An Evaluation of Erythropoietin's Role in the Treatment of Anemia of Chronic Kidney Disease

Pharmacotherapy Rounds
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Learning Objectives:
1. Understand the risks and impact of untreated CKD-related anemia
2. Understand the stepwise therapy for treating anemia of CKD
3. Critically evaluate the findings of the major trials of erythropoietin in CKD-related anemia
4. Be able to implement an individualized CKD-related anemia treatment regimen using evidence based treatment goals
1) Anemia Background
   a) A decrease of the hemoglobin (Hgb) content in the blood¹
   b) NHANES III (1988-1994)²
      i) Anemia: <12 g/dl (men), <11 g/dl (women)
      ii) Prevalence of anemia at a given GFR
          (1) 60 ml/min: 1%
          (2) 30 ml/min: 9%
          (3) 15 ml/min: 33-67%
   c) Life-impact of CKD-related anemia³⁻⁹
      i) Dyspnea
      ii) Fatigue
      iii) Decreased mental clarity
      iv) Decreased sexual function
      v) Depression
   d) Cardiovascular Implications of CKD-Related Anemia³⁻⁹
      i) Hypoxia eventually results in left ventricular hypertrophy (LVH)
         (1) 20-50% of Stage III & IV CKD patients have LVH
         (2) 80% of dialysis patients have LVH
      ii) Heart failure with anemia and CKD termed "Cardiorenal anemia syndrome"
      iii) CVD is the most common cause of death in CKD patients

2) Current Approach to Treating CKD Patients Presenting With Anemia¹⁰
   a) Rule out and treat other etiologies of the anemia
   b) Evaluate iron stores
      i) Low available iron may cause primary anemia
      ii) Low available iron slows the formation of red blood cells
   c) Manage and monitor blood pressure
      i) Lower the risk of cardiovascular events in a high-risk population
   d) What are the potential benefits of initiating erythropoietin therapy?
      i) Reduced mortality, cardiovascular outcomes, or progression to ESRD?
      ii) Decreased transfusions or increased quality of life?

3) Clinical Trial Timeline: 1987-2010
   a) 1987: Combined Phase I and II Erythropoietin Trials by Eschbach, et al.¹⁴
      i) CKD-related anemia pathophysiology¹⁶,¹⁷
         (1) Reduced erythropoietin production
         (2) Shortened RBC survival
      ii) CKD-related anemia previously treated with red blood cell transfusions or androgens¹⁸,¹⁹
iii) Trial consisted of 25 hemodialysis patients with a mean Hgb of 6.5 g/dl
   1) Subjects were randomized to doses between 1.5 units/kg/week – 500 units/kg/week
   2) Lowest dose producing clinical effects was 15 units/kg/week
      a) Functional iron deficiency appeared at these doses
   3) No ADRs directly attributable to erythropoietin
   4) 4 patients developed or had worsened hypertension
   5) 1 patient had a seizure associated with hypertension

b) 1989: Phase III Erythropoietin trial in ESRD by Eschbach, et al.\(^\text{15}\)
   i) 13-month study of 333 hemodialysis patients with average Hgb of 7.5 g/dl
      1) Designed to measure quality of life, safety, and consequences of near-normalization of hemoglobin
      2) Excluded patients with TSAT ≤20% or ferritin ≤100 μg/l
      3) Erythropoietin dosed to achieve average Hgb of 11.5 g/dl
      4) Impact on transfusions
         a) Averaged 0.5 transfusions per month at baseline
         b) All but 2 were transfusion independent by end of study
      5) Changes in iron
         a) 43% of participants developed iron deficiency

   6) Quality of Life
      a) Karnofsky score (0-100, 100 best)
         i) 25.9% of the participants had a Karnofsky score of 100 at baseline
         ii) 43.5% of the participants had a Karnofsky score of 100 at 10 months
         iii) \(p<0.01\)
         b) Nottingham Health Profile (0-100, 100 worst)
            i) Average score of 47 at baseline
            ii) Improved to 27.7 at 10 months
            iii) \(p<0.01\)

c) 1990-1997: Studies of CKD-Related Anemia\(^\text{20-27}\)
   i) Data from small, observational studies had shown that partial correction of anemia could
      1) Reduce exercise-induced cardiac ischemia
      2) Reduce left ventricular hypertrophy
   ii) Correction to normal hematocrit levels in small, observational studies had shown
      1) No increase in BP, no thrombosis of vascular access site, no seizures, nor cardiovascular events
      2) Improved quality of life, shorter hospitalizations, increased exercise performance, better cognitive function, better immune function, etc...
   iii) What impact does correcting anemia with erythropoietin have on mortality or cardiovascular outcomes?
<table>
<thead>
<tr>
<th>The Effects of Normal as Compared with Low Hematocrit Values in Patients with Cardiac Disease Who are Receiving Hemodialysis and Epoetin (The Normal Hematocrit Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[EDIT: The researchers derived study Hct values by multiplying measured Hgb by a factor of three. The Hgb listed below are the Hct listed in the trial divided by three.]</td>
</tr>
</tbody>
</table>

| Design | Prospective, randomized, open-label, multicenter study in dialysis patients with congestive heart failure or ischemic heart disease |
| Objective | To examine the risks and benefits of increasing hemoglobin to 14 g/dl vs. 10 g/dl in hemodialysis patients with cardiac disease |
| Population | Inclusion criteria |
| | • On hemodialysis |
| | • Documented congestive heart failure or ischemic heart disease |
| | • TSAT ≥20% |
| Exclusion criteria | • DBP ≥100 mm HG |
| | • NYHA Class IV CHF |
| | • MI, PTCA, or CABG within 3 months |
| | • Recipient of androgen therapy |
| Outcome | Primary |
| | • Time to death or first nonfatal MI |
| Secondary | • CHF or angina requiring hospitalization |
| | • CABG or PTCA |
| | • All cause hospitalization |
| | • Red cell transfusions |
| | • QOL (SF-36) |
| Methods | • Randomly assigned to normal (14 g/dl) or low (10 g/dl) hemoglobin groups |
| | • Planned duration of 3 years after last patient enrolled |
| | • Normal Hgb group had dose increased by 50% upon entry to study |
| | • Iron was reevaluated if the patient was a non-responder to increased Epoetin doses |
| Statistical Analysis | • Trial terminated after median duration of 14 months |
| | • Boundaries for significance not crossed |

| Results | Patients |
| | 1233 patients |
| | • Baseline Hgb of ~10 g/dl |
| | • 70% had hypertension |
| | • 56% had diabetes (44% had diabetes-induced nephropathy) |

Epoetin Use |

| | Normal group required 450 units/kg/week of Epoetin compared to 115 units/kg/week in the low group |
Primary Endpoint (Death or 1st nonfatal MI @ 29 months)
- Normal: 183 deaths and 19 1st nonfatal MI
- Low: 150 deaths and 14 1st nonfatal MI
  - HR: 1.3 (95% CI: 0.9-1.9)
  - Separation in Kaplan-Meier curve seen at approximately 7 months, increasing until month 14.
  - 50% of the patients remaining in study between months 12 and 15

Secondary Endpoints
- Red cell transfusions
  - Normal: 129 (21%)
  - Low: 192 (31%)
  - \( p < 0.001 \)
- SF-36 Physical-Function Score
  - No between-group analysis was discussed
  - Each 1 g/dl increase in Hgb over baseline produced a 1.8 point increase on SF-36 physical-function
  - \( p = 0.03 \)
- No difference in all cause hospitalization, nonfatal MI, CHF requiring hospitalization, angina pectoris requiring hospitalization, CABG, or PTCA

Conclusions of Authors
- Targeting a Hgb value of 14 g/dl in dialysis patients with congestive heart failure or ischemic heart disease is not recommended

Conclusion
- NHS showed there was definitely no mortality or MI reduction with Hgb target of 14 g/dl vs. 10 g/dl
- Quality of life data compared between groups was not published
- Amgen, Inc. was running all aspects of study
- Led to the boxed warnings on Epoetin Alfa
• FDA released a statement saying that poor outcomes possibly due to:
  - Rapid increases in erythropoiesis
  - Oscillations in Hgb/Hct
  - Overshooting the target level

### Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease
(Correction of Hemoglobin and Outcomes in Renal Insufficiency – CHOIR)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Design</td>
<td>Prospective, randomized, open-label, multicenter study in PRE-dialysis patients</td>
</tr>
<tr>
<td>Objective</td>
<td>To determine whether a high (13.5 g/dl) Hgb target would decrease the risk of complications from cardiovascular cause compared to a low (11.3 g/dl) Hgb target</td>
</tr>
<tr>
<td>Population</td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td></td>
<td>• Hgb &lt; 11 g/dl</td>
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<tr>
<td></td>
<td>• CKD (GFR 15-50 ml/min/1.73 m² BSA)</td>
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<tr>
<td></td>
<td>Exclusion criteria</td>
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<tr>
<td></td>
<td>• Uncontrolled hypertension</td>
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<tr>
<td></td>
<td>• Gastrointestinal bleeding</td>
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<tr>
<td></td>
<td>• Iron overloaded state</td>
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<tr>
<td></td>
<td>• &quot;Frequent&quot; transfusions over 6 months prior to study initiation</td>
</tr>
<tr>
<td></td>
<td>• Refractory iron deficiency anemia</td>
</tr>
<tr>
<td></td>
<td>• Active cancer</td>
</tr>
<tr>
<td></td>
<td>• Prior Epoetin Alfa therapy</td>
</tr>
<tr>
<td></td>
<td>• Unstable angina</td>
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<tr>
<td>Outcome</td>
<td>Primary Outcomes</td>
</tr>
<tr>
<td></td>
<td>• Composite of death, MI, stroke, or hospitalization for CHF (excluding those who received RRT)</td>
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<tr>
<td></td>
<td>• CHOIR added hospitalization for CHF and stroke to primary outcome of NHS</td>
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<tr>
<td></td>
<td>Secondary Outcomes</td>
</tr>
<tr>
<td></td>
<td>• Individual components of the primary outcome</td>
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<tr>
<td></td>
<td>• Time to RRT</td>
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<td></td>
<td>• Any-cause and cardiac-cause hospitalization</td>
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<tr>
<td></td>
<td>• QOL (LASA, KDQ, SF-36)</td>
</tr>
<tr>
<td>Methods</td>
<td>Randomly assigned to high or low hemoglobin group</td>
</tr>
<tr>
<td></td>
<td>Received subcutaneous Epoetin therapy on a weekly basis</td>
</tr>
<tr>
<td></td>
<td>Patients removed from study if initiated on RRT</td>
</tr>
<tr>
<td>Statistical Analysis</td>
<td>1352 patients needed for 80% power to detect a 25% relative risk reduction in composite event rate in the high hemoglobin group over 3 years assuming:</td>
</tr>
<tr>
<td></td>
<td>• 30% event rate in low-hemoglobin group</td>
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<tr>
<td></td>
<td>• ≥295 composite events</td>
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<tr>
<td></td>
<td>• 30% rate of early withdrawal for reasons other than primary endpoint</td>
</tr>
</tbody>
</table>
• O'Brien-Fleming alpha-spending boundary
  o Four interim analysis planned
  o 2% chance of type I error
• Kaplan-Meier to analyze time to first event
• Log-rank to compare times to event between groups
• Repeated ANOVA used to evaluate hemoglobin levels over time
• Duke Clinical Research Institute (DCRI) served as the independent data and safety monitoring board responsible for monitoring and reviewing the data
  o DCRI acquired and queried all data
  o DCRI performed primary analysis
  o Sponsor performed all secondary analysis with DCRI verification

### Results

#### Patients
- 1432 patients were randomized
  - 49% had diabetes-induced nephropathy
  - Hypertension
    - 95.8% in 13.5 g/dl group
    - 93.2% in 11.3 g/dl group
    - p<0.03
- Baseline Hgb of 10.1 g/dl
- TSAT ≥20% and ferritin ≥100 µg/l
- ~26% were on oral iron therapy at baseline

#### Early Termination of CHOIR
- Study terminated after 2nd (of 4) interim analysis by DCRI
- 16 month mean and median duration of participation
- 549 patients (38.2%) withdrew before termination of the study without a composite event
- 112 patients (8%) completed 36 months of the study

#### Hemoglobin Levels and Erythropoietin Requirements
- Low group achieved target of 11.3 g/dl at 6,276 units/week
- High group had a mean Hgb consistently below target of 13.5 g/dl (average 12.6 g/dl) while using 11,215 units/week

#### Iron Usage During Study
- 52% in high group
- 48% in low group
- P=0.18
Primary Outcome (Composite of death, MI, stroke, or hospitalization excluding for RRT)
- 222 total composite events occurred over 16 months
  - 125 (17.5%) in high group
  - 97 (13.5%) in low group
  - HR: 1.34 (95% CI: 1.03-1.74; p=0.03)

Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>High n(%)</th>
<th>Low n(%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>52 (7.3%)</td>
<td>36 (5%)</td>
<td>1.48 (0.97-2.27)</td>
<td>0.07</td>
</tr>
<tr>
<td>CHF Hospitalization (excluding RRT)</td>
<td>63 (9%)</td>
<td>47 (6.6%)</td>
<td>1.41 (0.97-2.05)</td>
<td>0.07</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>18 (2.5%)</td>
<td>20 (2.8%)</td>
<td>0.91 (0.48-1.73)</td>
<td>0.78</td>
</tr>
<tr>
<td>Stroke</td>
<td>12 (1.7%)</td>
<td>12 (1.7%)</td>
<td>1.01 (0.45-2.25)</td>
<td>0.98</td>
</tr>
<tr>
<td>Any renal replacement therapy</td>
<td>155 (21.7%)</td>
<td>134 (18.7%)</td>
<td>1.19 (0.94-1.49)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cardiac Hospitalization</td>
<td>233 (32.6%)</td>
<td>197 (27.5%)</td>
<td>1.23 (1.01-1.48)</td>
<td>0.03</td>
</tr>
<tr>
<td>Any Cause Hospitalization</td>
<td>369 (51.6%)</td>
<td>334 (46.6%)</td>
<td>1.18 (1.02-1.37)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Quality of Life
- Changes from baseline to 16 months
  - Both groups had p-values between <0.001 and 0.02 on all scales except for SF-36 pain, social function, and emotional role
- High vs. low target comparison
  - No difference on LASA or KDQ
  - Only difference on SF-36 was emotional role (p=0.01)
Conclusions of Authors

- Overall quality of life improved when treated with Epoetin Alfa, however, there were no additional benefits when the high and low Hgb groups were compared.
- No apparent benefits from a higher Hgb target, increased cost of Epoetin therapy, conclude that the high Hgb target provides no cost benefit for either patients or payers, even before considering the risk.
- This study does not support the NKF’s goal Hgb range of 11-13 g/dl and supports the use of an 11-12 g/dl goal

Comments

- Outcome difference driven by death and CHF-hospitalization
- Would death and CHF hospitalizations reached significance had study continued for 36 months?
- More hospitalizations in high hemoglobin group
- No difference seen in the rate of stroke between two groups
- Patients needing renal replacement therapy were statistically the same, though favored the low hemoglobin group
- Stronger evidence yet of no benefit to mortality, cardiovascular outcomes, or renal replacement therapy with a higher hemoglobin target

4) FDA Alert 2006\textsuperscript{33}
   a) Maintain hemoglobin levels between 10 to 12 g/dl
   b) Monitor ESA therapy frequently
   c) Make sure patients keep lab appointments
   d) Patients should be alerted of when to contact their physician

5) Black Box 2007\textsuperscript{11-13}
   a) Current Epoetin Alfa and Darbepoetin Alfa Black Box (emphasis added)
      i) “Increased mortality, serious cardiovascular events, thromboembolic events, stroke, and increased risk of tumor progression or recurrence.”
      ii) Pertaining to CKD
         (1) “In clinical studies, patients experienced greater risks for death, serious cardiovascular events, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target hemoglobin levels of 13 g/dL and above.”
         (2) “Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.”

6) Medication Guide 2008\textsuperscript{34}
   a) Medication guide replaced patient package insert
   b) Boxed warnings strengthened and modifications made to indications/usage and dosage/administration
### A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease (Trial to Reduce Cardiovascular Events with Aranesp Therapy – TREAT)

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<td><strong>Design</strong></td>
<td>Prospective, randomized, double-blind, placebo-controlled, multicenter, multination study in PRE-dialysis patients</td>
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<tr>
<td><strong>Objective</strong></td>
<td>To determine whether targeting a Hgb of 13 g/dl would lower rates of death, cardiovascular events, and end stage renal disease as compared with placebo</td>
</tr>
</tbody>
</table>
| **Population** | Inclusion criteria:  
  - Type II Diabetes Mellitus  
  - Hgb <11 g/dl  
  - CKD (GFR 20-60 ml/min/1.73 m² BSA)  
  - TSAT ≥15%  
  Exclusion criteria:  
  - Uncontrolled hypertension  
  - ESA use within 12 weeks  
  - Previous or scheduled renal transplant  
  - Current use of IV antibiotics  
  - Chemotherapy  
  - Radiation therapy  
  - Cancer (except basal-cell or squamous cell skin carcinoma)  
  - HIV or hematological disease  
  - Active bleeding  
  - Pregnancy |
| **Outcome** | Primary  
  - Time to composite of death or nonfatal CV event (nonfatal MI, CHF, stroke, MI-related hospitalization)  
  - Time to composite of death or ESRD  
  Secondary  
  - Components of primary outcomes  
  - Time to death  
  - Death from CV causes  
  - Rate of decline in GFR  
  - Changes in outcomes (FACT-Fatigue and SF-36)  
  - SF-36 added after 2nd interim analysis |
| **Methods** |  
  - Data collection and management by Amgen, Inc.  
  - University of Wisconsin Data Analysis Center did all data analysis  
  - Patients randomly assigned to treatment of placebo in 1:1 ratio  
  - Darbepoetin and placebo were supplied in matching prefilled syringes in 12 different strengths  
  - Very conservative dosing algorithm was used (Appendix B)  
  - Placebo group patients could get erythropoietin therapy if the Hgb <9 g/dl with a return to placebo once >9 g/dl |
Statistical Analysis

- Event driven
- 1203 composite cardiovascular events needed for 80% power to detect a 20% risk reduction
- Aimed for 4000 patient enrollment assuming
  - 12.5 annualized rate of events in placebo group
  - 15% loss to follow-up
  - Attenuation of treatment effect due to anticipated use of ESAs in patients who had progression to ESRD
- O'Brien-Fleming alpha-spending boundary
- Time-to-event analysis performed with life-table methods using ITT
- Kaplan-Meier cumulative incidence curves were compared using two-sided log-rank test
- Hazard ratios were determined using Cox-proportional hazards models

Results

Patients

- 4038 patients were randomized
  - 2012 in treatment group (Target: 13 g/dl)
  - 2026 in placebo group
- Baseline Hgb of 10.4 g/dl
- TSAT ≥20% and ferritin ≥100 µg/l at baseline
- 43.2% were on iron therapy at baseline
- Study continued for 29.1 months
- 87% of the patients were still being followed or had died
- More patients in placebo group had CHF
  - Treatment: 31.5%
  - Placebo: 35.2%
  - p=0.01

Hemoglobin Results and Darbepoetin Alfa Requirements (median)

- Separation of Hgb occurred prior to the 1st month
- Placebo group achieved 10.6 g/dl on 0 µg per month
  - 46% received at least one dose of treatment
- Treatment group achieved 12.5 g/dl 176 µg per month

Iron Usage

- Overall iron use
  - 66.8% in treatment
  - 68.6% in placebo
  - p=0.25
- IV Therapy
  - 14.8% in treatment
  - 20.4% in placebo
  - p<0.001
Red Cell Transfusions

- 298 patients (14.8%) treatment
- 496 patients (24.5%) placebo
  - HR 0.56 (95% CI: 0.49-0.65; p<0.001)

Primary Outcomes

- Death or a nonfatal cardiovascular event
  - 632 patients (31.4%) treatment
  - 602 patients (29.7%) placebo
  - HR: 1.05 (95% CI: 0.94-1.17; p=0.41)

Secondary Outcomes

- Death or ESRD
  - 652 patients (32.4%) treatment
  - 618 patients (30.5%) placebo
  - HR 1.06 (95% CI, 0.95-1.19; p=0.29)

- No statistically significant difference in
  - Death from any cause, myocardial infarction, heart failure, myocardial ischemia, ESRD, hypertension, or death from cardiovascular causes

- Stroke
  - 101 patients (5%) treatment
  - 53 patients (2.6%) placebo
  - HR 1.92 (95% CI: 1.38-2.68; p<0.001)
Cardiac revascularization
- 84 patients (4.2%) treatment
- 117 patients (5.8%) placebo
- HR 0.71 (95% CI: 0.54-0.94; p<0.02)

Venous thromboembolism
- 41 patients (2%) treatment
- 23 patients (1.1%) placebo
- P=0.02

Arterial thromboembolism
- 178 patients (8.9%) treatment
- 144 patients (7.1%) placebo
- P=0.04

Quality of Life
- FACT-Fatigue increase of ≥3 points
  - 963 of 1762 (54.7%) treatment
  - 875 of 1769 (49.5%) placebo
  - P=0.002

- SF-36
  - No difference in total score or any subsection of scale

<table>
<thead>
<tr>
<th>Conclusions of Authors</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results do not support the results of CHOIR, as CHOIR showed no difference in stroke but an increased risk of composite outcome driven by death and CHF-related hospitalization.</td>
<td>Trial establishes a proper risk/benefit of treating vs. not treating moderate CKD-related anemia in diabetic patients</td>
</tr>
<tr>
<td>The results of our study demonstrate the importance of completing planned follow-up of trials and the potential to draw misleading conclusions when premature discontinuation results in an insufficient number of events to allow for a reliable estimation of the effect of treatment.</td>
<td>Increased risk of stroke was seen in a meta-analysis, but not in NHS, CHOIR or CREATE</td>
</tr>
<tr>
<td>The risks outweigh the potential benefits of ESA therapy in pre-dialysis patients with diabetes and CKD with moderate anemia given increased risk of stroke and possibly death among patients with a history of a malignant condition.</td>
<td>Negligible quality of life improvement with treatment</td>
</tr>
</tbody>
</table>
7) Risk Evaluation and Mitigation Strategy (REMS) 2010
   a) ESA APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs) Oncology program for ESA patients with cancer
   b) A demonstrated increase in the risk of tumor growth and shorten survival in patients with cancer
   c) ESAs can increase the risk of heart attack, heart failure, stroke, or blood clots

8) What is Erythropoietin’s Role in the Treatment of CKD-Related Anemia?
   a) The pathophysiology of cardiovascular disease in CKD-related anemia seemed to indicate that eliminating anemia should have beneficial effects on cardiovascular disease outcomes.
   b) Smaller observational studies found benefit using surrogate cardiovascular endpoints with partial anemia correction and even better results with full anemia correction with little to no indication of potential harm.
      i) Many of these studies were in severely anemic hemodialysis patients
   c) The results of TREAT, a large, randomized, placebo-controlled trial demonstrated that the use of erythropoietin does not provide a decrease in mortality, cardiovascular complications, or time to renal replacement therapy in diabetic patients with mild to moderate anemia.
   d) The combined lack of outcome benefit, and possible harm, seen in NHS, CHOIR, and TREAT along with the negligible difference in quality of life scores between low (~10 g/dl) and high (>12.5 g/dl) hemoglobin levels, with erythropoietin therapy, do not support the use of high hemoglobin targets in clinical practice.
   e) The results of these large studies show the need for studies better designed to detect harm from erythropoietin therapy
   f) Greatest utility, among data reviewed, appears to be in patients with more severe anemia at high risk for cardiovascular complications.
References:

Appendix A:
Abbreviations

- ADR: Adverse Drug Reaction
- ANOVA: Analysis of Variance
- CABG: Coronary Artery Bypass Grafting
- CHF: Congestive Heart Failure
- CHOIR: Correction of Hemoglobin and Outcomes in Renal Insufficiency
- CI: Confidence Interval
- CKD: Chronic Kidney Disease
- CREATE: Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta
- CVD: Cardiovascular Disease
- DCRI: Duke Clinical Research Institute
- ESA APPRISE: Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs
- ESA: Erythropoiesis Stimulating Agent
- ESRD: End Stage Renal Disease
- FACT: Functional Assessment of Cancer Therapy
- FDA: Food and Drug Administration
- GFR: Glomerular Filtration Rate
- Hct: Hematocrit
- Hgb: Hemoglobin
- HR: Hazard Ratio
- IHD: Ischemic Heart Disease
- IV: Intravenous
- KDQ: Kidney Disease Questionnaire
- LASA: Linear Analogue Self Assessment Questionnaire
- MI: Myocardial Infarction
- NHANES: National Health and Nutrition Examination Survey
- NHS: Normal Hematocrit Study
- NTE: Not To Exceed
- NYHA: New York Heart Association
- PTCA: Percutaneous Transluminal Coronary Angioplasty
- QOL: Quality of Life
- REMS: Risk Evaluation and Mitigation Strategy
- SF-36: Short-Form 36
- SQ: Subcutaneous
- TREAT: Trial to Reduce Cardiovascular Events with Aranesp Therapy
- TSAT: Transferrin Saturation (Serum Iron divided by Total Iron Binding Capacity)
### Appendix B: TREAT Dosing Algorithm

#### Darbepoetin alfa Dosing Algorithm

<table>
<thead>
<tr>
<th>Hb (g/dL)</th>
<th>Hb rate of rise (g/dL/2 weeks)</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12.5</td>
<td>&lt; 0.5</td>
<td>Increase to next higher dose</td>
</tr>
<tr>
<td></td>
<td>≥ 0.5 - &lt; 1.0</td>
<td>Maintain dose</td>
</tr>
<tr>
<td></td>
<td>≥ 1.0</td>
<td>Decrease to next lower dose</td>
</tr>
<tr>
<td>12.5 - &lt; 13.5</td>
<td>&lt; 0.5</td>
<td>Maintain dose</td>
</tr>
<tr>
<td></td>
<td>≥ 0.5 - &lt; 1.0</td>
<td>Maintain dose</td>
</tr>
<tr>
<td></td>
<td>≥ 1.0</td>
<td>Decrease to next lower dose</td>
</tr>
<tr>
<td>13.5-14.0</td>
<td>Any</td>
<td>Decrease to next lower dose</td>
</tr>
<tr>
<td>&gt; 14.0</td>
<td>Any</td>
<td>Administer placebo until Hb value is below 13.0, then resume darbepoetin alfa at next lower dose</td>
</tr>
</tbody>
</table>

#### Rescue Therapy Dosing Algorithm

<table>
<thead>
<tr>
<th>Hb (g/dL)</th>
<th>Hb rate of rise (g/dL/2 weeks)</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 9.0</td>
<td>&lt; 0.5</td>
<td>Initiate or increase to next higher dose</td>
</tr>
<tr>
<td>&lt; 9.0</td>
<td>≥ 0.5, but &lt; 1.0</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>&lt; 9.0</td>
<td>≥ 1.0</td>
<td>Decrease to next lower dose</td>
</tr>
<tr>
<td>≥ 9.0</td>
<td>Any</td>
<td>Resume placebo administration</td>
</tr>
</tbody>
</table>