ADVANCES IN THE TREATMENT OF ANEMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Disclosures

Pablo E. Pergola, MD, PhD, has disclosed the following relevant financial relationships:

• Served as an advisor or consultant for: AbbVie Inc.; Akebia Therapeutics; Gilead Sciences, Inc.; Keryx Biopharmaceuticals, Inc.; Vifor Pharma

• Served as a speaker or member of a speaker bureau for: Keryx Biopharmaceuticals, Inc.
Background and Epidemiology
Almost half of patients with chronic kidney disease have anemia

- Based on WHO criteria, anemia is defined as:
  - Hemoglobin <12 g/dL in women
  - Hemoglobin <13 g/dL in men
- Both the prevalence and severity of anemia correlate with the progressive decline in eGFR
- Anemia affects the majority of patients with GFR category G5

Anemia is a common occurrence in CKD; the prevalence and severity increases with CKD progression.

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eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; WHO, World Health Organization.

Anemia increases the risk of complications and mortality in patients with chronic kidney disease

In patients with CKD, anemia can lead to 1–3

- Increased cardiovascular risk, such as myocardial infarction and stroke
- Increased hospitalization rates
- Increased all-cause mortality
- Increased risk of kidney failure progression
- Reduced exercise capacity
- Reduced quality of life

Higher hemoglobin levels are associated with reduced risk of hospitalization and mortality

<table>
<thead>
<tr>
<th>Patient hemoglobin, g/dl</th>
<th>RR mortality</th>
<th>p-value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8</td>
<td>1.06</td>
<td>0.34</td>
<td>2740</td>
</tr>
<tr>
<td>8–9.99</td>
<td>1.09</td>
<td>0.08</td>
<td>2202</td>
</tr>
<tr>
<td>10–10.99</td>
<td>1</td>
<td></td>
<td>1936</td>
</tr>
<tr>
<td>11–11.99</td>
<td>0.92</td>
<td>0.19</td>
<td>1403</td>
</tr>
<tr>
<td>≥12</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OVERALL RR = 0.95 (p=0.003) per 1 g/dl higher hemoglobin

<table>
<thead>
<tr>
<th>Patient hemoglobin, g/dl</th>
<th>RR hospitalization</th>
<th>p-value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8</td>
<td>1.55</td>
<td>&lt;0.0001</td>
<td>435</td>
</tr>
<tr>
<td>8–9.99</td>
<td>1.16</td>
<td>0.001</td>
<td>2484</td>
</tr>
<tr>
<td>10–10.99</td>
<td>1.09</td>
<td>0.05</td>
<td>1994</td>
</tr>
<tr>
<td>11–11.99</td>
<td>1</td>
<td></td>
<td>1789</td>
</tr>
<tr>
<td>≥12</td>
<td>1.01</td>
<td>0.77</td>
<td>1296</td>
</tr>
</tbody>
</table>

OVERALL RR = 0.94 (p=0.0001) per 1 g/dl higher hemoglobin

CKD, chronic kidney disease.
Key Players
Transferrin is a 90 Kd globulin that binds and transports iron in the plasma → transferrin receptors.

The liver is the primary synthesis site.

The “Iron Uber” (Csaba P. Kovesdy, MD)

Ferritin: The Origin

• A ubiquitous protein with a MW of 450,000
• Originates from reticuloendothelial system (RES) and is produced mainly in the liver and erythroid cells
• Functions as an iron binding protein for storage (represents body iron stores)
• Ferritin is NOT a transport protein
• "Hemosiderin" = condensed ferritin molecules

Tissue Ferritin vs Serum Ferritin

• Serum ferritin results from the leakage of tissue ferritin
• While tissue ferritin clearly plays a role in intracellular iron handling, the role of serum ferritin is less clearly understood

Serum ferritin contains little or no iron

Serum Ferritin

- Serum ferritin is the result of balance between its secretion/leakage (related to intracellular iron synthesis or inflammation) and its clearance, mainly in liver.

- Liver dysfunction and inflammatory factors may interfere with the synthesis and clearance of ferritin, thereby increasing serum ferritin levels due to circumstances not related to iron metabolism.

Ferroportin -- The Iron Exporter

- The only cellular iron exporter known in vertebrates
- Member of the major facilitator superfamily (MFS)
- Mechanism: alternating access, anion symporter?

Hepcidin

- An iron-regulatory peptide hormone
  - Made in the liver as 84 aa preprohepcidin
  - Cleaved to 25 aa bioactive hepcidin by furin
  - Circulates in blood plasma

Serum Hepcidin Is Very High in CKD

<table>
<thead>
<tr>
<th></th>
<th>2009 [a]</th>
<th>Median Hepcidin, mg/mL</th>
<th>2010 [b]</th>
<th>Median Hepcidin, mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Controls (n = 20)</td>
<td>25.3</td>
<td></td>
<td>Pediatric Controls (n = 20)</td>
<td>25.3</td>
</tr>
<tr>
<td>Adult Controls (n = 24)</td>
<td>72.9</td>
<td></td>
<td>Adult Controls (n = 24)</td>
<td>72.9</td>
</tr>
<tr>
<td>PCKD2-4 (n = 48)</td>
<td>127.3</td>
<td></td>
<td>PCKD2-4 (n = 30)</td>
<td>240.5</td>
</tr>
<tr>
<td>ACKD2-4 (n = 32)</td>
<td>269.9</td>
<td></td>
<td>Adult HD (n = 33)</td>
<td>690.2</td>
</tr>
<tr>
<td>PCKD5D (n = 26)</td>
<td>652.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Hepcidin-Mediated Inhibition of Ferroportin (hFPN)

- Hepcidin binds to the hFPN C lobe, inhibiting its state transition toward the inward-facing state
- Hepcidin binding may also change the conformation of the intracellular side of hFPN
  - Triggers the ubiquitination and subsequent internalization

Intestinal Iron Transport

Regulation of Intestinal Iron Absorption

- **Dietary iron uptake**
- **Food**
- **Dietary iron uptake**
- **Iron release into plasma**
- **Ferritin**
- **Fpn**
- **Fe**
- **Hepcidin**

**Low hepcidin**

**High hepcidin**
• Enterocytes take up elemental Fe from the gut via DMT1
• Fe passage is stimulated by HIF2α and inhibited through Fe sequestration in ferritin
• Fe utilization by the erythroid marrow and its recycling by RES macrophages account for the major iron fluxes
• Peritubular fibroblasts of the kidney sense Fe and O2 deficiency and release EPO
• Low Fe and/or O2 inactivate PHD2, leading to HIF2α accumulation and stimulation of EPO transcription
Iron Metabolism in Erythroid Cells

• Iron acquisition in erythroid cells is dependent on endocytosis of Fe$^{2+}$ transferrin via the transferrin receptor

• In mitochondria, iron is inserted into protoporphyrin IX to produce heme
  – Heme is transported outside of mitochondria for incorporation into hemoglobin

• In the cytosol, excess iron is sequestered within ferritin

• Cellular iron efflux is mediated by ferroportin and requires iron oxidation on the extracellular side
Anemia Associated With CKD
Available Treatments

1. **ERYTHROPOIETIN ANALOGUES (ESA)**
2. **PO IRON**
3. **IV IRON**
4. **DIALYSATE IRON**

**Erythropoietin Deficiency**
- "Absolute or functional"

**Absolute Iron Deficiency**

**Functional Iron Deficiency**
- Iron sequestration due to inflammation

**Less Iron Available for Erythropoiesis**

**Improved Hemoglobin**

Iron: Why is it Important?

• Most abundant element on Earth: 35% of Earth’s mass!
• Essential trace element used by almost all living organisms
  – Catalyst of oxidative reactions
  – Transport of soluble gases
• Essential component of hemoglobin

• 200 billion RBCs are produced every day
  – 20 mL of blood being produced each day
  – 6 g of hemoglobin and 20 mg of iron
• More than $2 \times 10^{15}$ iron atoms are needed every second to maintain adequate erythropoiesis
Physiologic Iron Trafficking

Dietary iron (10-15 mg/d) → Iron losses (1-2 mg/d) → Duodenum → Absorbed iron (1-2 mg/d) → Iron Transferrin (3 mg Iron) → Bone marrow (300 mg iron) → Red blood cells (1800 mg iron) → Macrophage (600 mg iron) → Liver and Spleen (1000 mg iron)

Estimated Annual Iron Loss in Patients With HD

Average annual iron loss due to:
- Repeated laboratory tests ~ 0.5 g
- Accidental losses during HD and other bleeding events ~ 1.0 g
- Blood retention in dialyzer and tubing ~ 1.0 g
- Normal iron losses ~ 0.5 g
- Total annual iron loss ~ 3.0 g

Systemic Iron Homeostasis Under Pathologic Conditions

Response to hemorrhage, iron deficiency:
- Dietary absorption of iron increased
- Stored iron released from macrophages and hepatocytes

Response to iron overload:
- Dietary absorption of iron decreased

Response to infection or inflammation:
- Iron release from macrophages and hepatocytes decreased
- Dietary iron absorption decreased
- Hypoferremia
Iron homeostasis is dysregulated in CKD
  - Several factors lead to upregulation of hepcidin production

Hepcidin reduces iron bioavailability:
  - Blocks absorption in gut
  - Blocks iron release from the cells of the RES

Iron-Restricted Anemias

Overview of Iron Metabolism in CKD and ESRD

- Iron stores decreased by blood losses
- Hepcidin levels increased by inflammation and decreased renal clearance, despite counter effects from EPO-stimulated erythroferrone
  - High hepcidin blocks iron efflux from macrophages and hepatocytes
  - High hepcidin decreases absorption of dietary iron
- Iron availability for erythropoiesis is restricted
- Intermittent stimulation by EPO therapy requires intermittently high iron flows into the marrow
- Iron may be limiting for erythropoiesis
- Ferritin is an unreliable marker of iron stores

Iron Deficiency Anemia in CKD

KDIGO Anemia Guidelines

- Initial evaluation: CBC, absolute reticulocyte count, serum ferritin levels and transferrin saturation, B12 and folate levels
- Give iron supplementation when TSAT ≤ 30% and ferritin ≤ 500 ng/mL

Aim is to:
- Raise Hb without use of ESA
- Make sufficient iron available for erythropoiesis and other iron-dependent functions
## Treatment Options
### IV Iron Preparations

<table>
<thead>
<tr>
<th></th>
<th>INFeD</th>
<th>CosmoFer</th>
<th>Ferrlecit</th>
<th>Venofer</th>
<th>Feraheme</th>
<th>Injectafer</th>
<th>Monofer (not in US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Name</td>
<td>Low Mw Iron Dextran</td>
<td>Sodium Ferric Gluconate</td>
<td>Iron Sucrose</td>
<td>Ferumoxytol</td>
<td>Ferric Carboxy-maltose</td>
<td>Iron Isomaltoside</td>
<td></td>
</tr>
<tr>
<td><strong>Carbohydrate</strong></td>
<td>Dextran Polysaccharides</td>
<td>Gluconate</td>
<td>Sucrose</td>
<td>Polyglucose sorbitol carboxy-methyl ether</td>
<td>Carboxy-maltose</td>
<td>Isomaltoside</td>
<td></td>
</tr>
<tr>
<td>Molecular weight (Da)</td>
<td>165K Low-MW iron dextran</td>
<td>289K-444K</td>
<td>34K–60K</td>
<td>750K</td>
<td>150K</td>
<td>150K</td>
<td></td>
</tr>
<tr>
<td>Max dose (mg)</td>
<td>100</td>
<td>125</td>
<td>200 (300-400 if PD)</td>
<td>510</td>
<td>1000 mg if patient weighs &gt;66 Kg</td>
<td>20 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Test dose required</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Black box warning</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Preservative</td>
<td>None</td>
<td>Benzyl alcohol</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

## Treatment Options

### PO and IV Iron

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Potential Benefits</th>
<th>Potential Risks</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Iron[^a]</td>
<td>Improved Hb levels</td>
<td>Accumulation in tissue</td>
<td>More costly than oral iron (drug, travel, and administration costs)</td>
</tr>
<tr>
<td></td>
<td>Delayed need for transfusion or ESA use</td>
<td>Transient increase in oxidative stress (?)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduce ESA dosing</td>
<td>Risk of infection (?)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased fatigue and improved physical performance</td>
<td>Increase in plasma NTBI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improved QoL and mental performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO Iron[^b]</td>
<td>• Same as IV</td>
<td>• Interference with concomitant medications</td>
<td>• Pill burden</td>
</tr>
<tr>
<td></td>
<td>• Limited use in patients with chronic inflammatory bowel disease</td>
<td>• Limited intestinal absorption</td>
<td>• Limited intestinal absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GI AEs</td>
<td></td>
</tr>
</tbody>
</table>
### IV and Oral Iron Therapy in Patients With Anemic NDD-CKD Without Concomitant ESA Therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>n</th>
<th>Treatment Period, wk</th>
<th>Mean Change in Hb From Baseline, g/dL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal</td>
<td>IV sodium ferric gluconate -- 250 mg iron weekly x 4</td>
<td>36</td>
<td>6</td>
<td>0.40</td>
<td>&lt; .01</td>
</tr>
<tr>
<td></td>
<td>Oral ferrous sulphate -- 65 mg iron 3x/d</td>
<td>39</td>
<td>6</td>
<td>0.20</td>
<td>NS</td>
</tr>
<tr>
<td>Spinowitz</td>
<td>IV ferumoxytol -- 510 mg iron, 2 doses within 5 days</td>
<td>145</td>
<td>5</td>
<td>0.62</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Oral iron (ferrous fumarate) -- 100 mg iron 2x/d for 21 days</td>
<td>43</td>
<td>5</td>
<td>0.13</td>
<td>n/a</td>
</tr>
<tr>
<td>Tagboto</td>
<td>IV iron sucrose -- 200 mg iron/wk x 4</td>
<td>82</td>
<td>4</td>
<td>0.53</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Tagboto</td>
<td>IV ferric carboxymaltose -- 800 mg iron (single infusion)</td>
<td>30</td>
<td>4</td>
<td>0.73</td>
<td>n/a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>IV Iron</th>
<th>Oral Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.57</td>
<td>0.17</td>
</tr>
<tr>
<td>Median</td>
<td>0.58</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Anemia Associated With CKD

**Iron Deficiency**
- Absolute
  - IRON PO or IV

**Iron Deficiency**
- Functional
  - IRON IV

**IMPoved**
**HEMOglobin**
DOPPS analyzed associations between IV iron dose and outcomes in >32,000 patients on hemodialysis over 9 years.

Increased risk of mortality among patients given higher doses of **IV iron >300 mg/mo**.

For monthly iron doses normalized to body weight, there was an increased risk of CV-related mortality at >6 mg/kg per month vs 1-2 mg/kg/mo.

Hospitalization risk was elevated at IV iron dose >300 mg/mo vs 100–199 mg/mo.

# IV Iron and Infection: REVOKE Study

<table>
<thead>
<tr>
<th></th>
<th>Oral Ferrous Sulfate</th>
<th>IV Iron Sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>Study Period</td>
<td></td>
<td>104 weeks</td>
</tr>
<tr>
<td>SAE, (%)</td>
<td>40 (58)</td>
<td>37 (55)</td>
</tr>
<tr>
<td>SAE infections, (%)</td>
<td>11 (16)</td>
<td>19 (28)</td>
</tr>
</tbody>
</table>

## IV Iron and Infection: FIND-CKD Study

<table>
<thead>
<tr>
<th></th>
<th>Oral Ferrous Sulfate</th>
<th>IV Ferric Carboxymaltose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>312</td>
<td>304</td>
</tr>
<tr>
<td>Study Period</td>
<td>56 weeks</td>
<td></td>
</tr>
<tr>
<td>SAE, (%)</td>
<td>59 (19)</td>
<td>75 (25)</td>
</tr>
<tr>
<td>SAE infections, (%)</td>
<td>12 (3.8)</td>
<td>11 (3.6)</td>
</tr>
</tbody>
</table>

Studies in HD, PD, and non-dialysis CKD patients provide conflicting evidence for the association between IV iron and infection risk

- Most data are derived from observational studies in HD (subject to confounding) and the few RCTs conducted to date were of short duration or underpowered to assess the risk of infection

Current KDIGO recommendations are still prudent, which call for\textsuperscript{[a]}:

- Balancing potential benefits vs risks of IV iron
- Avoiding IV iron use in patients with active systemic infections

Which of the following agents is *not* an iron replacement?

1. Venofer (iron sucrose)
2. Ferrous sulfate
3. Velphoro (Sucroferric oxyhydroxide)
4. Auryxia (Ferric citrate)
5. Ferrous fumarate
Which of the following agents is **not** an iron replacement?

1. Venofer (iron sucrose)
2. Ferrous sulfate
3. **Velphoro (Sucroferric oxyhydroxide)**
4. Auryxia (Ferric citrate)
5. Ferrous fumarate
Velphoro (Sucroferric oxyhydroxide) is not a source of iron

Velphoro is Not Absorbed

- The active moiety of Velphoro, polynuclear iron(III)-oxyhydroxide (pn-FeOOH), is practically insoluble and therefore not absorbed.
- Velphoro works by binding phosphate in the gastrointestinal tract.
- Non-clinical studies in rats and dogs showed that systemic absorption was very low (≤1% of the administered dose).
- The iron uptake from radiolabelled Velphoro (2,000 mg/day) was:
  - 0.06% (range 0.008 – 0.44%) in CKD patients not on dialysis
  - 0.02% (range 0-0.04%) in hemodialysis patients, and
  - 0.43% (range 0.16 – 1.25%) in healthy volunteers with low iron stores (serum ferritin <100 mcg/L)
- Blood levels of radiolabelled iron were very low and confined to the erythrocytes.
Erythropoiesis Stimulating Agents (ESA)
EPO controls the rate of erythropoiesis

- Inhibits hepcidin expression through ERFE
- Adjusts iron efflux from macrophages and enterocytes

History of Erythropoiesis Stimulating Agents

- **Epoetin α** (1989)
- **Epoetin β** (1990)
- **Darbepoetin α** (2001)
- **Epoetin δ** (2002)
- **Methoxy PEG-epoetin β (CERA)** (2007)

**THE FIRST ESA EPOETIN ALFA WAS APPROVED BY THE US FDA IN 1989**

**SINCE THEN SEVERAL EPOETINS HAVE BEEN APPROVED FOR ANEMIA**

**CERA, continuous erythropoietin receptor activator.**

## Treatment Options

### ESAs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Potential Benefits</th>
<th>Potential Risks</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESAs</td>
<td>Decrease need for RBC transfusions</td>
<td>CV events</td>
<td>FDA black box warning</td>
</tr>
<tr>
<td></td>
<td>Improvement in quality of life</td>
<td>Stroke</td>
<td>Goal Hb &lt; normal</td>
</tr>
<tr>
<td></td>
<td>Slower CKD progression</td>
<td>Vascular thrombosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>
Which of the following agents produces the fastest increase in hemoglobin?

1. EPOGEN (erythropoietin alpha) 3 x a week
2. EPOGEN (erythropoietin alpha) 1 x a week
3. ARANESP (Darbepoetin alfa)
4. MIRCERA (Sucroferric oxyhydroxide)
5. All about the same
Question

Which of the following agents produces the fastest increase in hemoglobin?

1. EPOGEN (erythropoietin alpha) 3 x a week
2. EPOGEN (erythropoietin alpha) 1 x a week
3. ARANESP (Darbepoetin alfa)
4. MIRCERA (Sucroferric oxyhydroxide)
5. All about the same
Erythropoiesis Requires Epo and Iron in the Bone Marrow

**BFU-E:** early-stage burst-forming unit-erythroid progenitor
**CFU-E:** later stage colony-forming unit-erythroid progenitor
**Proerythroblast:** earliest morphologically recognizable erythroblast that undergoes mitosis
**EPO binding** to Proerythroblast activates expression of **erythroferrone (ErFe)** that suppresses **hepcidin**
**Erythroblasts:** expel their nuclei to become reticulocytes
**Transferrin receptor:** takes up Tf-bound iron; highly expressed during all maturation stages but absent in mature RBC

Adapted from Gassmann and Muckenthaler. J Appl Physiol 2015;119:1432-1440
Anemia Associated With CKD

EPO Deficiency
- Absolute

EPO Deficiency
- Functional: EPO Hyporesponsive

EPO Analogue

IMPROVED HEMOGLOBIN
Red-Flags Raised With ESA Use

### Four randomized controlled trials of hemoglobin-raising in chronic kidney disease

<table>
<thead>
<tr>
<th></th>
<th>NHCT&lt;sup&gt;52&lt;/sup&gt;</th>
<th>CHOIR&lt;sup&gt;53&lt;/sup&gt;</th>
<th>CREATE&lt;sup&gt;54&lt;/sup&gt;</th>
<th>TREAT&lt;sup&gt;55&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Patients with chronic heart failure and end-stage renal disease on dialysis</td>
<td>Chronic kidney disease</td>
<td>Chronic kidney disease</td>
<td>Chronic kidney disease with diabetes</td>
</tr>
<tr>
<td><strong>Hemoglobin target</strong></td>
<td>10 vs 14 g/dL</td>
<td>13.5 vs 11.3 g/dL</td>
<td>&gt; 13 vs 11 g/dL</td>
<td>&gt; 13 vs 9 g/dL</td>
</tr>
<tr>
<td><strong>Target achieved?</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td>Time to death or first myocardial infarction</td>
<td>Composite of death, myocardial infarction, hospitalization for chronic heart failure, stroke</td>
<td>Time to first cardiovascular event</td>
<td>Composite of death or a cardiovascular event and death or end-stage renal disease</td>
</tr>
<tr>
<td><strong>Risks with higher hemoglobin level</strong></td>
<td>Trend toward increased risk of primary outcome resulted in early study interruption</td>
<td>Increased risk of primary outcome</td>
<td>Trend toward risk increase that was nonsignificant: no benefits</td>
<td>No risk increase or reduction</td>
</tr>
<tr>
<td><strong>Other results</strong></td>
<td>Higher rate of thrombosis in high-target group</td>
<td>Improved quality of life</td>
<td>Higher rate of stroke</td>
<td></td>
</tr>
</tbody>
</table>

Based on these data, KDIGO and the US FDA released new recommendations (2011) stressing the need to balance the potential benefits of reducing blood transfusions with potential cardiovascular risks.

Anemia Associated With CKD: Challenges and Treatment Needs

Iron Deficiency
Functional: EPO Hyporesponsive

EPO Deficiency
Functional: EPO Hyporesponsive

IRON IV

HEMOGLOBIN AT OR BELOW TARGET
Approved and Investigational Therapies
New and Emerging Treatment Options for Anemia in CKD

• Dialysate Iron Replacement:
  – Ferric Pyrophosphate Citrate

• Oral Iron Replacement:
  – Ferric Citrate
  – Ferric maltol

• Oral Hypoxia Inducible Factor Modulators:
  – ...dustats
Ferric Pyrophosphate Citrate (Triferic, Rockwell Medical)
Ferric Pyrophosphate Citrate

- New water-soluble IV iron
- Carbohydrate free
- Indicated for iron replacement and hemoglobin maintenance in patients with CKD on hemodialysis
- Added to bicarbonate dialysate solution; transfers across dialyzer membrane
- Donates iron directly to transferrin; delivers iron directly to the bone marrow
- Must be given in low doses
- Common AEs in trials
  - Procedural hypotension, muscle spasms, headache, extremity pain, peripheral edema, dyspnea, pyrexia

Ferric Pyrophosphosphate Citrate Role in Iron-Restricted Anemias

Safety and Efficacy of Ferric Pyrophosphate Citrate: CRUISE-1 and CRUISE-2

Ferric Citrate
(Auryxia, Keryx)
Ferric Citrate Phase 3 Dialysis Study

**Safety Assessment Period**
- Ferric Citrate
  - n = 292

**Efficacy Assessment Period**
- Ferric Citrate
  - n = 96
- Placebo
  - n = 96

**Open Label Ext**
- Ferric Citrate

**Randomization**
- Active Control (AC)
  - (sevelamer and/or calcium)
  - n = 149

**Secondary endpoints:**
- Mean change in serum ferritin
- Mean change in TSAT
- Cumulative iron use
- Cumulative ESA use
- Mean change in hemoglobin

**52-week Long-term safety data**

**Up to 2 y**
- Wk 56

**Primary efficacy:**
- Mean change in serum phosphorus

Ferric Citrate Increased Serum Ferritin in Dialysis Patients

Means and SDs shown.

*p < .0001.

Ferric Citrate Increased TSAT In Dialysis Patients

Hb Remains Stable With Long-Term PO Ferric Citrate Use in Dialysis Patients

<table>
<thead>
<tr>
<th>Mean Hb, g/dL</th>
<th>Active Control (n = 132)</th>
<th>Ferric Citrate (n = 245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (Day 0)</td>
<td>11.7</td>
<td>11.6</td>
</tr>
<tr>
<td>Week 52</td>
<td>11.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Change From Baseline</td>
<td>-0.6</td>
<td>-0.2</td>
</tr>
<tr>
<td>Least Squares Mean Difference</td>
<td>0.4</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

Ferric Citrate Decreased IV Iron Use

- Ferric citrate demonstrated a 52% decrease in median IV iron intake compared with the active control group over 52 weeks ($P < .0001$)

**Last 6 and 9 Months with No IV Iron in the Study**

<table>
<thead>
<tr>
<th></th>
<th>Active Control</th>
<th>Ferric Citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Months</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>6 Months</td>
<td>24</td>
<td>58</td>
</tr>
</tbody>
</table>

• Ferric citrate demonstrated a 24% decrease in median ESA intake compared with the active control group over 52 weeks ($P < .05$)
Reduction in cardiac and infection SAEs noted after 52 weeks of treatment with ferric citrate

<table>
<thead>
<tr>
<th>Type of SAE</th>
<th>Ferric Citrate N = 292</th>
<th>Active Control N = 149</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SAEs</td>
<td>113 (39.1)</td>
<td>73 (49.0)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>21 (7.3)</td>
<td>18 (12.1)</td>
</tr>
<tr>
<td>Infections</td>
<td>36 (12.5)</td>
<td>27 (18.1)</td>
</tr>
<tr>
<td>GI</td>
<td>20 (6.9)</td>
<td>19 (12.8)</td>
</tr>
</tbody>
</table>

As CKD progresses, patients become iron deficient and anemic; however:

- Many nephrologists refrain from administering IV-iron and EPO in their offices due to safety and logistical concerns
- > 80% of US pre-dialysis clinics do not have IV equipment
- Current oral iron formulations (mostly ferrous iron) are marginally effective, with inadequate absorption and significant GI AEs

Consequently, an effective oral ferric iron supplement could be an ideal solution

- No oral iron supplements are FDA approved
Safety and Efficacy of Ferric Citrate for Treatment of Iron Deficiency Anemia in Patients With NDD-CKD

Primary endpoint: proportion of patients who achieved a ≥ 1.0 g/dL increase in hemoglobin at any time during a 16-week randomized period

Ferric Citrate Increases TSAT and Ferritin in Patients with NDD-CKD

Ferric Citrate Increases Hgb in Patients With NDD-CKD

The increase in hemoglobin in the ferric citrate arm is comparable to IV iron in studies with no ESA background therapy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ferric Citrate (n=117), n (%)</th>
<th>Placebo (n=116), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent AE</td>
<td>93 (79.5)</td>
<td>75 (64.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (20.5)</td>
<td>19 (16.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>22 (18.8)</td>
<td>15 (12.9)</td>
</tr>
<tr>
<td>Feces discolored</td>
<td>17 (14.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (11.1)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (6.0)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0)</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>8 (6.8)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (4.3)</td>
<td>6 (5.2)</td>
</tr>
</tbody>
</table>

Events occurring during the randomized period (randomization to week 16).
Ferric Maltol
(Feraccrue, Shield Therapeutics)
Ferric Maltol

• Novel oral ferric iron currently approved in the United Kingdom for treatment of IDA in adults with IBD
• Phase 3 study AEGIS-CKD for the treatment of iron deficiency anemia in CKD is currently underway
  – eGFR < 60 and ≥ 15 mL/min/1.73m²
  – Iron deficiency anemia (Hb < 11.0 and > 8.0 g/dL; Ferritin < 250 ng/mL and TSAT < 25%)
  – 16-week randomized, placebo-controlled study
  – 160 patients with predialysis CKD in the United States
  – The primary endpoint of the study will be the change in Hb from baseline to week 16

ClinicalTrials.gov. NCT02968368.
Significant improvements in Hb were observed with ferric maltol versus placebo at weeks 4, 8, and 12: mean (SE) 1.04 (0.11) g/dL, 1.76 (0.15) g/dL, and 2.25 (0.19) g/dL, respectively ($P < .0001$ at all time-points). Hb was normalized in 2/3 of patients by week 12. The safety profile of ferric maltol was comparable with placebo, with no impact on inflammatory bowel disease severity.

Treatments

HIF-PHI
(the ...dustats)
New Drugs: HIF-PHI (the ...dustats)

Low Oxygen (eg, high altitude)

HIF-PH Enzymes

HIF-α

HIF-β

Gene Transcription

HIF-α degrades rapidly

Normal Oxygen

HIF-α

HIF-PH Enzymes

Degradation (No Gene Transcription)

High altitude is associated with improved anemia conditions among hemodialysis patients

- Retrospective cohort study – US Renal Data System (N=341,737 incident HD patients) combined with elevation data from the US Geological Survey

**Average Hct**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;250 ft</td>
<td>31</td>
<td>31.5</td>
<td>32</td>
<td>33</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>250–1999 ft</td>
<td>31.5</td>
<td>32</td>
<td>32.5</td>
<td>33</td>
<td>33.5</td>
<td>34</td>
</tr>
<tr>
<td>2000–3999 ft</td>
<td>32</td>
<td>32.5</td>
<td>33</td>
<td>33.5</td>
<td>34</td>
<td>34.5</td>
</tr>
<tr>
<td>4000–5999 ft</td>
<td>32.5</td>
<td>33</td>
<td>33.5</td>
<td>34</td>
<td>34.5</td>
<td>35</td>
</tr>
<tr>
<td>6000+ ft</td>
<td>33</td>
<td>33.5</td>
<td>34</td>
<td>34.5</td>
<td>35</td>
<td>36</td>
</tr>
</tbody>
</table>

**Average dose of EPO analogue**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;250 ft</td>
<td>11</td>
<td>11.5</td>
<td>12</td>
<td>12.5</td>
<td>13</td>
<td>13.5</td>
</tr>
<tr>
<td>250–1999 ft</td>
<td>11.5</td>
<td>12</td>
<td>12.5</td>
<td>13</td>
<td>13.5</td>
<td>14</td>
</tr>
<tr>
<td>2000–3999 ft</td>
<td>12</td>
<td>12.5</td>
<td>13</td>
<td>13.5</td>
<td>14</td>
<td>14.5</td>
</tr>
<tr>
<td>4000–5999 ft</td>
<td>12.5</td>
<td>13</td>
<td>13.5</td>
<td>14</td>
<td>14.5</td>
<td>15</td>
</tr>
<tr>
<td>6000+ ft</td>
<td>13</td>
<td>13.5</td>
<td>14</td>
<td>14.5</td>
<td>15</td>
<td>15.5</td>
</tr>
</tbody>
</table>

**EPO resistance by elevation group**

<table>
<thead>
<tr>
<th>Elevation group</th>
<th>EPO dose (U/week)/ hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;250 ft</td>
<td>0.35</td>
</tr>
<tr>
<td>250–1999 ft</td>
<td>0.40</td>
</tr>
<tr>
<td>2000–3999 ft</td>
<td>0.50</td>
</tr>
<tr>
<td>4000–5999 ft</td>
<td>0.45</td>
</tr>
<tr>
<td>6000+ ft</td>
<td>0.50</td>
</tr>
</tbody>
</table>

EPO, erythropoietin; Hct, hematocrit.
New Drugs: HIF-PHI

Role of HIF-PHI in Iron-Restricted, EPO-Deficient Anemias

# Emerging HIF-PHIs (the ...dustats)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roxadustat</td>
<td>3</td>
<td>Phase 3 trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active since May 2013</td>
</tr>
<tr>
<td>Vadadustat</td>
<td>3</td>
<td>Phase 3 trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active since December 2015</td>
</tr>
<tr>
<td>Daprodustat</td>
<td>3</td>
<td>Phase 3 trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active since fall 2016</td>
</tr>
<tr>
<td>Molidustat</td>
<td>2</td>
<td>Phase 2 studies completed</td>
</tr>
<tr>
<td>DS-1093</td>
<td>1</td>
<td>Pilot/dosing studies completed</td>
</tr>
<tr>
<td>JTZ-951</td>
<td>1</td>
<td>Phase 1 studies completed</td>
</tr>
</tbody>
</table>

Recruitment goal for Phase III trials - Roxadustat 4025 pts; Vadadustat 5700 pts; Daprodustat 7500 pts
Vadadustat treatment increased Hb levels and maintained them at the clinically desired range while minimizing excursions ≥13.0 g/dL

- Met primary endpoint (54.9% vs. 10.3%, \( P < .0001 \))
- Mean Hb change of 1 g/dL
- Only 4.4% of patients experienced excursions beyond 13 g/dL (6 patients)

Box and whiskers plot represents 10\(^{th}\), 25\(^{th}\), 75\(^{th}\), and 90\(^{th}\) percentiles, median is the line within the box, mean is symbol within the box.

MITT population – included patients in the ITT population who had a baseline and at least one post-baseline Hb measurement.

Vadadustat treatment improved iron mobilization in patients with NDD-CKD.

- **Total Iron-Binding Capacity**
- **Ferritin**
- **Hepcidin**

Box and whiskers plot represents 10th, 25th, 75th, and 90th percentiles, median is the line within the box, mean is symbol within the box.

MITT population – included patients in the ITT population who had a baseline and at least one post-baseline Hb measurement.

The HIF pathway is an oxygen-sensitive pathway that regulates genes involved in EPO production and iron homeostasis, thus promoting the production of red blood cells.

- HIF activation stimulates EPO synthesis in multiple cell types
- HIF activity suppresses hepcidin expression to promote intestinal iron absorption and transport

Phase 3 clinical trials are underway for several HIF-PHI inhibitors for the treatment of anemia in patients with CKD.
Conclusions: Ferritin and “Iron Overload”

• Hyperferritinemia is not synonymous with iron overload

• Serum ferritin does not differentiate iron stored in parenchymal cells or RES
  – Serum ferritin does not always correlate with liver iron content

• Experience from patients with hemochromatosis suggests that combination of high TSAT and ferritin may be better indices as markers of parenchymal iron excess
Iron: Conclusions

• Available data do not allow any firm statement to be made on the potential dangers of high-dose iron use and high ferritin levels

• RCTs are needed to assess the safety and efficacy of IV iron therapy using hard clinical endpoints
  – The ongoing, event-driven PIVOTAL trial, recruiting > 2000 HD patients across 50 UK sites, randomized to a high and low IV iron regimen (planned follow-up of 2 to 4 years) will help to fill this evidence gap

• Meanwhile, nephrologists would do well to recognize the benefits and limitations of IV iron therapy
Summary: Anemia of CKD

Causes and effects

• ↓ EPO production
• ↑ hepcidin (2° to ↓ renal clearance and ↑ IL-6)
  – Iron sequestration in macrophages
  – Iron-restricted erythropoiesis, resistance to EPO
• True iron deficiency (2° to increased blood loss and hepcidin-mediated decrease in intestinal iron absorption)
• Suppression of erythropoiesis by inflammatory cytokines (important in acute inflammation)
• Shortened erythrocyte lifespan (2° to inflammation, uremia, blood loss)

Summary: Anemia of CKD

Treatments and modulators

• Exogenous EPO
  – Causes pulsatile erythropoiesis and transient high demand for iron
  – High doses ↓ hepcidin but at the cost of AEs

• Iron treatment
  – Overcomes hepcidin-induced blockade of iron release from macrophages
  – Decreases resistance to EPO
  – PO Iron:
    ▪ New Ferric iron preparations
  – Dialysate Iron

• Future HIF-PH Modulators (…dustats)

Summary and Conclusions

- Despite disparate effects on serum ferritin levels, drugs that increase delivery of iron to bone marrow help maintain Hb while decreasing ESA (and IV iron) use.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Route</th>
<th>TSA T</th>
<th>Ferritin</th>
<th>ESA Dose</th>
<th>IV Iron Use</th>
<th>Safety c/w IV Iron</th>
<th>MACE Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>IV</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓</td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Ferric Pyrophosphate Citrate</td>
<td>Dialysate</td>
<td>↑</td>
<td>↓</td>
<td>↓(^a)</td>
<td>↓</td>
<td>↔↔</td>
<td>No</td>
</tr>
<tr>
<td>Ferric Citrate</td>
<td>PO</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>No</td>
</tr>
<tr>
<td>HIF-PHI</td>
<td>PO</td>
<td>↑</td>
<td>↓</td>
<td>N/A</td>
<td>? (↓)</td>
<td>?</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

*Compared with placebo, IV iron use restricted in placebo patients.
THANK YOU