Evolving Evidence on Anemia, Transfusion, Intravenous Iron and Patient Outcomes

A Need for Updated Intravenous Iron Coverage

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Overview

- Requested changes in the Policy Article
- Defining anemia, the "*at risk*" population and why they are at risk
- Prevalence of anemia – an epidemic
- Current attitude (practice)
- Anemia and the surgical patient
  - Risks
  - Management

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NGS Limitations on IV Iron Use

- Requirement that patients first **fail a trial of oral iron** (due to intolerance or lack of efficacy) **before IV iron will be covered**
  - **IV iron has superior efficacy and fewer ADE's**
- **IV iron will not be reimbursed if co-administered with an ESA** regardless of transferrin saturation or ferritin results, comorbidities such as CKD, or prior attempts to increase the TSAT to > 20%
  - **Co-administration of IV iron reduces ESA use by 30% or more and may reduce number of clinic visits**
- **Not all IV iron preparations** available in the U.S. **are covered** by the Policy Article
- The existence of **iron deficiency independent of anemia** is not recognized

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Requested Changes:

Expanded Inclusion Criteria for Coverage

- Eliminate requirement of "failure to respond to oral iron"
- Provide coverage for:
  - Both elective ***and*** non-elective surgery
  - Inflammatory process if documented by an hs-CRP > 4 or TSAT < 20% with elevated ferritin
  - Known IBD or RA regardless of disease activity
  - CKD, Stage 3 or higher (eGFR < 60 ml/min)
  - Chronic heart failure with ferritin <100 ng/ml or TSAT <20% regardless of hemoglobin level[1]
  - Iron deficiency **without anemia** (TSAT less than 20% **and** ferritin < 100 ng/ml

[1] Anker NEJM 2011

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Requested Changes:

Expanded Inclusion Criteria for Coverage of IV Iron

- Provide coverage for:
  - TSAT <20% and malignancy
  - Ferritin <100 and TSAT <20% and total iron deficit ≥ 1,000 mg
  - Iron deficiency (TSAT < 20% and ferritin <100 and pregnancy or within 8 weeks after delivery
  - Any patient being treated with an ESA, if transferrin saturation < 35% and ferritin < 1200 ng/ml, including coverage for iron administered on same day as ESA
  - Obesity
  - Status post bariatric surgery

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Current Qualifying ICD – 9 Codes

Diagnoses for Iron Therapy:

Iron deficiency anemia secondary chronic blood loss [280.0]
Iron deficiency anemia, unspecified [280.9]
Iron deficiency anemia due to inadequate iron dietary intake [280.1]
Personal hx of other specified digestive system diseases [V12.79]
Postsurgical non-absorption, other and unspecified [579.3]
Unspecified adverse effect of other drug, medicinal, and biological substance [995.29]

Renal failure unspecified [586.0]

Other:_____
Chemotherapy related anemia [285.22]
CKD, Stage 3: (mod) GFR 30 to 59 [585.3]
CKD, Stage 4: (severe) GFR 15 to 29 [585.4]
CKD, Stage 5: GFR less than 15 [585.5]
Intestinal malabsorption, unspecified [579.9]
Iron deficiency anemias, other specified [280].

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Additional Qualifying Diagnosis Codes Requested

- Functional iron deficiency
- Inflammatory states, unspecified, acute and chronic
- Chronic heart failure
- Obesity
- Malignancy
- Dysfunctional uterine bleeding and related codes
- Pregnancy
- Bariatric surgery
- Iron deficiency as defined by ferritin or TSAT who do **NOT** have anemia

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Prevalence of Anemia and Why We Need to Treat It

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Age, Anemia and Iron Deficiency

- 35% of adults over the age of 65 have unexplained anemia (defined as Hgb less than 12 g/dl)
- 17% of adults over the age of 65 have iron deficiency
  - Of those with iron deficiency anemia, only 50% normalized their hemoglobin with oral iron therapy

Blood Cells Mol Dis. 2011;46(2):159

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Prevalence of Iron Deficiency Anemia

- Walsh TS et al. - 35% of patients have red cell indices consistent with functional iron deficiency at ICU admission [1]
- Lasocki S et al. Iron deficiency may affect up to 40% of critically ill patients [2]
- Rodriguez RM et al. 9% of ICU patients were iron deficient, 2% B12 deficient, and 2% folic acid deficient[-3]

1. Walsh TS. Br J Anaesth. 2006
2. Lasocki S. Anesthesiology, 2011
3. Rodriguez RM . J Crit Care. 2001

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Prevalence of Iron Deficiency Anemia

- 30-60% of patients with RA have anemia
- 30-80% of patients with IBD have anemia
- 30-50% of patients with CHF have anemia
- 20-40% of diabetics *without* overt renal failure have anemia
- 40-60% of patients with chronic kidney disease have anemia

All of these are related to iron absorption and metabolism

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Journal of HOSPITAL MEDICINE www.journalofhospitalmedicine.com

ORIGINAL RESEARCH

Hospital-Acquired Anemia: Prevalence, Outcomes, and Healthcare Implications

Colleen G. Koch, MD[1,2*], Liang Li, PhD[3], Zhiyuan Sun, MS[3], Eric D. Hixson, PhD[4], Anne Tang, MS[3], Shannon C. Phillips, MD[2], Eugene H. Blackstone, MD[3,5], J. Michael Henderson, MD[2,6]

10 hospitals, from1/09 to 08/11 188,447 Hospitalizations
Endpoints: Mortality, Charges and LOS

	Mild	Mod	Severe
Definition	>11 – 12F >11-13M	9.1 - ≤ 11	≤ 9.0
HAA (74%)	29%	41%	30%
Mort RR	1.0	1.51	3.28
LOS	1.08	1.28	1.88
Charges	1.06	1.18	1.80

J Hosp Med 2013

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Anemia is often "*accepted*" or ignored

- A long tradition of accepting anemia as a "harmless" problem that can be easily corrected with transfusion
- For the medical community transfusion as treatment for anemia remains a default position
- New paradigm: Anemia is an independent risk of morbidity and mortality regardless of the level of hemoglobin
- Transfusion as a treatment of anemia compounds the problem and increases costs
  - Cost of transfusion range from $800 to over $1200 per transfusion done through activity=based costing, excluding ANY complications of transfusion

Isbister J. Shander A. TMR 2011
Shander Transfusion 2010

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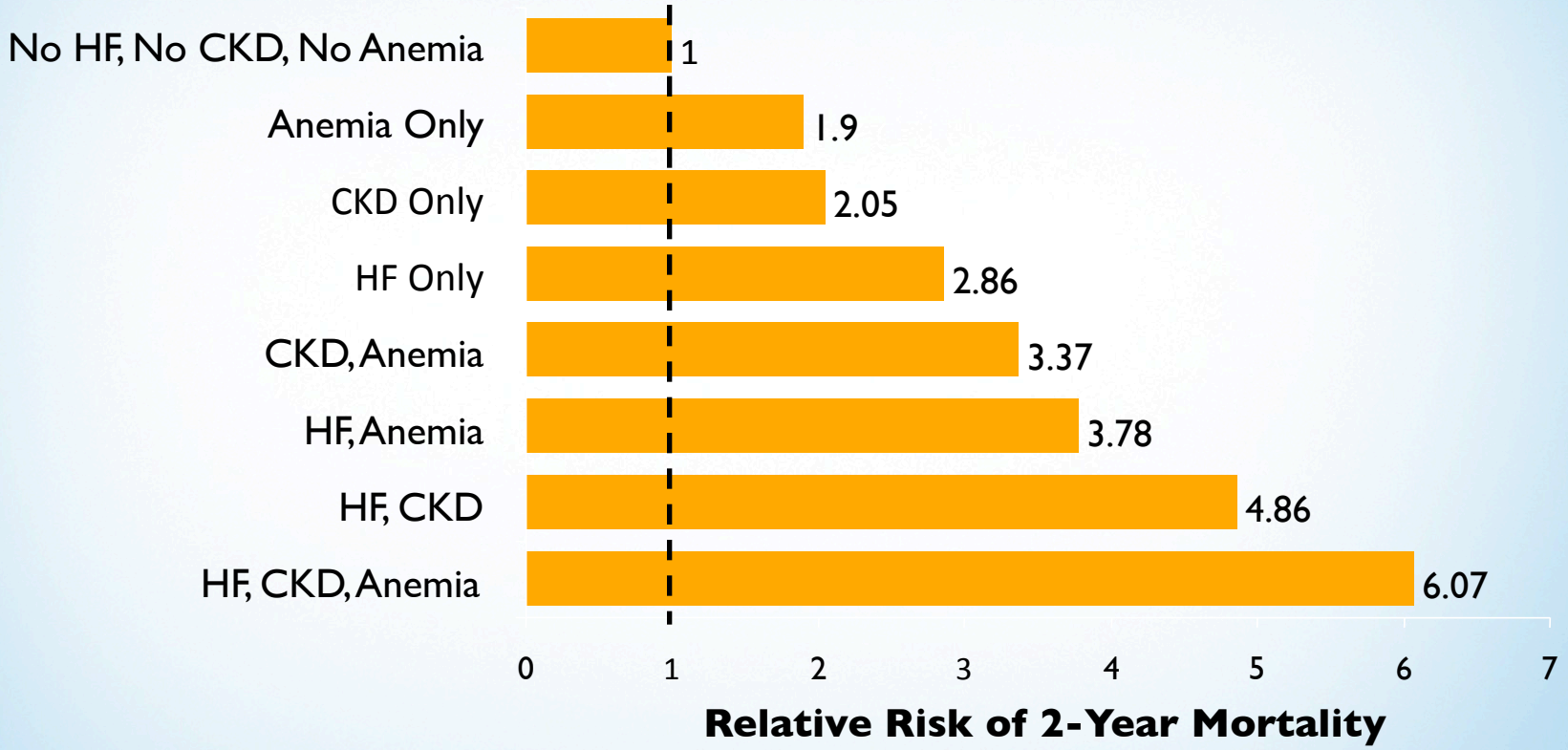
Anemia—A Potent Multiplier of Mortality



N = 1.1 million (5% Medicare sample, 1996-1997)

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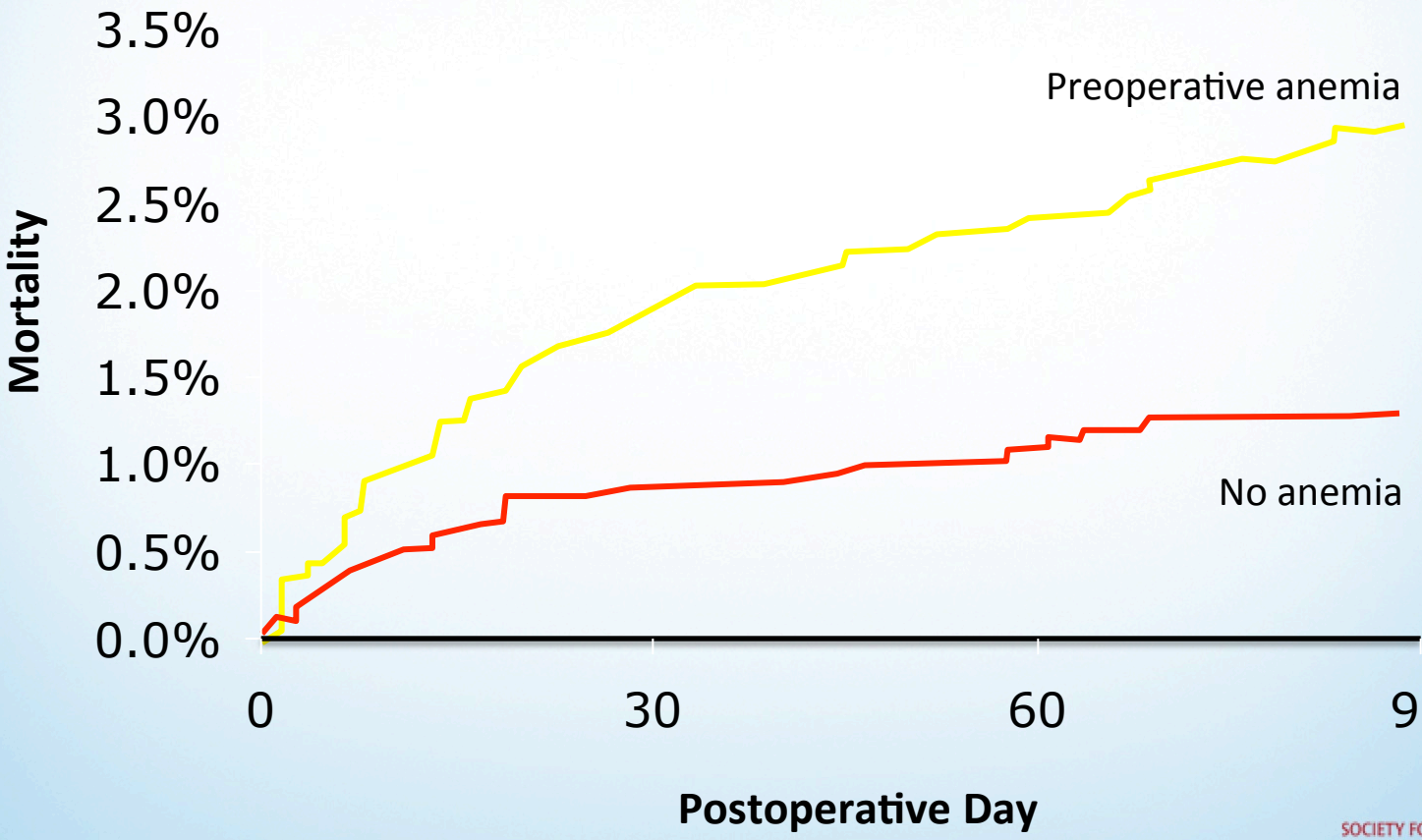
Herzog CA, Muster HA, Li S, Collins AJ. Impact of congestive heart failure, chronic kidney disease, and anemia on survival in the Medicare population. J Card Fail 2004; 10:467–472.

Preoperative Anemia Is Associated With Postoperative Mortality

N – 7759 2003 – 2006

Hb<12 g/dL for women and <13 g/dL for men



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Beattie WS et al. *Anesthesiology.* 2009;110:574-581.

Does Preoperative Anemia Adversely Affect Colorectal Surgery Outcomes?

- 2005-2008 - NSQIP (251 hospitals)
- CO – MI, CVA, AKI, Mortality and HLOS
- N – 23,348 – 47.4 % Anemic
- Uni, multi, logistic regression and propensity scoring

Anemia	HCT	N	CO - OR	HLOS
None	(>38%)	12,281	1.0	-
Mild	(30-37%)	9037	1.47	-
Moderate	(26-29%)	1726	1.87	1.2
Severe	(21-25%)	304	2.1	1.6

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Leichtle S.W. et. al. *J Am Coll Surg 2011;* 212 (2):187-94

Who Gets Transfused?

- 94% of transfusions in surgical patients can be attributed to:
  - Low preoperative hemoglobin levels
  - Excessive (uncontrolled) surgical blood loss, and/or
  - Inappropriate transfusion practices

ALL MODIFIABLE RISKS

Shander A, Javidroozi M, Perelman S, Puzio T, Lobel G. Mt Sinai J Med 2012

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Anemia Management in Surgical Patients – Published Clinical Pathway

1. Surgical patients have a Hb level determination as close to 28 - 30 days before the scheduled surgical procedure
2. Patient's target **Hb be within the normal range** (female ≥ 12 g/dL, male ≥ 13 g/dL) before surgery
3. Laboratory testing take place to further evaluate for nutritional deficiencies, chronic renal insufficiency, and/or chronic inflammatory disease
4. Nutritional deficiencies be treated - **including iron deficiency !**
5. ESA therapy be used for anemic patients in whom nutritional deficiencies have been ruled out and/or corrected

Goodnough LT, Shander A, et al. *Anesth Analg.* 2005.
Goodnough LT, et al. BJA 2011

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Safety and Efficacy of Iron Preparations

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Side Effects with Oral Iron

- Constipation and Diarrhea
- Gastric Cramping
- Metallic Taste
- Thick, green tenacious stool
- Leads to significant non-compliance!
- Oral iron is low cost but ineffective in many patients and **delays effective anemia treatment**

Kruske SG, et al. Paediatr Child Health 1999; 35:153.

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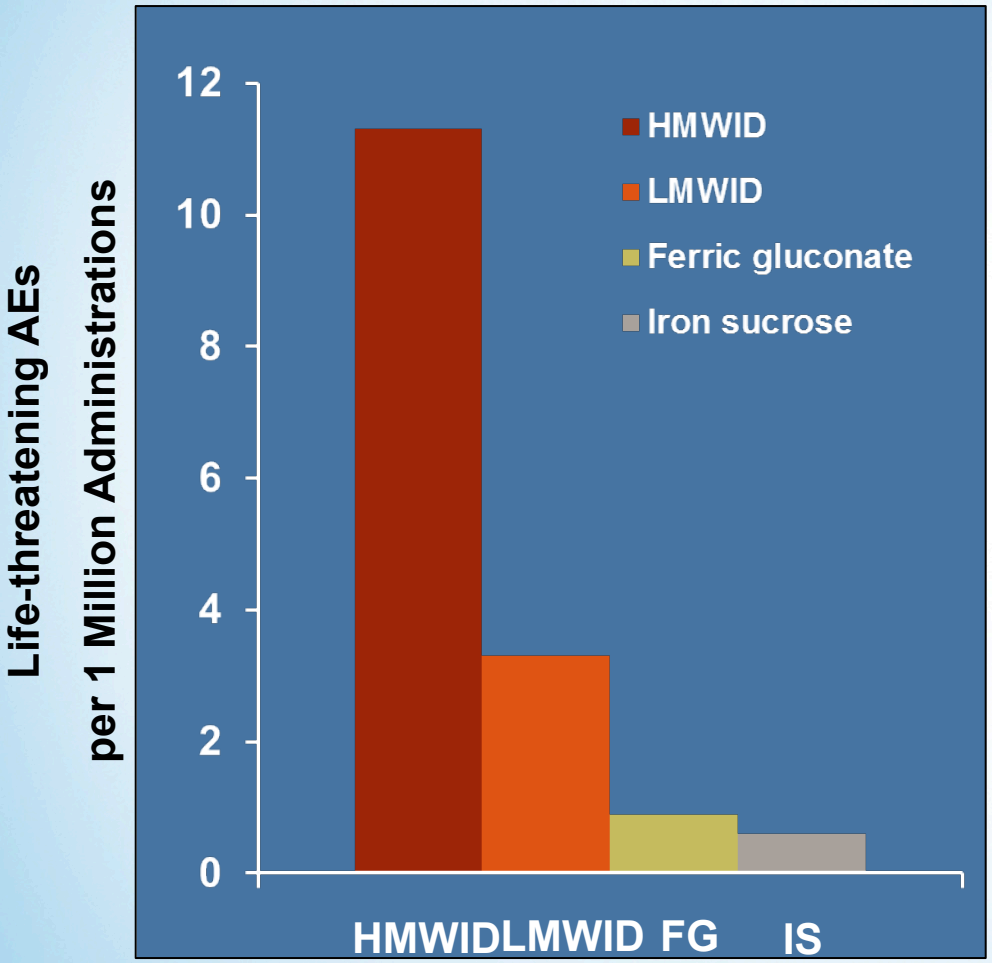
AEs and IV Iron Therapy



- FDA MedWatch reports (2001-2003) show HMWID was associated with a 3.4-fold increase in odds of life-threatening AEs
- This analysis likely overestimates AEs with LMWID (all AEs reported by generic name only where attributed to LMWID)
- **In tens of thousands of patients in prospective studies SAEs with IV iron are vanishingly rare**

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Chertow GM, et al. *Nephrol Dial Transplant*. 2006;21:378-382.

Maintenance Therapy With IV vs Oral Iron in EPO-Treated Patients

	Baseline	2 Months	4 Months
Hct, %			
IV Iron	32.5 ±0.6	36.3 ±0.9*	34.4 ±0.7*
PO Iron	31.8 ±0.3	32.1 ±0.3	31.8 ±0.4
EPO, U/Rx			
IV Iron	7100 ±571	3350 ±689*	4050 ±634*
PO Iron	6750 ±419	7250 ±409	7563 ±378

PO Iron = 200-300 mg/d; IV Iron = 200 mg/wk.
***P*<.05 compared to PO iron group.**

Fishbane *et al.* Am J Kidney Dis. 1995;26:41-46.

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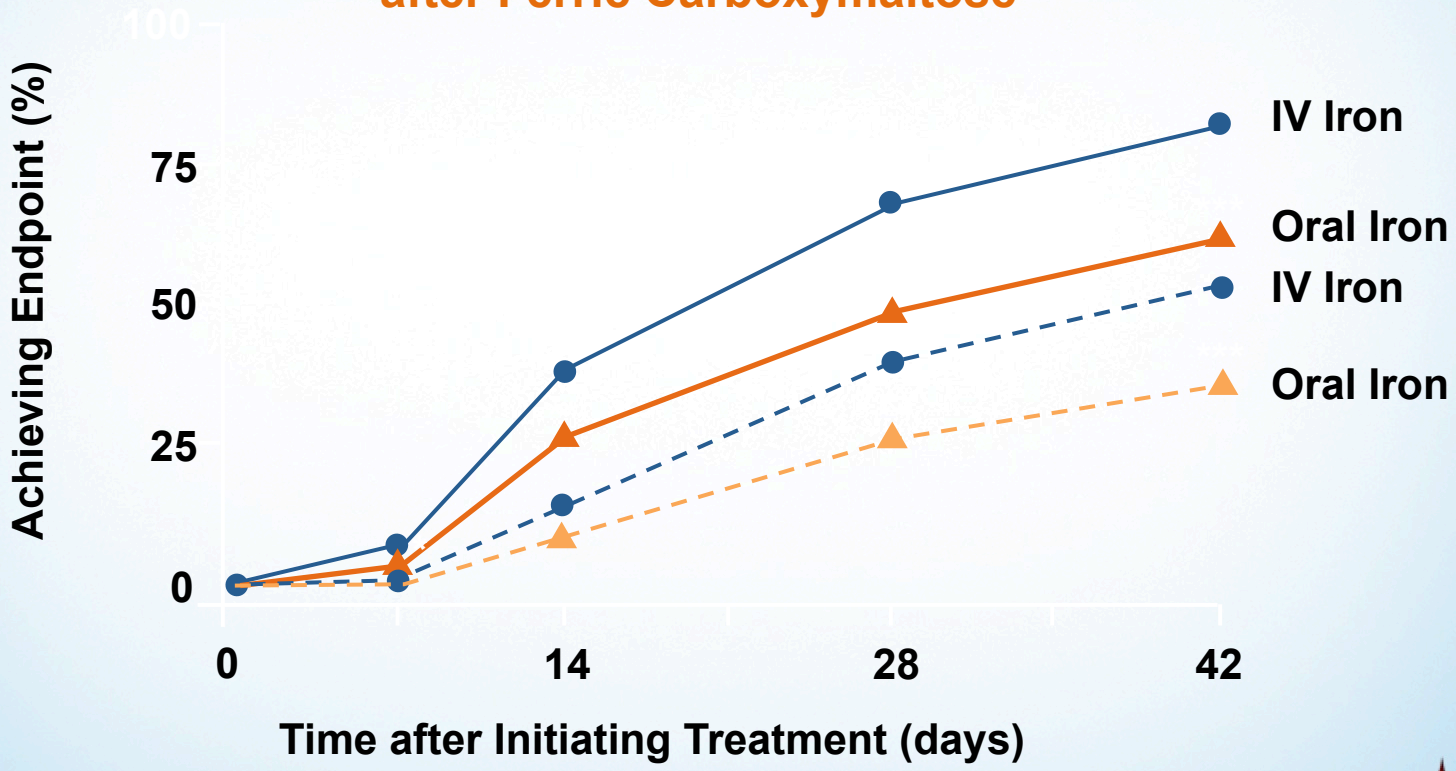
IV Iron Improves Anemia in Women with Menorrhagia

Proportion of 477 Patients Achieving an Hgb Increase of 2 g/dL or 3 g/dL after Ferric Carboxymaltose



Proportion of patients achieving an Hgb increase of more than 2.0 g/dL or 3.0 g/dL according to treatment assignment; significant between-group differences.

*P<0.05. **P<0.01. ***P<0.001.

Van Wyck DB, et al. *Transfusion*. 2009;49:2719-2728.

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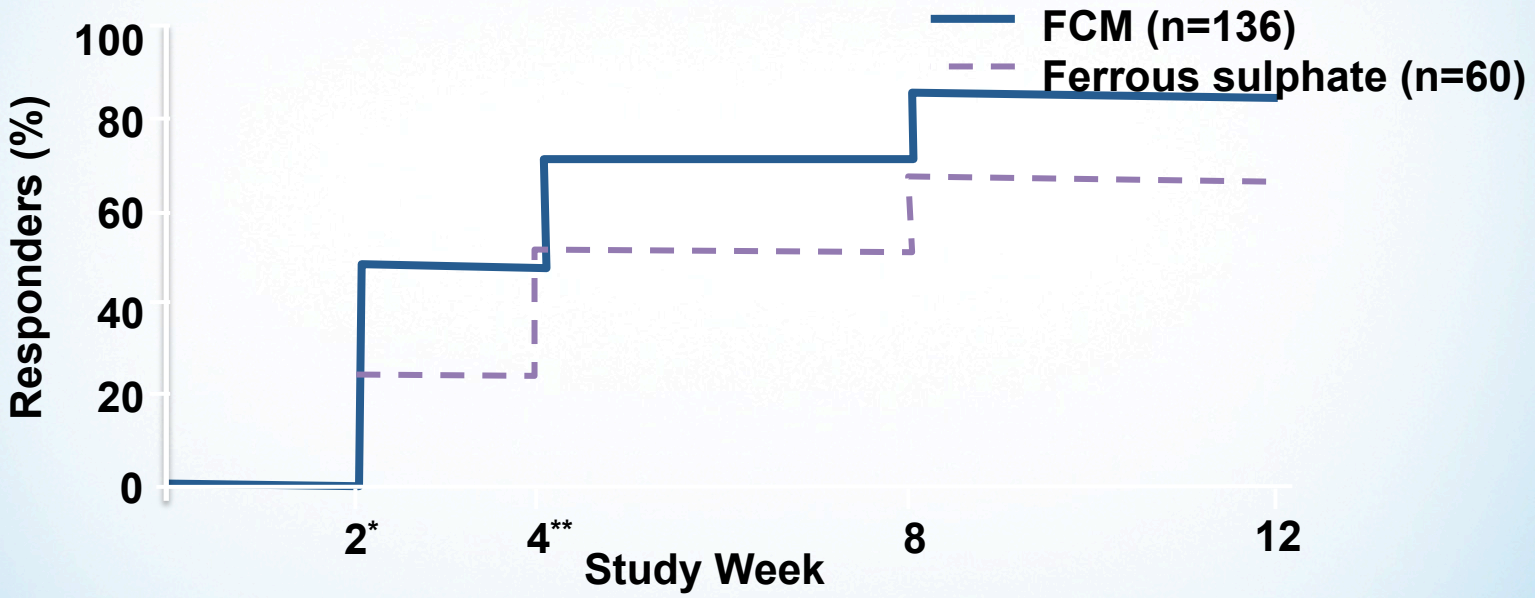
Ferric Carboxymaltose in IBD Patients

Significantly Faster Hb Response vs. Oral Iron (Kaplan-Meier Analysis: Increase in Hb ≥2 g/dL at Weeks 2 and 4)



DOSING **Ferric carboxymaltose:** The median calculated iron deficit was 1405.5 mg (range 937–2102 mg), requiring 1–3 administrations on an individual basis at 1 week intervals.

Ferrous sulfate: 2x100 mg/day for 12 weeks (total 16,800 mg). Non-inferiority of ferric carboxymaltose confirmed in primary endpoint.

Treatment comparison log-rank test 0.009.
*P=0.0051; **P=0.0346.
Kulnigg S, et al. *Am J Gastroenterol.* 2008;103:1182-1192.

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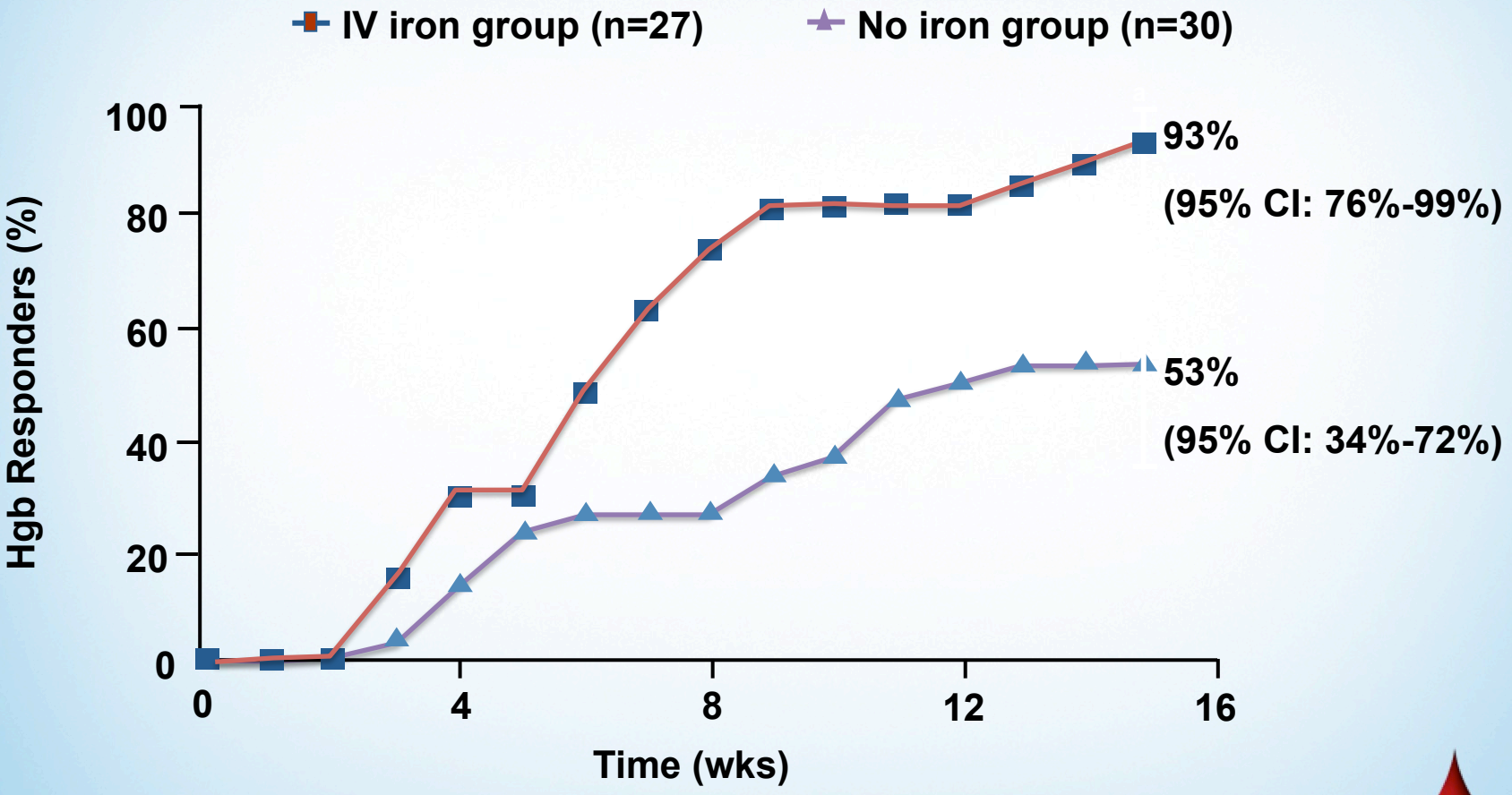
Addition of IV Iron to EPO Increases Hgb Response in Cancer-associated Anemia



Increase in Hgb of ≥2 g/dL during the study without transfusion.
[a]Significant difference (P=0.0012) between treatment arms.
Hedenus M, et al. *Leukemia*. 2007;21:627-632.

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Summary of Literature Review

- Superiority of IV iron over enteric iron in the management of IDA and functional IDA (iron sequestration syndromes) in multiple disease states
- Requiring a failed course of enteric iron before IV iron unnecessarily delays needed treatment and increased ADEs
- Clinical and economic benefits of concomitant use of IV iron and ESAs is demonstrated

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