INSIGHTS INTO ANEMIA IN CHRONIC KIDNEY DISEASE AND BEYOND
NEW DISCOVERIES, STRATEGIES, AND MODELS OF CARE
1) Appraise recent shifts in treatment patterns that have occurred in the management of anemia in CKD and the potential implication for patients and the healthcare system.

2) Evaluate current controversies in the safety of anemia management in CKD and the trial data that have led to increased precautions for this condition.

3) Examine the pathophysiology of anemia in kidney disease and how the role of hepcidin in iron metabolism contributes to this process.

4) Explore hypoxia-inducible factor (HIF) as a novel treatment target in anemia in CKD and the clinical trial data that is available for investigational HIF-PH inhibitors.

5) Examine the therapeutic potential of HIF-PH inhibitors in myelodysplastic syndromes and review emerging clinical trial data.

6) Discuss the potential impact of HIF-PH inhibitors on clinical outcomes in CKD, MDS, etc., and explore how these emerging agents compare to traditional ESAs and ESA biosimilars.
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Disclosures: Dr. Glaspy has disclosed that he receives research support from Fibrogen.
Trends in CKD Anemia Management

Changes in Care, Patient Outcomes, and Public Health

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Minneapolis, Minnesota
Objectives

- Review CKD anemia pathophysiology
  - Iron deficiency
  - Other factors
- Examine current trends/knowledge in CKD anemia treatment
- Describe public health issues with CKD anemia
I have no relevant financial relationships to disclose in relation to the content of this activity.
Pathophysiology of CKD Anemia

Iron Homeostasis
Effect of Hypoxia Inducible Factor (HIF) on Iron Metabolism

Absorption

- DCYTB
- DMT1
- FPN
- HIF

Enterocyte (Mainly duodenum)

Transportation

- TF
- EPO
- HIF

Mobilization

- GDF15
- Erythroferrone
- FPN
- HIF

Liver

Other Reticuloendothelial system

Bone Marrow

Adapted from Koury MJ, et al. Nat Rev Nephrol. 2015. Used with permission from Bruce Spinowitz.
Signs and Symptoms of Anemia

- Angina
- Impaired cognition
- Dyspnea
- Impaired exercise capacity
- Heart failure
- Angina
- Left ventricular hypertrophy
- Weakness
- Decreased physical function
- Fatigue
- Cold intolerance
- Lethargy
- Palpitations
- Pallor

November 2006: CHOIR and CREATE trials published. CKD-ND patients. **CHOIR**: Higher composite of death, MI, CHF, stroke. **CREATE**: Trend toward higher CV events and mortality in higher hematocrit groups (13–15 g/dL vs 10.5–11.5 g/dL).

September 2007: KDOQI updates anemia CPGs and changes target back to 11–12 g/dL
November 2009: TREAT Study results published. No difference in primary endpoint (death or CV event); increased risk of stroke in higher Hb group (13 g/dL) vs no treatment (rescue DPO if Hb <9 g/dL) in CKD-ND patients with diabetes.

January 2011: ESRD Prospective Payment System went into effect. ESA and IV iron payment included in bundled payment to dialysis providers. Quality Incentive Program (Hb: %>12 and <10 g/dL).

August 2012: KDIGO Anemia CPGs published. Removes target range. Suggests starting ESA when Hb 9–10 g/dL, not going above 11.5 g/dL. “Individualize.”

June 2011: FDA approved ESA label removes target Hb range. Essentially...initiate if Hb <10, goal in dialysis <11 g/dL. “Use lowest ESA dose sufficient to reduce need for RBC transfusions.”

In February 2018:
- 84% of dialysis patients received ESA in last month
- Of those, 63% received long-acting ESAs
In February 2018:
- 80% of dialysis patients received IV iron dose in last 3 months, mainly iron sucrose
- 8% received an iron-containing phosphate binder (ferric citrate or sucroferric oxyhydroxide)
UK Study on High-dose vs Low-dose Iron

**PIVOTAL Study**

- **N=2141 new HD patients; median: 2.1 years follow-up**
- **Reactive:** 0-400 mg IV iron if ferritin <200 ng/mL or TSAT <20%
- **Proactive:** 400 mg IV iron (unless ferritin >700 ng/mL or TSAT >40%)
- **Composite Outcome:** MI, stroke, HHF, death

**Primary Efficacy End Point**

Hazard ratio, 0.88 (95% CI, 0.76–1.03) P<0.001 for noninferiority P=0.11 for superiority

Non-Dialysis Dependent CKD Anemia

Anemia is Common in CKD
- Prevalence in CKD stage 3–5
  - 52% in older (Medicare)
  - 28% in younger patients (18–63 years old)
- Increases with CKD stage
- Less variability in prevalence with sex or race compared to general population

Treatment is Less Common
- ESA use
  - 10.8% younger
  - 12.7% older
- RBC transfusions
  - 11.7% younger
  - 22.2% older
- IV iron*
  - 9.4% younger
  - 6.7% older
- Combination therapy: ~6% in both

*Unable to assess oral iron therapy.

Policy Issues in CKD Anemia Treatment

- FDA product labels for ESAs (since 2011)\(^1\)
  - Initiate therapy when Hgb <10
  - Decrease or terminate therapy if
    - Hgb exceeds 10 g/dL (non-dialysis)
    - Hgb approaches 11 g/dL (dialysis)
  - Use minimal ESA dose to avoid transfusions

- CMS quality oversight in dialysis\(^2\)
  - No hemoglobin measures in Quality Incentive Program (QIP)
  - Standardized transfusion ratio (STrR) will be 22% of the QIP score in performance year 2019
  - Medicare state surveyors use Hgb 10–11 g/dL as the target for quality

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\(^1\) https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103234s5363s5366lbl.pdf;
<table>
<thead>
<tr>
<th>Compound</th>
<th>Status of clinical development</th>
<th>HIF-α stabilization</th>
<th>HIF-PHD targets</th>
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<tr>
<td>AKB-6548 (Vadadustat)</td>
<td>Phase 3</td>
<td>HIF-2α &gt; HIF-1α</td>
<td>PHD3 &gt; PHD2</td>
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<td>Akebia Therapeutics</td>
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<td>GSK-1278863 (Daprodustat)</td>
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<td>BAY 85-3934 (Molidustat)</td>
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<td>HIF-1α and HIF-2α</td>
<td>PHD2 &gt; PHD1/PBD3</td>
</tr>
<tr>
<td>Bayer</td>
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Some Unanswered Questions

Dialysis

• Is high-dose IV iron (400 mg/month) safe beyond 2 years?
• What is target ferritin?

CKD

• Is IV vs oral iron better (and type)? Dosing?
• When (what Hb) should ESAs or other (HIF stabilizers) be started?

Dialysis and NDD-CKD

• What should be the target Hb? Or should we treat symptoms?
• What is best treatment strategy ESAs vs new HIF stabilizers?
Summary and Key Take-aways

- ESA use affected by trial results, CMS policy, FDA action
- Epoetin alfa use down, long-acting ESAs on rise
- First biosimilar epoetin alfa approved in United States in May 2018
  - Epoetin alfa-epbx (Retacrit, Pfizer)
- Higher proactive vs lower reactive dose iron during HD reduces ESA dose with similar outcomes
- Anemia management challenging in NDD-CKD due to need for parenteral ESAs-unmet needs
- Several HIF stabilizers in Phase 3 clinical trials
Taking It to the Limit?

Changes in Hemoglobin Targets and Cardiovascular Data from Clinical Trials

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Consultant for GlaxoSmithKline
Anemia in CKD Patients and Outcomes

- Observational Studies suggest that increased Hb associated with improved outcomes
  - Problems of confounding

- RCTs of correction anemia
  - No benefit in CVD or Renal Outcomes with correction
  - Increased risk for death and CVD [CHOIR]; stroke/malignancy [TREAT]
  - No improvement in hrQOL

Summary of Trials Data

- **1989 EPO Approved**
- **2001 Darbepoetin approved**
- **Sept 2007 CHOIR FDA Advisory Meeting**
- **July 2008**
  - Label changes from EMEA and FDA upper limit of 12 g/dL
- **June 2011**
  - Label changes new FDA Hb guidelines: 10 ND & 11 HD
- **1998 NHS HD Study**
  - Subjects show higher mortality at Hb 14 vs 10
- **2006 CHOIR stopped**
  - Interim analysis ND—higher mortality at Hb 13 vs 11
- **2009 TREAT**
  - ND study—higher mortality and stroke at Hb 13 vs control
- **Oct 2010 TREAT**
  - FDA Advisory Meeting

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The Normal Hematocrit Study
*Published 1998, NEJM*

- Tested hypothesis that patients with normal Hb 13–14 g/dL will have better outcomes than patients with Hb 9–10 g/dL
- 1233 HD patients with CAD or CHF
- Primary end-point: death or MI
- Study terminated early due increased risk
- Higher rate of vascular access thrombosis in normal Hct group: 243 patients (39%) vs 176 patients (29%); \( P=0.001 \).
Normal Hematocrit Study

N=1233 HD patients with CAD or CHF

<table>
<thead>
<tr>
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<th>Low Hct</th>
<th>Normal Hct</th>
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<tr>
<td>n</td>
<td>618</td>
<td>615</td>
</tr>
<tr>
<td>Hct</td>
<td>30</td>
<td>42 (achieved 39%)</td>
</tr>
<tr>
<td>Epoetin dose</td>
<td>160</td>
<td>460</td>
</tr>
<tr>
<td>Total deaths</td>
<td>150</td>
<td>183</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>RR</td>
<td>1.3 (0.9–1.9)</td>
<td></td>
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</tbody>
</table>

Primary Composite Endpoint
Death, MI, CHF hosp (no RRT) and/or stroke

N=1432, median FU 16 m
11.3 g vs 13.5 g
10,952 units/w higher arm

Randomized Treatment
Hemoglobin Target 13.5 g/dL
Hemoglobin Target 11.3 g/dL

Kaplan-Meier Failure Estimate (%)

Hazard ratio 1.337 (1.025, 1.743)
P= 0.0312

**CHOIR**

**Components of Primary Endpoint**

Death
- 65 deaths

CHF Hospitalization (where RRT did not occur)
- 65 deaths

**Stroke**
- Randomized treatment
- Hemoglobin target 13.5 g/dL
- Hemoglobin target 11.3 g/dL

**Myocardial Infarction**
- Randomized treatment
- Hemoglobin target 13.5 g/dL
- Hemoglobin target 11.3 g/dL

TREAT Study
Primary Results

N=4038
N= 2012 to darbe with goal Hb 13 g/dL
N=2026 to placebo with rescue darbe
TREAT 8800 units per week (darbepoetin group)

Death, MI, Myocardial Ischemia, HF, Stroke

- Darbepoetin alfa 632 (31.4%)
- Placebo 602 (29.7%)

HR: 1.05 (0.94–1.17)  
P=0.41

Renal Composite
Death or ESRD

- Darbepoetin alfa 652 (32.4%)
- Placebo 618 (30.5%)

HR: 1.06 (0.95–1.19)  
P=0.29

TREAT—Fatal and Nonfatal Stroke

### Patients With Events (%)

- **Darbepoetin alfa 101 (5.0%)**
- **Placebo 53 (2.6%)**

### Hazard Ratio (HR)

- **HR: 1.92 (1.38–2.68)**
- **P < 0.001**

### Nominal P-value (log-rank)

<table>
<thead>
<tr>
<th>Hx of Stroke</th>
<th>DA</th>
<th>Placebo</th>
<th>HR (adjusted)</th>
<th>95% CI</th>
<th>Nominal P-value (log-rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx of Stroke</td>
<td>27/231 (12%)</td>
<td>9/216 (4%)</td>
<td>2.97</td>
<td>(1.40, 6.33)</td>
<td>0.0047</td>
</tr>
<tr>
<td>No Hx of Stroke</td>
<td>74/1781 (4%)</td>
<td>44/1810 (2%)</td>
<td>1.70</td>
<td>(1.17, 2.47)</td>
<td>0.0054</td>
</tr>
</tbody>
</table>

**CHOIR**

**Association between Dose and Primary Outcome**

**CHOIR (9-Month Landmark Analysis)**

Time to the Primary Endpoint between Randomization and Termination

Target Hb 13.5 g/dL (Group A) [N=519, Events=62]

Dashed lines = 95% confidence bounds

*If a patient experienced a primary event, only doses prior to the event were used to determine average weekly dose.*

Summary of CKD Anemia Studies

- Recombinant erythropoietin successfully corrects anemia in CKD patients
- At high doses and with normalizing Hb, increased CVD risk and higher mortality has been reported
- New therapies—prolyl hydroxylase inhibitors (PHI) promising strategy
Breakthroughs in the Pathophysiology of Anemia in CKD
The Role of Hepcidin and HIF-α

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Disclosures

- I have no relevant financial relationships to disclose in relation to the content of this activity.
• Severe anemia among patients with chronic renal failure/ESRD was almost universal (CKD was not called CKD yet)
  • Hb levels of 5–7 g/dL were very common among patients on dialysis
  • Average transfusion rate ~0.5 units/month among HD patients
• Treatment options
  • CRF—transfusions for severe anemia
  • Dialysis patients—transfusions, iron dextran, nandrolone decanoate
    • Deferoxamine to chelate excess iron
• First clinical trial with recombinant human erythropoietin reported in HD patients
Multiple ESAs, “biosimilar epoetins,” and new iron preparations available

Severe anemia among patients with CKD/ESRD is rare

ESA use has gone from highly profitable to costly for dialysis providers

Enthusiasm for Hb normalization tempered by clinical trial data

New understanding of EPO regulation $\rightarrow$ HIF-PH inhibitors in clinical trials

New understanding of iron metabolism $\rightarrow$ discovery of hepcidin and other iron regulatory proteins

Studies ongoing to understand role of hepcidin and its pharmacologic manipulation in patients with CKD and other causes of anemia
Anemia of CKD
More Than Just EPO Deficiency

Hepcidin

• “Master regulator” of iron metabolism
  • 25 amino acid peptide synthesized in hepatocytes
• Controls iron transport by binding to cell membrane iron transport protein ferroportin
• Ferroportin transports ferrous iron out of cells
  • Is the only known exporter of iron from mammalian cells
• Results in internalization and lysosomal degradation of ferroportin
• Reduces GI tract iron absorption
• Promotes iron sequestration in macrophages

Regulation of Hepcidin Expression

BMP, bone morphogenic protein; HJV, hepatic hemojuvelin; Tfr2, Transferrin receptor 2.

Many Clinical Conditions Influence Hepcidin Levels

Hepcidin Assays

- Theoretically could be useful to identify patients who might benefit from more (or less) iron, ESA although correlates highly with ferritin
- No value over low ferritin in those with iron deficiency
- Assays are not standardized or harmonized
- Diurnal rhythm

Plasma Hepcidin Levels are Elevated in CKD/ESRD


R = -0.530
CKD

- Reduced GFR
- Iron Supplementation
- Inflammation
- Vitamin D Deficiency

↑ HEPCIDIN

- Reduced Iron Release from Cells of RES
- Reduced Gut Iron Absorption

Iron Restricted Erythropoiesis

Hepcidin and ESA Hyporesponsiveness

• Some studies have found high hepcidin levels with greater ESA hyporesponsiveness...others the opposite
• Hepcidin levels fall during HD treatments
• Hepcidin levels fall with ESA administration; higher ESA doses reduce levels more
• Higher hepcidin levels associate with higher ferritin levels, which associate with higher iron stores and ESA responsiveness

Hepcidin Levels Correlate with Ferritin and Both Decline in Response to EPO Initiation

But not CRP or IL-6 in CKD/ESRD (variable)

![Graph showing the correlation between Hepcidin and Ferritin levels before and after iron and EPO initiation.](image)

Role of Hepcidin in ASCVD?

Hepcidin and TNF-α associated with arterial stiffness in HD patients

HIF-PH Inhibitor Effect on Hepcidin Levels

Effects of an Oral HIF-PH Inhibitor on Total Cholesterol

Conclusion

• Dramatic changes in anemia management in patients with kidney disease over last several decades

• Hepcidin levels are elevated in patients with CKD/ESRD

• Unclear relationship with ESA-hyporesponsiveness

• Emerging evidence implicates hepcidin and other iron metabolism components in anemia of CKD

• Oral HIF-PH inhibitors reduce hepcidin levels and increase iron availability and utilization

• ? Role of hepcidin in vascular disease and atherosclerosis

• Studies are examining pharmacologic manipulation of hepcidin
  • Vitamin D—mixed results
HIF-PH Inhibitors and CKD

Emerging Clinical Trial Data

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Exogenous Recombinant EPO Therapy

- Revolutionized management of anemia in CKD patients
- Convenient dosing
- QoL benefits for treatment of severe anemia

- Increased mortality and CVD complications
- Increased cancer-related deaths
  - **Black Box Warnings in USA**
  - Risk of hypertension
  - Risk of thrombovenous embolism
  - No benefit on progression of CKD
  - Immunogenicity
  - Storage and stability (~4°C)
Effects of ESA Dosing on EPO Levels

Hypothetical erythropoietin level following administration of 7000 IU of epoetin-alpha

EPO upper level represents estimated epo level following a 2 unit volume venesection

EPO Stimulates Erythropoiesis by Activating EPO Receptors

- Homodimeric EPO Receptor
- Heterodimeric EPO Receptor

- Bone Marrow
- Heart, Brain, Kidney, endothelial cells

rHuEPO

High doses of rHuEPO
Gene Regulation

- Hypoxia inducible factor (HIF) stabilizing agents
  - Prolyl hydroxylase inhibitors
  - Inhibit enzyme that break down HIF
    - HIF is a transcription factor that regulates erythropoietin gene transcription
    - Fibrogen/Astellas/AstraZeneca, GlaxoSmithKline, Akebia, Bayer

- GATA inhibitors
  - GATA inhibits epo promoter activity and increase epo production
  - K-11706, oral

• Semenza and Wang\textsuperscript{1} discover HIF-1—protein with DNA binding activity
  • Identify the presence of hypoxia response element (HRE; 5’-RCGTG-3’) in the erythropoietin gene

• The two isoforms or subunits of HIF-1—HIF-1α (inducible) and HIF-1β(constitutive) form heterodimeric complex to regulate target gene in response to hypoxia

• HIF-1α is mainly under the control of oxygen sensing HIF-1α dioxygenases (prolyl-4-hydroxylase-domain (P4HD) containing enzymes)\textsuperscript{2}

HIF-1α is mainly under the control of oxygen sensing HIF-1α dioxygenases (prolyl-4-hydroxylase-domain (P4HD) containing enzymes)

Normoxia

Attaches to von Hippel-Lindau (pVHL)

HIFα

Prolyl Hydroxylase

O₂

OH

OH

OH

degradation by 26S Proteosome

STOP

No epo gene transcription
HIF-1α is mainly under the control of oxygen sensing HIF-1α dioxygenases (proline 4-hydroxylase domain (P4HD) containing enzymes).

Hypoxia

Prolyl Hydroxylase

HIF stabilized

HIFα/ß combine to form heterodimer

Translocate to nucleus

HIFα

EPO Promoter

GATA-2

AGTCCCTGGGC

NF-xB

EPO Gene

A/GCGTG

EPO Enhancer

+ epo gene transcription

Hypoxia

Four-color diagram showing the interaction of HIFα and HIFß to form a heterodimer, which translocates to the nucleus for epo gene transcription.
HIF-1α is mainly under the control of oxygen sensing. HIF-1α dimerizes with HIF-ß, which together form a heterodimer. HIFα/ß combine to form the heterodimer. Under hypoxia, HIFα is stabilized and translocates to the nucleus, where it induces the transcription of target genes.

PHI Agents (e.g., daprodustat, roxadustat, vadadustat, molidustat)
<table>
<thead>
<tr>
<th>Compound</th>
<th>HIF-α stabilization</th>
<th>HIF-PHD targets</th>
<th>Half-life (hours)</th>
<th>Dosing frequency</th>
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<tr>
<td>FG-4592 (Roxadustat)</td>
<td>HIF-1α and HIF-2α</td>
<td>PHD1, 2, and 3</td>
<td>12-13</td>
<td>3x/week</td>
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<td>Fibrogen/Astellas/AstraZeneca</td>
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<td>AKB-6548/MT-6548 (Vadadustat)</td>
<td>HIF-2α &gt; HIF-1α</td>
<td>PHD3 &gt; PHD2</td>
<td>4.5</td>
<td>Daily</td>
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<td>Akebia/Mitsubishi</td>
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<td>GSK-1278863 (Daprodustat)</td>
<td>HIF-1α and HIF-2α</td>
<td>PHD2 and PHD3</td>
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<td>BAY 85-3934 (Molidustat)</td>
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<td>PHD2&gt;PHD1/PHD3</td>
<td>~5-10</td>
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## HIF-PH Inhibitors Phase 2 Experience (CKD Anemia)

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<tr>
<th>Company</th>
<th>Agent</th>
<th>Name</th>
<th>Phase</th>
<th>Study Population</th>
<th>No. of studies</th>
<th>Study size</th>
<th>Aggregate N</th>
<th>Dates</th>
<th>Endpoints</th>
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<tr>
<td>Fibrogen/Astellas/AstraZeneca</td>
<td>FG-4592</td>
<td>Roxadustat</td>
<td>Phase 2</td>
<td>HD, PD, ND-CKD</td>
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<td>N=60–145</td>
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<td>2010–2015</td>
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<td>Akebia/Mitsubishi</td>
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<td>Vadadustat</td>
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<td>N=123–301</td>
<td>450</td>
<td>2015</td>
<td>Safety Efficacy</td>
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Daprodustat (GSK 1278863)  
Effect on Hemoglobin

**Two Studies**

- **Non-dialysis**
  - N≈73, Non-dialysis CKD epo naïve, baseline Hb 8.5–11.0 g/dL

- **Dialysis**
  - N≈ 83, Stable HD patients on epo, baseline Hb 9.5–12.0 g/dL

Randomized to 0.5 mg, 2 mg, 5 mg, or control (placebo for epo naïve ND-CKD, and epo in D-CKD)

Roxadustat (FG-4592) Effect on Hemoglobin

**NDD Study**

<table>
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<tr>
<th>Treatment</th>
<th>n</th>
<th>ΔHb_{mean} (g/dL)</th>
<th>SE</th>
<th>p-value (^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>low dose</td>
<td>30</td>
<td>1.82 ±0.21</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>high dose</td>
<td>31</td>
<td>2.59 ±0.26</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>30</td>
<td>0.65 ±0.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DD Study**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Successful Hb Maintenance (^b)</th>
<th>p-value (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>low dose</td>
<td>22</td>
<td>13 (59.1)</td>
<td>n. s.</td>
</tr>
<tr>
<td>mid dose</td>
<td>16</td>
<td>16 (88.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>high dose</td>
<td>20</td>
<td>20 (100)</td>
<td>0.0008</td>
</tr>
<tr>
<td>epoetin alfa</td>
<td>22</td>
<td>11 (50.9)</td>
<td></td>
</tr>
</tbody>
</table>
**Vadadustat (AKB-6548)**

*Effect on Hemoglobin*

- Phase 2, 20-week, randomized, placebo-controlled study in CKD Stages 3–5 (n=160—*per protocol population*)

## Daprodustat (GSK 1278863) 
**Effect on EPO Levels**

### Erythropoietin Levels

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=18)</th>
<th>Daprodustat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 mg (n=19)</td>
</tr>
<tr>
<td><strong>EPO, mIU/mL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline, n</strong></td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>5.6</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Min, max</strong></td>
<td>2.5, 12.5</td>
<td>2.5, 22.3</td>
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<tr>
<td><strong>Peak, n</strong></td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>11.7</td>
<td>33.3</td>
</tr>
<tr>
<td><strong>Min, max</strong></td>
<td>3.4, 23.2</td>
<td>8.2, 111.1</td>
</tr>
</tbody>
</table>

5 subjects
(1 subject on 6 mg, 2 subjects on 8 mg, and 2 subjects on 10 mg) exceeding 500 mIU/mL
Roxadustat (FG-4592) 
Effect on EPO Levels

# Daprodustat (GSK 1278863) Effect on VEGF

## VEGF Levels

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=18)</th>
<th>Daprodustat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 mg (n=19)</td>
</tr>
<tr>
<td>VEGF, ng/L</td>
<td></td>
<td></td>
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<tr>
<td>Baseline, n</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Median</td>
<td>139.1</td>
<td>149.1</td>
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<tr>
<td>Min, max</td>
<td>19.1, 415.5</td>
<td>93.6, 478.5</td>
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<tr>
<td>Peak, n</td>
<td>17</td>
<td>18</td>
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<tr>
<td>Median</td>
<td>169.5</td>
<td>180.3</td>
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<tr>
<td>Min, max</td>
<td>115.6, 332.4</td>
<td>97.8, 382.8</td>
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</table>

Vadadustat (AKB-6548)  
Effect on VEGF

![Graph showing the effect of Vadadustat and Placebo on VEGF levels over time. The graph compares VEGF levels in the Vadadustat treatment group and the Placebo group from baseline (B) to the end of treatment (EOT) and follow-up (FU). The y-axis represents VEGF levels in pg/mL, and the x-axis represents time in weeks. The graph indicates a significant decrease in VEGF levels in the Vadadustat group compared to the Placebo group.]

## Balancing Benefits/Risks of HIF Stabilization

<table>
<thead>
<tr>
<th>Effect of PH Inhibition</th>
<th>Potential Beneficial Effect</th>
<th>Potential Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO production</td>
<td>• Raise Hb to treat anemia</td>
<td>• Promote thrombosis and CV events</td>
</tr>
<tr>
<td>VEGF production</td>
<td>• Promote angiogenesis in ischemic tissues</td>
<td>• Promote tumor angiogenesis</td>
</tr>
<tr>
<td></td>
<td>• Reduced retinopathy</td>
<td>• Worsen retinopathy/macular edema</td>
</tr>
<tr>
<td>Reduce hepcidin</td>
<td>• Promote iron mobilization</td>
<td>• ↑ iron availability for pathogens</td>
</tr>
<tr>
<td>Potential pulmonary hypertension</td>
<td>• No analogy to Chuvash polycythemia</td>
<td>• Potential increase in pulmonary hypertension</td>
</tr>
</tbody>
</table>
# Phase 3 Trials with Oral HIF-PH Inhibitors

*(CKD Anemia)*

<table>
<thead>
<tr>
<th>Name</th>
<th>Sponsor</th>
<th>Phase 3 Randomized Trials</th>
<th>Primary Completion Date</th>
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</thead>
<tbody>
<tr>
<td><strong>Roxadustat</strong></td>
<td>FibroGen/Astellas/AstraZeneca</td>
<td>7 active/enrolling (n=7,950) 8 completed (n=2,428)</td>
<td>Late 2018 Early 2017–Mid 2018</td>
</tr>
<tr>
<td>(FG-4592)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Daprodustat</strong></td>
<td>GlaxoSmithKline</td>
<td>1 completed (n=271 Japan) 5 underway (n=8,802 US)</td>
<td>Japan (late 2018) US (mid 2020)</td>
</tr>
<tr>
<td>(GSK 1278863)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vadadustat</strong></td>
<td>Akebia/Mitsubishi-Tanabi</td>
<td>8 active/enrolling (n= 6,900 US; n=660 Japan)</td>
<td>Japan (late 2018) US (Jan–Aug 2018)</td>
</tr>
<tr>
<td>(AKB-6548; MT-6548)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Molidustat</strong></td>
<td>Bayer</td>
<td>5 active/enrolling (n=628, Japan)</td>
<td>Late 2018/2019</td>
</tr>
<tr>
<td>(BAY 85-3934)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Future of HIF-PH Inhibitors Beyond CKD
Examining the Therapeutic Potential in Myelodysplastic Syndromes

John Glaspy, MD
Division of Hematology, Oncology
Department of Medicine
David Geffen School of Medicine at UCLA
Los Angeles, California
• Dr. Glaspy has disclosed that he receives research support from Fibrogen.
Potential Pleiotropic Effects of HIF-PH Inhibitors

Altered cell survival - Angiogenesis - Cell cycle and growth control - Erythropoietin production - Iron homeostasis - Energy metabolism - Epigenetic regulation - pH regulation

HIF-1α - HIF-2α

PHD1 - PHD2 - PHD3

On target

PHD enzyme inhibitors

Off target (enzymes structurally related to PHD enzymes)

KDM family - Altered histone methylation
ALKB family - Altered RNA and DNA methylation
FIH - Decreased hydroxylation of ankyrin repeats
JMJD family - Altered ribosome function?
PLOD family - Altered RNA splicing?
P4HA family - Altered matrix formation

Non-HIF targets?
Unknown effects

Potential Applications of HIF-PH Inhibitors

- Renal anemia (increased EPO production)
- Myelodysplastic syndromes (EPO, Fe, + ?)
- Anemia of chronic illness (Fe homeostasis)
  - Inflammatory disease
  - Cancer
- Hemoglobinopathies (increased Hb F)
- Ischemia and modulation of ischemic injury (vasodilation, angiogenesis, decreased free radical production)
  - Myocardial
  - Stroke
  - Limb
  - Organ transplant
HIF-PH Inhibitors in Clinical Trials

Also in development:

• Vadadustat (AKB-6548/MT6548) Akebia/Mitsubishi
• Enarodustat (JTZ-951) Japan Tobacco

PHD, HIF, and Iron Homeostasis

A: HIF = Iron sensor?

- Poor tissue oxygenation → ANEMIA
- Low iron → PHD mediated ubiquitination

B: HIF = Iron regulator

- ↑ Transferrin, Tfr
- ↑ ceruloplasmin
- ↑ HO-1
- ↑ ferroportin
- ↓ hepcidin

- ↑ Iron transport
- ↑ Iron oxidation
- ↑ Heme catabolism / Iron recycling
- ↑ Iron uptake, Iron availability

Iron → Red blood cells

Transcriptional Regulation of the Hepcidin (*HAMP*) Gene by HIFs

Potential Applications of HIF-PH Inhibitors

- Renal anemia (increased EPO production)
- Myelodysplastic syndromes (EPO, Fe, + ?)
- Anemia of chronic illness (Fe homeostasis)
  - Inflammatory disease
  - Cancer
- Hemoglobinopathies (increased Hb F)
- Ischemia and modulation of ischemic injury (vasodilation, angiogenesis, decreased free radical production)
  - Myocardial
  - Stroke
  - Limb
  - Organ transplant
Myelodysplastic Syndrome (MDS)

- Very heterogeneous
  - Cytopenias
  - Acute leukemia risk
  - Toxins and aging

- Diagnosis—marrow dysplasia

- Prognosis
  - Cytopenia(s)
  - % blasts
  - Cytogenetics
  - IPSS or IPSS-R
MDS Risk-Adapted Therapy

• Low-risk goals
  • Reduce transfusion burden
  • Resist transformation to higher risk disease

• High-risk goals
  • Prolong survival

• Tools
  • Transfusions, chelation
  • Growth factors (EPO +/- G-CSF)
  • Hypomethylating agents (epigenetic therapy)
  • Lenalidomide (5q-)
  • BMT
### WHO classification-based Prognostic Scoring System (WPSS) of primary myelodysplastic syndromes

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Category</td>
<td>RA, RARS, 5q-</td>
<td>RCMD, RCMD-RS</td>
<td>RAEB-1</td>
<td>RAEB-2</td>
</tr>
<tr>
<td>Karyotype*</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>—</td>
</tr>
<tr>
<td>Transfusion requirement**</td>
<td>No</td>
<td>Regular</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Good: normal, -Y, del(5q), del(20q); Poor: complex, chromosome 7 anomalies; Intermediate: other abnormalities.

**Transfusion dependency: at least one transfusion every 8 weeks over a period of 4 months.

Risk groups: very low (score 0), low (score 1), intermediate (score 2), high (score 3–4), very high (score 5–6).
Hepcidin Levels, Iron, and MDS

Erythroid bone marrow expansion combined with ineffective erythropoiesis

Release of molecules that suppress hepcidin production (BMP/TGF-β superfamily members like GDF15, or other similar molecules)

Hepcidin levels that are inappropriately low for the body iron

Increased reticuloendothelial iron recycling (crucial mechanism in patients receiving regular red cell transfusions)

Increased iron absorption from the gut (crucial mechanism in patients with the so-called iron loading anemias)

Parenchymal iron loading

Driver Mutations in MDS

A

Leukemia-free survival

0 driver mutations identified (n=116)
1 driver mutations identified (n=138)
2 driver mutations identified (n=167)
3 driver mutations identified (n=111)
4-5 driver mutations identified (n=50)
≥6 driver mutations identified (n=13)

p < 0.0001

Time (months)

Number of patients

0 1 2 3 4 5 6 7 8

Number of oncogenic mutations and driver cytogenetic lesions

RA
RARS
RARS-T
RCMD
RCMD-RS
RAEB
5q−
CMML
MDS-MPN
MDS-U
MDS-AML

Evolution of Anemia in MDS Not Transfused

Iron Overload May Be Involved in Progression of MDS

IFN, interferon; LCI, labile cell iron; LPI, labile plasma iron; NO, nitric oxide; ROS, reactive oxygen species.

Iron Chelation and Survival in Low-risk MDS

Anemia and Iron in MDS Subtypes

A

B

C

- Controls: beta-coefficient=0.529; P<0.001
- RA: beta-coefficient=0.558; P=0.004
- 5q-: beta-coefficient=0.660; P=0.002
- RARS: beta-coefficient=1.059; P=0.088
- CMML: beta-coefficient=0.055; P=0.952
- RAEB: beta-coefficient=0.104; P=0.649

MDS Anemia Trials

Questions

MDS Subtype

• Transfusion independent (WPSS very good)
• Transfusion dependent (WPSS good)

Endpoint

• Hemoglobin change
• Transfusions
• Liver iron
• QoL
• Leukemic progression
• Survival
US/ROW Phase 3 MDS Study
- **Patient pop**—transfusion dependent, ESA naïve (no ESA use within 8 weeks prior to randomization) lower risk MDS patients
- **Open label lead-in**—N up to 24
  - starting doses (8 each): 1.5 mg/kg; 2.0 mg/kg; 2.5 mg/kg
- **Double-blind, placebo controlled**—N=160
  - 3:2 randomization
- **Primary endpoint at 28 weeks**
  - Cumulative % patients achieved transfusion independence (over at least 8 weeks)
- **Safety exposure**—up to 52 weeks

China Phase 2/3 MDS Study
- **Patient pop**—non-transfusion dependent w/BL Hb 6–10 g/dL, lower risk MDS patients, ESA-naïve (less than 4 weeks of ESA treatment in total and not within 30 days of randomization)
- **Open label**—N up to 40
- **Double-blind, placebo controlled**—N=135
  - 2:1 randomization
- **Primary endpoint at 26 weeks**
  - % patients with Hb increased by 1.5 g/dL from BL
- **Treatment duration**—26 weeks
- ~ 30 sites in China

Cancer and Chemotherapy Induced Anemia

- A common problem resulting in fatigue and transfusions
- Recombinant erythropoietin (rEPO) therapy; some efficacy but problematic
  - Relative resistance with modest response rates and high rEPO doses (? hepcidin)
  - Safety issues (hypertension, thrombosis, +/- tumor effects) especially at higher hemoglobin concentrations (? very high EPO levels)
  - HIF-PH inhibitors may have advantages over rEPO due to effects on iron homeostasis and lower effects on EPO levels
- 2 years of exposure to roxadustat in CD-1 mice and SD rats was not associated with increased observed cancers
FG4497 (roxadustat) treatment increased hemoglobin levels without increased initiation, progression, or metastases in a VGEF-sensitive spontaneous mouse breast cancer model.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD</td>
<td>atherosclerotic cardiovascular disease</td>
</tr>
<tr>
<td>BIW</td>
<td>twice per week</td>
</tr>
<tr>
<td>BL</td>
<td>baseline</td>
</tr>
<tr>
<td>BMP</td>
<td>bone morphogenetic protein</td>
</tr>
<tr>
<td>BMT</td>
<td>bone marrow transplant</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CKD-ND</td>
<td>chronic kidney disease non-dialysis</td>
</tr>
<tr>
<td>CMML</td>
<td>chronic myelomonocytic leukemia</td>
</tr>
<tr>
<td>CMS</td>
<td>Centers for Medicare and Medicaid Services</td>
</tr>
<tr>
<td>CPG</td>
<td>clinical practice guidelines</td>
</tr>
<tr>
<td>CRF</td>
<td>chronic renal failure</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>DA</td>
<td>darbepoetin alfa</td>
</tr>
<tr>
<td>Dcytb</td>
<td>duodenal cytochrome B</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
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<tr>
<td>DMT1</td>
<td>divalent metal transporter 1</td>
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<td>DPO</td>
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<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<tr>
<td>EMEA</td>
<td>European Medicines Evaluation Agency</td>
</tr>
<tr>
<td>EMT</td>
<td>end of trial</td>
</tr>
<tr>
<td>EPO</td>
<td>erythropoietin</td>
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<tr>
<td>ESA</td>
<td>erythropoiesis stimulating agent</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<td>ESRD</td>
<td>end-stage renal disease</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FIH</td>
<td>factor inhibiting hypoxia-inducible factor</td>
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<tr>
<td>FPN</td>
<td>ferroportin</td>
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<td>FU</td>
<td>follow-up</td>
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<td>G-CSF</td>
<td>granulocyte-colony stimulating factor</td>
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<td>glomerular filtration rate</td>
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<td>GI</td>
<td>gastrointestinal</td>
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<tr>
<td>Hb</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>Hb F</td>
<td>fetal hemoglobin</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
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<td>hematocrit</td>
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<tr>
<td>HD</td>
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<tr>
<td>HIF</td>
<td>hypoxia inducible factor</td>
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<tr>
<td>HIF-PH</td>
<td>hypoxia-inducible factor prolyl hydroxylase</td>
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<td>HJV</td>
<td>hepatic hemojuvelin</td>
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<td>health-related quality of life</td>
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<td>Hx</td>
<td>history</td>
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<tr>
<td>IDA</td>
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<td>IFN</td>
<td>interferon</td>
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<td>IL-6</td>
<td>interleukin-6</td>
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<td>IPSS</td>
<td>international prognostic risk score</td>
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<tr>
<td>IPSS-R</td>
<td>revised international prognostic risk score</td>
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<tr>
<td>IV</td>
<td>intravenous</td>
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<tr>
<td>KDIGO</td>
<td>Kidney Disease: Improving Global Outcomes</td>
</tr>
<tr>
<td>KDOQI</td>
<td>Kidney Disease Outcomes Quality Initiative</td>
</tr>
<tr>
<td>LCI</td>
<td>labile cell iron</td>
</tr>
<tr>
<td>LPI</td>
<td>labile plasma iron</td>
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<tr>
<td>MCP-1</td>
<td>monocyte chemoattractant protein-1</td>
</tr>
<tr>
<td>HHF</td>
<td>hospitalization for heart failure</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>HH</td>
<td>hereditary haemochromatosis</td>
</tr>
<tr>
<td>HIF</td>
<td>hypoxia inducible factor</td>
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<tr>
<td>HJV</td>
<td>hepatic hemojuvelin</td>
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<td>Hx</td>
<td>history</td>
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<td>Hx</td>
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<tr>
<td>IDA</td>
<td>iron-deficiency anemia</td>
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<td>IL-6</td>
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<td>IPSS</td>
<td>international prognostic risk score</td>
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<td>IPSS-R</td>
<td>revised international prognostic risk score</td>
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<td>intravenous</td>
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<td>labile cell iron</td>
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<td>labile plasma iron</td>
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<td>MCP-1</td>
<td>monocyte chemoattractant protein-1</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>MCV</td>
<td>mean corpuscular volume</td>
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<td>MDS</td>
<td>myelodysplastic syndrome</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>MMP-2</td>
<td>matrix metalloproteases-2</td>
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<tr>
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<td>NDD-CKD</td>
<td>non-dialysis dependent chronic kidney disease</td>
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<td>NHS</td>
<td>National Health Service (UK)</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>PD</td>
<td>peritoneal dialysis</td>
</tr>
<tr>
<td>PHD</td>
<td>prolyl hydroxylase</td>
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<td>QIP</td>
<td>Quality Incentive Program</td>
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<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>QW</td>
<td>once per week</td>
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<tr>
<td>RA</td>
<td>refractory anemia</td>
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<tr>
<td>RAEB</td>
<td>refractory anemia with excess blasts</td>
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References


