* in 2003. We detected implausibilities of serious concern.

<table>
<thead>
<tr>
<th></th>
<th>Losartan (n=89)</th>
<th>Trandolapril (n=86)</th>
<th>Combination (n=88)</th>
<th>( \chi^2 ) test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>48 (54%)</td>
<td>46 (53%)</td>
<td>47 (53%)</td>
<td>( p=0.997 )</td>
</tr>
<tr>
<td><strong>Renal disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerular</td>
<td>58 (65%)</td>
<td>56 (65%)</td>
<td>57 (65%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (17%)</td>
<td>16 (19%)</td>
<td>15 (17%)</td>
<td></td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>3 (3%)</td>
<td>5 (5%)</td>
<td>4 (5%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (15%)</td>
<td>9 (10%)</td>
<td>12 (14%)</td>
<td>( p=0.972 )</td>
</tr>
<tr>
<td><strong>ACE gene polymorphism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>9 (11%)</td>
<td>11 (13%)</td>
<td>10 (11%)</td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>49 (49%)</td>
<td>41 (48%)</td>
<td>42 (48%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>40 (40%)</td>
<td>34 (39%)</td>
<td>36 (41%)</td>
<td>( p=0.9876 )</td>
</tr>
</tbody>
</table>

Table: Categorical variables from Nakao and colleagues’ table 1

Effect of calcitriol on NFκB pathway

Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials

Strippoli G et al. BMJ 2008;336:645-651
Effect of statins compared with placebo or no treatment on cardiovascular mortality in pre-dialysis, dialysis, and transplant patients

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Statin n/N</th>
<th>Placebo n/N</th>
<th>Relative risk (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (random) (95% CI)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dialysis patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rayner 1995</td>
<td>0/42</td>
<td>2/45</td>
<td></td>
<td>0.11</td>
<td>0.21 (0.01 to 4.33)</td>
<td>1995</td>
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<tr>
<td>PPP 2004</td>
<td>476/8376</td>
<td>527/8448</td>
<td></td>
<td>66.07</td>
<td>0.80 (0.70 to 0.90)</td>
<td>2004</td>
</tr>
<tr>
<td>PREVEND II 2004</td>
<td>4/433</td>
<td>4/431</td>
<td></td>
<td>0.54</td>
<td>1.00 (0.25 to 3.95)</td>
<td>2004</td>
</tr>
<tr>
<td>Lemmon 2005S</td>
<td>3/150</td>
<td>3/160</td>
<td></td>
<td>0.61</td>
<td>1.07 (0.32 to 3.50)</td>
<td>2005</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>9001</td>
<td>9084</td>
<td></td>
<td>67.14</td>
<td>0.80 (0.70 to 0.90)</td>
<td></td>
</tr>
<tr>
<td>Total events: 423 (statin), 536 (placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 0.96$, df = 3, $p = 0.31$, $I^2 = 0%$</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $z = 3.58$, $p &lt; 0.001$</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dialysis patients</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PERFECT study 1997</td>
<td>0/54</td>
<td>1/53</td>
<td></td>
<td>0.10</td>
<td>0.33 (0.01 to 7.66)</td>
<td>1997</td>
</tr>
<tr>
<td>Lins 2004</td>
<td>0/23</td>
<td>1/19</td>
<td></td>
<td>0.10</td>
<td>0.28 (0.01 to 6.45)</td>
<td>2004</td>
</tr>
<tr>
<td>AD trial 2005</td>
<td>121/419</td>
<td>140/436</td>
<td></td>
<td>22.78</td>
<td>0.83 (0.47 to 1.03)</td>
<td>2005</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>696</td>
<td>708</td>
<td></td>
<td>22.98</td>
<td>0.83 (0.47 to 1.02)</td>
<td></td>
</tr>
<tr>
<td>Total events: 121 (statin), 151 (placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 0.80$, df = 2, $p = 0.67$, $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 1.76$, $p = 0.08$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transplant patients</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Katsmeen 1996</td>
<td>0/24</td>
<td>1/24</td>
<td></td>
<td>0.10</td>
<td>0.33 (0.01 to 7.60)</td>
<td>1996</td>
</tr>
<tr>
<td>Kasiske 2001</td>
<td>2/53</td>
<td>0/52</td>
<td></td>
<td>0.11</td>
<td>4.91 (0.24 to 99.82)</td>
<td>2001</td>
</tr>
<tr>
<td>Holdaas 2002</td>
<td>26/1050</td>
<td>54/1052</td>
<td></td>
<td>6.05</td>
<td>0.67 (0.44 to 1.01)</td>
<td>2002</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1127</td>
<td>1128</td>
<td></td>
<td>6.27</td>
<td>0.68 (0.46 to 1.03)</td>
<td></td>
</tr>
<tr>
<td>Total events: 38 (statin), 55 (placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 1.86$, df = 2, $p = 0.39$, $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 1.83$, $p = 0.07$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A significant (approximately 20%) reduction in the risk of cardiovascular mortality

Strippoli G et al. BMJ 2008;336;645-651
## Recommended route and frequency of administration

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient type</th>
<th>CKD stages 1–5 not on dialysis</th>
<th>HD</th>
<th>PD</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended route</strong> of administration</td>
<td>s.c.</td>
<td>s.c. or i.v.</td>
<td>s.c.</td>
<td>s.c.</td>
<td></td>
</tr>
<tr>
<td><strong>Recommended frequency</strong> of administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Correction</strong></td>
<td><strong>EA</strong>: N/A</td>
<td><strong>EA</strong>: 3×/week (i.v. only)</td>
<td><strong>EA</strong>: N/A</td>
<td><strong>EA</strong>: N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>EB</strong>: 1–3×/week</td>
<td><strong>EB</strong>: 3×/week (i.v. or s.c.)</td>
<td><strong>EB</strong>: 3×/week</td>
<td><strong>EB</strong>: 1–3×/week</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>DA</strong>: 1×/week</td>
<td><strong>DA</strong>: 1×/week (i.v. or s.c.)</td>
<td><strong>DA</strong>: 1×/week</td>
<td><strong>DA</strong>: 1×/week</td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td><strong>EA</strong>: N/A</td>
<td><strong>EA</strong>: 3×/week (i.v. only)</td>
<td><strong>EA</strong>: N/A</td>
<td><strong>EA</strong>: N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>EB</strong>: 1–3×/week</td>
<td><strong>EB</strong>: 1–3×/week (s.c.)</td>
<td><strong>EB</strong>: 1–3×/week</td>
<td><strong>EB</strong>: 1–3×/week</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>DA</strong>: 1×/week</td>
<td><strong>DA</strong>: 2–3×/week (i.v.)</td>
<td><strong>DA</strong>: 1×/week</td>
<td><strong>DA</strong>: 1×/week</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to 1×/2 weeks</td>
<td><strong>DA</strong>: 1×/week</td>
<td>to 1×/2 weeks</td>
<td>to 1×/2 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to 1×/2 weeks (i.v. or s.c.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EA = epoetin alfa; EB = epoetin beta; DA = darbepoetin alfa; N/A = not applicable because not licensed for use by this route. Supporting evidence levels can be found in Recommendations II and III.

---

**Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure**

Recommendation

II. Exact target Hb concentrations > 11 g/dl should be defined for individual patients, taking gender, age, ethnicity, activity and co-morbid conditions into account. In HD patients, pre-dialysis Hb concentrations above 14 g/dl are not desirable due to the risks associated with the effects arising from post-dialysis haemoconcentration. (Evidence level C)
Recommendation

III. The optimal target Hb concentration may vary in patients with significant co-morbidity:

- Hb concentrations >12 g/dl are not recommended for patients with severe cardiovascular disease [defined as class III and above of the New York Heart Association Classification of Congestive Heart Failure (Table 2, Appendix C)] unless continuing severe symptoms (e.g. angina) dictate otherwise. *(Evidence level A)*
- Until data become available, it seems prudent to recommend a cautious approach to raising Hb concentrations to levels >12 g/dl in patients with diabetes, especially with concurrent peripheral vascular disease. *(Evidence level C)*
- Patients with chronic hypoxaemic pulmonary disease may benefit from a higher Hb target. *(Evidence level C)*
Cardiovascular disease mortality in the USRDS

Advances in the treatment with Erythropoiesis Stimulating Agents (ASA)

Anaemia not related to CKD

• Old indications
  ▪ Cancer diseases
  ▪ Chronic inflammation
  ▪ Prematurity
  ▪ Autologic blood transfusion

• New indications
  ▪ Acute renal failure

Anemia in CKD patients

1. New therapeutic options (prevention)

2. New drugs
darbepoietin alfa
CERA

• New therapeuetic concepts

Strategies for treating renal

Hemoglobin (g/dL)

Time or creatinine

Dialysis
Prevention
Earlier start
Uremic cardiomiopathy: an inadequate LVH

Hematocrit and LV cavity diameter

$r = -0.62$  $P < 0.001$

$N = 57$

Effect of partial anaemia correction on LV mass

LVMI (g/m²)

Time (weeks)

15 studies

Target Hb in Anaemia Management Guidelines

DOQI 1997
11-12 g/dL

EBPG 1999
>11 g/dL
(upper limit
not defined)

K/DOQI 2001
11-12 g/dL

EBPG 2004
>11 g/dL
(upper limit
individualised)

K/DOQI 2006
>11 g/dL
(caution with
maintenance >13 g/dL)

CSN-Canada 1999
11-12 g/dL

CARI 2000
11-12 g/dL CVD
12-14 g/dL no CVD

CARI 2003
>11 g/dL CVD
12-14 g/dL no CVD

UK 2002
>10 g/dL

KDIGO 2008

CVD=cardiovascular disease
Hb distribution in women: 13.3 ± 0.9 g/dL
Hb distribution in men: 15.2 ± 0.9 g/dL

N=40,000 (NHANES III, 1988-1994)

Target Hb in CKD Patients Versus Normal Hb Distribution

Hb distribution in women: 13.3 ± 0.9 g/dL

Hb distribution in men: 15.2 ± 0.9 g/dL

N=40,000 (NHANES III, 1988-1994)

## Target Hb in Anaemia Management Guidelines

<table>
<thead>
<tr>
<th>Europe</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European Best Practice Guideline (EBPG) of anaemia management in CKD</strong></td>
<td><strong>National Kidney Foundation guideline of anaemia management in CKD (K/DOQI)</strong></td>
</tr>
<tr>
<td>• Only lower Hb limit</td>
<td>• Lower and upper Hb limit</td>
</tr>
<tr>
<td>• Target Hb &gt;11 g/dL</td>
<td>• Target Hb range 11-12 g/dL</td>
</tr>
<tr>
<td></td>
<td>• Lower Hb limit ≥11 g/dL (2006)</td>
</tr>
<tr>
<td></td>
<td>• Caution with maintaining Hb &gt;13 g/dL</td>
</tr>
</tbody>
</table>

2 NKF-K/DOQ *AJKD* 2001;37(Suppl 1):S182-238
3 NKF-K/DOQI *AJKD* 2006; 47(Suppl 3): S11-145
National Kidney Foundation Releases Anemia Guideline Update

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 Initiative (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.
The National Kidney Foundation Releases Preliminary Anemia Guideline Update. Full Evidence-based re-examination of 2006 Recommendations. Click here to download the complete Anemia Update, PDF (2.33 MB).

- Diabetes and Kidney Failure: A New Tool to Break the Cycle
- KDOQI Transparencies and COI policies

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™)

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™)
Hemoglobin Level Variability:
Associations with Mortality

Hazard ratios for mortality based on the first classification system. Monthly hemoglobin values were categorized as low (L, 11 g/dl), intermediate (I, 11 to 12.5 g/dl) and high (H, 12.5 g/dl); variability groups were classified on the basis of the lowest and highest categories seen in the 6-mo observation period. Each $P$ value tests the corresponding variability group hazard ratio compared with the reference group (consistently intermediate).

Hemoglobin Level Variability: Associations with Mortality

Hazard ratios for mortality based on the second classification system. Number of months with hemoglobin 11 g/dl and first or second half of the 6-mo exposure period. For example, 2-F represents 2 mo with hemoglobin 11 g/dl during the first 3 mo; 4-F-S represents 4 mo with hemoglobin 11 during both the first and the second 3-mo periods. I-I, consistently intermediate (11 to 12.5 g/dl), represents the reference group.

Hemoglobin Level Variability: Associations with Mortality

Interval Poisson model examining the change in hazard ratios over follow-up time. Number of months with hemoglobin 11 g/dl and first or second half of the 6-mo exposure period, as explained in Figure 2. I-I, consistently intermediate (11 to 12.5 g/dl), represents the reference group.

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)
### Cross-sectional study in the US (NHANES III)

#### Comparison of CREATE and CHOIR

<table>
<thead>
<tr>
<th></th>
<th>CREATE – baseline</th>
<th></th>
<th>CHOIR – baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low arm</td>
<td>High arm</td>
<td>Low arm</td>
<td>High arm</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>58.8</td>
<td>59.3</td>
<td>66.3</td>
<td>66.0</td>
</tr>
<tr>
<td><strong>DM as cause of CKD</strong></td>
<td>21 %</td>
<td>20 %</td>
<td>51 %</td>
<td>47 %</td>
</tr>
<tr>
<td><strong>Hypertension as cause of CKD</strong></td>
<td>19 %</td>
<td>23 %</td>
<td>28 %</td>
<td>30 %</td>
</tr>
<tr>
<td><strong>BP systolic</strong></td>
<td>139</td>
<td>139</td>
<td>136</td>
<td>137</td>
</tr>
<tr>
<td><strong>BP diastolic</strong></td>
<td>80</td>
<td>79</td>
<td>71</td>
<td>72</td>
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</table>
Lesson learned from CREATE and CHOIR

From an Editorial Comment by Adeera Levin

*Nephrol Dial Transplant*

## PROSPECTIVE STUDIES

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PUBLICATION</th>
<th>CONVERSION FACTOR</th>
<th>LENGTH OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raymond et al.</td>
<td>ASN 2004, F-PO522</td>
<td>1:281 i.v 1:224 s.c</td>
<td>3 months</td>
</tr>
<tr>
<td>Giotta N et al.</td>
<td>ASN 2004, SU-PO434</td>
<td>1:246 i.v.</td>
<td>6 months</td>
</tr>
<tr>
<td>Roger et al.</td>
<td>Nephrology 2004; 9: 223</td>
<td>1:275 s.c vs i.v</td>
<td>3 months</td>
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<tr>
<td>Barril et al.</td>
<td>ASN 2004, SA-PO321</td>
<td>1:198 HD 1:190 CADO</td>
<td>6 months</td>
</tr>
<tr>
<td>Nissenson et al.</td>
<td>AJKD 2002; 40: 110</td>
<td>1:252 in the correction phase</td>
<td>6 months</td>
</tr>
<tr>
<td>Brunkhorst et al.</td>
<td>NDT 2004; 19: 1224</td>
<td>1:234 i.v. 1:214 s.c</td>
<td>6 months</td>
</tr>
<tr>
<td>Tolman et al.</td>
<td>ASN 2004, MO-46</td>
<td>44% higher doses of erythropoietin beta than darbepoetin</td>
<td>9 months</td>
</tr>
<tr>
<td>Vanrenterghem et al.</td>
<td>Kidney Int 2002; 62: 2167</td>
<td>ca. 1:250 i.v.</td>
<td>12 months</td>
</tr>
</tbody>
</table>
Summary: CERA Clinical Profile

- CERA Phase II results (>1 year) indicate with extended administration intervals
  - a large number of patients are maintained within recommended ranges
  - keeping Hb in recommended ranges is achieved with few dose changes
  - overall, generally well tolerated

adverse events profile characteristic of this
Thank You for your attention!

A. Więcek

Katowice
Poland
<table>
<thead>
<tr>
<th>ERYTHROPOIESIS STIMULATING AGENTS (ESA)</th>
<th>Half-life (h, mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>i.v.</td>
</tr>
<tr>
<td>CERA(^1)</td>
<td>133 ± 9.83</td>
</tr>
<tr>
<td>Darbepoetin alfa(^2)</td>
<td>25.3 ± 2.2</td>
</tr>
<tr>
<td>Epoetin beta(^3)</td>
<td>8.8 ± 0.5</td>
</tr>
<tr>
<td>Epoetin alfa(^3)</td>
<td>6.8 ± 0.6</td>
</tr>
</tbody>
</table>

1 from multiple dose studies  
2 Macdougall et al. JASN 1999  