

Challenging the Status Quo in Hereditary Hemorrhagic Telangiectasia:



A Comprehensive Review of IV Iron Best Practices at the Hematology-Primary Care Interface



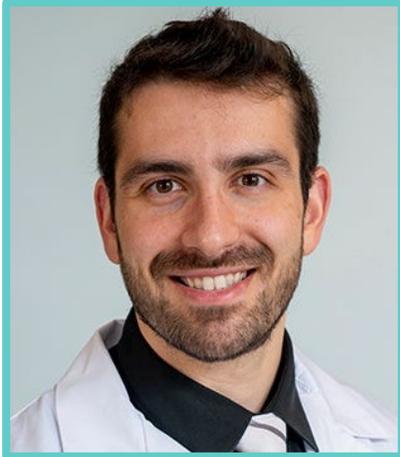
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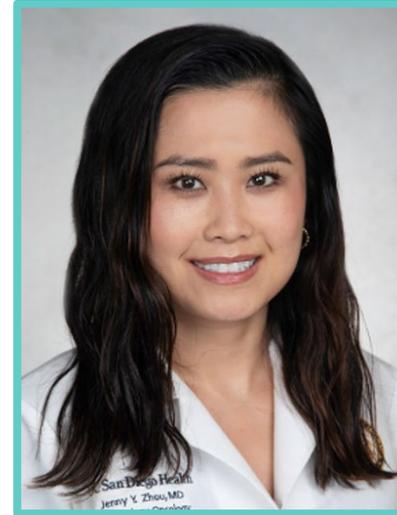


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Faculty Disclosures

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Learning Objectives



Take the Activity Pre-Test using this QR code (or by visiting <https://form.jotform.com/AcademyCME/25CHHT2PRE>)



- Examine the prevalence, genetic genesis, and overwhelming patient burden of illness associated with HHT.
- Identify the hallmark disease manifestations and diverse clinical presentation of HHT, with a focus on chronic bleeding and consequent iron deficiency (ID) and iron deficiency anemia (IDA).
- Summarize current international HHT guideline recommendations, highlighting early and accurate diagnosis, screening protocols, and timely linkage to evidence-based treatment.
- Evaluate guideline-directed approaches to testing for HHT-associated ID and IDA and implementing treatment using iron replacement strategies.
- Compare and contrast the clinical utility of oral iron and intravenous (IV) iron supplementation in patients with HHT according to current expert consensus and real-world experience.
- Describe the paradigmatic placement of specific IV iron products in the guideline-directed treatment of HHT-associated IDA, emphasizing patient convenience and hypophosphatemia as core differentiators.
- Collaborate with your multidisciplinary team to design individualized, guideline-concordant treatment plans for patients with HHT-associated IDA using IV iron.



Patient Case: Part 1, Meet Jack

- **44-year-old man** presents to clinic with fatigue, reduced energy, brain fog, recurrent epistaxis, and dark stools.
 - Symptoms **are severe enough to impact work**
- Recurrent nosebleeds started in his 20s and have worsened over time
 - **Diagnosed: “mild” von Willebrand disease**
- **7 years ago:** mildly anemic, prescribed oral iron (takes on and off due to constipation and GI upset)
- **Over past 2 years:** intermittent dark stools his provider attributed to oral iron and swallowed epistaxis blood
- **Today:** Hb 8.9 g/dL, MCV 69, ferritin 9 ng/mL, TSAT 5%
 - He has taken oral ferrous sulfate daily for past 3 months

What is the most appropriate next step to diagnose Jack?



The Spectrum of (Non-Platelet) Bleeding Disorders



**Coagulation
Factor Problem**

Hemophilia

- **1 in 10,000** people
- Coagulation factor deficiency
- **Normal** angiogenesis

Von Willebrand Disease

- **1 in 1,000** people
- Coagulation factor deficiency
- **Disordered** angiogenesis

**Vascular Structural
Problem**

Hereditary Hemorrhagic Telangiectasia

- **1 in 5,000** people
- **NO** coagulation factor deficiency
- **Disordered** angiogenesis

Ferry AM, et al. *Am J Rhinol Allergy*. 2020; <https://curehht.org/understanding-hht/what-is-hht/medical-summary/>; Viteri-Noel A, et al. *J Clin Med*. 2022; Zhang E, et al. *Blood Adv*. 2024.



HHT: Multisystem Hereditary Bleeding Disorder with Numerous Morbid and Potentially Fatal Manifestations

- Progressive, multisystem bleeding disorder consequent to abnormal vessel formation
 - As such, requires a multidisciplinary and interprofessional management approach
 - Mucocutaneous telangiectasias → chronic gastrointestinal hemorrhage and severe recurrent epistaxis
 - *Severe iron deficiency (ID) and/or iron deficiency anemia (IDA)*
 - IV iron infusions or RBC transfusions
 - Visceral AVMs in lung, liver, brain, others → morbidity/mortality
- **Bleeding most important to patients**
 - AVMs and anemia tied for 2nd

***No FDA-approved
therapies to-date***

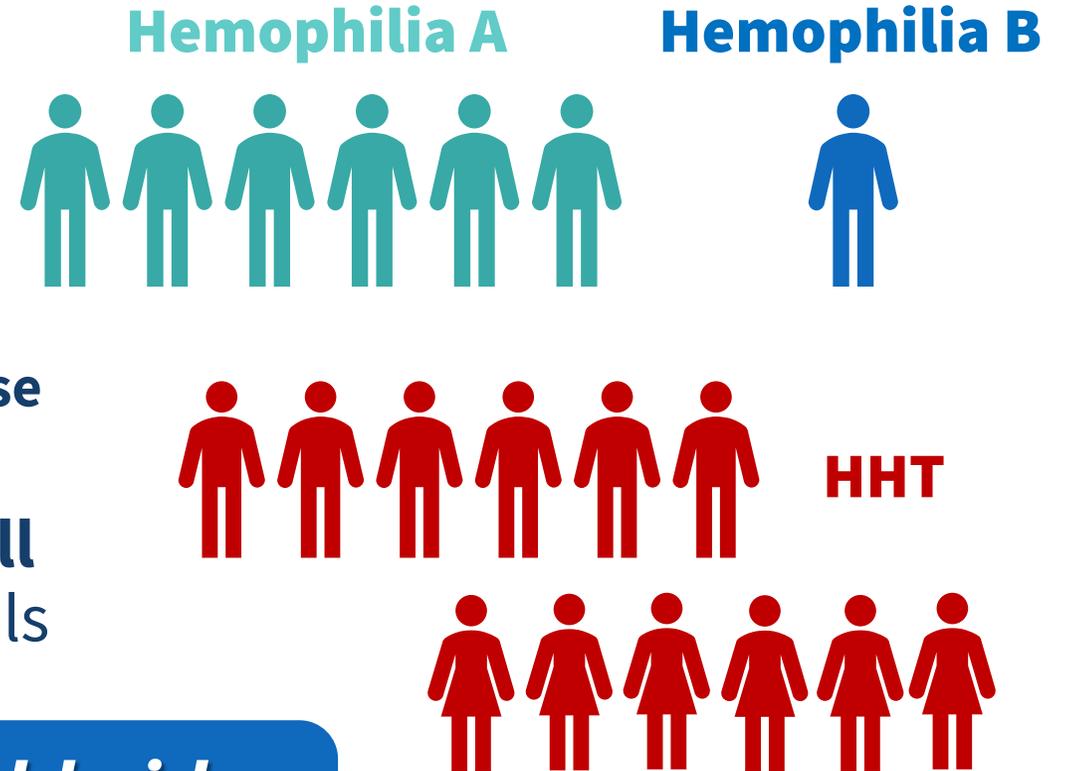
AVM: ArterioVenous Malformations

Viteri-Noel A, et al. *J Clin Med.* 2022; Ferry AM, et al. *Am J Rhinol Allergy.* 2020; <https://curehht.org/understanding-hht/what-is-hht/medical-summary/>; Faughnan M, et al. *Ann Intern Med.* 2020; Droege F, et al. *Vasc Med.* 2018; Zarrabeitia R, et al. *Health Qual Life Outcomes.* 2017; Kasthuri R, et al. *Blood Adv.* 2022; <https://curehht.org/understanding-hht/what-is-hht/signs-and-symptoms/>.



HHT is the Second Most Common Inherited Bleeding Disorder

- Autosomal dominant inheritance
- 1:1 male to female prevalence
- Most clinically significant and morbid inherited bleeding disorder of women
 - **More severe bleeding and visceral disease manifestations in women**
- Patients with HHT have **reduced overall survival** compared with healthy controls

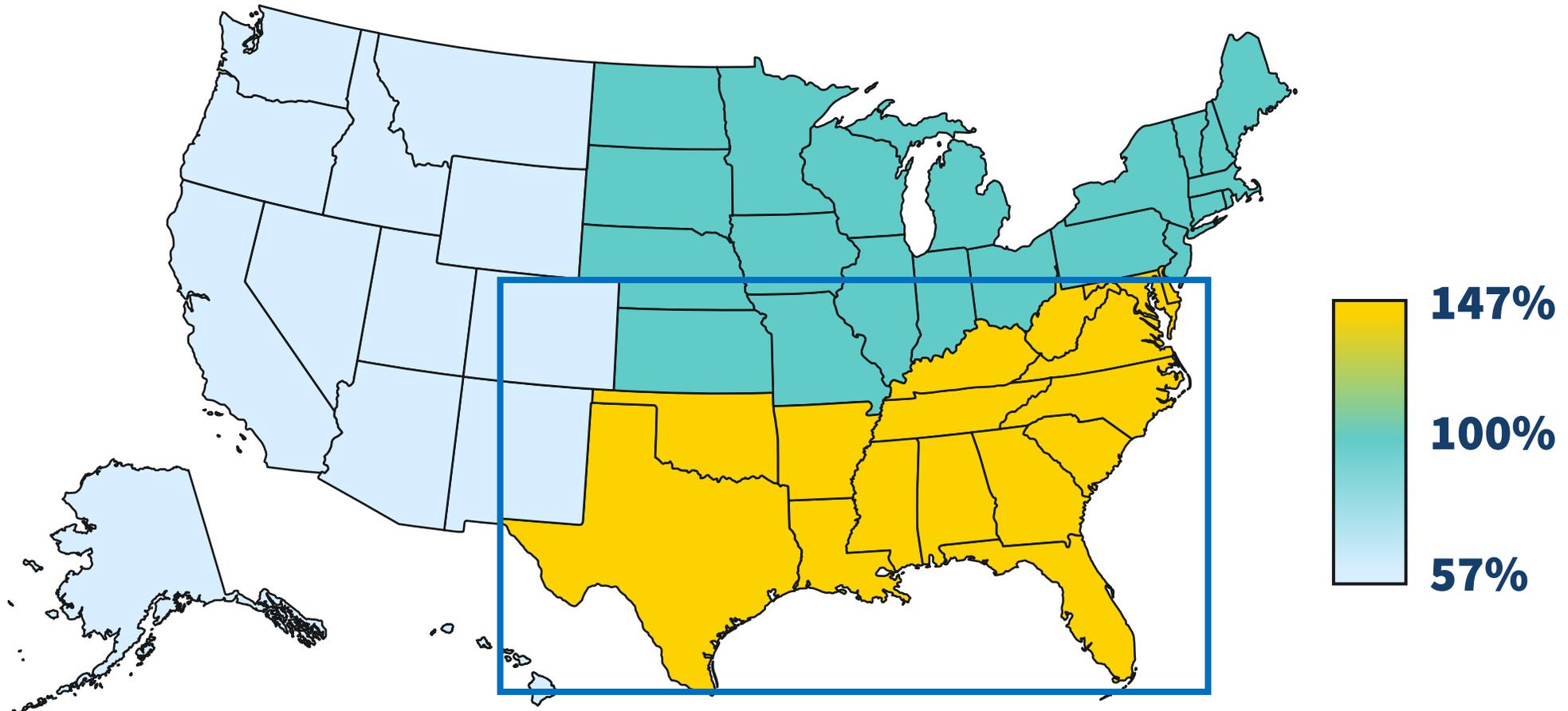


HHT Affects 1.4 Million Worldwide

Zhang E, et al. *Blood Adv.* 2024; Ferry AM, et al. *Am J Rhinol Allergy.* 2020; Viteri-Noel A, et al. *J Clin Med.* 2022; Faughnan M, et al. *Ann Intern Med.* 2020; McDonald J, et al. *Front Genet.* 2015.



Important HHT Epidemiologic Trends

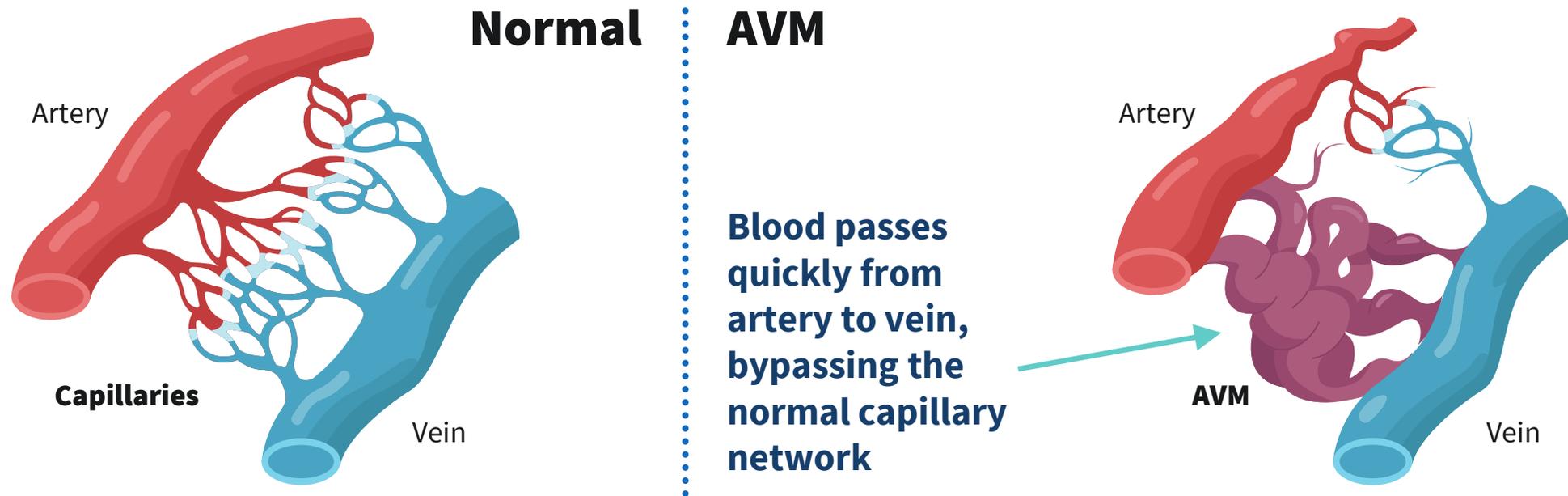


Ferry AM, et al. *Am J Rhinol Allergy*. 2020.



AVM: The Empiric Pathologic Lesion of HHT

- “**AVM**”: visceral organs (lung, liver, brain, etc.)
- “**Telangiectasia**”: AVM in Skin, GI mucosa, upper aerodigestive tract



Ferry AM, et al. *Am J Rhinol Allergy*. 2020; <https://curehht.org/understanding-hht/what-is-hht/medical-summary/>; Viteri-Noel A, et al. *J Clin Med*. 2022; Droege F, et al. *Vasc Med*. 2018.



Diagnosis of HHT is Primarily Clinical and a MAJOR Clinical Practice Gap

- Only **10% of cases accurately diagnosed**
- Average delay in diagnosis = **27 years!**

Curaçao Criteria

- Spontaneous or recurrent **epistaxis** (nosebleeds)
- **Mucocutaneous telangiectasias** (hands, lips, face, internal mucosa of nose or mouth)
- **Visceral AVMs** (lungs, brain, liver, intestines, stomach, and/or spinal cord)
- **Family history** (first-degree relative with HHT who met the prior three criteria)

Definitive HHT Diagnosis:

3-4 Criteria

Possible HHT: 1-2 Criteria

Can (Should Ideally) Confirm with Genetic Testing

- *ENG* Mutation: HHT Type 1
- *ACVRL1* Mutation: HHT Type 2

<https://curehht.org/understanding-hht/what-is-hht/signs-and-symptoms/>; Viteri-Noel A, et al. *J Clin Med.* 2022; Faughnan M, et al. *Ann Intern Med.* 2020; McDonald J, et al. *Front Genet.* 2015; Garg N, et al. *J Blood Med.* 2014; Shovlin CL, et al. *Am J Med Genet.* 2000.

Jack's Case Continued

- Review of Jack's medical records demonstrate the following:

- **VWF: Ag** 60%
- **VWF: RCo** 62%
- **FVIII: C** 68%
- **ABO blood group: O**

-
- Repeat VWF testing today **confirms these numbers.**
 - In addition to recurrent epistaxis, Jack has red spots (**telangiectasias**) on his fingers/lips and a **strong family history of nosebleeds**
 - **Meeting 3 out of 4 Curaçao Criteria, Jack is diagnosed with HHT**, and the prior VWD diagnosis is removed.
 - Jack **begins IV iron therapy.**





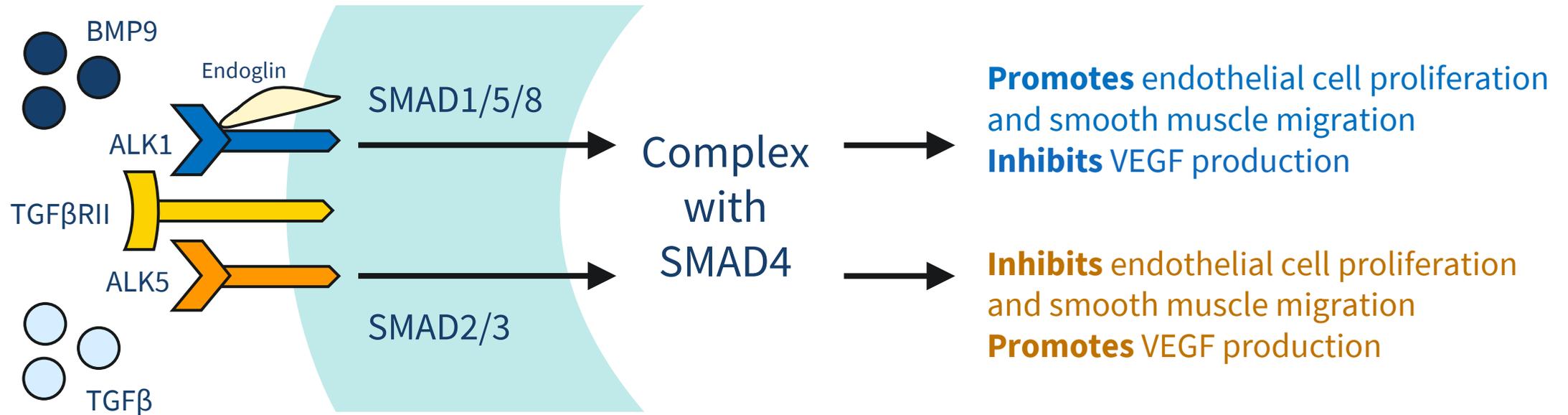
Fundamentally, HHT is a Disease of the TGF- β Signaling Pathway

Mutation in *ENG*, *ACVRL1/ALK1*, or *BMP9/GDF2*

▶ ↓Endoglin, ↓ALK1, or ↓BMP9 leads to reduced signaling through **ALK1** and increased signaling through **ALK5**

▶ ↑VEGF leads to increased endothelial proliferation (exacerbated by stress or hypoxia)

▶ **AVMs**
Telangiectasias
HHT manifestations



Kritharis A, et al. *Haematologica*. 2018; Viteri-Noel A, et al. *J Clin Med*. 2022; McDonald J, et al. *Front Genet*. 2015.



Classifying HHT Disease Subtypes

| Disease | Genetic Mutation (locus) | Primary Visceral Manifestations |
|--|-------------------------------|--|
| HHT type 1 | <i>ENG</i> (9q34.11) | <ul style="list-style-type: none">• Pulmonary AVMs• Brain AVMs |
| HHT type 2 | <i>ACVRL1</i> (ALK1;12q13.13) | <ul style="list-style-type: none">• Liver AVMs• Pulmonary hypertension• Spinal AVMs |
| JP-HHT (Combined syndrome of HHT and juvenile polyposis) | <i>MADH4</i> (SMAD4; 18q21.2) | <ul style="list-style-type: none">• Gastrointestinal polyps• Visceral AVMs• Pulmonary hypertension |

Kritharis A, et al. *Haematologica*. 2018; McDonald J, et al. *Front Genet*. 2015.



Mucocutaneous Telangiectasias: Skin



Images provided courtesy of Dr. Hanny Al-Samkari.



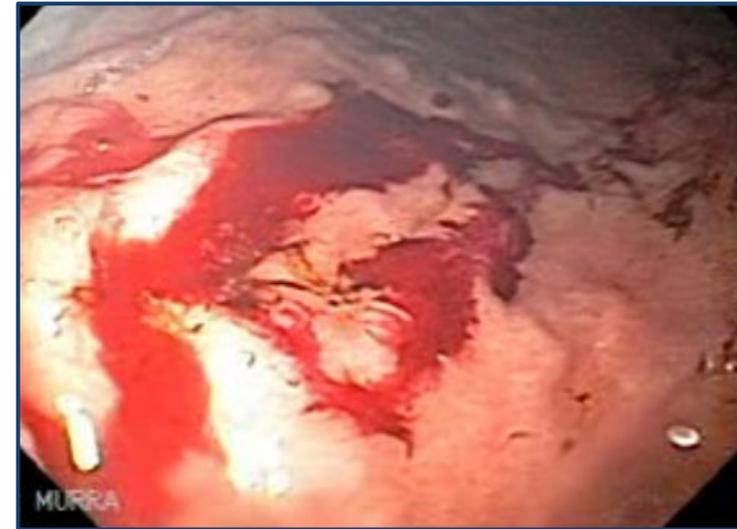
Mucocutaneous Telangiectasias: Oral Cavity



Images provided courtesy of Dr. Hanny Al-Samkari.



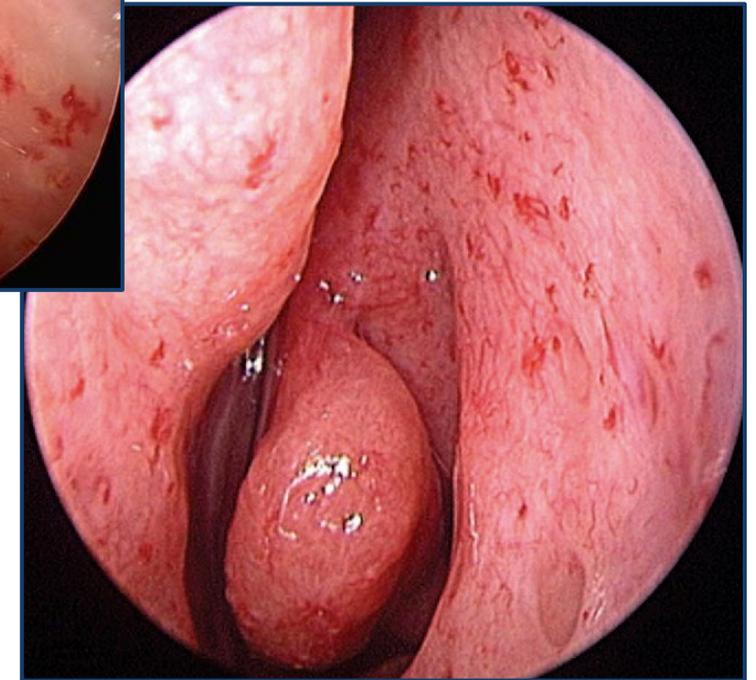
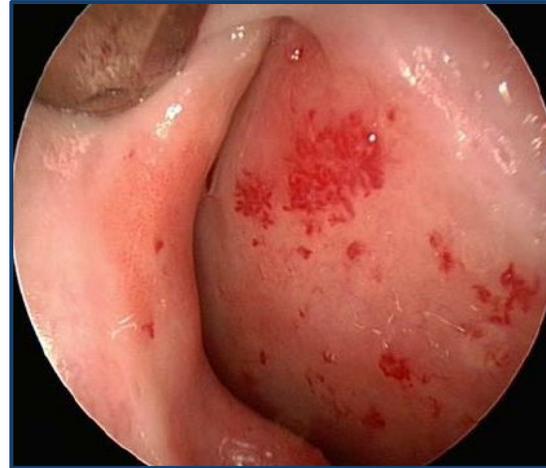
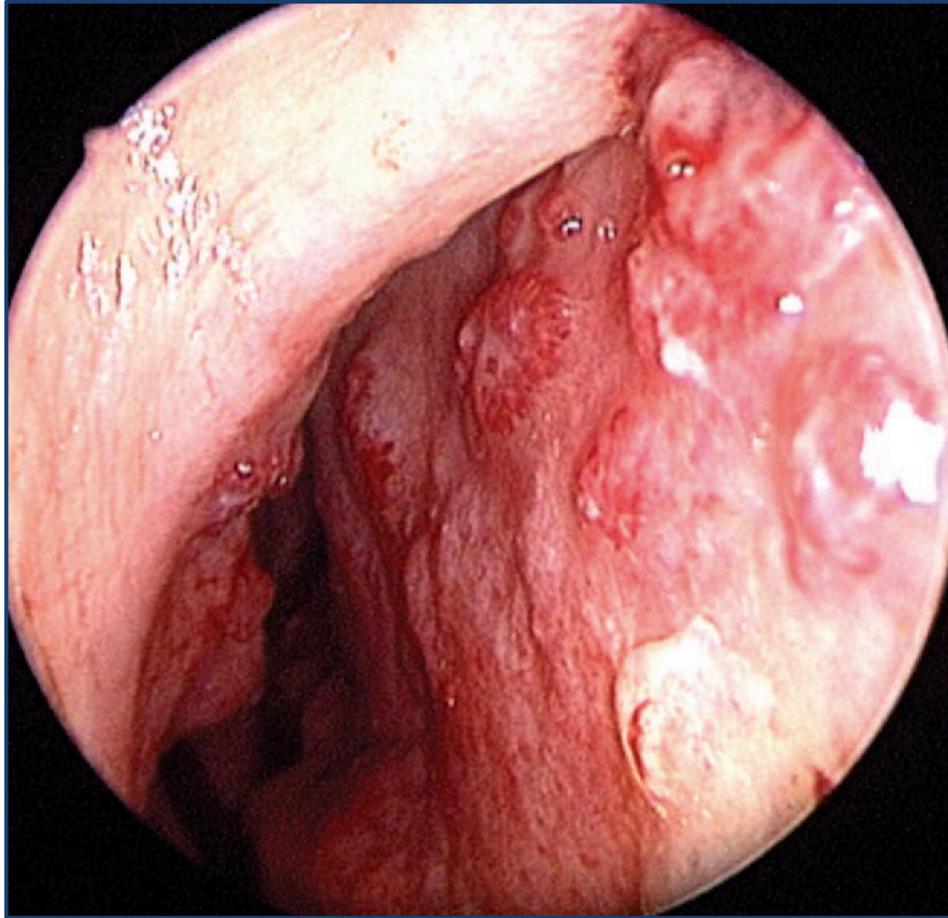
Mucocutaneous Telangiectasias: GI Tract



Images provided courtesy of Dr. Hanny Al-Samkari.



Mucocutaneous Telangiectasias: Nasal Cavity



Images provided courtesy of Dr. Hanny Al-Samkari.



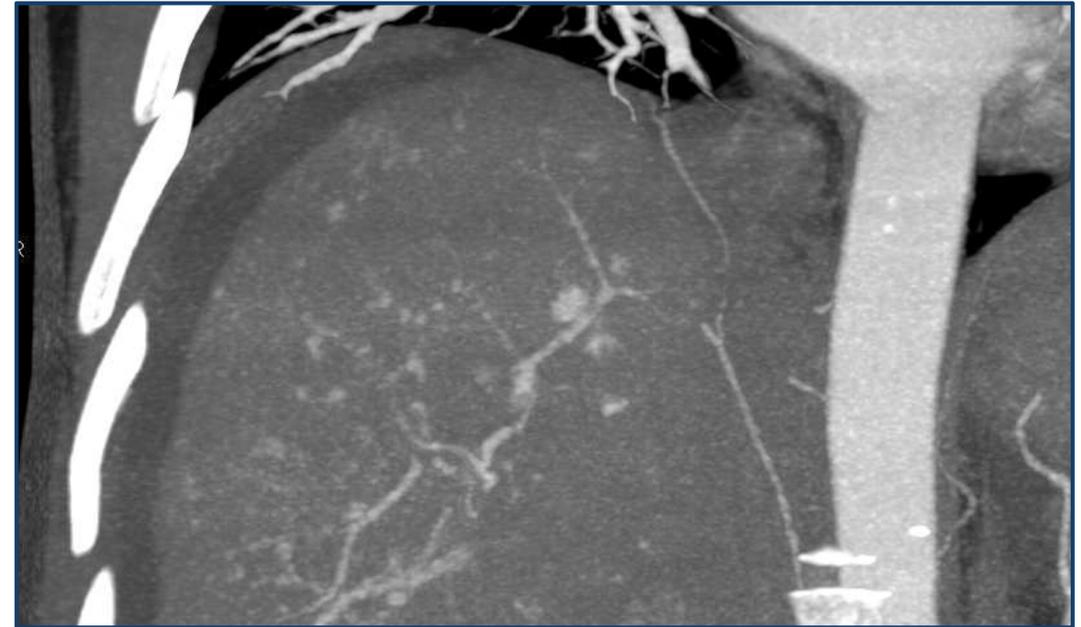
Pulmonary AVMs (>50%)



Images provided courtesy of Dr. Hanny Al-Samkari; Viteri-Noel A, et al. *J Clin Med.* 2022; Faughnan M, et al. *Ann Intern Med.* 2020; McDonald J, et al. *Front Genet.* 2015; Droege F, et al. *Vasc Med.* 2018.



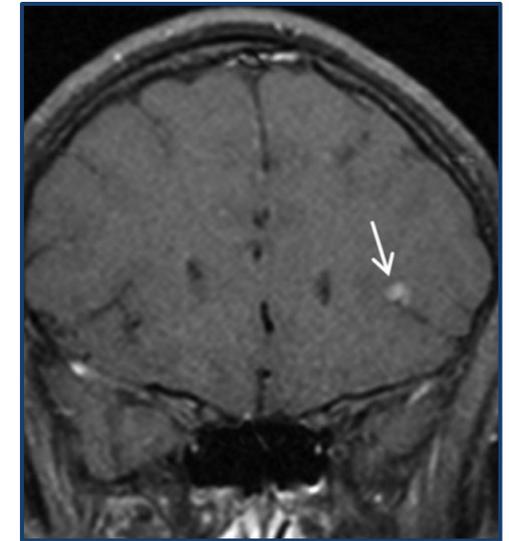
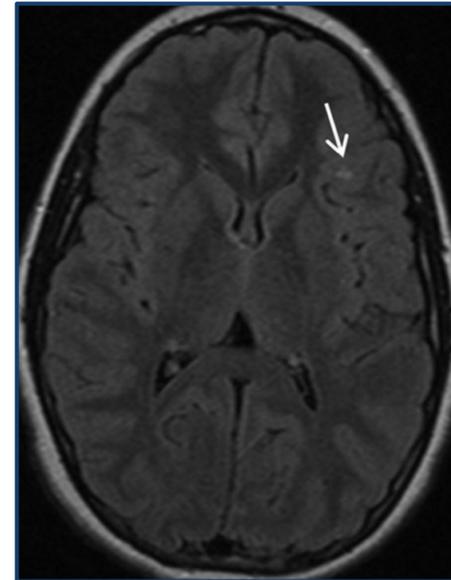
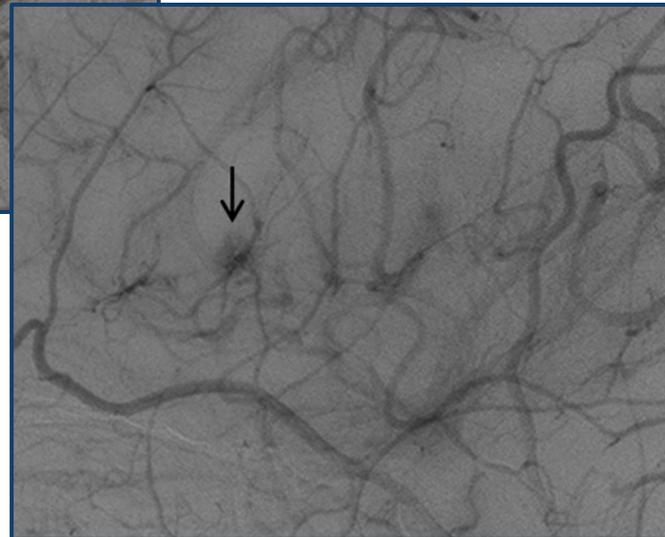
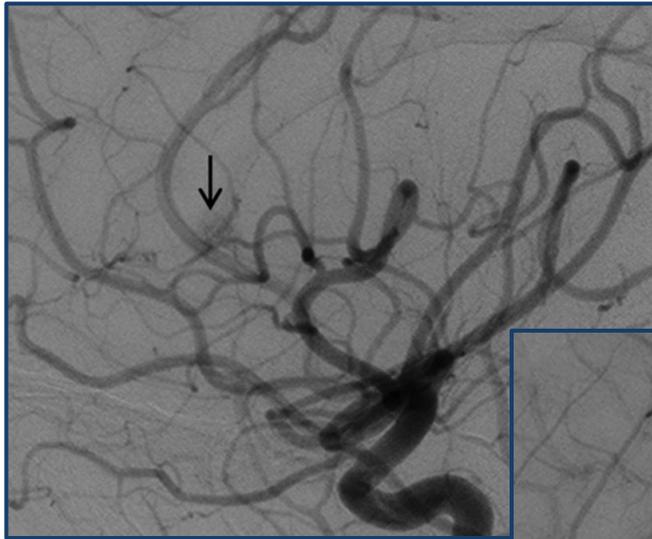
Hepatic AVMs (~70%)



Images provided courtesy of Dr. Hanny Al-Samkari; Viteri-Noel A, et al. *J Clin Med.* 2022; Faughnan M, et al. *Ann Intern Med.* 2020; McDonald J, et al. *Front Genet.* 2015; Droege F, et al. *Vasc Med.* 2018.



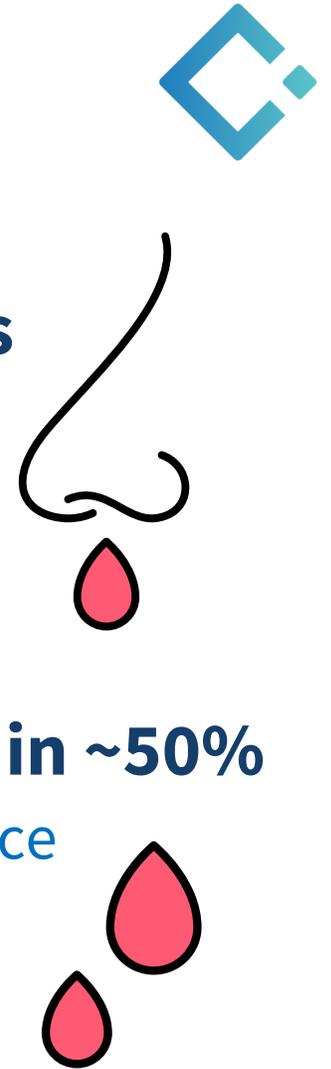
Brain AVMs (~10-20%)



Images provided courtesy of Dr. Hanny Al-Samkari; Viteri-Noel A, et al. *J Clin Med.* 2022; Faughnan M, et al. *Ann Intern Med.* 2020; McDonald J, et al. *Front Genet.* 2015; Droege F, et al. *Vasc Med.* 2018.

Telangiectasias are Fragile and Bleed, Acutely and Chronically

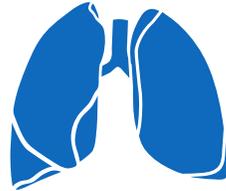
- Recurrent, severe epistaxis: **50% of children, >95% of adults**
 - Common to have **multiple nosebleeds daily**
 - Not uncommon to have an hour or more of nose bleeding daily
 - Result: **ID/IDA, social isolation, unemployment, no travel, depression, anxiety, PTSD**
- GI telangiectasias are present in 75% → **chronic GI bleeding in ~50%**
 - May result in severe anemia, RBC transfusion, and IV iron dependence
- **50% of patients with HHT have chronic IDA**
 - May be an underestimation due to lack of screening



Viteri-Noel A, et al. *J Clin Med.* 2022; Faughnan M, et al. *Ann Intern Med.* 2020; Droege F, et al. *Vasc Med.* 2018; Jackson SB, et al. *Dig Dis Sci.* 2017; <https://curehht.org/understanding-hht/what-is-hht/medical-summary/>.



Recommended AVM Workup



Pulmonary AVMs (pAVMs)

- All patients should have an **echocardiogram with agitated saline contrast** (“**echo bubble study**”) to screen for pAVMs
- **Repetition necessary** every few years



Brain AVMs (bAVMs)

- All patients should have **brain MRI** to screen for bAVMs
- **If negative, probably do not need to repeat** unless patient develops concerning symptoms



Hepatic AVMs (hAVMs)

- **Liver imaging** (i.e., doppler ultrasound) to screen for hAVMs is controversial but currently recommended

Viteri-Noel A, et al. *J Clin Med.* 2022; Faughnan M, et al. *Ann Intern Med.* 2020; Garg N, et al. *J Blood Med.* 2014.



Jack's Case Continued

- Jack undergoes echo with bubble study, brain MRI, and doppler ultrasound of liver
 - **Two brain AVMs are found**
 - Jack referred to neurology for evaluation
- He continues IV iron therapy, **initially with ferumoxytol**
 - He receives 4 infusions, 510 mg per infusion, administered over 4 weeks
 - Hb: 11.2 g/dL (an improvement from 8.9 g/dL, but suboptimal)
 - **Remains anemic and serum ferritin/TSAT are low = IDA**
- Epistaxis severity: moderate
- Jack's refractory anemia is disproportionate to the severity of his nosebleeds, so he undergoes endoscopy
 - **Reveals telangiectasias throughout stomach and small bowel**
 - **None are actively bleeding, so no intervention is undertaken**



Jack's Case Continued

- Jack feels “a lot better” after receiving IV iron, but lives far from the infusion center
- He asks you...

**Is it possible to
receive more IV iron
with each infusion?**





Second International HHT Guidelines





Iron Deficiency and Anemia

Recommendation #1

The following HHT patients should be **tested for iron deficiency and anemia**:

- All adults, regardless of symptoms.
- All children with recurrent bleeding and/or symptoms of anemia.

Quality of Evidence:

High

(Agreement 98%)

Strength of Recommendation:

Strong

(Agreement 96%)

Faughnan M, et al. *Ann Intern Med.* 2020; <https://www.hhtguidelines.org/anemia>.



Screening for Iron Deficiency in HHT

- CBC, serum ferritin, iron/total iron binding capacity (TIBC), transferrin saturation (TSAT)
- Bleeding, and risk for/severity of anemia, is a moving target
 - Often worsens with age, entering menopause
- Screening interval should always mirror bleeding symptoms
 - ***When in doubt, screen more often at first***
 - Can always space out interval later

Faughnan M, et al. *Ann Intern Med.* 2020; <https://www.hhtguidelines.org/anemia>.



Iron Deficiency and Anemia

Recommendation #2

Iron replacement for treatment of iron deficiency and anemia as follows:

- Initial therapy with **oral iron**
- **IV iron** replacement for when oral is not effective, not absorbed or not tolerated, or for patients presenting with severe anemia

Quality of Evidence:

Moderate

(Agreement 88%)

Strength of Recommendation:

Strong

(Agreement 100%)

Faughnan M, et al. *Ann Intern Med.* 2020; <https://www.hhtguidelines.org/anemia>.



Oral Iron in HHT

- Start with **one pill once daily**
- **35-65 mg of elemental iron**
- If inadequate, but well-tolerated, **go to twice daily dosing**



- Take **in between meals** → 2 hours before or 1 hour after
- Co-prescribe **stool softener**

- If not tolerated, consider another formulation (success unlikely) and/or every-other-day dosing



- Expect **>1.0 g/dL improvement** in hemoglobin (Hb) within **4-6 weeks**
 - **Anything less = clinically insufficient for an HHT patient with IDA**

Faughnan M, et al. *Ann Intern Med.* 2020; <https://www.hhtguidelines.org/anemia>.



IV Iron in HHT

NO

↑Hb by >1 g/dL
within 4-6 weeks?

NO

Normalized Hb and iron
studies (ferritin >100 ng/mL,
TSAT >20%) within ~10 weeks?

YES

Tolerability
a concern?



**Initiate
IV Iron**

- *Low threshold for initiating IV iron in HHT*
- If degree of iron losses are not adequately replaced by diet +/- PO iron, intermittent ongoing IV iron is requisite

Auerbach M, et al. *Lancet Haematol.* 2020; Lopez A, et al. *Lancet.* 2016; DeLoughery TG. *Acta Haematol.* 2019; Faughnan M, et al. *Ann Intern Med.* 2020; <https://www.hhtguidelines.org/anemia>.



IV Iron in HHT

Determine Dose

- Calculate total body iron deficit (using Ganzoni formula)

OR

- Administer 1000 mg empirically and recheck CBC and iron studies after 3-4 weeks



Once Receiving IV Iron

- Monitor serum ferritin, TSAT (Q1-3 months) to determine appropriate infusion interval
- Repeat infusion when serum ferritin <50-70 ng/mL, transferrin saturation <20-25%

- In HHT, **do not wait until patient is iron deficient or anemic again to re-treat**
- **Longitudinal repeat/regular IV iron infusions are usually needed** in HHT

Ganzoni AM. *Schweiz Med Wochenschr.* 1970; Auerbach M, et al. *Lancet Haematol.* 2020; Lopez A, et al. *Lancet.* 2016; Faughnan M, et al. *Ann Intern Med.* 2020; <https://www.hhtguidelines.org/anemia>.

Differentiating IV Iron Products for HHT

Current FDA Labels



| Iron Product | Dosing and Administration | Approved Indications | Common Adverse Drug Effects | Warnings |
|--|---|---|--|---|
| Low-Molecular-Weight Iron Dextran | <ul style="list-style-type: none"> 100 mg daily via IV push over at least 2 minutes Total dose is calculated based on iron deficit May repeat daily | Iron deficiency (ID) in adult and pediatric patients 4 months of age and older for whom oral therapy is unsatisfactory or intolerable | Pruritis, abdominal pain, nausea, vomiting, diarrhea | Black box: risk for anaphylactic-type reactions, including fatalities |
| FMX | <ul style="list-style-type: none"> 510 mg via IV infusion over at least 15 minutes 2nd (510 mg) dose 3–8 days later | Iron deficiency anemia (IDA) in adult patients who have intolerance or unsatisfactory response to oral iron, or who have a diagnosis of CKD | Dizziness, hypotension, constipation, nausea | Black box: fatal and serious hypersensitivity reactions, including anaphylaxis |
| FDI | <ul style="list-style-type: none"> For patient weighing ≥ 50 kg, give 1,000 mg (<i>single dose TDI</i>) over at least 20 minutes For patients weighing <50 kg, give 20 mg/kg in a single dose | IDA in adult patients who have intolerance or unsatisfactory response to oral iron, or who have non-hemodialysis-dependent CKD | Nausea, injection site reactions, rash, hypotension | Hypersensitivity reactions, iron overload |

FDA Prescribing Information.

Differentiating IV Iron Products for HHT

Current FDA Labels



| Iron Product | Dosing and Administration | Approved Indications | Common Adverse Drug Effects | Warnings |
|--------------------------------|---|---|--|---|
| Iron Sucrose | <ul style="list-style-type: none"> 100–400 mg, by setting Doses may be repeated based on clinical response and iron indices | IDA in adult and pediatric patients (2 years of age and older) with CKD | Diarrhea, nausea, vomiting, headache, hypotension, pruritus | Hypersensitivity reactions, hypotension, iron overload |
| FCM | <ul style="list-style-type: none"> For patients weighing ≥ 50 kg, may give 15 mg/kg up to 1,000 mg (<i>single-dose TDI</i>) or 750 mg infusion over at least 15 minutes If 750 mg is given, may be repeated in 7 days, for a total dosage per course of 1,500 mg For patients weighing < 50 kg, give 15 mg/kg in 2 doses, separated by at least 7 days | <p>IDA in patients 1 yo and older who have intolerance or unsatisfactory response to oral iron, and in adults who have non-dialysis-dependent CKD (NDD-CKD)</p> <p>ID in adult patients with heart failure and NYHA class II/III to improve exercise capacity</p> | Nausea, hypertension, hypophosphatemia , flushing | Hypersensitivity reactions, symptomatic hypophosphatemia , hypertension |
| Sodium Ferric Gluconate | <ul style="list-style-type: none"> 125 mg (adults) via IV infusion over 1 hour, per dialysis 1.5 mg/kg in peds Repeated weekly for up to 8 weeks | IDA in patients 6 years old and older who are receiving hemodialysis and supplemental EPO therapy for CKD | Chest pain, leg cramps, dizziness, dyspnea, nausea, vomiting, diarrhea | Hypersensitivity reactions, hypotension, iron overload, benzyl alcohol toxicity |

FDA Prescribing Information.

Differentiating IV Iron Products for HHT

Total Dose Infusion (TDI) Capacity by IV Iron Product



| Iron Product | TDI on the Label | HHT Considerations |
|-----------------------------------|------------------|--|
| Low-Molecular-Weight Iron Dextran | No | Adherence challenges |
| FMX | No | Adherence challenges; notable MRI interference |
| FCM | Yes | <i>Hypophosphatemia risk, especially high in HHT (see product label)</i> |
| FDI | Yes | None beyond mild, transient side effects listed on label |

HHT Guidelines Advise Against*

**Due to high risk for IV iron-induced hypophosphatemia*

FCM, ferric carboxymaltose; FDI, ferric derisomaltose; FMX, ferumoxytol

TDI always preferred in HHT

Faughnan M, et al. *Ann Intern Med.* 2020; Avni T, et al. *Mayo Clin Proc.* 2015; Wang C, et al. *JAMA.* 2015; DeLoughery TG. *Acta Haematol.* 2019; Adkinson NF, et al. *Am J Hematol.* 2018; Abdulrehman J, et al. *Transfusion.* 2019; Glaspy JA, et al. *Adv Ther.* 2021; Auerbach M, et al. *Am J Hematol.* 2021; Wolf M, et al. *JCI Insight.* 2018; Kalantar-Zadeh K, et al. *Am J Hematol.* 2021; Wolf M, et al. *JAMA.* 2020.

Ferric Carboxymaltose (FCM) Label Update

January 3, 2025



HHT formally added to product label as a “possible risk factor” for *FCM-induced hypophosphatemia*:

- “Symptomatic hypophosphatemia with serious outcomes including osteomalacia and fractures requiring clinical intervention has been reported in patients treated with FCM in the post-market setting...*possible risk factors for hypophosphatemia include...hereditary hemorrhagic telangiectasia (HHT)*. Check serum phosphate levels...in any patient who receives a second course of FCM within three months.”

FDA Prescribing Information.



Iron Deficiency and Anemia

Recommendation #3

RBC transfusions in the following settings:

- Hemodynamic instability/shock
- Comorbidities that require a higher Hb target
- Need to increase the Hb acutely, such as prior to surgery or during pregnancy
- Inability to maintain an adequate Hb despite frequent IV iron infusions

Quality of Evidence:

Low

(Agreement 92%)

Strength of Recommendation:

Strong

(Agreement 100%)

Faughnan M, et al. *Ann Intern Med.* 2020; <https://www.hhtguidelines.org/anemia>.



Iron Deficiency and Anemia

Recommendation #4

Consider evaluation for additional causes of anemia if inadequate response to iron replacement:

- **Consider:** folate, B12, MCV, smear, reticulocyte counts, TSH, hemolysis workup
- In **unresolved cases, hematology referral is appropriate**

Quality of Evidence:

Low

(Agreement 100%)

Strength of Recommendation:

Strong

(Agreement 100%)

Faughnan M, et al. *Ann Intern Med.* 2020; <https://www.hhtguidelines.org/anemia>.



Jack's Case Continued

- Jack switched to FCM: 750 mg given over 15 min infusion
- After 2 infusions (7 days apart), Hb normalized to 14.8 g/dL, ferritin 67 ng/mL, and TSAT 24%
- Systemic **bevacizumab, a disease-modifying therapy in HHT**, initiated due to severity of ongoing epistaxis and GI bleeding to reduce chronic blood loss
 - Bevacizumab is successful and IV iron frequency is reduced from **750 mg/month** to **750 mg/every 4 months**
- **With IDA and bleeding improved, Jack resumes working full time**





Summary

- Chronic bleeding in patients with HHT nearly always requires iron supplementation
- Mild bleeding can be addressed with oral iron alone in some cases
 - Limited efficacy and tolerability concerns limit utility for many patients
- **The majority of patients with HHT will require IV iron**
- Patients requiring IV iron once usually need it again and again, so products with TDI capacity should be preferred
- Interval for IV iron infusion is patient-dependent and a moving target



Summary

- Any patient with HHT-associated ID/IDA requiring IV iron should receive 1000-1500 mg IV iron at minimum to replete iron stores
- Clinical pearl: I use a **ferritin of <50 ng/mL** or **transferrin saturation of <20%** as a **trigger for IV iron repletion in non-anemic patients** (i.e., those with ID, not IDA) **with chronic bleeding** (and give ~1000 mg elemental iron at this time)



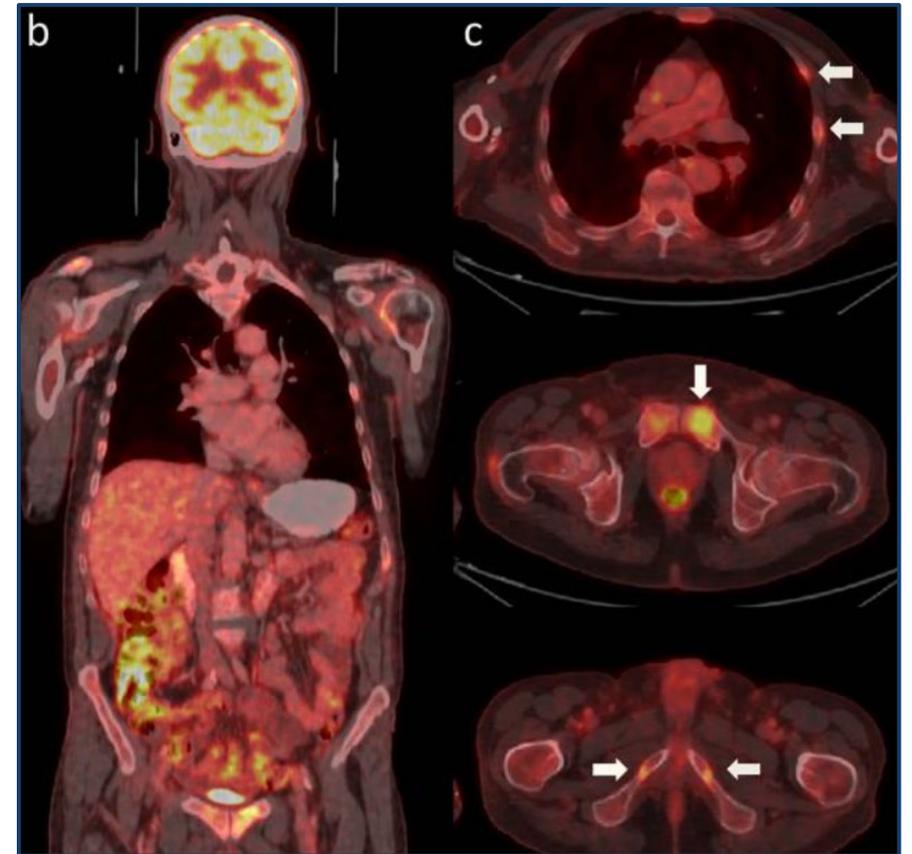
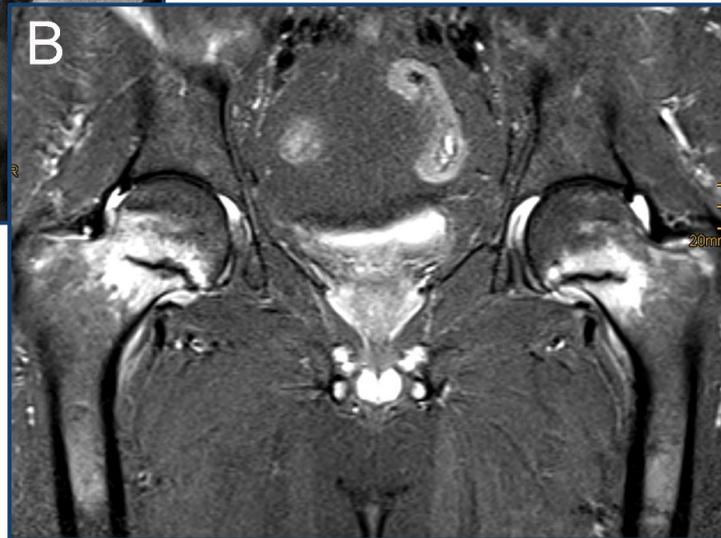
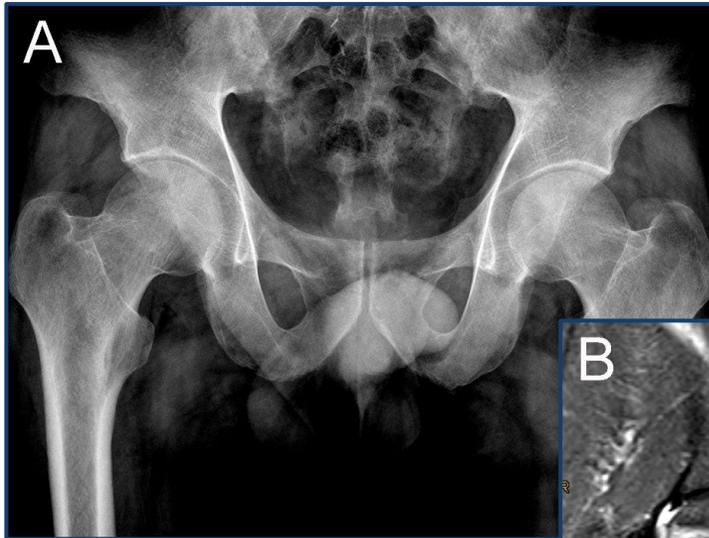
Jack's Case Continued

- 6 months later, Jack returns to clinic: IDA/bleeding still under control and sustained improvements in fatigue and brain fog
- However, he reports **recent-onset bilateral groin pain**
 - Began at work about 2 months ago as a “twinge”
 - Has since gotten progressively worse
- Lab results from recent hospitalization
 - **iFGF23:** 173 pg/mL
 - **Serum phosphate:** 1.8 mg/dL
- **Physical exam:** waddling gait and grimacing with movement
 - Jack's pain is acute, and at times during the exam, quite severe

The care team decides to conduct further testing, including imaging, to elucidate the cause



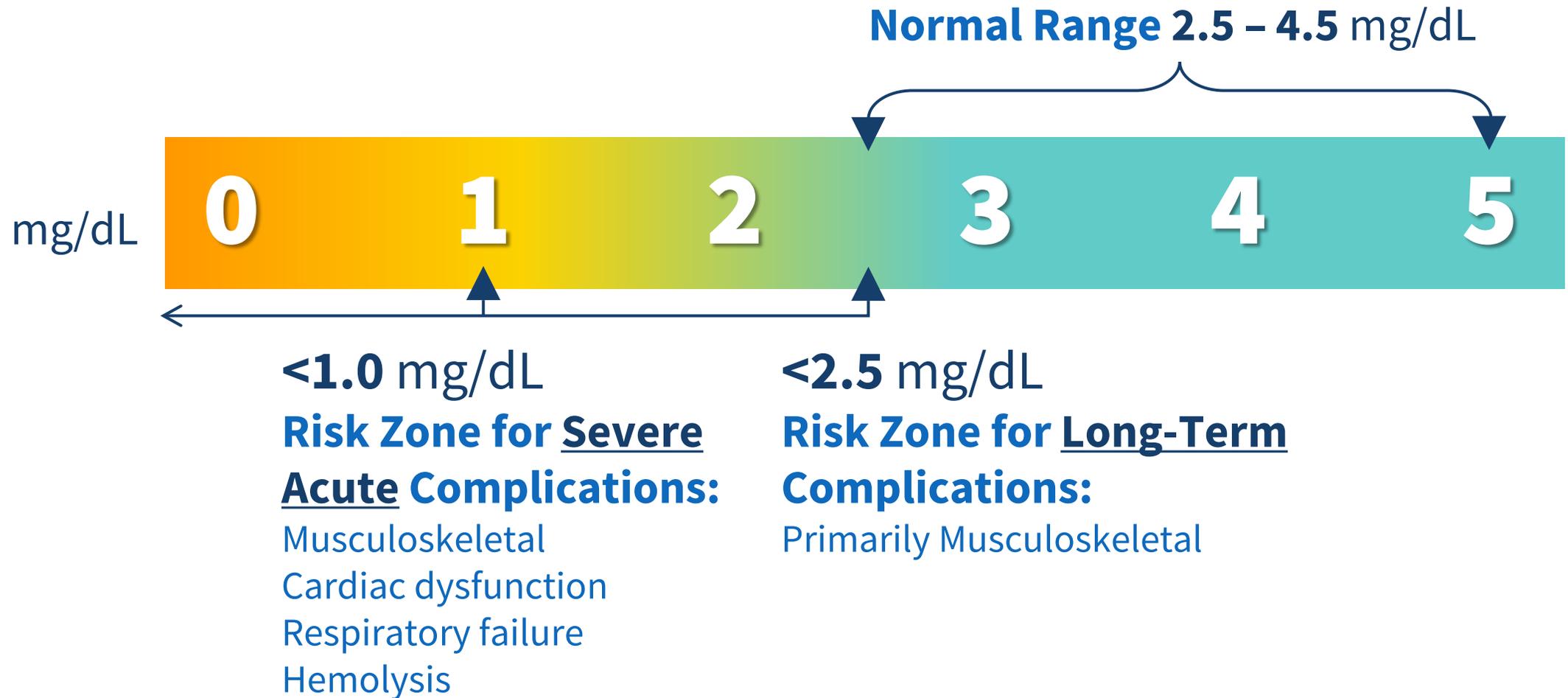
Jack's Imaging Results



Schaefer B, et al, *Gastroenterology*. 2017; Callejas-Moraga EL, et al. *Bone Rep*. 2020.



Hypophosphatemia

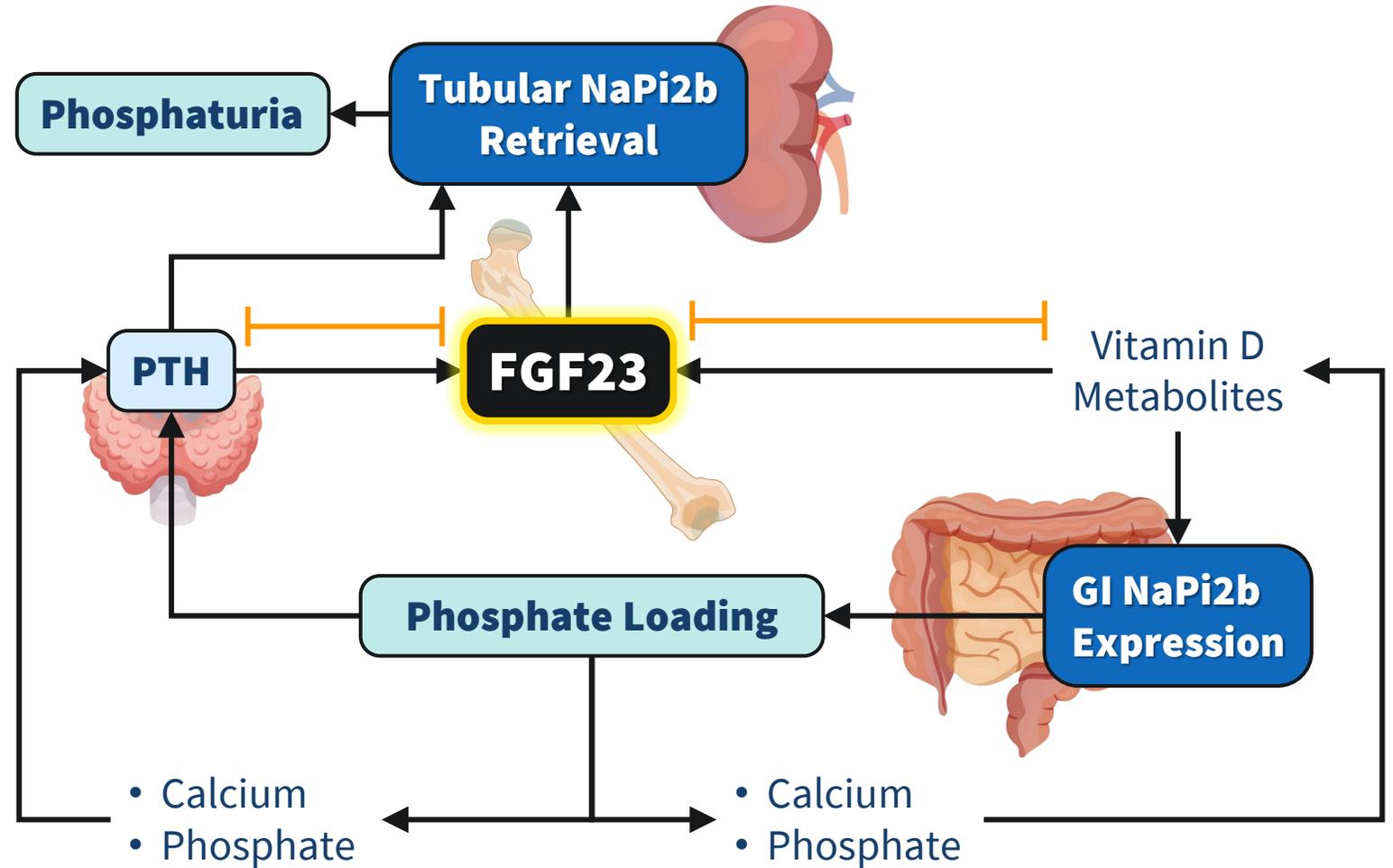


Felsenfeld AJ, Levine BS. *Am J Kidney Dis.* 2012; Kalantar-Zadeh K, et al. *Am J Hematol.* 2021; Glaspy J, et al. *Adv Ther.* 2021.



Fibroblast Growth Factor 23 (FGF23)

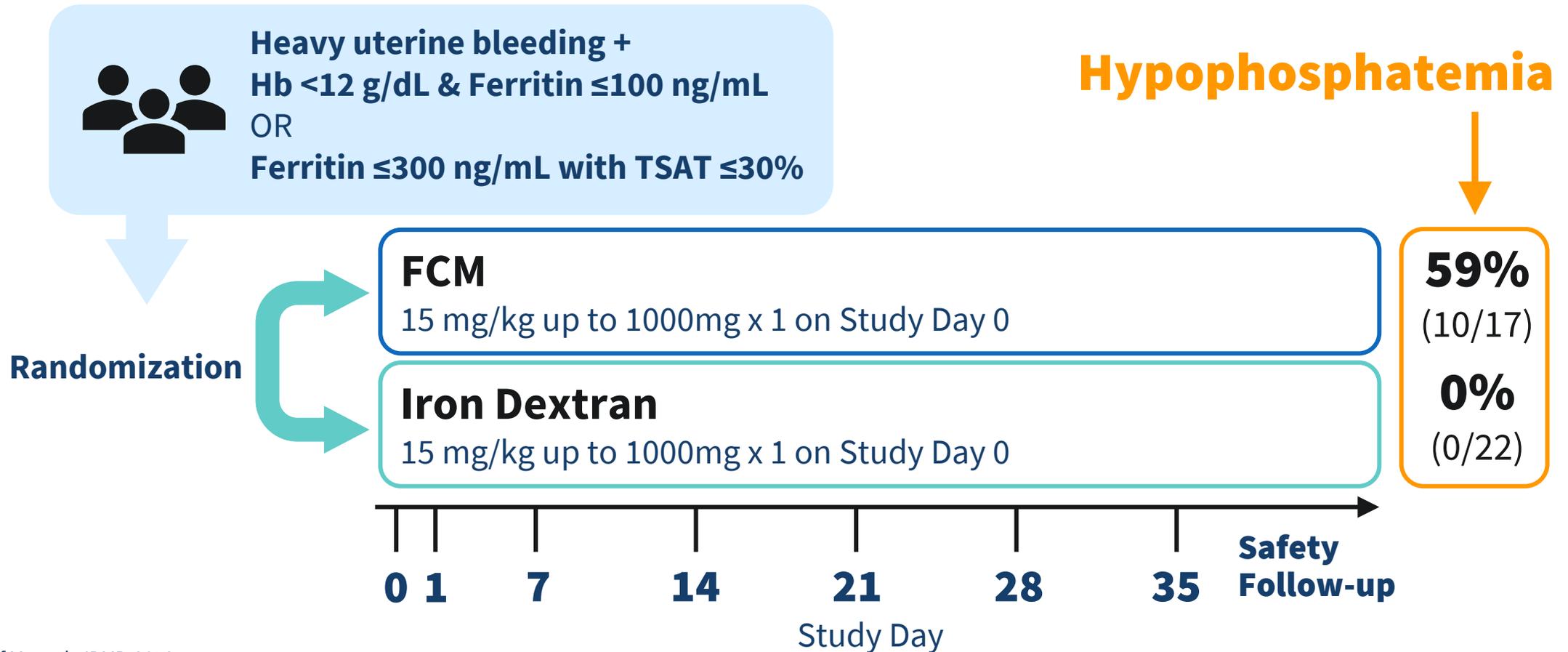
- Increased levels of intact FGF23 (iFGF23) **promote hypophosphatemia** via:
 - Urinary phosphate wasting
 - Reduced dietary absorption of phosphate in the gut
 - Reductions in biologically active vitamin D



Kalantar-Zadeh K, et al. *Am J Hematol.* 2021.



FCM vs Iron Dextran

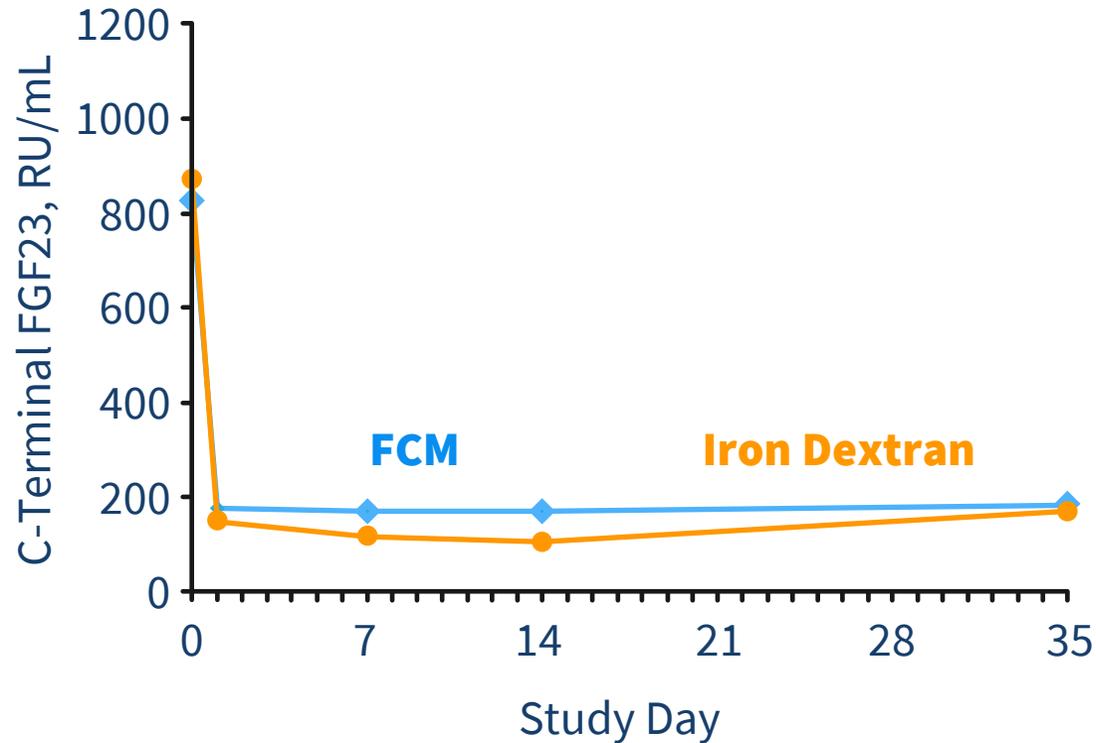


Wolf M, et al. *JBMR*. 2013.

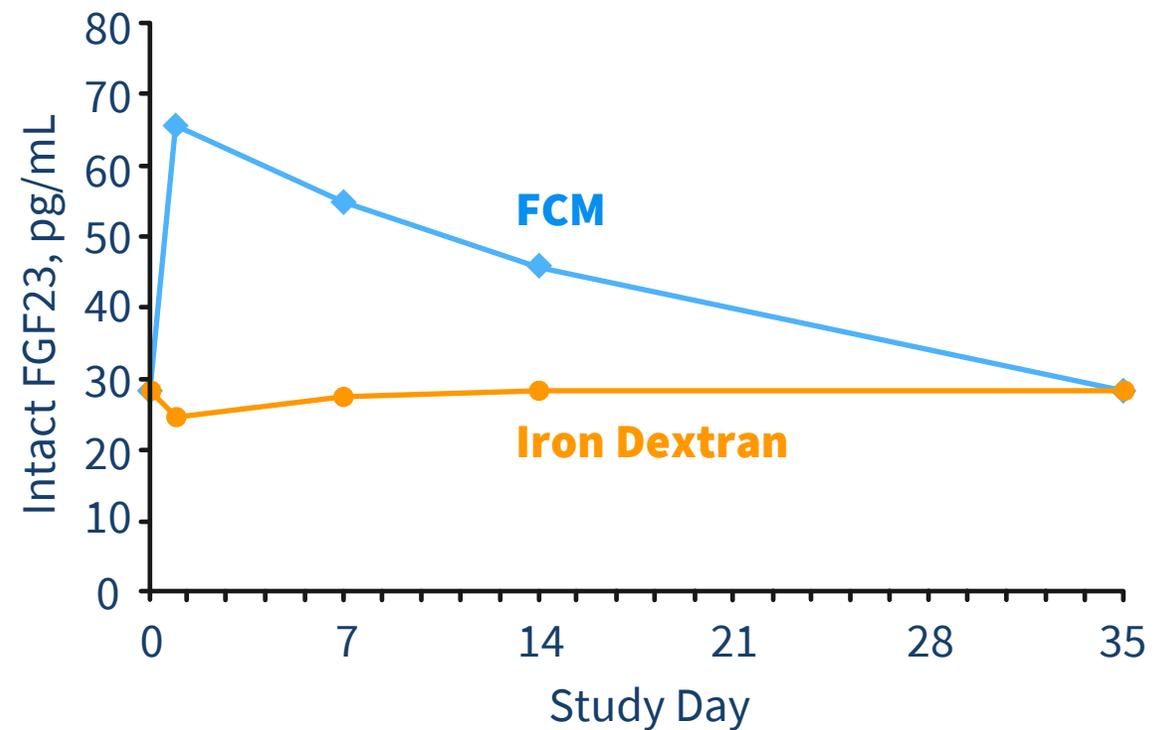


Formative Differential in iFGF23 Levels

cFGF23



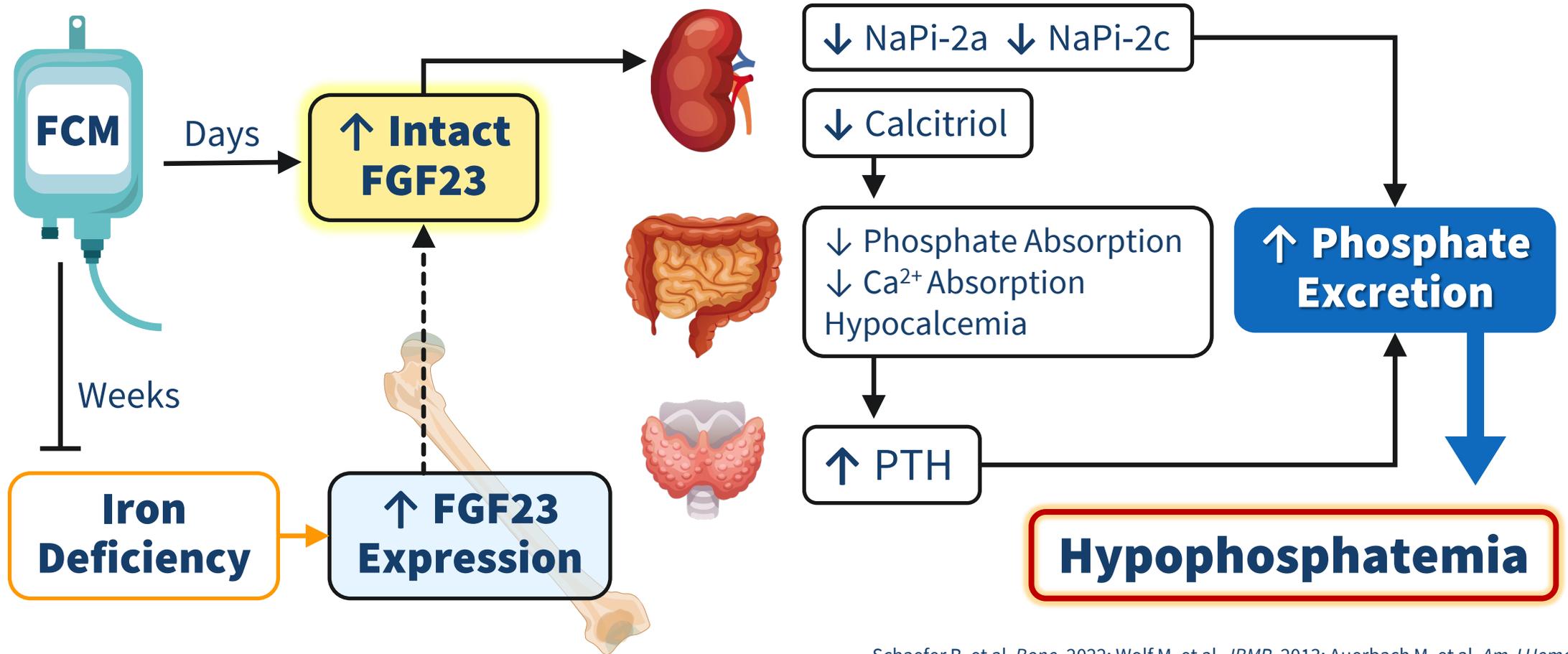
iFGF23



Wolf M, et al. *JBMR*. 2013.



Proposed Mechanism of FCM-Induced Hypophosphatemia



Schaefer B, et al. *Bone*. 2022; Wolf M, et al. *JBMR*. 2013; Auerbach M, et al. *Am J Hematol*. 2021.



The FIRM Trial

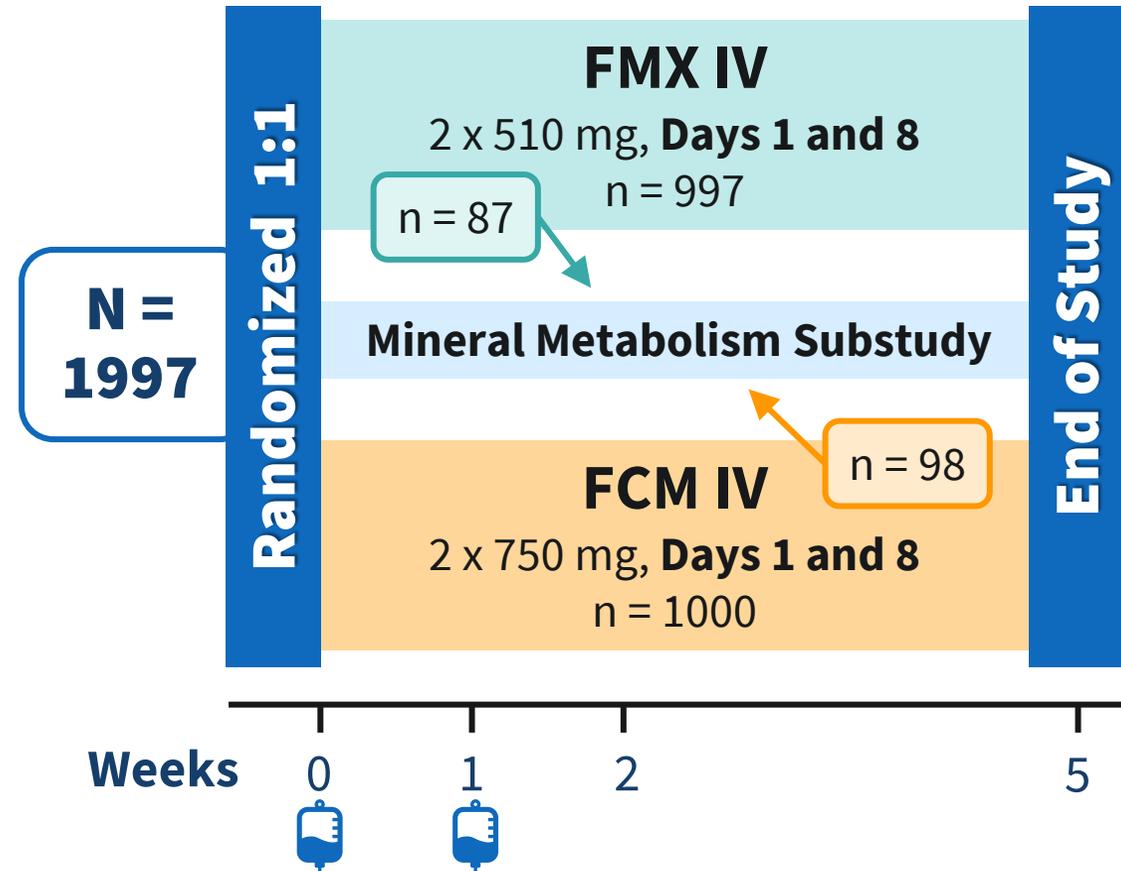
Multicenter, Double-Blinded RCT of Treatment of IDA of Diverse Causes

• Key inclusion criteria

- Adults ≥ 18 years
- **Women:** Hb < 12.0 g/dL
- **Men:** < 14.0 g/dL
- TSAT $\leq 20\%$ or ferritin ≤ 100 ng/mL
- Failed or did not tolerate oral Fe

• Assays: weeks 0, 1, 2, 5

- Serum phosphate & fractional excretion of phosphate (FePi) in all
- **Sub-study:**
 - cFGF23, iFGF23
 - 25D, 1,25D calcium, PTH

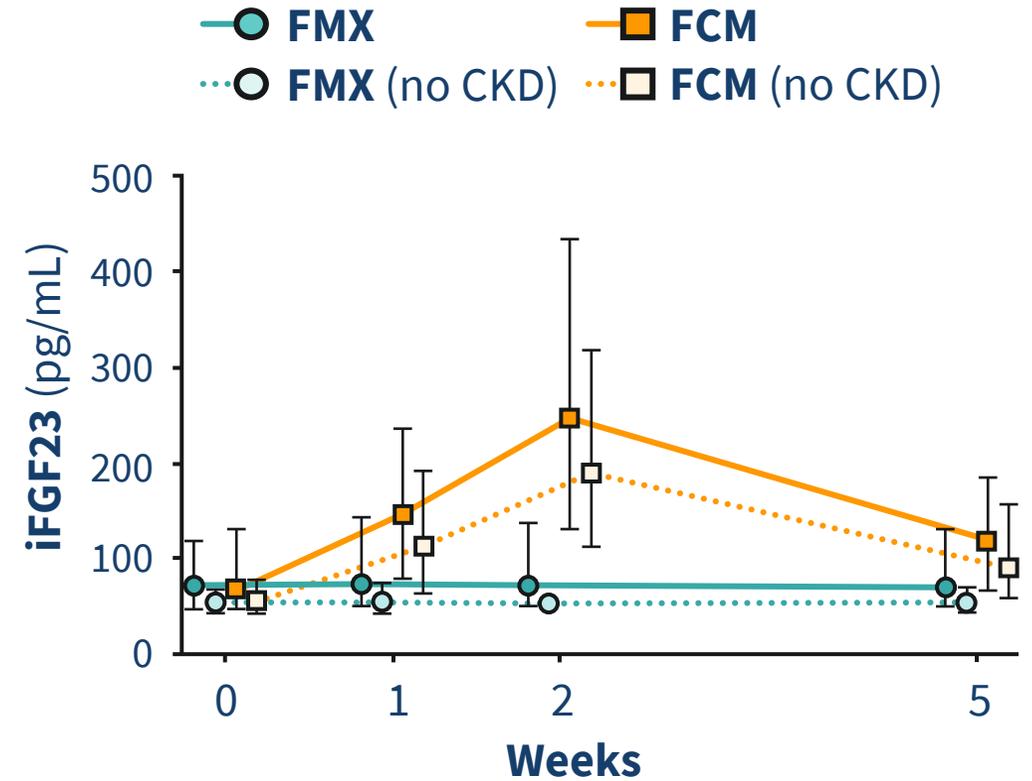
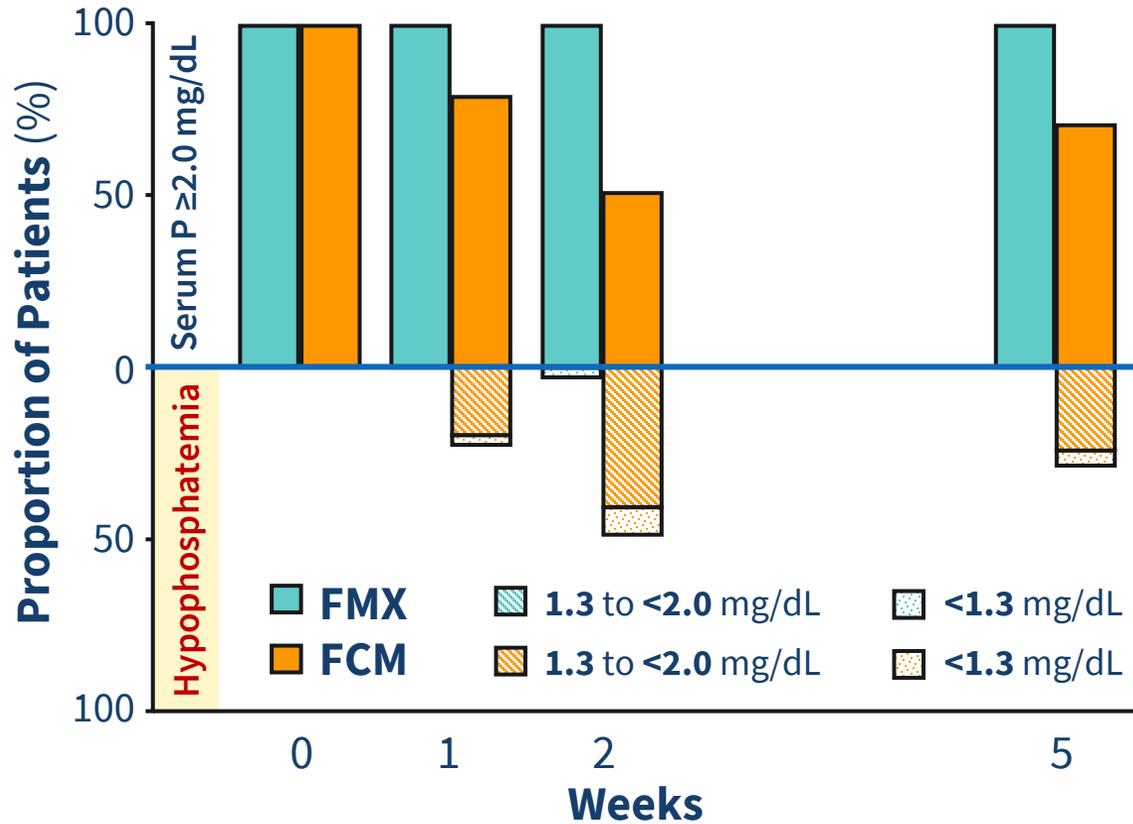


Wolf M, et al. *JCI Insight*. 2018



The FIRM Trial

Primary End Point: Serum Phosphate After IV Iron



Wolf M, et al. *JCI Insight*. 2018

Clinical Risk Factors for Incident and Persistent Hypo-P



| Risk Factor | Incident Hypophosphatemia | | Persistent Hypophosphatemia | |
|--|---------------------------|-------------|-----------------------------|--------------|
| | Odds Ratio | 95% CI | Odds Ratio | 95% CI |
| FCM vs FMX | 250.6 | 115.4-544.5 | 271.4 | 66.5-1-106.7 |
| eGFR, per 10 mL/min/1.73 m ² increase | 1.07 | 1.01-1.13 | - | - |
| Hb, per 1 g/dL increase | 1.24 | 1.12-1.38 | 1.30 | 1.16-1.46 |
| Weight, per 10 kg increase | 0.92 | 0.87-0.97 | 0.79 | 0.73-0.86 |
| Serum phosphate, per 1 mg/dL increase | 0.31 | 0.23-0.41 | 0.24 | 0.17-0.34 |
| Etiology of IDA | | | | |
| Uterine bleeding vs other/unknown | 1.81 | 1.18-2.76 | - | - |
| CKD vs other/unknown | 0.38 | 0.22-0.64 | 0.35 | 0.20-0.62 |
| Black vs White race | - | - | 1.87 | 1.26-2.79 |

Wolf M, et al. *JCI Insight*. 2018



The PHOSPHARE IDA Trials (A&B)

Study Design

- Two identically designed trials
- Adults >18 years with IDA, defined as hemoglobin (Hb) ≤ 11 g/dL, ferritin ≤ 100 ng/mL, eGFR ≥ 65 mL/min/1.73 m², serum phosphate >2.5 mg/dL
- **1:1 randomized patients to receive:**
 - Iron isomaltoside (**IIM**) 1000/**FDI**: single infusion of 1,000 mg on Day 0; **or**
 - **FCM**: FDA-approved dosing schedule: 750 mg on Day 0 & Day 7
- **Overall:**
 - IIM/FDI: n = 125
 - FCM: n = 117
- Collected blood, urine at Days 0, 1, 7, 8, 14, 21, and 35
- **Primary endpoint:** incidence of hypophosphatemia <2.0 mg/dL (<0.65 mmol/L)
- **Other endpoints:** IDA markers, mineral metabolites, safety

Wolf M, et al. *JAMA*. 2020.

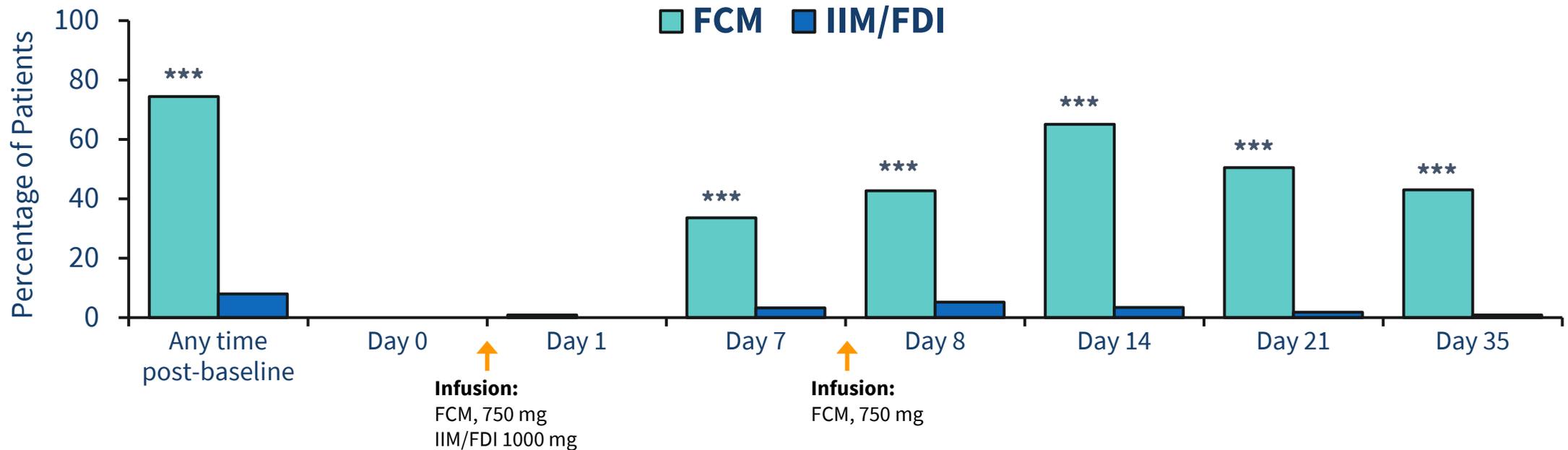


The PHOSPHARE IDA Trials (A&B)

Primary Endpoint: FCM vs. FDI

Incidence of **hypophosphatemia <2 mg/dL**:
IIM/FDI: **8.0%** vs FCM: **74.4%**
P<0.001

Incidence of **severe hypophosphatemia ≤1.0 mg/dL**:
IIM/FDI: **0.0%** vs FCM: **11.3%**
P<0.001



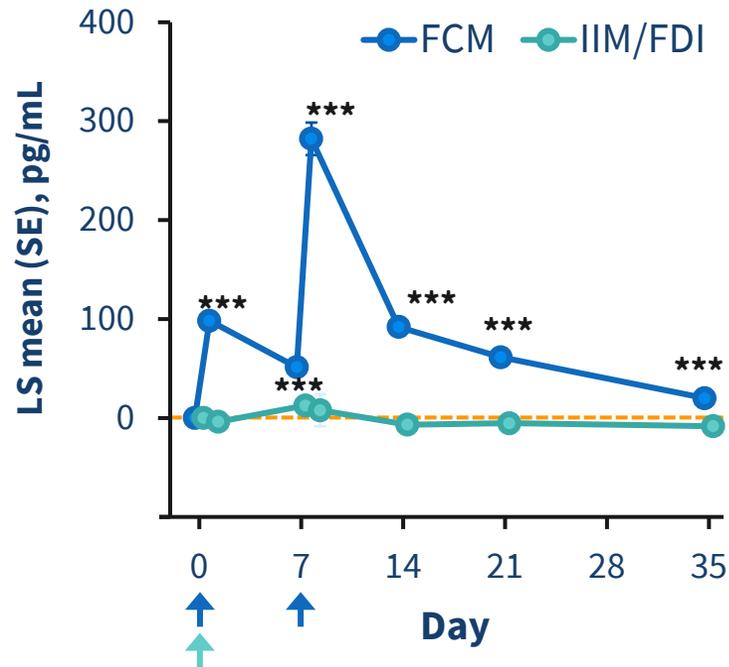
Wolf M, et al. *JAMA*. 2020.



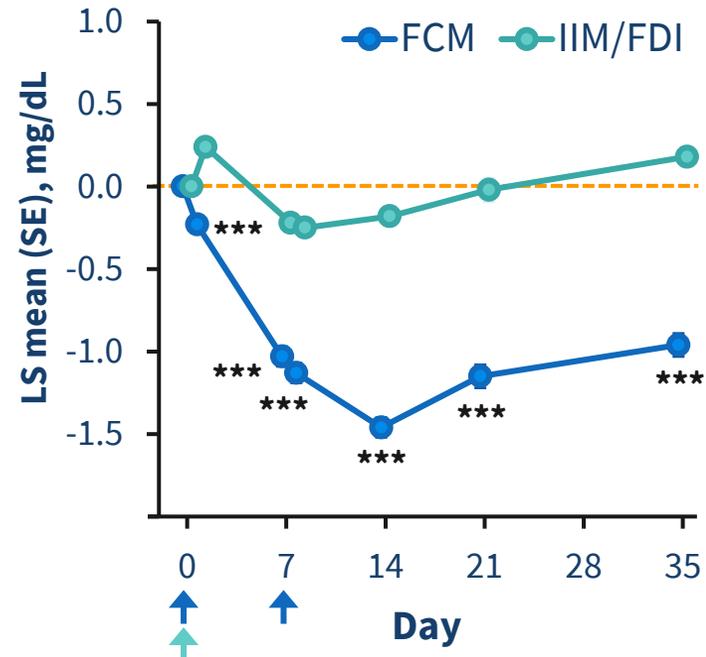
The PHOSPHARE IDA Trials (A&B)

Effects on iFGF23 & Phosphate: FCM vs. FDI

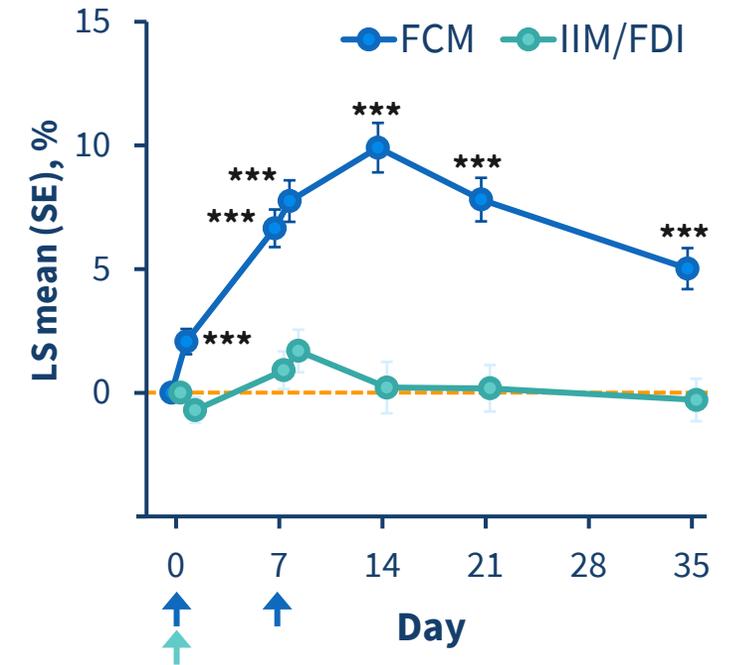
Intact FGF23



Serum Phosphate



Urinary Fractional Excretion of Phosphate



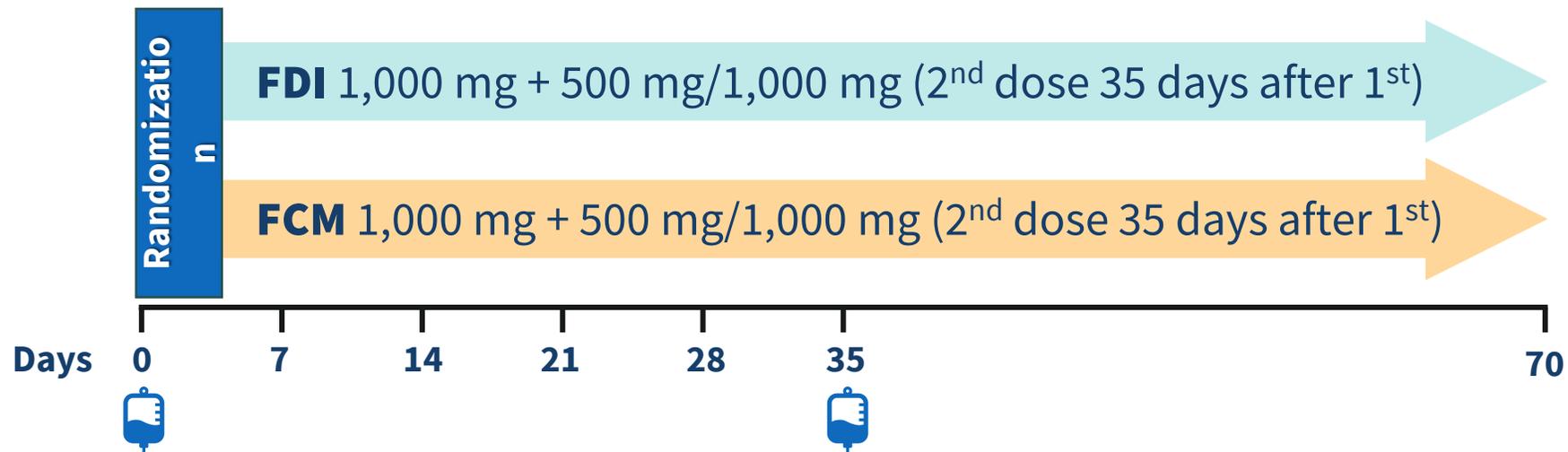
Wolf M, et al. *JAMA*. 2020.



The PHOSPHARE-IBD Trial

Study Design

- Double-blinded RCT of **FDI vs FCM**
- **Inclusion:** Adults >18 years with IDA due to IBD, Hb \leq 13 g/dL, ferritin \leq 100 ng/mL, serum phosphate >2.5 mg/dL, weight >50 kg; **failed oral iron**
- **Required >1000 mg IV iron:** dosing on **Day 0** (1000) & **Day 35** (500-1000)
- **Primary outcome:** Incident hypophosphatemia

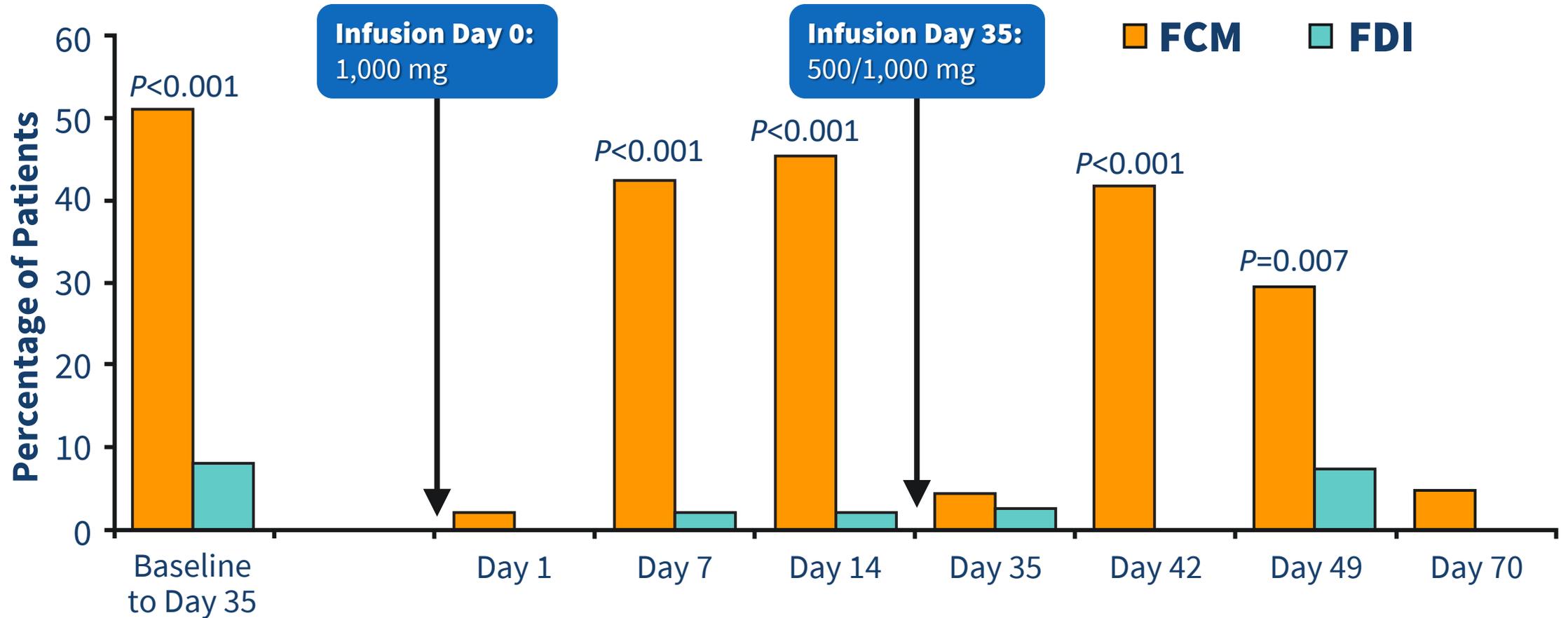


Zoller H, et al. *Gut*. 2023.



The PHOSPHARE-IBD Trial

Primary Outcome: Incident Hypophosphatemia

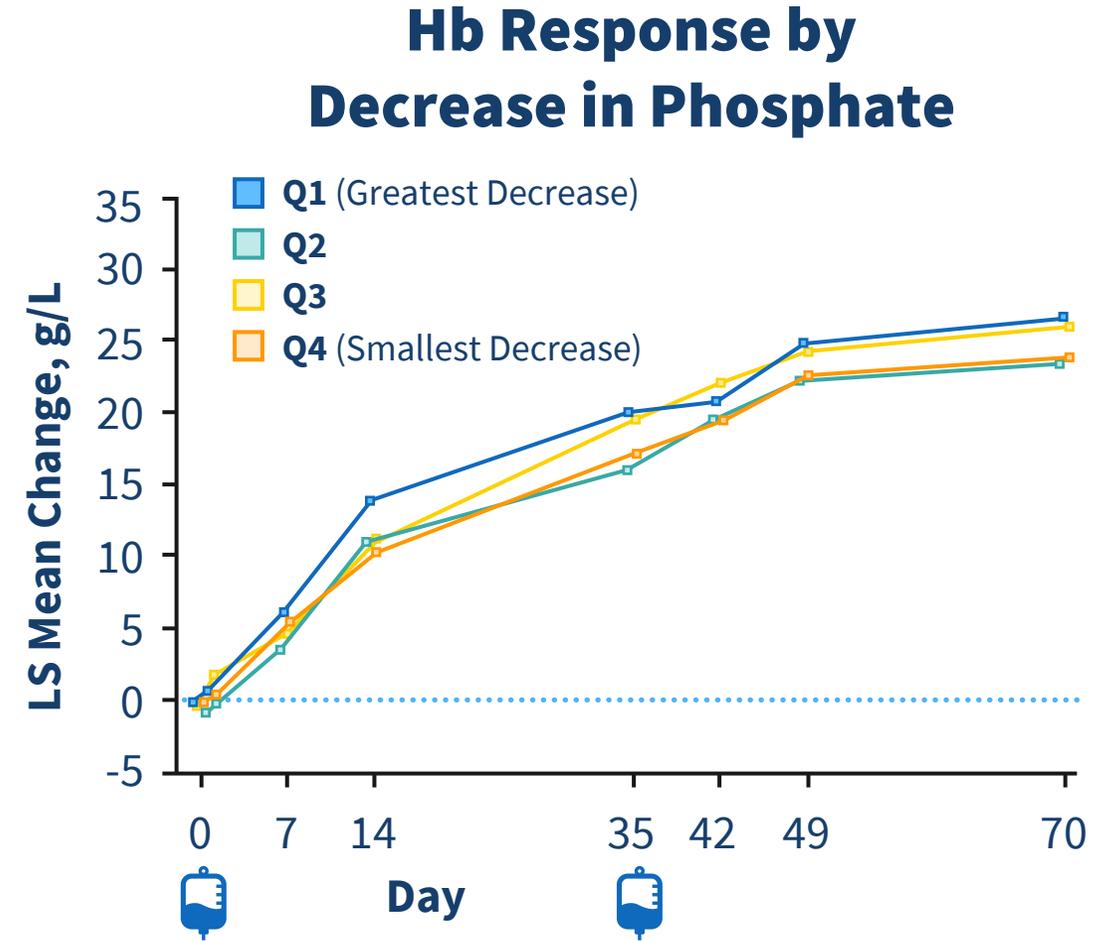
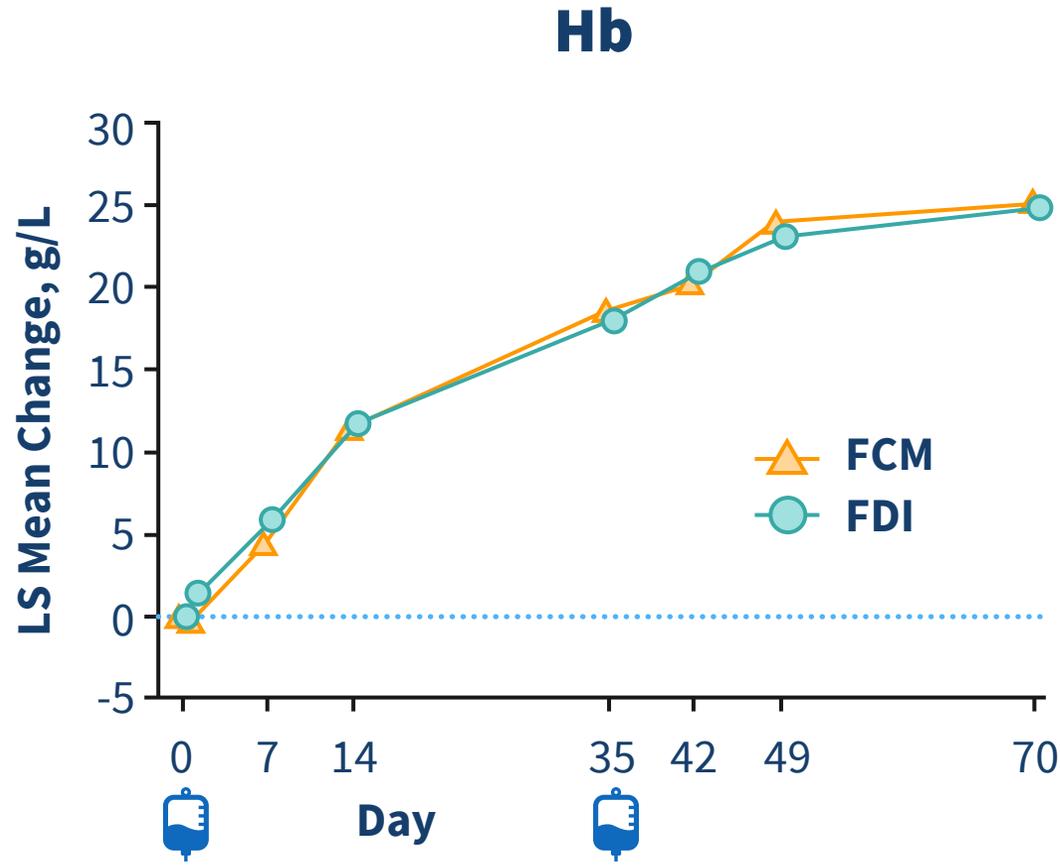


Zoller H, et al. *Gut*. 2023.



The PHOSPHARE-IBD Trial

Secondary Outcome: Hb



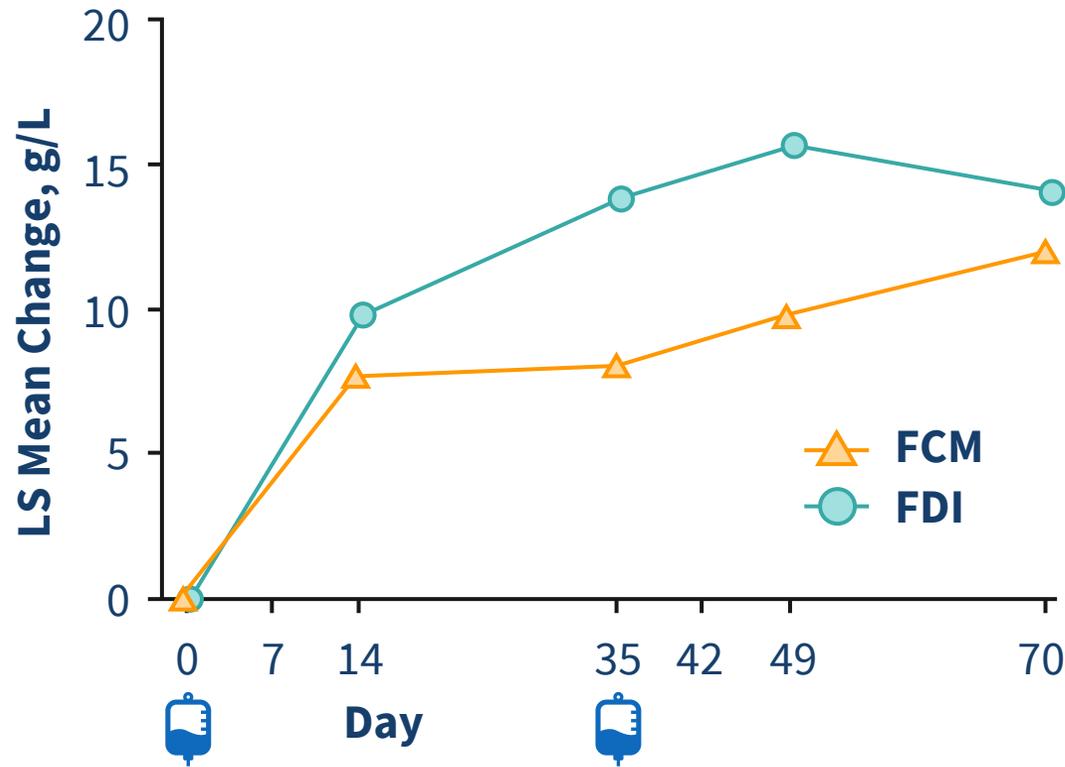
Zoller H, et al. *Gut*. 2023.



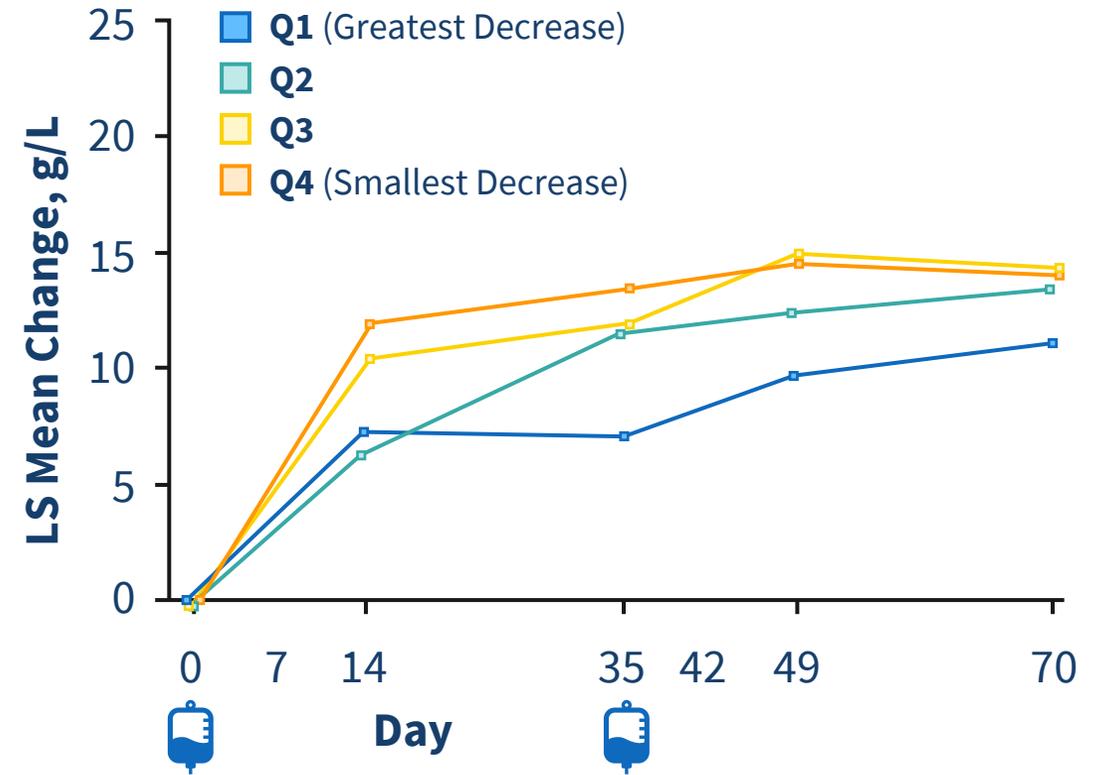
The PHOSPHARE-IBD Trial

Secondary Outcome: Fatigue

FACIT Fatigue Scale Score



FACIT Fatigue Scale Score by Decrease in Phosphate



Zoller H, et al. *Gut*. 2023.

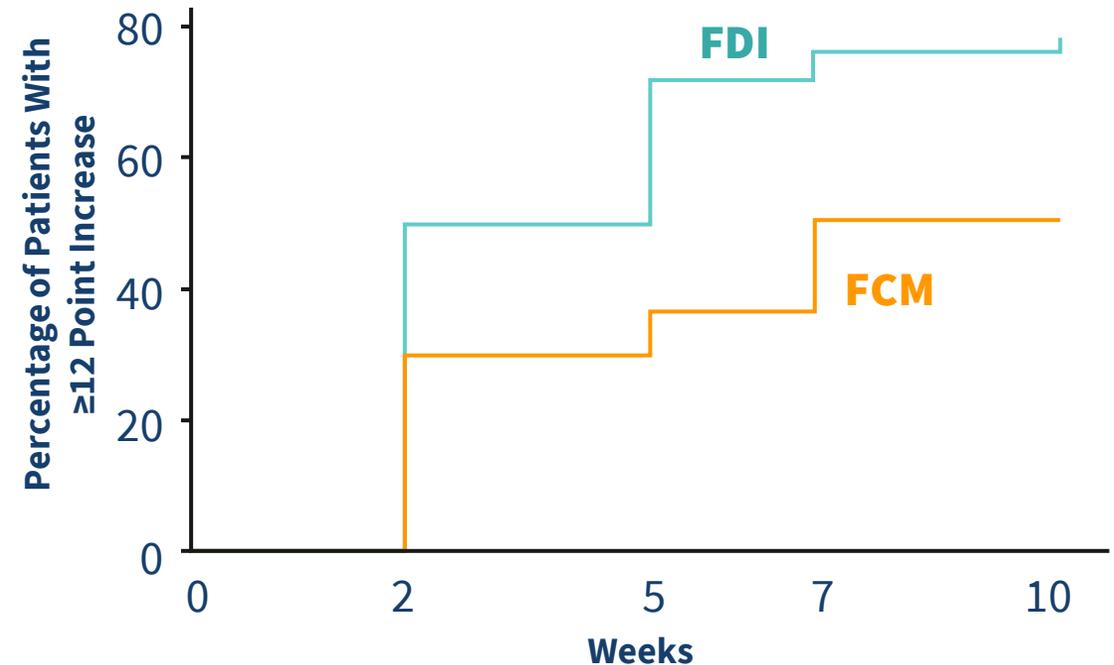


The PHOSPHARE-IBD Trial

Fatigue Subanalysis: Is Hypo-P the Key?

- Percent of patients achieving a **FACIT fatigue scale improvement of ≥ 12 points** at any time during study period:
 - FDI = 78.3% ($P=0.005$)
 - FCM = 48.9%
- **Patients on FDI** were statistically significantly ($P=0.003$) **more likely to achieve FACIT scale fatigue improvements of ≥ 12 points** vs. patients on FCM

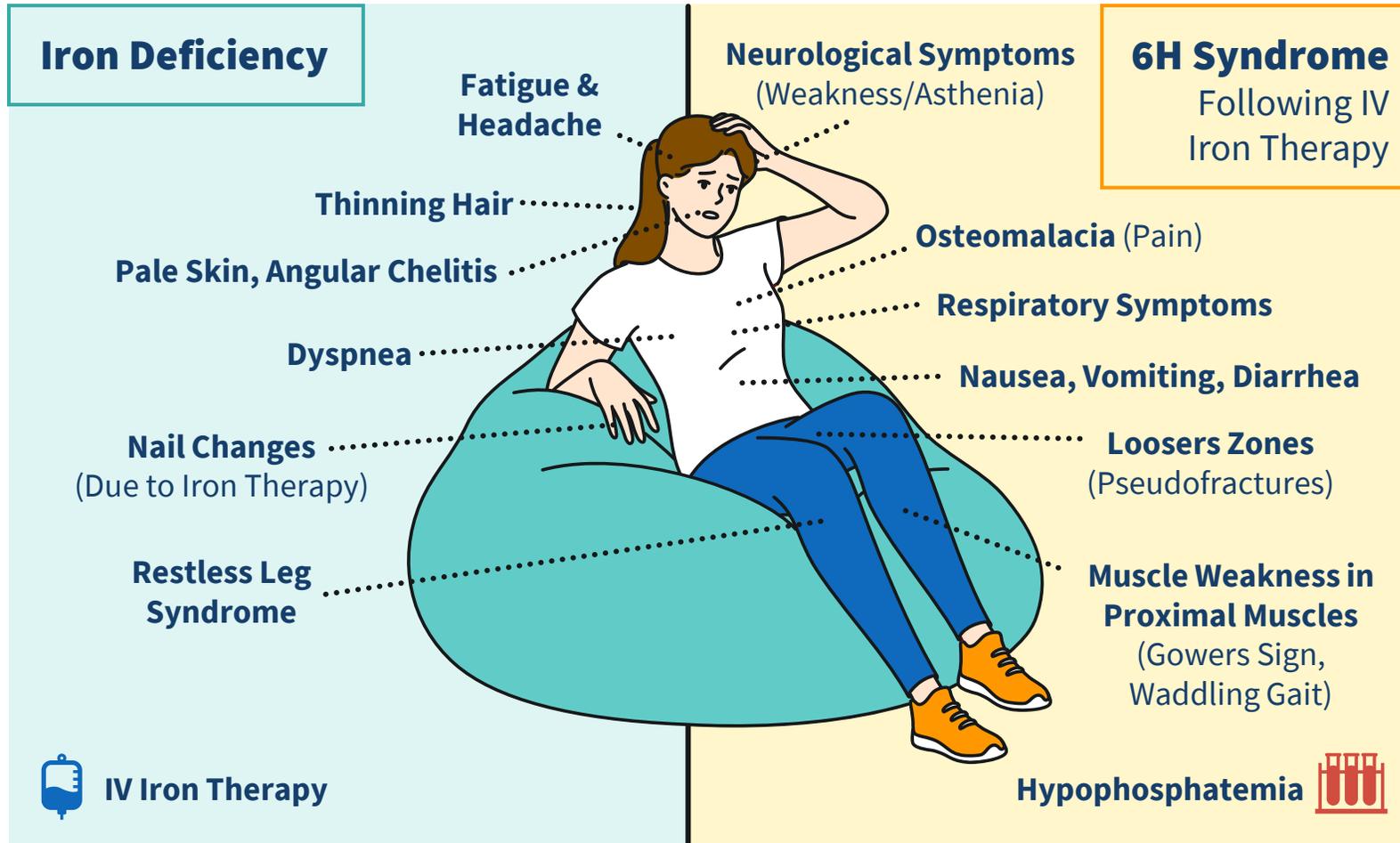
FACIT Fatigue Scale Improvement of ≥ 12 Points



Zoller H, et al. *Gut*. 2023; Mehta AR, et al. *Blood*. 2022.



Why Does Hypo-P Matter?



Pooled Analysis of Symptoms

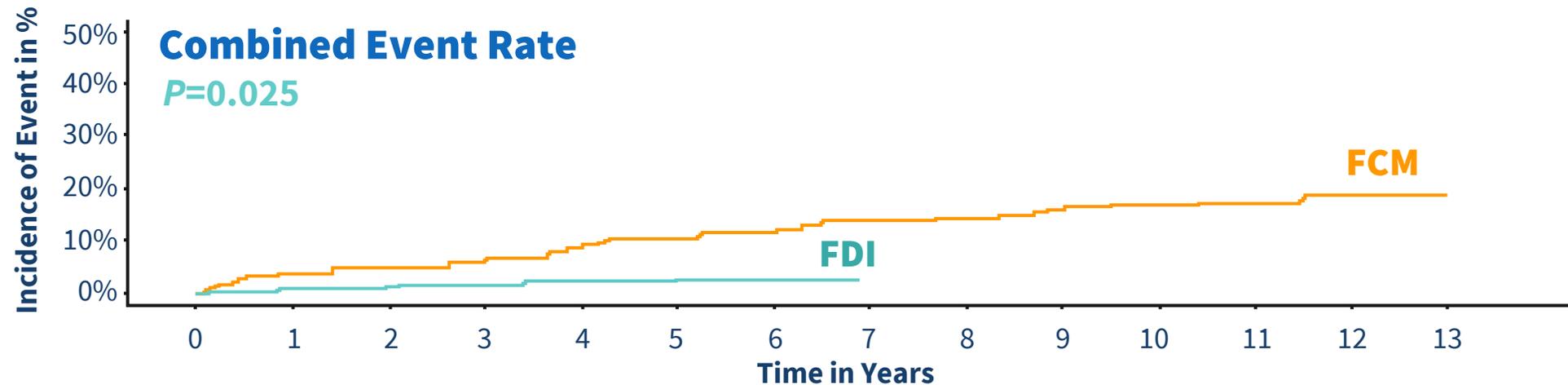
| Symptoms/Complications | Reported in [n] |
|-----------------------------|-----------------|
| General weakness/asthenia | 23/77 |
| Bone pain | 33/77 |
| Muscle pain/weakness | 20/77 |
| Osteomalacia with fractures | 34/77 |
| Gait disturbance | 14/77 |
| Nausea/vomiting/diarrhea | 8/77 |
| Neurological symptoms | 10/77 |
| Respiratory symptoms | 3/77 |

Schaefer B, et al. *Bone*. 2021.



FCM-Associated Fractures? A Closer Look

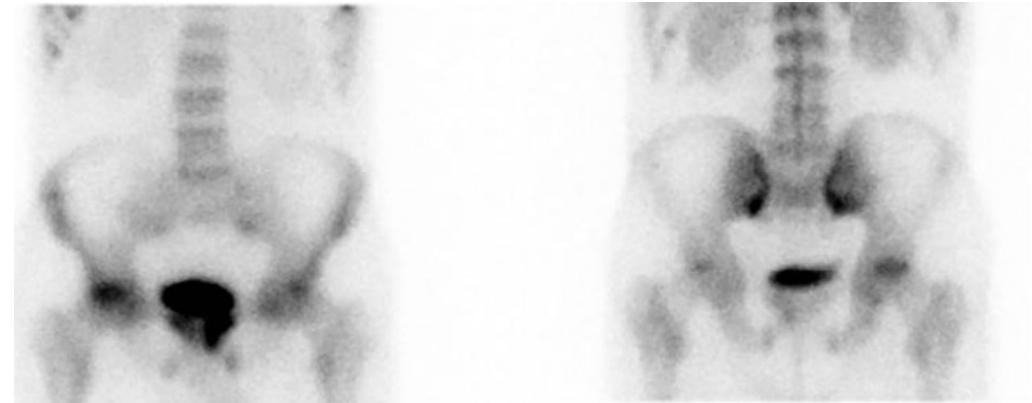
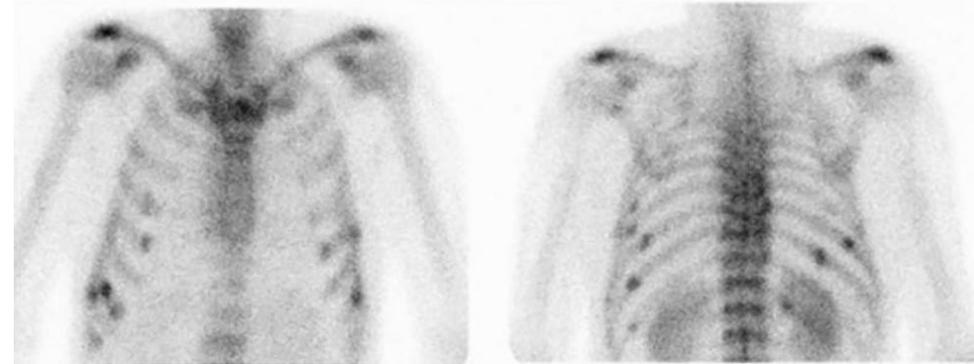
- Retrospective analysis of 289 patients
 - Median follow-up: 5.8 years – FCM vs. FDI
- Evaluated **combined event rate** of:
 - Fractures
 - Radiological signs of osteomalacia
 - Kidney stones
- Combined event rate was **significantly higher with FCM** vs. FDI ($P=0.025$)
- Specific to **fracture risk**, the **HR for FCM was 4.54 relative to FDI** ($P=0.04$)



Zoller H, et al. *ASH*. 2023. Poster #3838; Schaefer B, et al. *Bone*. 2021; Schaefer B, et al. *Br J Clin Pharmacol*. 2021.

Real-World Impact of FCM-Induced Hypo-P in HHT

- 65-year-old man with HHT
- Monthly FCM infusions x 2 years
- Reported chronic, progressive bone pain, worsened by movement
- Labs
 - **Phosphate:** 1.2 mg/dL
 - **C-terminal FGF23:** >3x ULN
- **Diagnosis:** FGF23-mediated hypophosphatemic osteomalacia with diffuse insufficiency fractures
- **Treatment:** PO phosphate supplementation, PO calcium/vitamin D, switched FCM to iron sucrose
- **Clinical Outcome:** pain and mobility limitations resolved; labs normalized

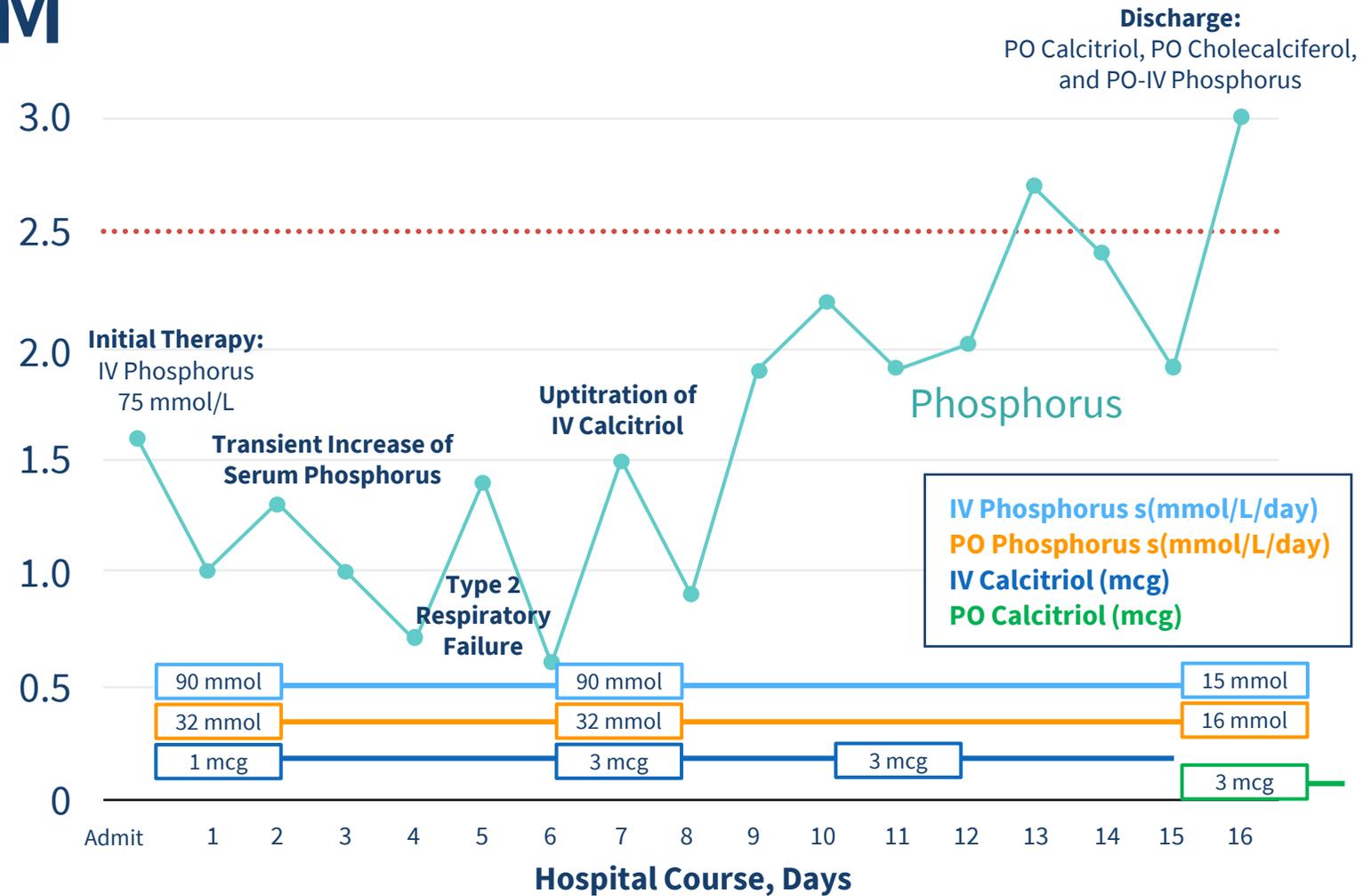


Callejas-Moraga EL, et al. *Bone Rep.* 2020.



Severe Hypophosphatemia After 1 Course of FCM

- 28-year-old woman
- Fatigue, muscle weakness, palpitations 2 weeks PTA
- Uterine bleeding → IDA
- FCM, 750mg x 2 doses 8 weeks PTA
- Presented with: hypophosphatemia, renal phosphate wasting
- Rx: PO, IV phosphate; 1,25D
- **Acute respiratory failure on day 7: serum phosphate 0.6**



Vasquez-Rios G, et al. *Nefrologia*. 2021.



FCM-Induced Hypo-P: The Latest Data

Magagnoli J, et al. *Am J Hematol.* 2025

- Systematic review of IV FCM
 - Comprising clinical trials, observational databases, and meta-analyses
 - FAERS data
- Findings:
 - Hypo-P rates = 50-92% with FCM (vs. 2-8% with other IV iron products)
 - FCM-induced hypo-p is a clinically important adverse events
 - Weakness
 - Fatigue
 - Bone/muscle pain
 - Osteomalacia
 - Fractures
- Recommendations:
 - FCM label updates are warranted
 - Serum phosphate monitoring prior to all doses
 - If hypo-p detected, stop FCM
 - Consider other IV products with lower rates of hypo-p

Outcome counts by Received Year

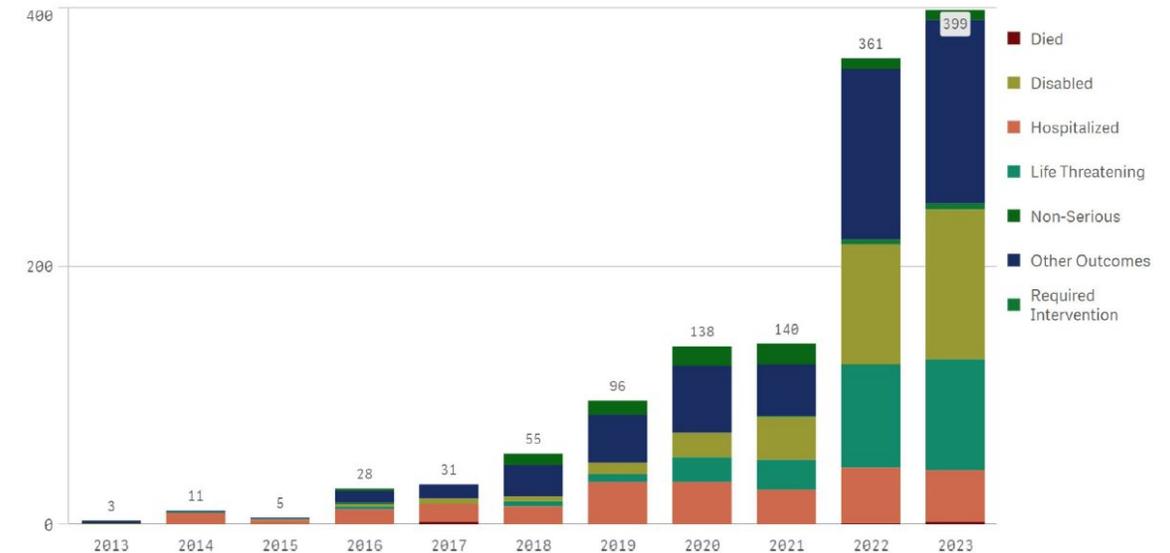


FIGURE 2 | Case report of FCM-associated HPP reported to FDA between 2014 and 2023.

Magagnoli J, et al. *Am J Hematol.* 2025; Auerbach M, Wolf M. *Am J Hematol.* 2025.



Managing IV Iron-Induced Hypo-P

Iron deficiency with impaired absorption or intolerance/
inadequate response to oral iron

- Evaluate/correct underlying etiology
- Start IV iron repletion therapy

Any of the following risk factors present?

- Severe iron deficiency (ferritin <10 ng/mL)
- Lower body weight
- Lower baseline serum phosphate level
- Abnormal uterine bleeding
- Need for repeat doses of IV iron

NO

YES

Assess institution-specific resources
and IV iron formulation availability

Non-FCM formulation available?

NO

YES

Repeat serum phosphate at
day 7 prior to second infusion

Phosphate >2.0 mg/dL

Phosphate ≤2.0 mg/dL

**Proceed with 2nd
infusion of IV FCM**

- **Avoid 2nd dose**
- Management based on symptoms
and severity of hypophosphatemia

Avoid IV FCM if alternate formulations available

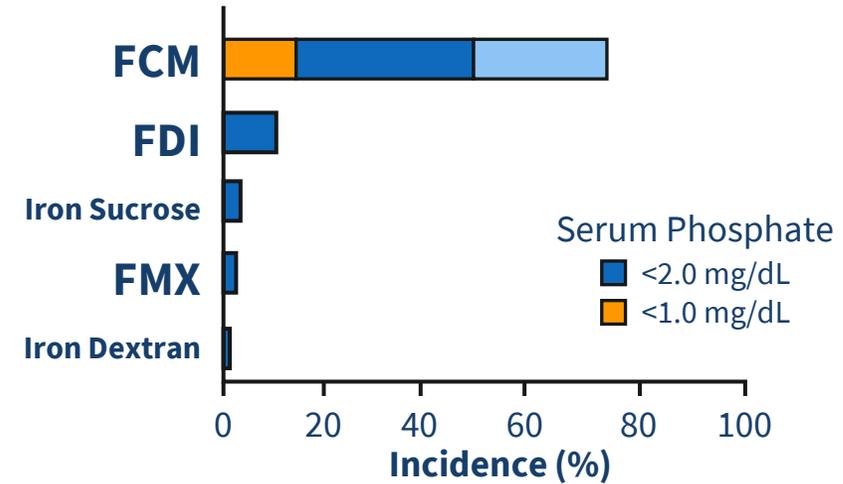
Martens KL, Wolf M. *Am Soc Hematol*. 2023.



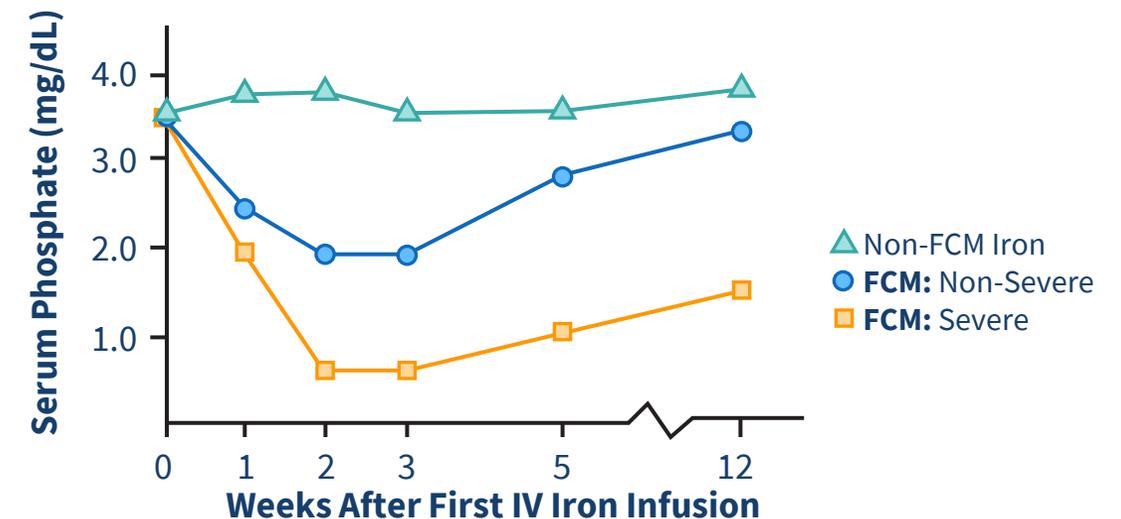
Summary

- **HHT patients are at an elevated risk for IV iron-induced hypophosphatemia because of repeated, longitudinal infusion needs**
- This risk is greatest with FCM
- IV iron-induced hypophosphatemia is **challenging to diagnose and treat**
 - Overlapping signs and symptoms with ID/IDA: fatigue, asthenia, lethargy, weakness, dyspnea
- Key Points in Management
 - Repletion strategies are ineffective due to renal leak
 - Repletion strategies stimulate FGF23 → worsens leak
 - **Primary prevention is best approach**

Incidence & Severity of Hypophosphatemia by IV Iron Formulation



Time Course of FCM-Induced Hypophosphatemia



Martens KL, Wolf M. *Am Soc Hematol*. 2023.



Jack's Case Conclusion

- Jack is diagnosed with IV iron-induced hypophosphatemic fractures
- You start oral phosphate, daily calcium + vit D tablet; his bevacizumab therapy is continued
- **You discontinue FCM and begin FDI 1,000 mg given over at least 20 minutes**
- After labs normalize and fractures heal, Jack returns to work and **continues IV FDI infusions every 4 months** for long term management of his HHT-associated IDA





Jack's Case Conclusion

The Collaborative Imperative in HHT

- *Multisystem nature of HHT requires interprofessional and multidisciplinary team-based care strategies*
- Jack's case is an illustrative example
 - Multidisciplinary collaboration
 - Primary Care
 - Hematology (+/- hem/onc)
 - Pulmonology
 - Radiology/Interventional Radiology
 - Gastroenterology
 - Otorhinolaryngology
 - Interprofessional collaboration
 - Physicians
 - Nurses/NPs/PAs
 - Pharmacists



Kritharis A, et al. *Haematologica*. 2018; Faughnan M, et al. *Ann Intern Med*. 2020; <https://www.hhtguidelines.org>.



Post-Test and Activity Evaluation



Take the Activity Post-Test and Evaluation
using this QR code (or by visiting
[https://form.jotform.com/AcademyCME/
25CHHT2Post](https://form.jotform.com/AcademyCME/25CHHT2Post))

Challenging the Status Quo in Hereditary Hemorrhagic Telangiectasia:



A Comprehensive Review of IV Iron Best Practices at the Hematology-Primary Care Interface



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