

# Evaluating the Impact of IV Iron on Bone Health



Expert Perspectives on Best Practices for Safely and Effectively Treating ID and IDA with IV Iron



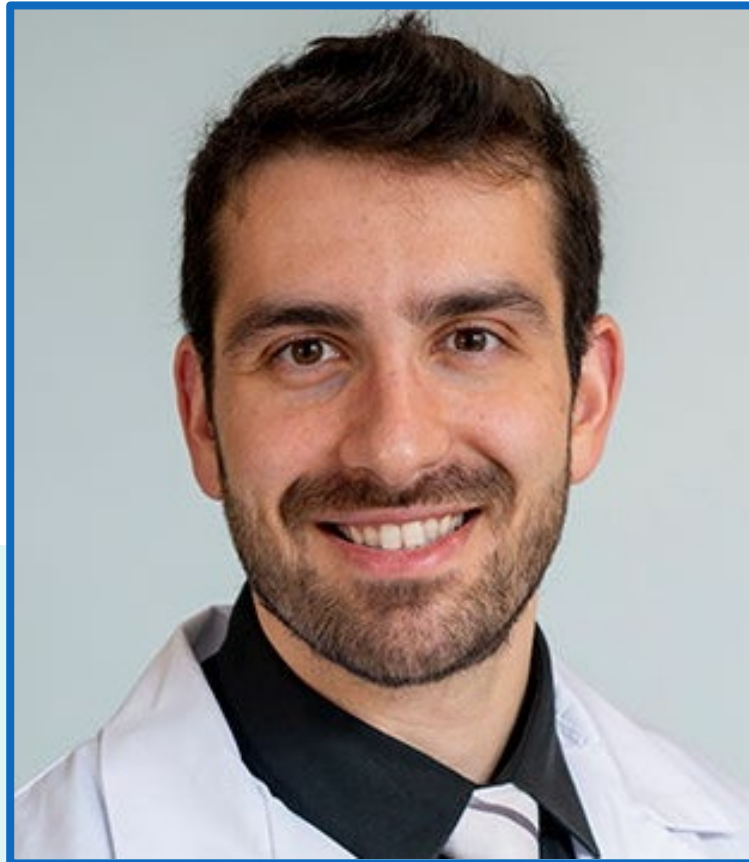
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# Faculty Information and Disclosures



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## Disclosures

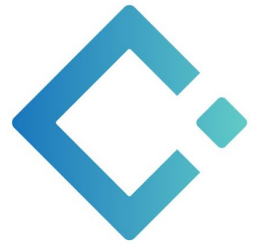
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# Learning Objectives

- Examine the comparative clinical utility of oral iron and intravenous (IV) iron for patients living with ID or IDA, irrespective of etiology, according to current expert consensus and real-world experience.
- Evaluate the relative risk and underlying molecular mechanisms associated with IV iron-related bone complications, including an increased rate of fractures.
- Recognize HHT disease manifestations, with a focus on chronic bleeding, resultant iron deficiency (ID) and iron deficiency anemia (IDA), and the effects of ID/IDA on clinical and patient-reported endpoints.
- Summarize current and emerging HHT guideline recommendations, highlighting the central role of IV iron in treating HHT-associated ID/IDA and the implications of bone compromise in this setting.
- Collaborate with your multidisciplinary team to develop safe, effective, and individualized treatment plans for patients living with ID or IDA using IV iron.



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# The IV Iron Imperative

**Iron Deficiency, Anemia, and the Impetus for IV Iron Replacement**

# The Age Old Mantra: “Start with Oral Iron, and if Not Adequate, Move to IV Iron”...*is this Really Correct in Modern Times?*



- 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**



# Though Nuanced, IV Iron Has Clear Benefits

- Numerous RCTs demonstrate **superiority of IV iron in successfully treating** iron deficiency and iron deficiency anemia in patients of all types.
  - Meta-analyses with thousands each of general population IDA, IBD, pregnant women, heart failure, etc. ***all demonstrate this clearly.***
- The same conclusions were made about tolerability: **IV iron is better tolerated than PO iron.**

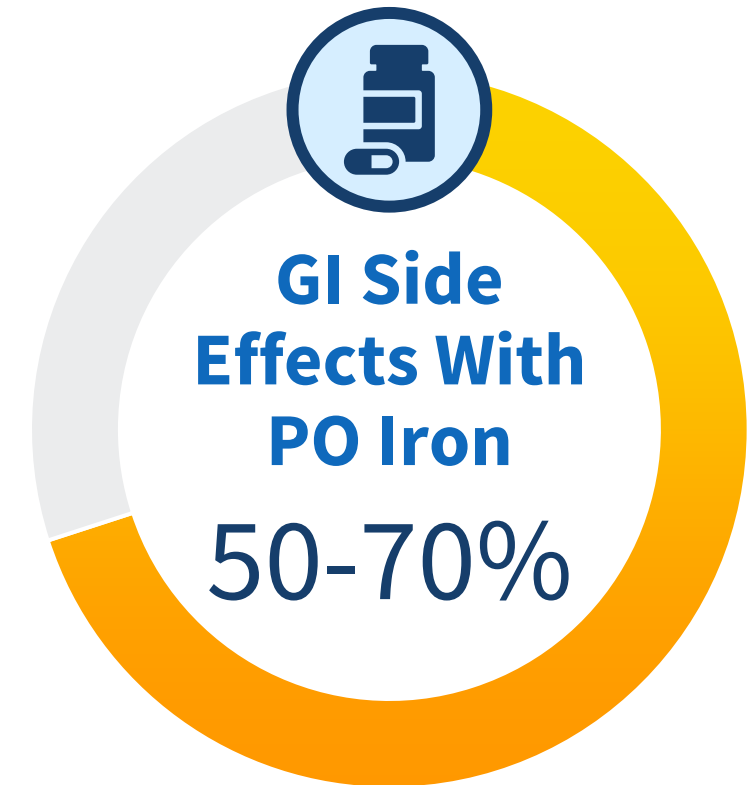


Tolkien Z, et al. *PLoS One*. 2015; DeLoughery T, et al. *Acta Haematol*. 2019; Pantopoulos K. *Haematologica*. 2024; Zhao C, et al. *Biomed Rep*. 2025; Alharbi B, et al. *Cureus*. 2025; Sultan P, et al. *Am J Obstet Gynecol*. 2019; Pandey A, et al. *Sci Rep*. 2024; Patel M, et al. *Cureus*. 2025.



# Understanding the Limitations of Oral Iron

- **90%+ of PO iron goes unabsorbed** and causes irritation and inflammation in the intestines.
- Constipation, nausea, vomiting, abdominal pain, diarrhea, heartburn.
- **Strategies to reduce side-effects** (taking with food, alternate day dosing) → **might also reduce efficacy.**
- Meta-analysis of Oral Ferrous Sulfate vs. either placebo or IV iron, 6831 patients.
  - **Odds ratio of GI adverse events 2.32 vs placebo, 3.05 vs IV iron.**
  - Subgroups of patients with IBD and pregnant women had similar findings.
  - No association between dose of oral iron and likelihood of side-effects (***any oral iron was enough to cause them***).

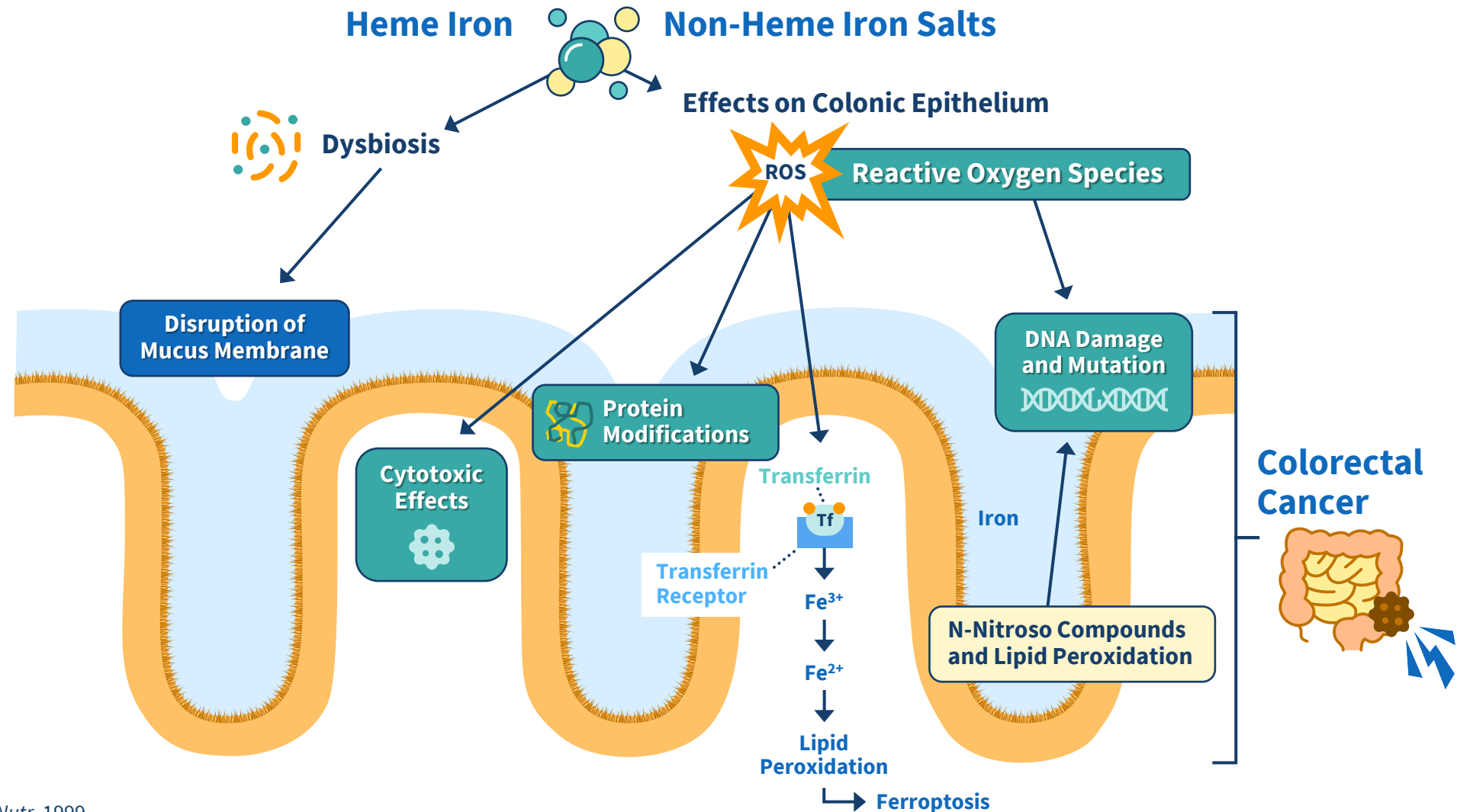


Tolkien Z, et al. *PLoS One*. 2015; DeLoughery T, et al. *Acta Haematol*. 2019; Pantopoulos K. *Haematologica*. 2024.

# Oral Iron and the Risk of Colorectal Cancer



- Concerning evidence  
→ **PO iron significantly increases potential risk of colorectal cancer.**
  - Postulated mechanism  
→ increased free radical generation in gut lining; disrupts gut microbiota.
  - Similar hypothesis as to why red meat intake increases colorectal cancer risk.

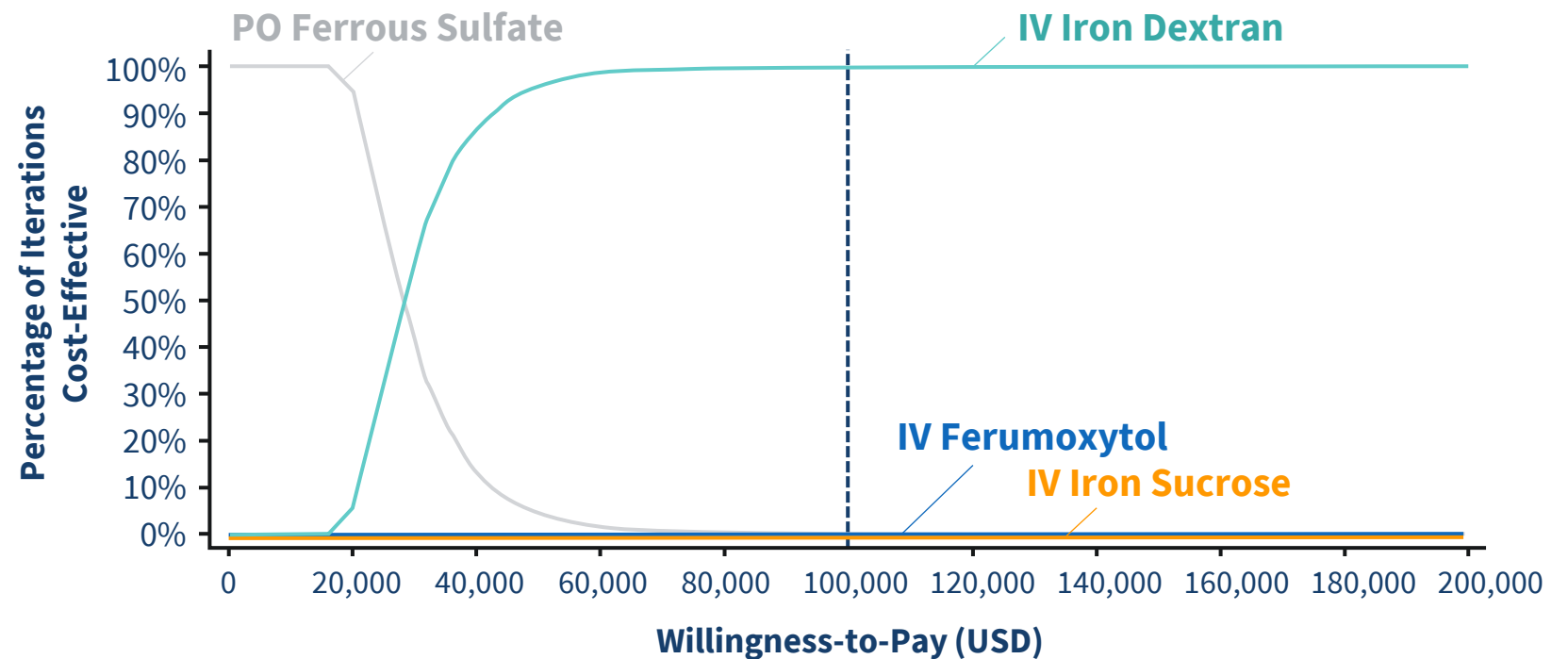




# What about Comparative Cost Burden?

- **IV iron can be quite *cost-effective*** compared with oral iron
  - Rigorous cost-effectiveness study of first-line IV vs oral iron for iron-deficiency anemia in women with heavy menstrual bleeding published in 2026.

**LMW Iron Dextran  
more cost effective  
than PO ferrous  
sulfate.**



Wang D, et al. *Blood Adv.* 2026.



# Patient Case 1: Meet Mary

- **32-year-old woman with heavy menstrual bleeding presents with fatigue and alopecia.**
  - Has heavy menstrual bleeding *despite* contraceptive use.
- Previously tried PO ferrous sulfate 1 tab daily, then PO iron polysaccharide 1 tab daily, but remained with **hemoglobin 10-11 g/dL** and **ferritin <30 ng/mL**.
- **Very anxious about receiving IV iron** because her sister had an **infusion reaction** to IV iron and she witnessed it.
- She asks to receive the formulation of IV iron with the lowest risk of an infusion reaction.



**How to best manage this patient?**

# Choose Your IV Iron Formulation Wisely



| Formulation                  | Dose (US Label)                                        | Time      | Clinical Considerations & Suitability                                                                                                                                                                                                                                                                              |
|------------------------------|--------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>LMW Iron Dextran</b>      | Hgb-based (label)<br>1000 mg (off-label)               | 1-4 H     | High quantity in single infusion, long infusion time                                                                                                                                                                                                                                                               |
| <b>Iron Sucrose</b>          | 200-400 mg (label)                                     | 1.5-4 H   | Inconvenient: 3-5 infusions to give 1000 mg, long infusion time                                                                                                                                                                                                                                                    |
| <b>Ferric Gluconate</b>      | 125 mg (label)<br>250 mg (off-label)                   | 1-2 H     | Inconvenient: 4-8 infusions to give 1000 mg, long infusion time<br>Contains <b>benzyl alcohol</b> (hypersensitivity reactions, local irritation, skin reaction); contraindicated in infants (“gasping syndrome”); avoid in pregnant patients (?crosses the placenta)                                               |
| <b>Ferumoxytol</b>           | 510 mg (label)<br>1020 mg (off-label)                  | 15-30 min | High quantity in single infusion<br><b>Notify radiologist if MRI is performed</b> within 3 months of infusion                                                                                                                                                                                                      |
| <b>Ferric Carboxymaltose</b> | 750 mg (label)                                         | 15 min    | <b>50-75% risk of treatment-emergent hypophosphatemia, with FDA Black Box Warning</b> (may last up to 3+ months after one infusion; no treatment)<br>May result in <b>serious decline in bone density, fractures bone demineralization, osteomalacia, and pseudofractures</b><br>Newer formulation, more expensive |
| <b>Ferric Derisomaltose</b>  | 1000 mg if $\geq 50$ kg, 20 mg/kg if $< 50$ kg (label) | 20 min    | High quantity in single infusion<br>Newer formulation, more expensive                                                                                                                                                                                                                                              |

Al-Samkari H. *Blood*. 2024; FDA Prescribing Information.

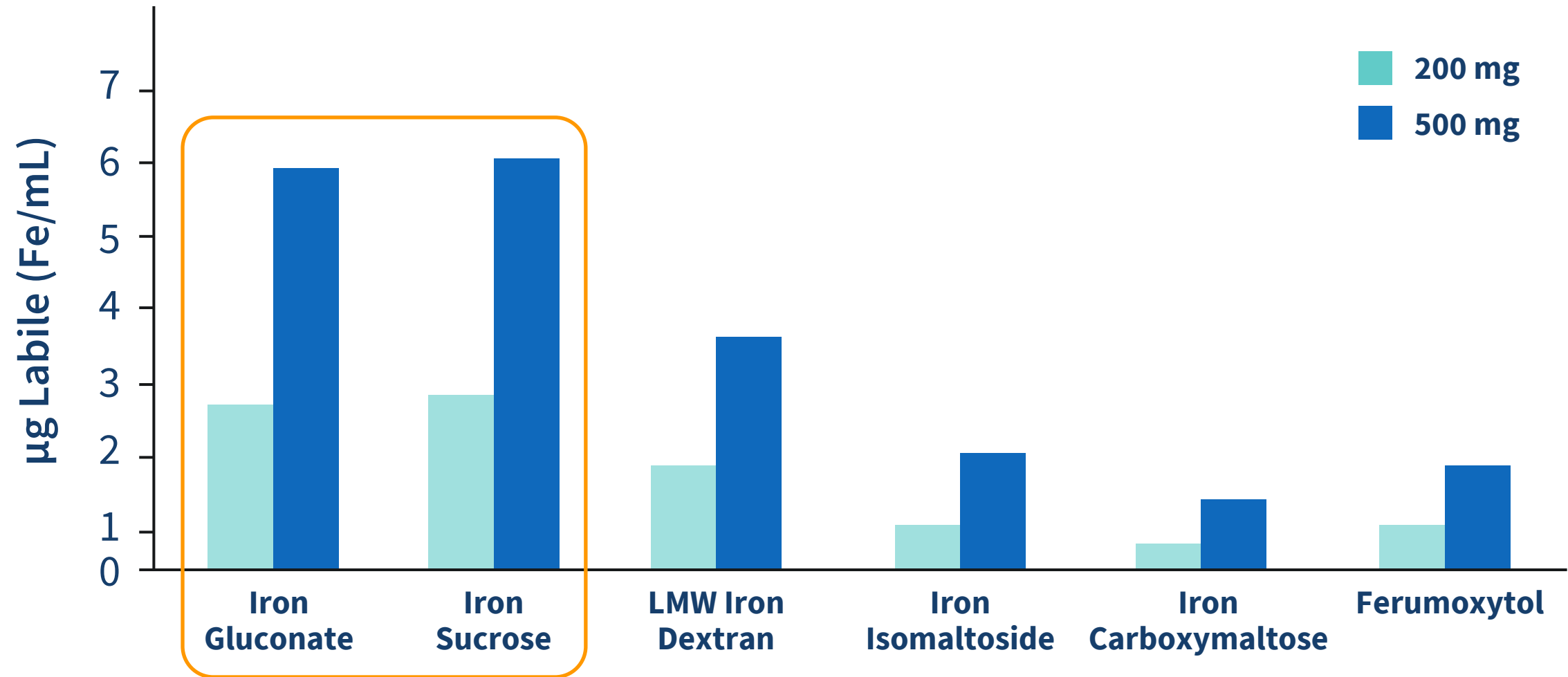


**Which IV iron formulation causes the *most* infusion reactions?**

**Which one causes the *fewest*?**



# Labile Free Iron



Van Doren L, et al. *Hematology Am Soc Hematol Educ Program*. 2023.

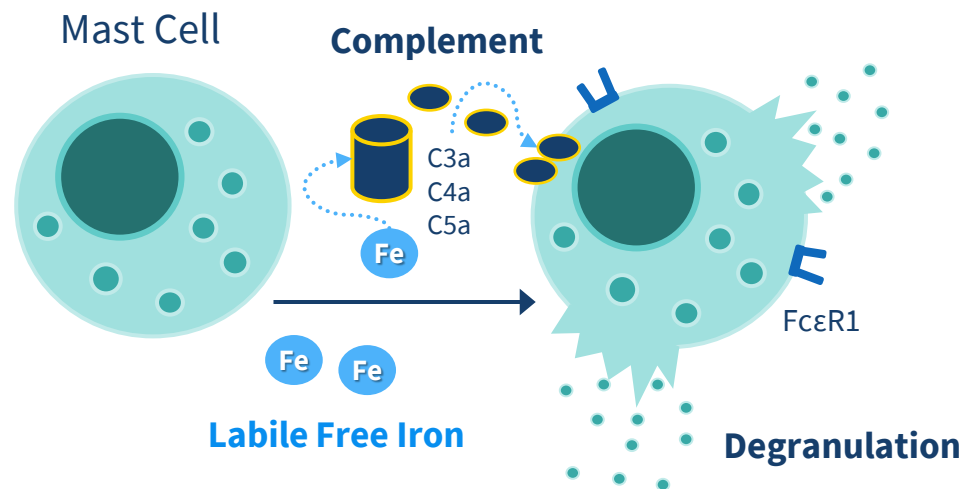
# Know Your Infusion Reaction

Adapted from Alsaleh N, et al. *Front Immunol.* 2020;  
Arastu A, et al. *JAMA Netw Open.* 2022; Van Doren L, et al.  
*Hematology Am Soc Hematol Educ Program.* 2023.



## CARPA (Complement Activation-Related Pseudo-Allergy)

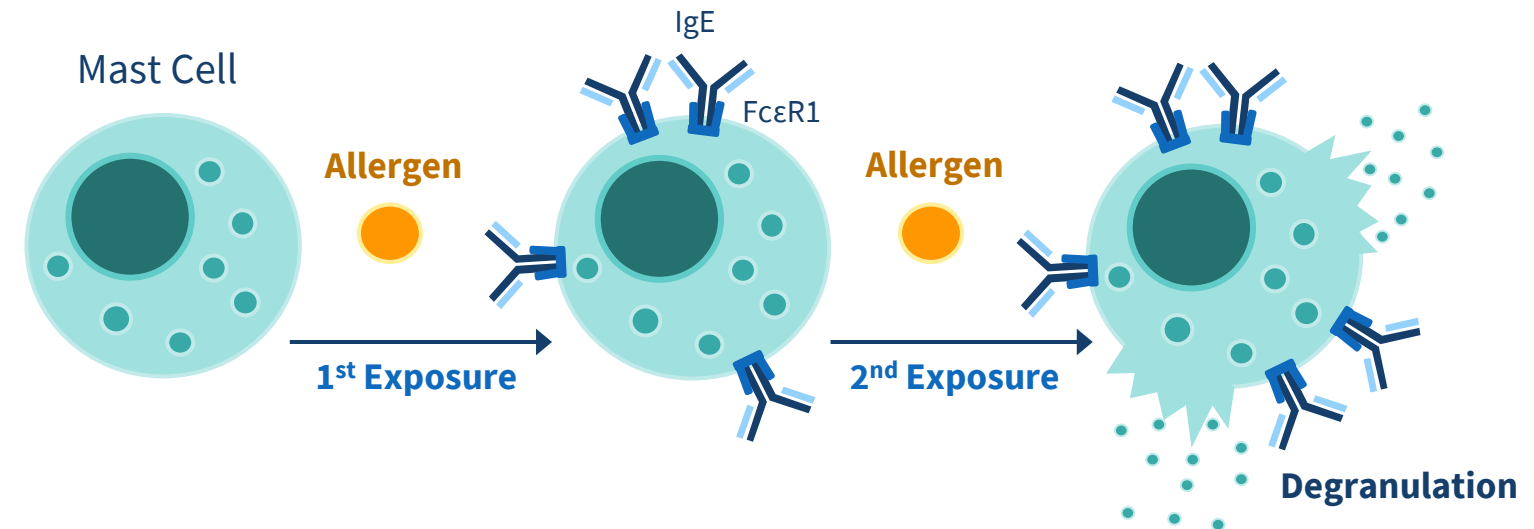
### No Prior Sensitization



- Pruritis
- Isolated Urticaria
- Flushing
- Chest Tightness
- Joint Pain

## Allergic (IgE)-Mediated Hypersensitivity

### Prior Sensitization Required



- Anaphylaxis
- Hypotension
- Angioedema
- Generalized Urticaria
- Stridor, Bronchospasm
- Vomiting, Abdominal Pain

- **Complement-mediated (Fishbane):** >99% of all IV iron infusion reactions; *not* anaphylactic; give steroid + H2 blocker
- **Anaphylactic:** Note the difference in symptoms; give epinephrine, H1 blocker, H2 blocker, steroid

# Systematic Review and Meta-Analysis of IV Iron-related Infusion Reactions

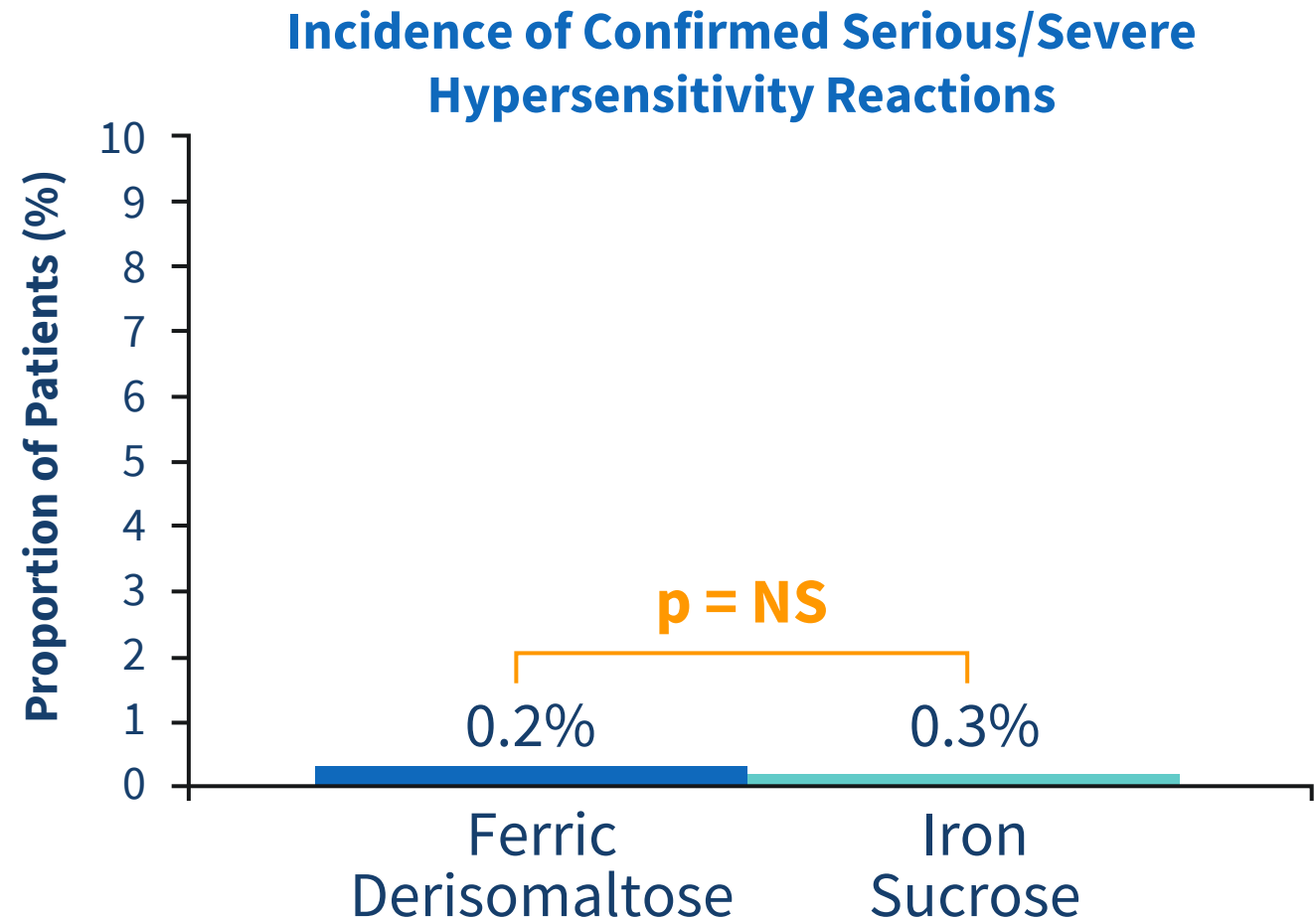


- **103 trials** performed between 1965 and 2013.
- 10,391 patients treated with IV iron and compared to:
  - 4,044 patients treated with PO iron.
  - 1,329 with no iron.
  - 3,335 with placebo.
  - 155 with IM iron.
- There was **no increase in the risk** of severe adverse events (SAEs) with IV iron compared to control, **RR 1.04** (95% CI 0.93-1.17).
- **No difference** in infusion reactions among different formulations.



# FERWON-NEPHRO and FERWON-IDA Trials

- Powered to assess **risk of hypersensitivity reactions**, comparing ferric derisomaltose with iron sucrose.



Auerbach M, et al. *Am J Hematol*. 2019; Bhandari S, et al. *Nephrol Dial Transplant*. 2021; Wolf M, et al. *JAMA*. 2020

# FIRM Trial: Huge Double-Blind RCT Designed to Evaluate HSR Risk (FMX vs. FCM)



|                                                     | Treatment Group, n (%)   |                   | Treatment Difference<br>(95% CI) | Relative Risk<br>(95% CI) | Non-Inferiority<br>P-Value |
|-----------------------------------------------------|--------------------------|-------------------|----------------------------------|---------------------------|----------------------------|
|                                                     | Ferumoxytol<br>(n = 997) | FCM<br>(n = 1000) |                                  |                           |                            |
| <b>Primary Endpoint:</b><br>Composite Incidence of: | <b>6 (0.6)</b>           | <b>7 (0.7)</b>    | <b>-0.1 (-0.8 to 0.6)</b>        | <b>0.9 (0.3-2.5)</b>      | <b>0.0001</b>              |
| <b>Moderate Hypersensitivity Reaction</b>           | <b>3 (0.3)</b>           | <b>6 (0.6)</b>    |                                  |                           |                            |
| <b>Severe Hypersensitivity Reaction</b>             | <b>1 (0.1)</b>           | <b>0 (0.0)</b>    |                                  |                           |                            |
| <b>Anaphylaxis</b>                                  | <b>0 (0.0)</b>           | <b>0 (0.0)</b>    |                                  |                           |                            |
| <b>Moderate Hypotension</b>                         | <b>2 (0.2)</b>           | <b>1 (0.1)</b>    |                                  |                           |                            |
| <b>Severe Hypotension</b>                           | <b>0 (0.0)</b>           | <b>0 (0.0)</b>    |                                  |                           |                            |

Adkinson N, et al. *Am J Hematol*. 2018; Wolf M, et al. *JCI Insight*. 2018.



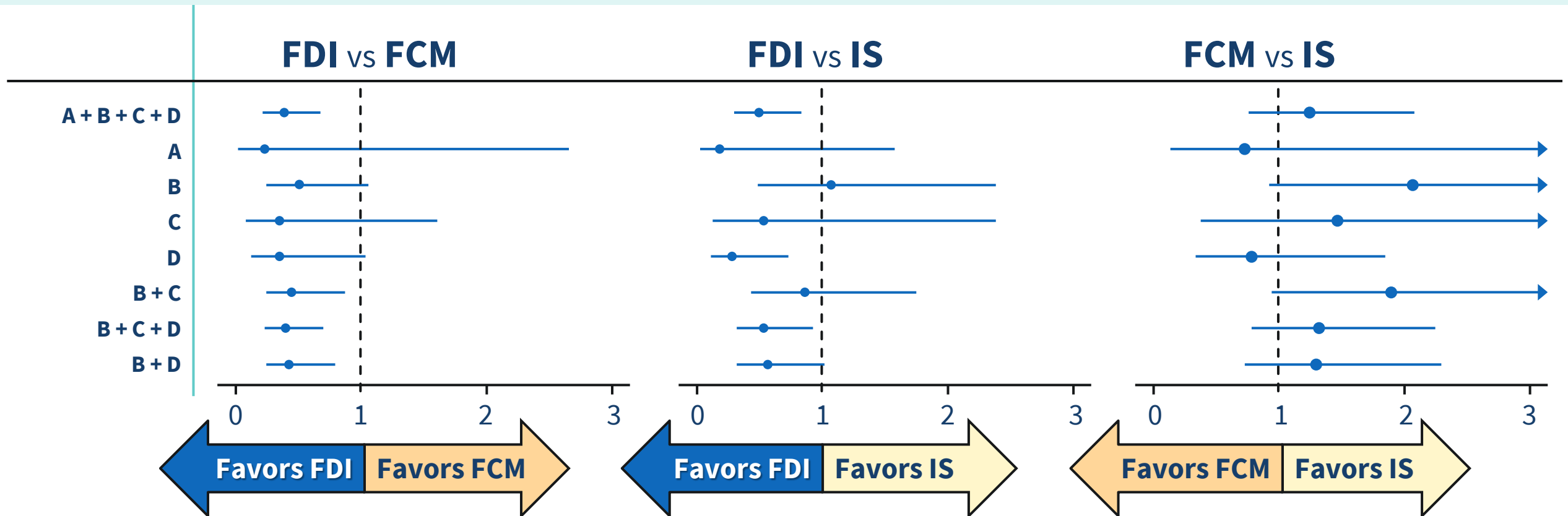
# Pooled Analysis of Safety Data from >20 Prospective Trials Including >8000 Patients: **FDI favored over FCM and IS; IS favored over FCM**

**A:** Anaphylactic Reactions

**B:** Respiratory Reactions Potentially Related to Hypersensitivity

**C:** Skin Reactions Potentially Related to Hypersensitivity

**D:** Cardiovascular Reactions Potentially Related to Hypersensitivity





# IV Iron and Bone Health

**Evidence, Product-Specific Risks, and IV Iron Case Studies in HHT**



# Patient Case 2: Meet Wanda

- 68-year-old woman with HHT c/b severe recurrent epistaxis, liver AVMs presents for follow up.
- Patient receiving **ferumoxytol 510 mg infusions q3 months** to maintain normal hemoglobin and iron stores given ongoing severe epistaxis.
  - Multi-drug refractory HHT, waiting for next clinical trial to open.
  - Has received **over 100 lifetime iron infusions**.
- Today, **ferritin is 341 ng/mL** and **TSAT is 68%**.
- She also has innumerable liver AVMs, causing a **high output cardiac state** (but not failure), being monitored by yearly liver MRI.





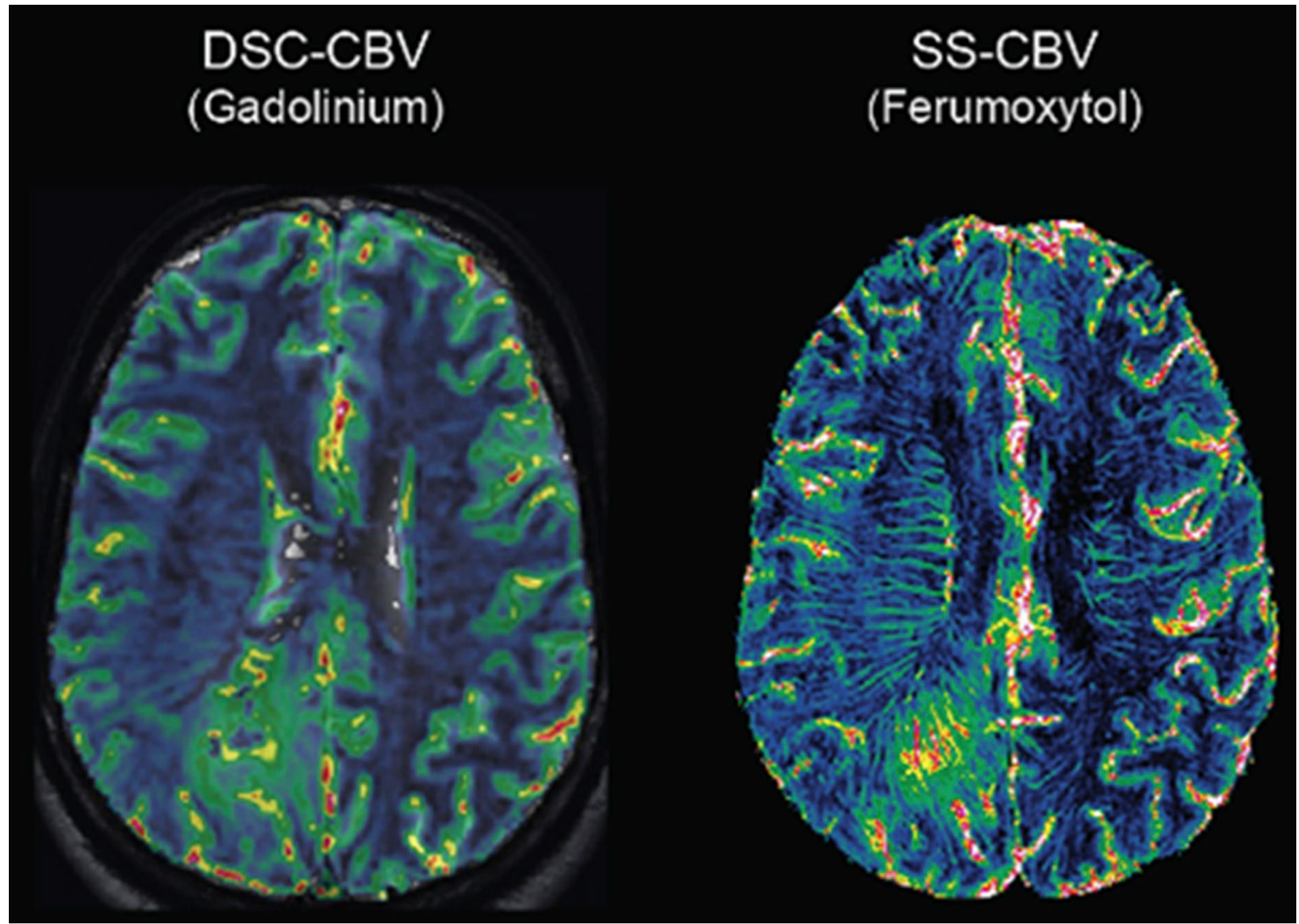
# Patient Case 2: Wanda's Imaging

- Wanda's most recent liver MRI done 3 week ago was interpreted as “**AVM burden stable, but evidence of severe iron overload**” and recommended liver MRI for iron quantitation.
- **Patient is scared**, has Googled iron overload and is worried about liver cancer risk, liver failure, and possible cardiac iron overload, and **requests cardiac MRI to evaluate iron burden**.

## As a next step, what would you do?

- |                                                               |                       |
|---------------------------------------------------------------|-----------------------|
| A. Order liver MRI for iron quantitation.                     | E. Both A and D.      |
| B. Order liver MRI for iron quantitation and cardiac T2* MRI. | F. Both B and D.      |
| C. Order repeat standard liver MRI in 1 month.                | G. Both C and D.      |
| D. Order <i>HFE</i> sequencing.                               | H. None of the above. |

# Ferumoxytol is MRI Contrast!

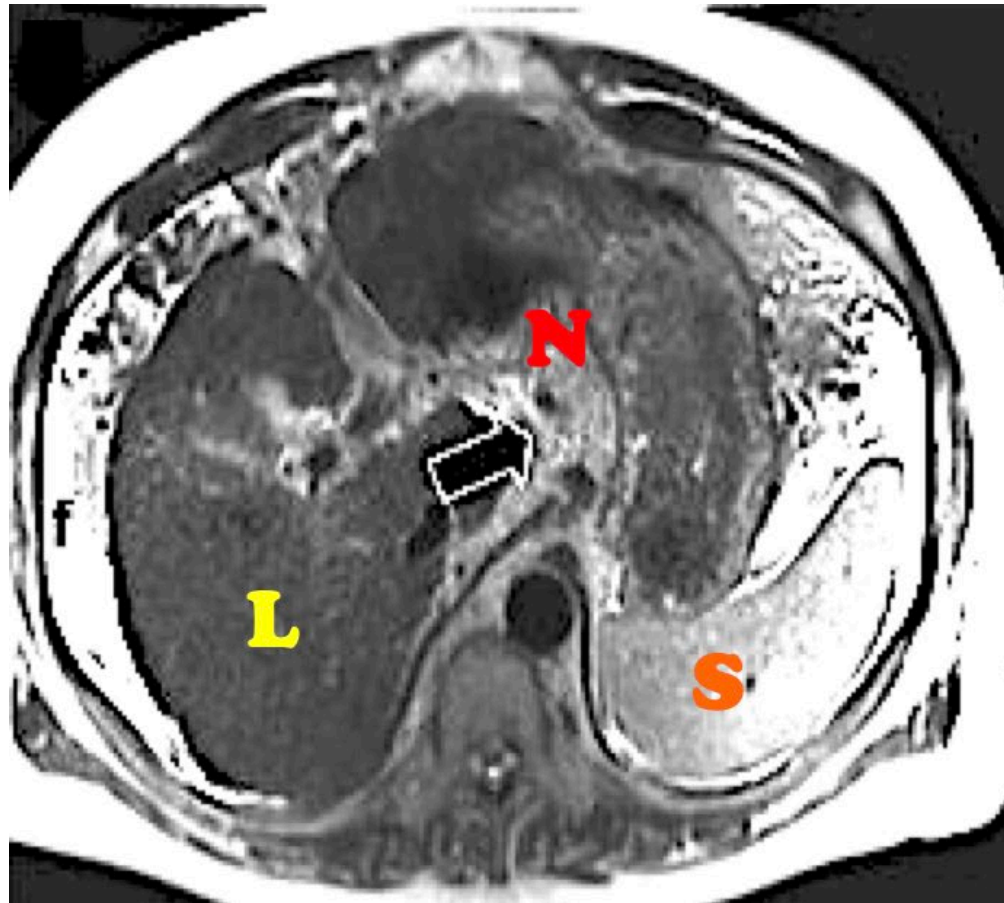


Toth G, et al. *Kidney Int.* 2017.

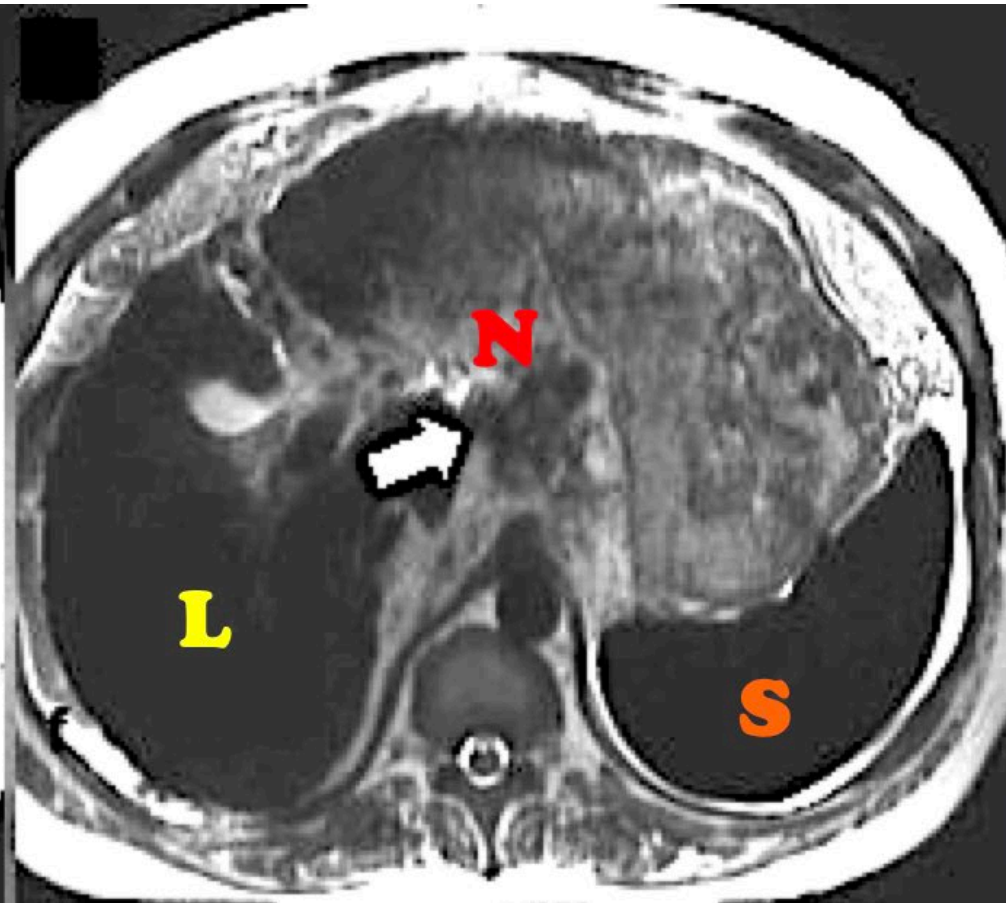
# Ferumoxytol Interferes with MRI Interpretation *for Months*



Before Ferumoxytol



After Ferumoxytol



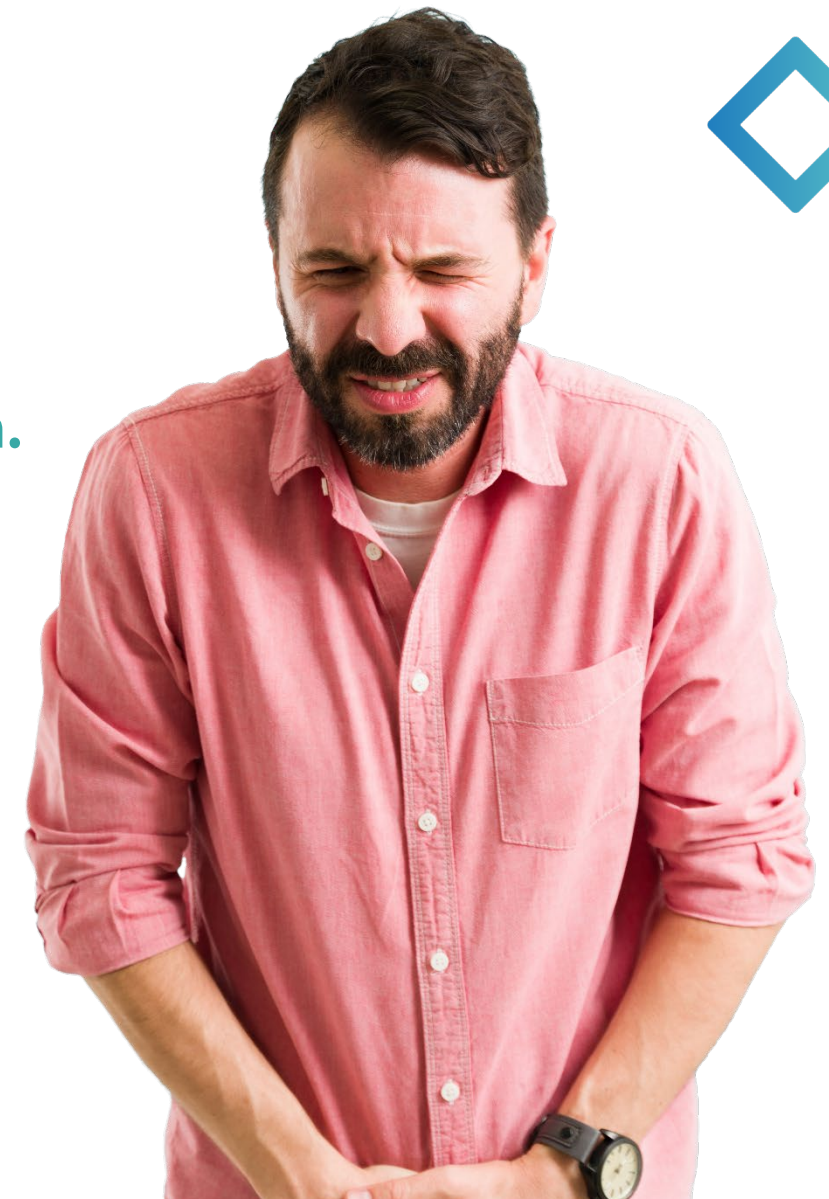
Note decreased signal of liver (L), spleen (S) and cluster of lymph nodes (N and arrow) due to iron retention in these structures following ferumoxytol infusion.

Image from <https://mriquestions.com/ferumoxytol.html>.



# Patient Case 3: Meet Joe

- **45-year-old man with HHT c/b epistaxis, chronic gastrointestinal bleeding presents with weakness, groin pain.**
- Has had **recurrent epistaxis** since early childhood, and it has worsened over time.
- First diagnosed with chronic GI bleeding 3 years ago when presented with hemoglobin of 6.2 g/dL; was started on ferric carboxymaltose 1000 mg approximately q3 months by his prior hematologist.
- **Presents with bilateral groin pain, waddling gait.**
- Hgb 12.4 g/dL, ferritin 88 ng/mL, transferrin saturation 11%.



**How to best manage this patient?**

# How to Best Care for Iron Deficiency Anemia in the Chronically Bleeding Patient?



**Monitor** CBC, Ferritin, Transferrin Saturation.

- Interval is patient-dependent but **frequent = better**).



**Goal iron studies:**

- Ferritin >50 ng/mL **and**
- Transferrin Saturation >20%.



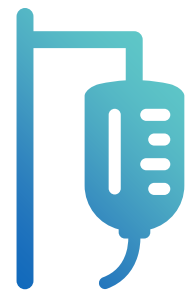
Oral iron **usually inadequate** (except with very mild bleeding).

- **Do not** “tread water”.



**Most will need IV iron** and will need **repeat infusions**.

- **Do not hesitate** if non-anemic.



Hgb goal for >90%: **Normal hemoglobin.**

- **Give 1000-1500 mg IV iron** per repletion.



**My trigger** for iron infusion:

- Ferritin <50 ng/mL **or**
- Transferrin Saturation <20%.



# Patient Case 3: Joe's Imaging

- 45-year-old man with HHT c/b epistaxis, chronic gastrointestinal bleeding presents with weakness, groin pain → **X-Ray**
- **Read as normal by radiologist.**

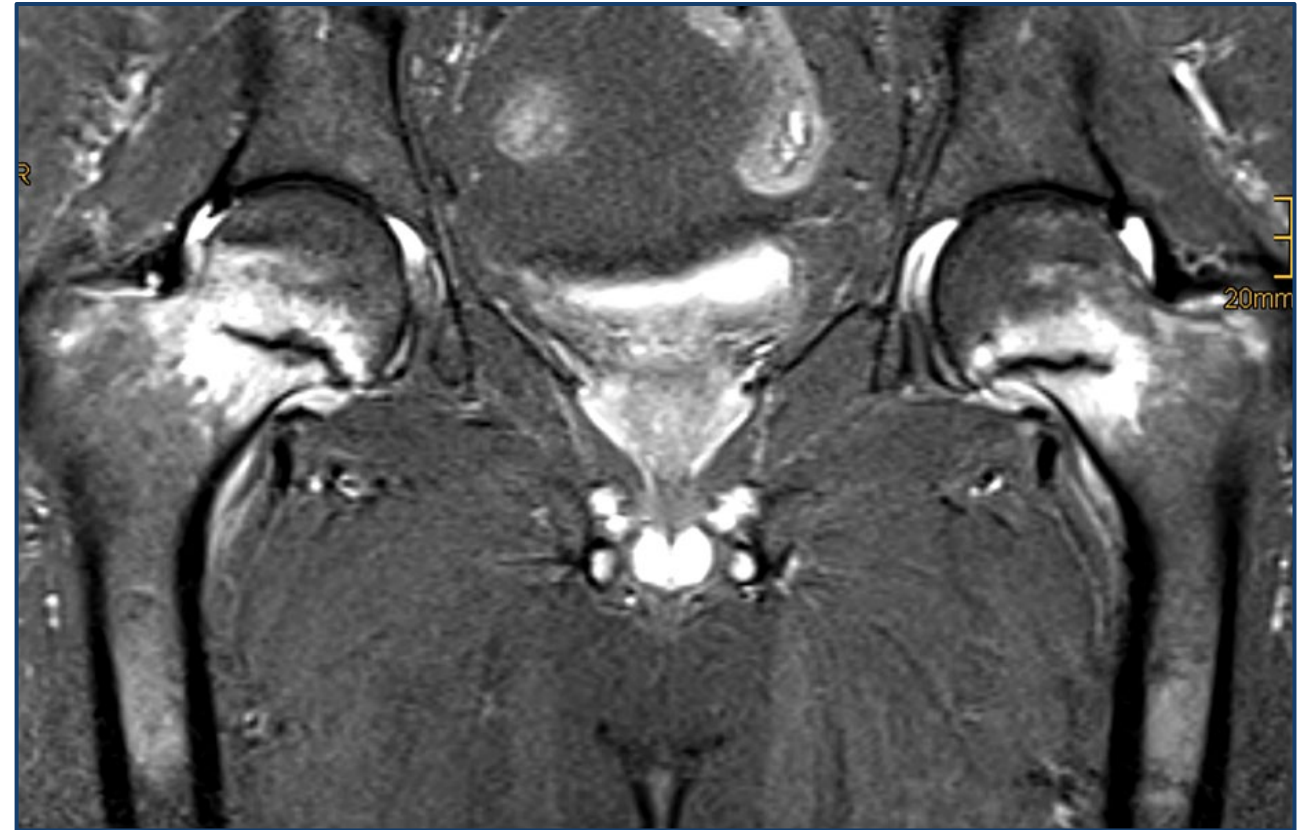


**What now?**



# Patient Case 3: Joe's Imaging

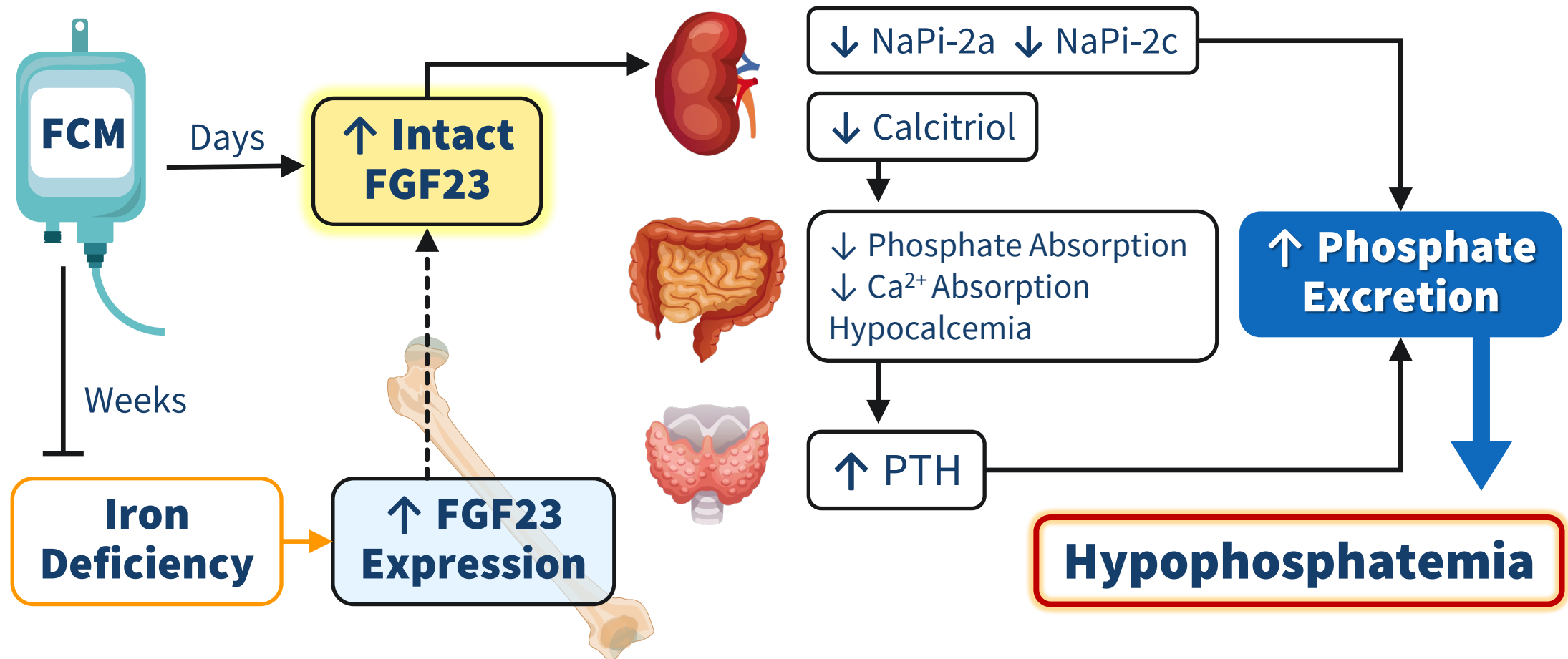
- 45-year-old man with HHT c/b epistaxis, chronic gastrointestinal bleeding presents with weakness, groin pain → **Hip MRI**



**What is going on here?**



# Treatment-Emergent Hypophosphatemia

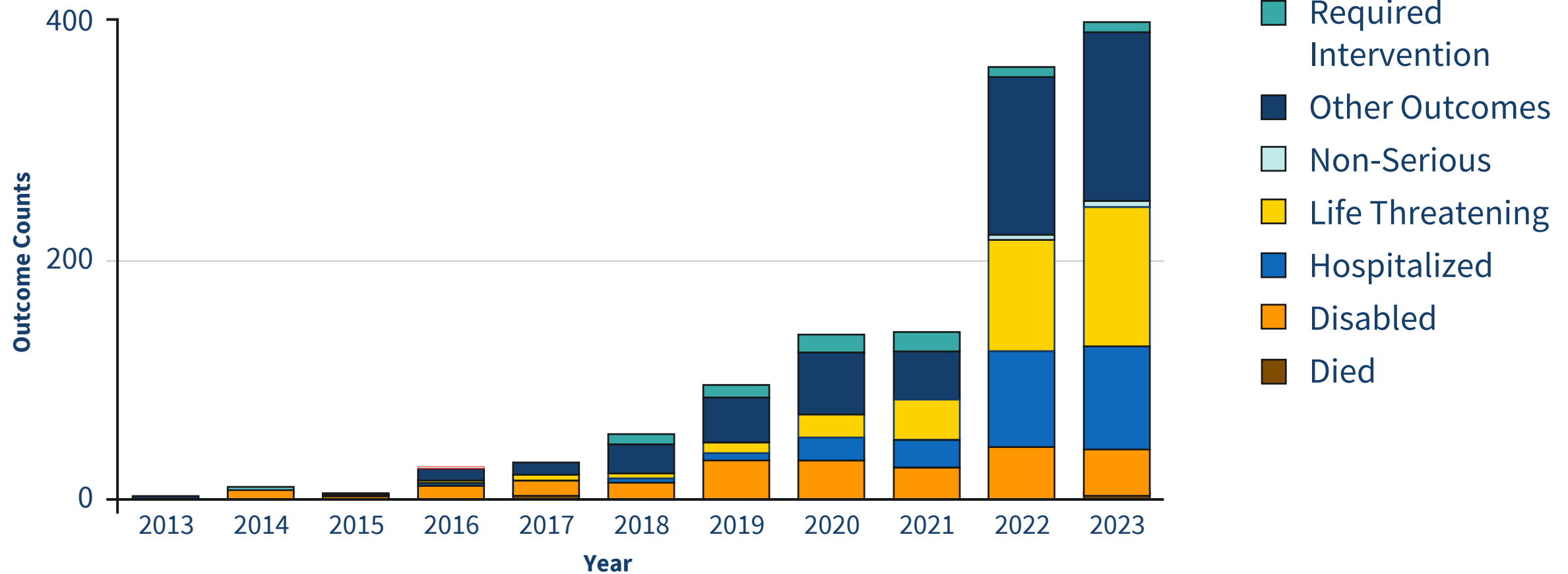


Schaefer B, et al. *Bone*. 2022; Wolf M, et al. *J Bone Miner Res*. 2013; Auerbach M, et al. *Am J Hematol*. 2021; Auerbach M, et al. *Am J Hematol*. 2025.

# A Rapidly Growing Iatrogenic *and Completely Preventable* Problem

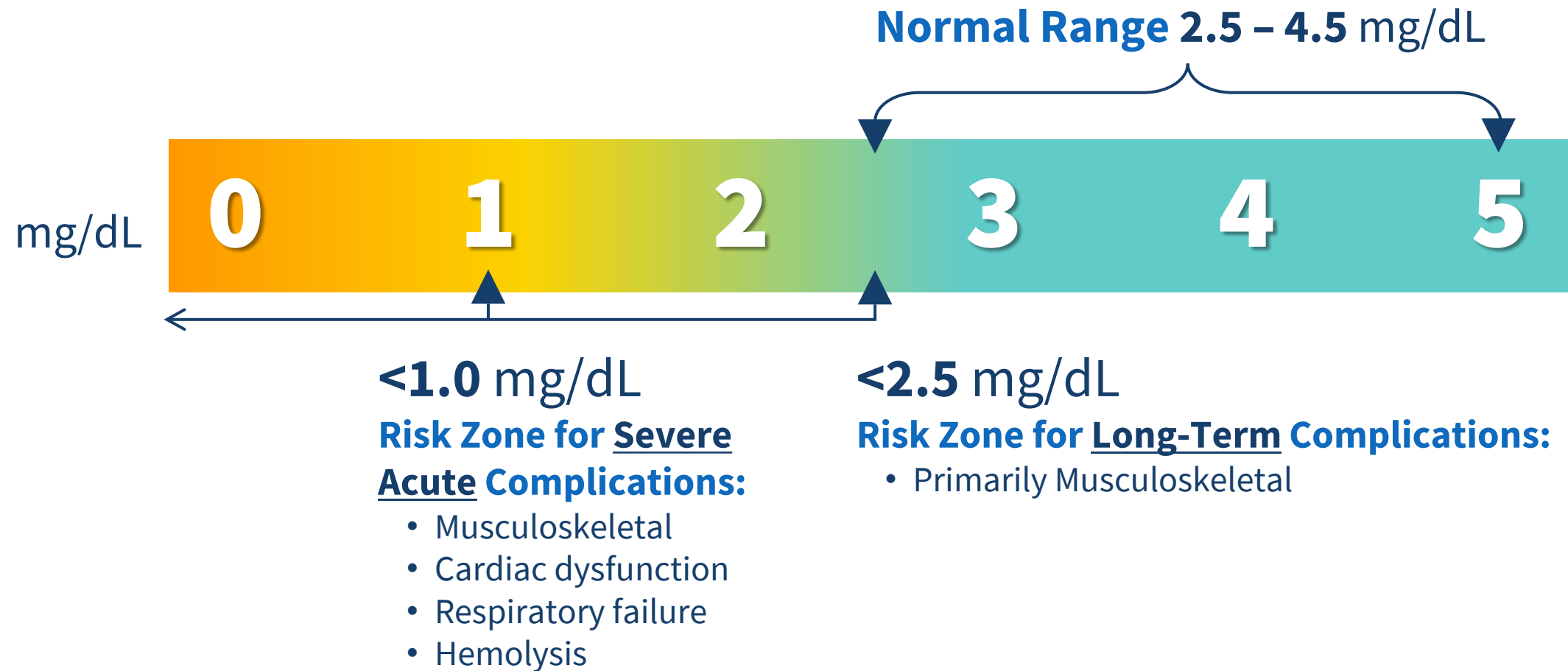


Case Report of FCM- Associated HPP Reported to FDA Between 2014 and 2023.



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

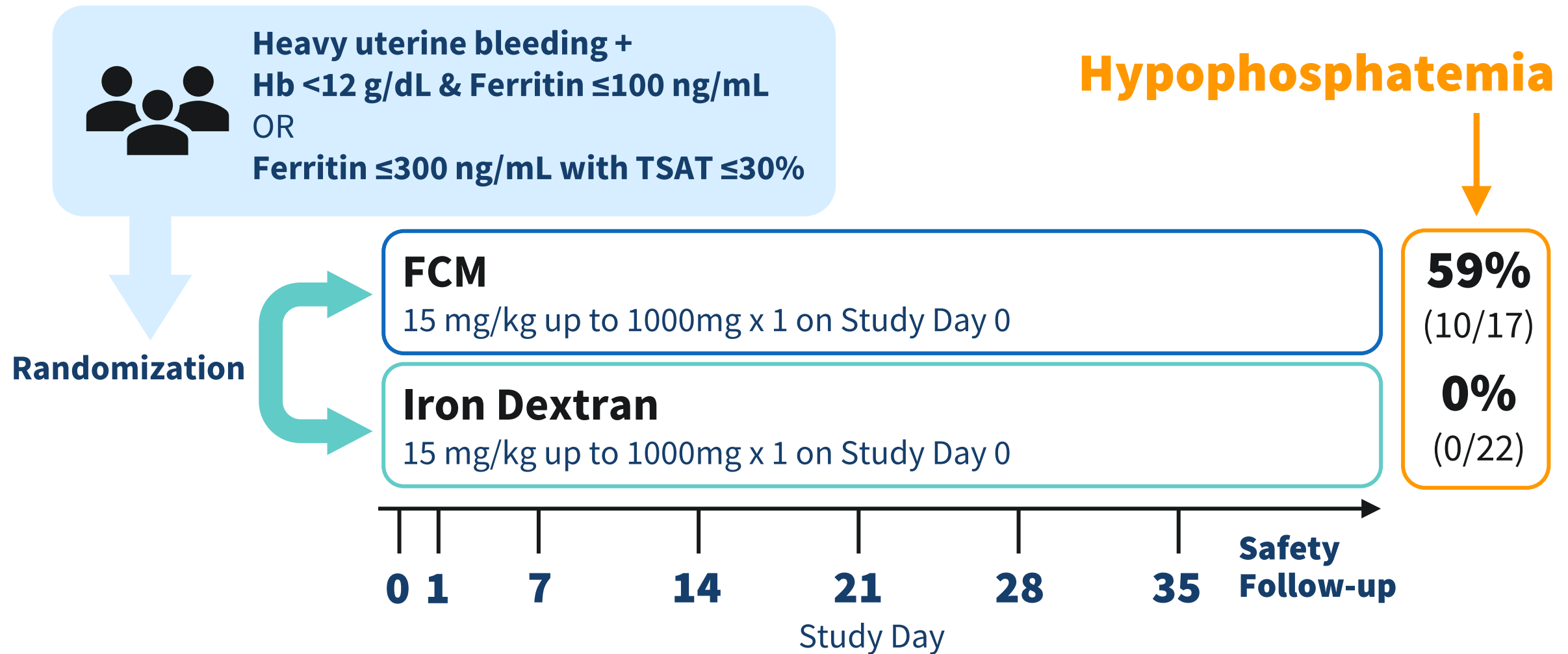
# Treatment-Emergent Hypophosphatemia May Be Serious and is **AVOIDABLE**



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



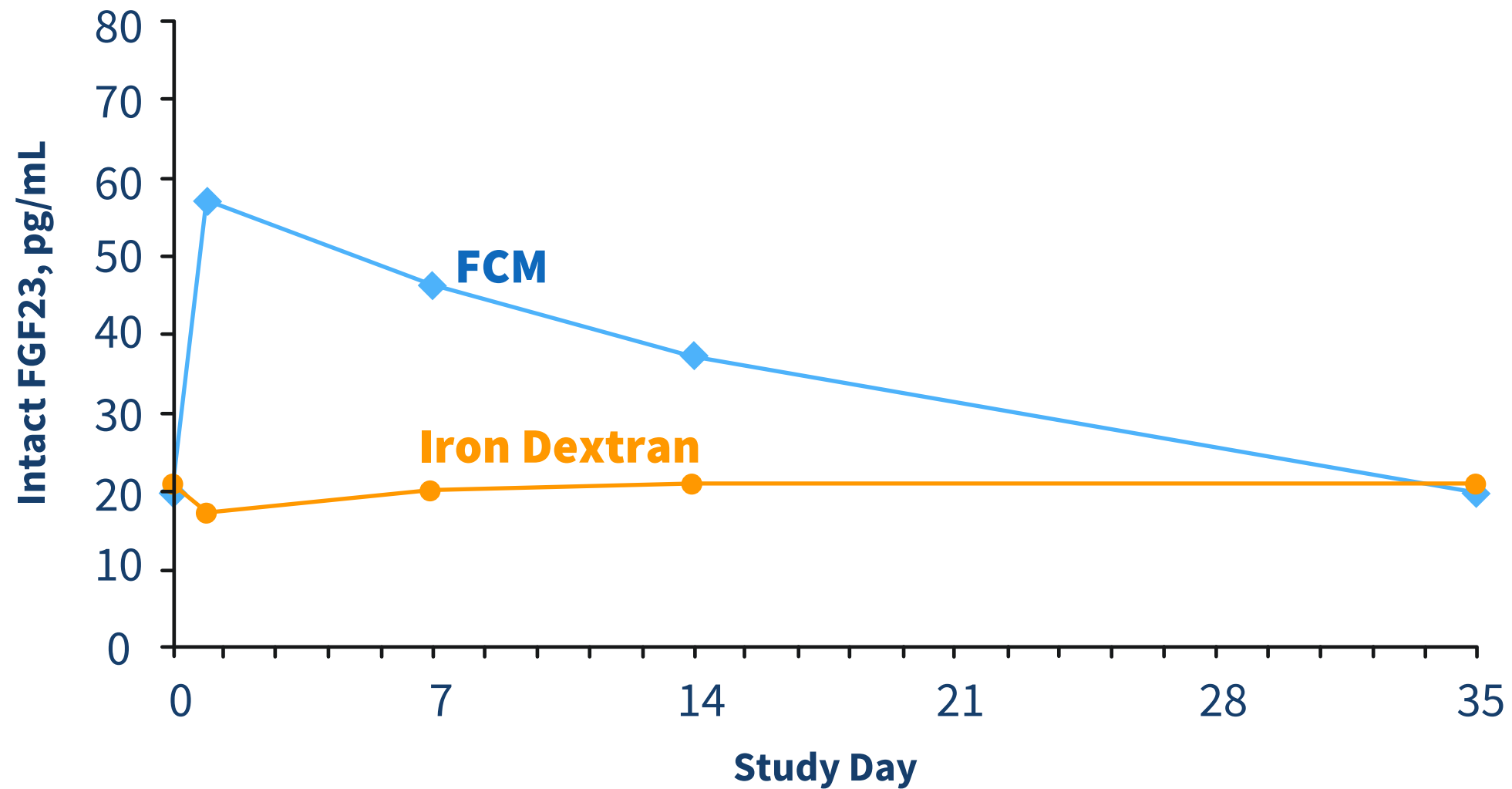
# FCM vs Iron Dextran



Wolf M, et al. *J Bone Miner Res.* 2013.



# Difference in iFGF23 Levels



Wolf M, et al. *J Bone Miner Res.* 2013.

# FIRM Trial: Multicenter, Double-Blind RCT of Treatment of IDA of Diverse Etiologies

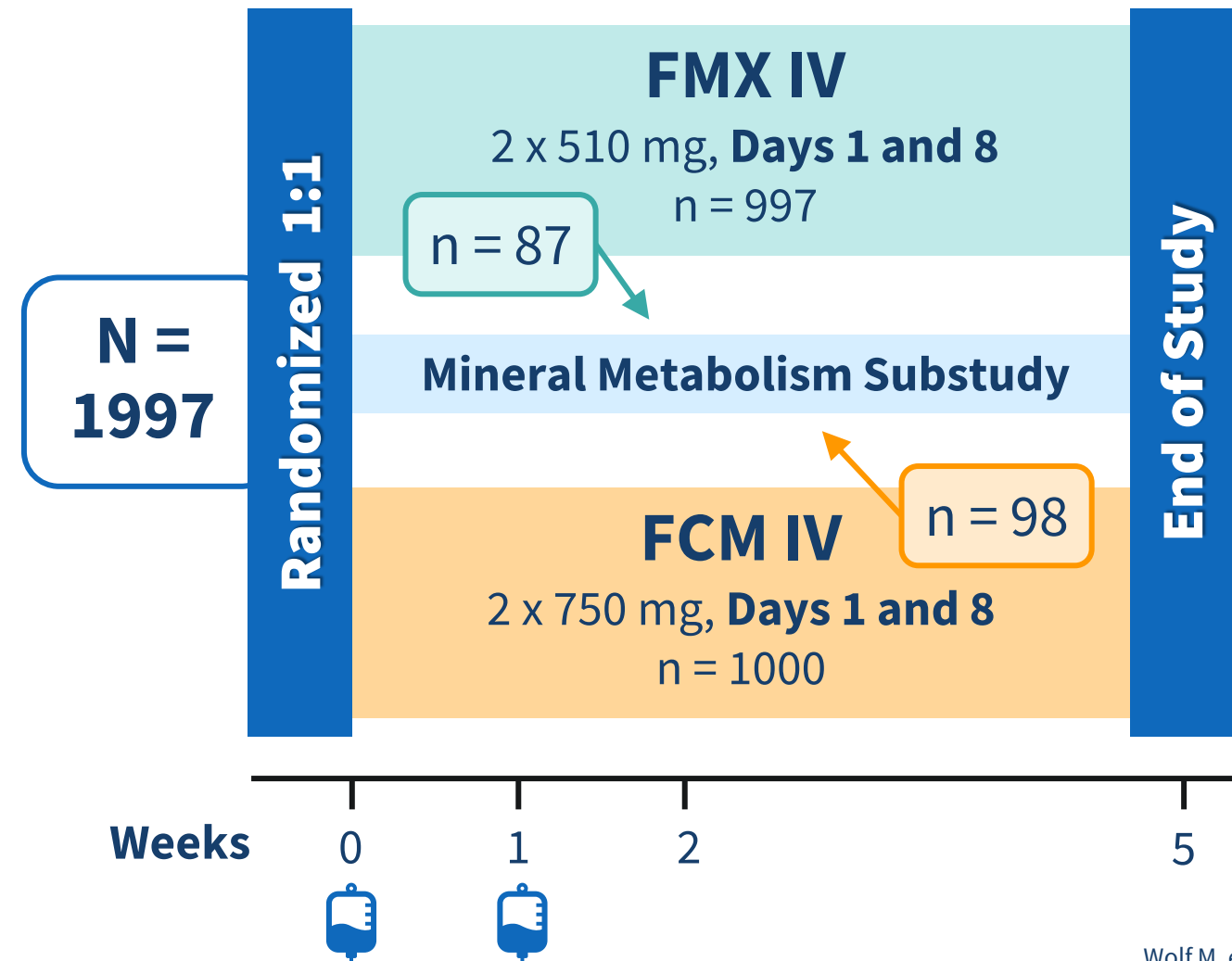


- **Key Inclusion Criteria**

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

- **Assays: Weeks 0, 1, 2, 5**

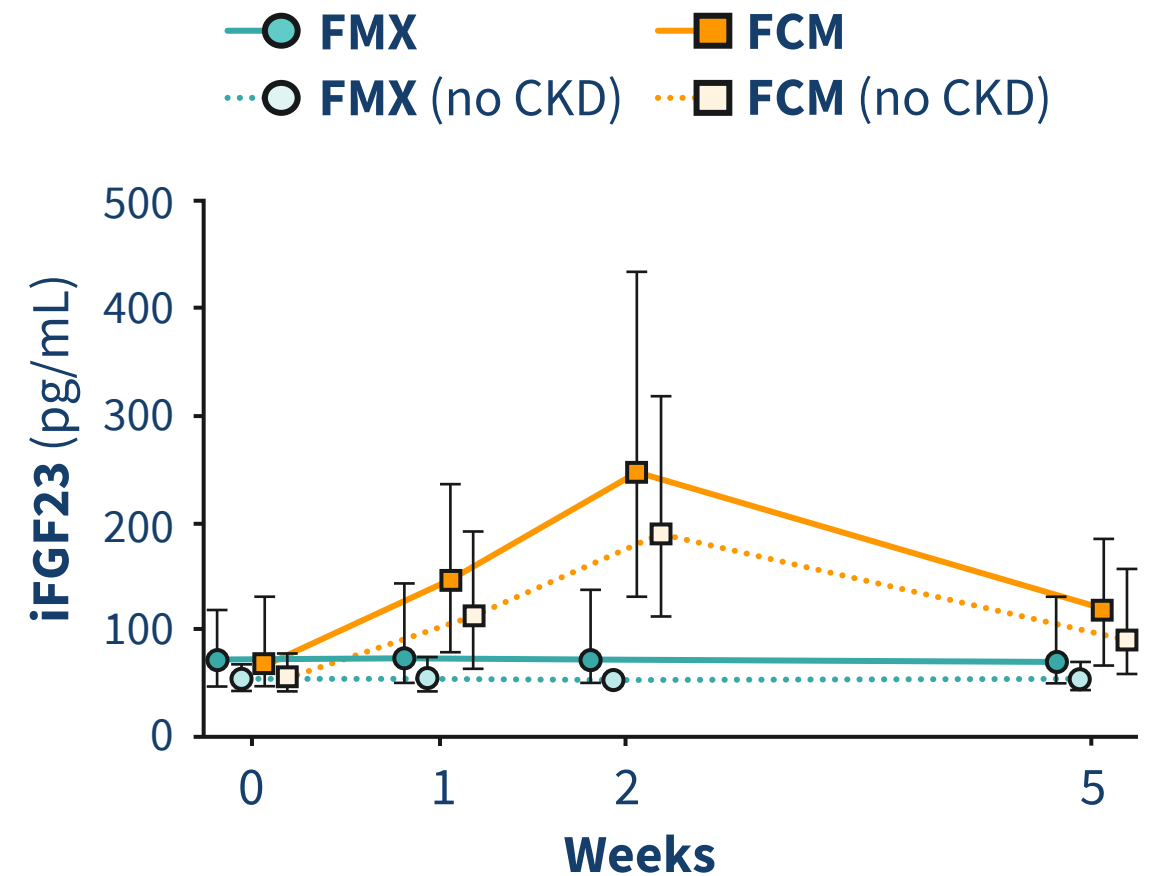
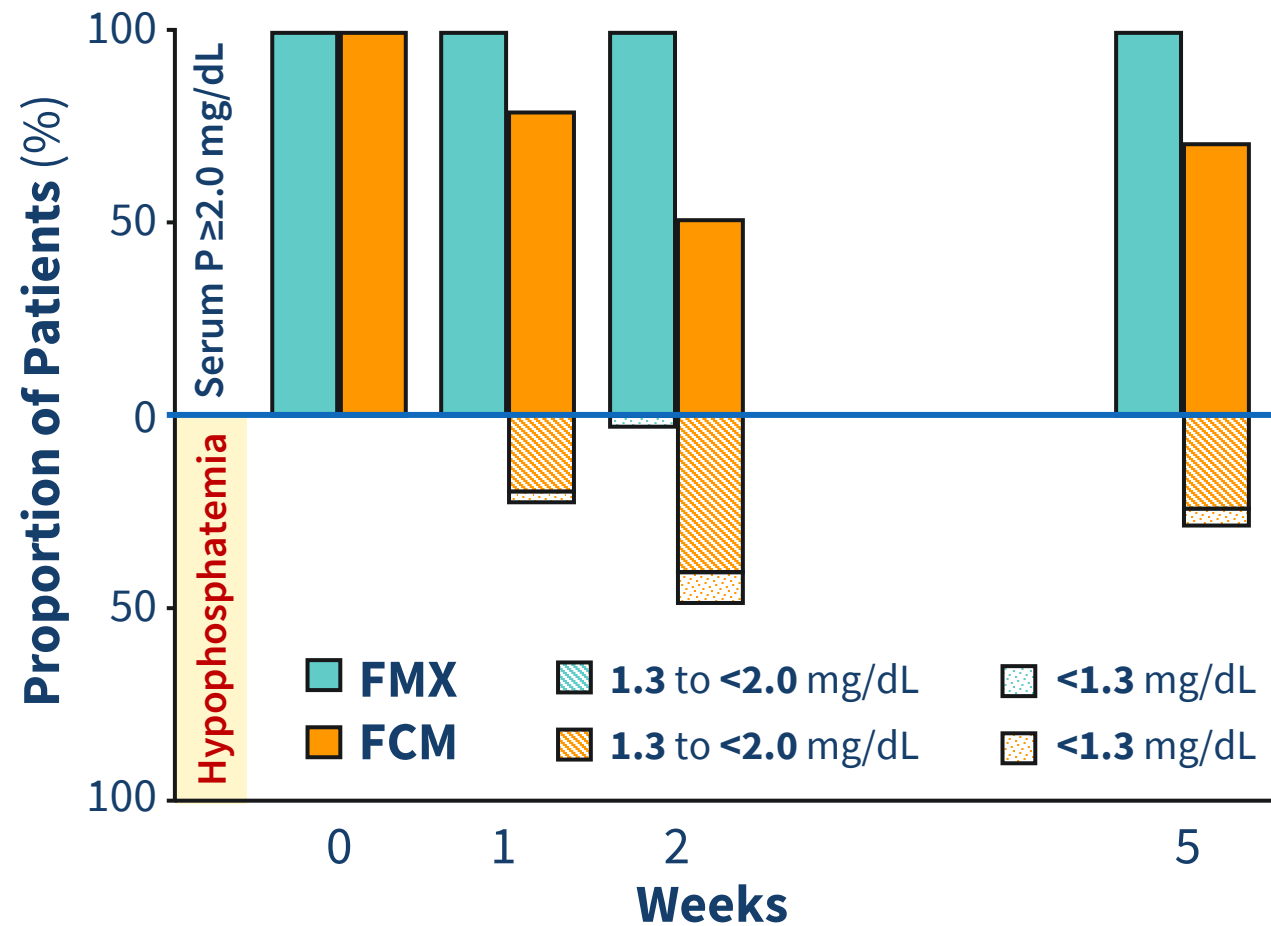
- Serum phosphate & fractional excretion of phosphate (FePi) in all
- **Sub-study:**
  - cFGF23, iFGF23
  - 25D, 1,25D calcium, PTH



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



# FIRM Trial: Primary Endpoint of Serum Phosphate After IV Iron



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

# The FIRM Trial: Clinical Risk Factors for Incident and Persistent Hypo-P



| Risk Factor                                              | Incident Hypophosphatemia |             | Persistent Hypophosphatemia |              |
|----------------------------------------------------------|---------------------------|-------------|-----------------------------|--------------|
|                                                          | Odds Ratio                | 95% CI      | Odds Ratio                  | 95% CI       |
| <b>FCM vs FMX</b>                                        | 250.6                     | 115.4-544.5 | 271.4                       | 66.5-1-106.7 |
| <b>eGFR</b> , per 10 mL/min/1.73 m <sup>2</sup> increase | 1.07                      | 1.01-1.13   | -                           | -            |
| <b>Hb</b> , per 1 g/dL increase                          | 1.24                      | 1.12-1.38   | 1.30                        | 1.16-1.46    |
| <b>Weight</b> , per 10 kg increase                       | 0.92                      | 0.87-0.97   | 0.79                        | 0.73-0.86    |
| <b>Serum phosphate</b> , per 1 mg/dL increase            | 0.31                      | 0.23-0.41   | 0.24                        | 0.17-0.34    |
| <b>Etiology of IDA</b>                                   |                           |             |                             |              |
| 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    |
| <b>Black vs White race</b>                               | -                         | -           | 1.87                        | 1.26-2.79    |

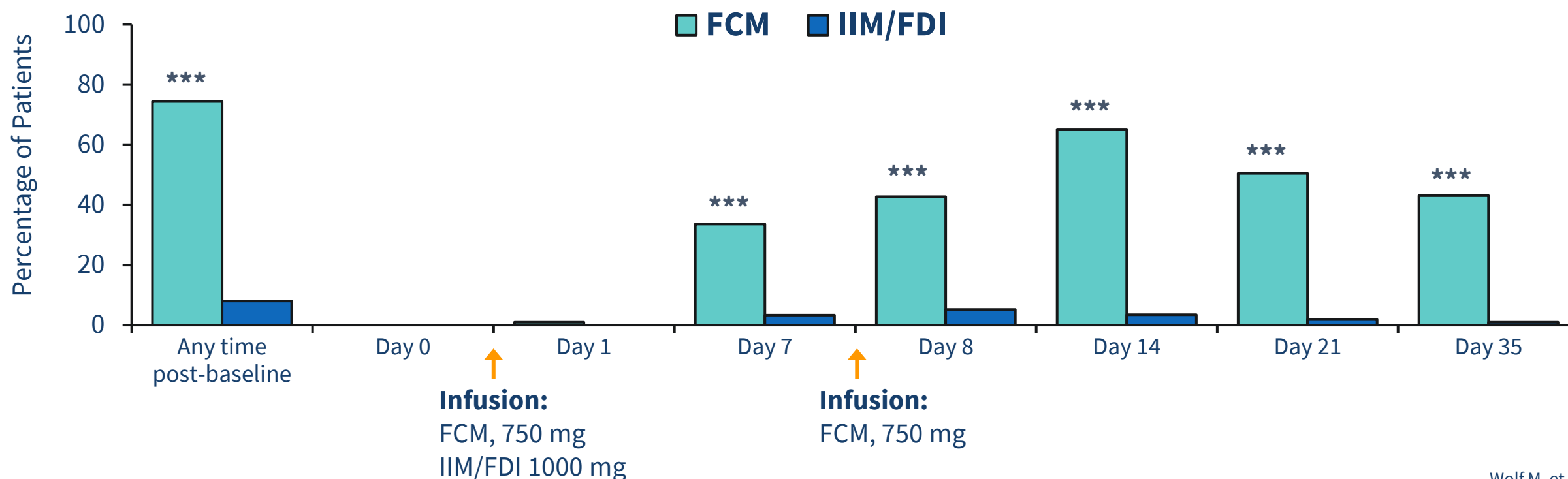
Wolf M, et al. *JCI Insight*. 2018.

# PHOSPHARE IDA Trials Comparing FDI with FCM: Primary Endpoint



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

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

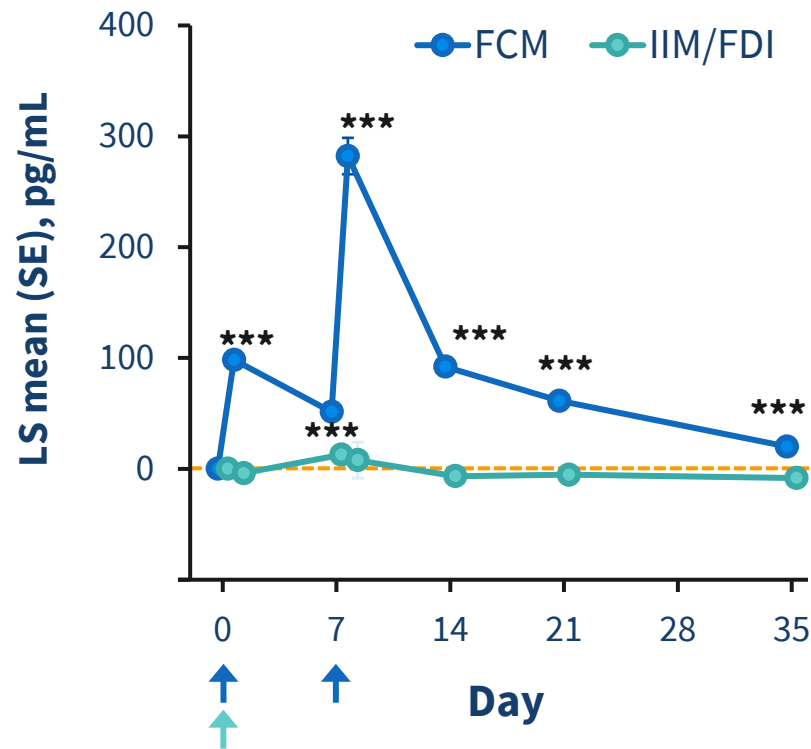


Wolf M, et al. JAMA. 2020.

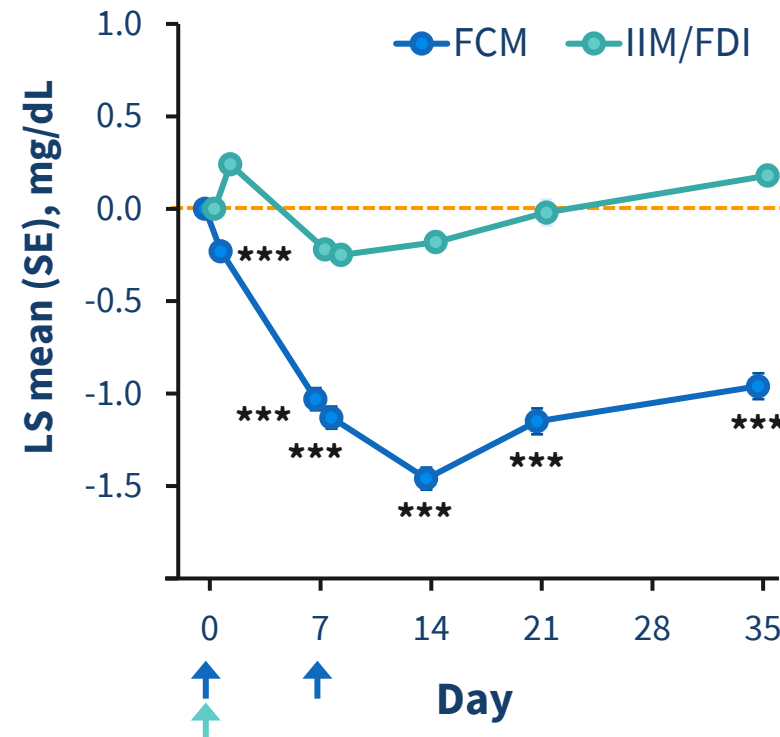
# PHOSPHARE IDA Trials (A&B): Effects on iFGF23 and Phosphate



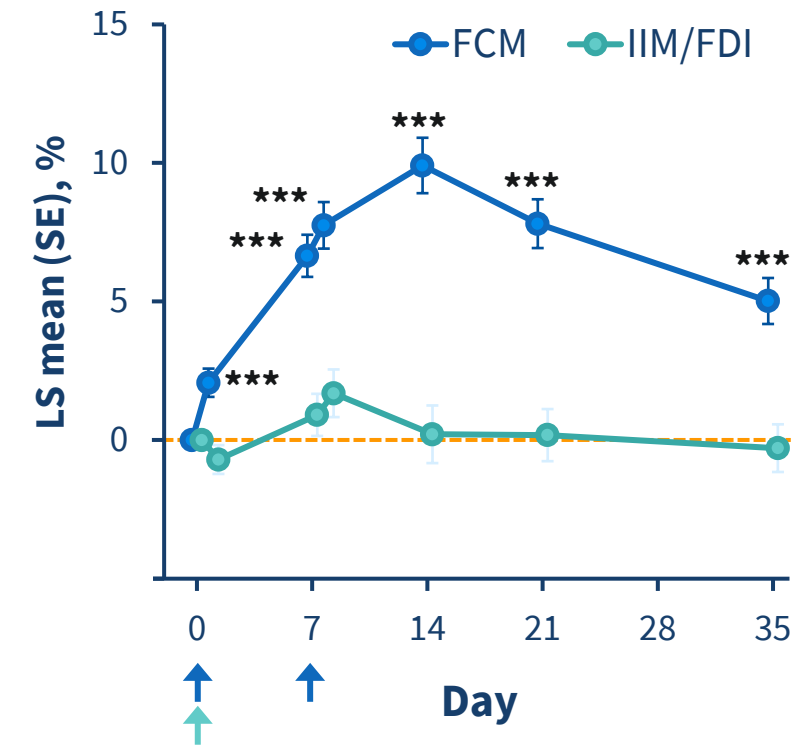
## Intact FGF23



## Serum Phosphate



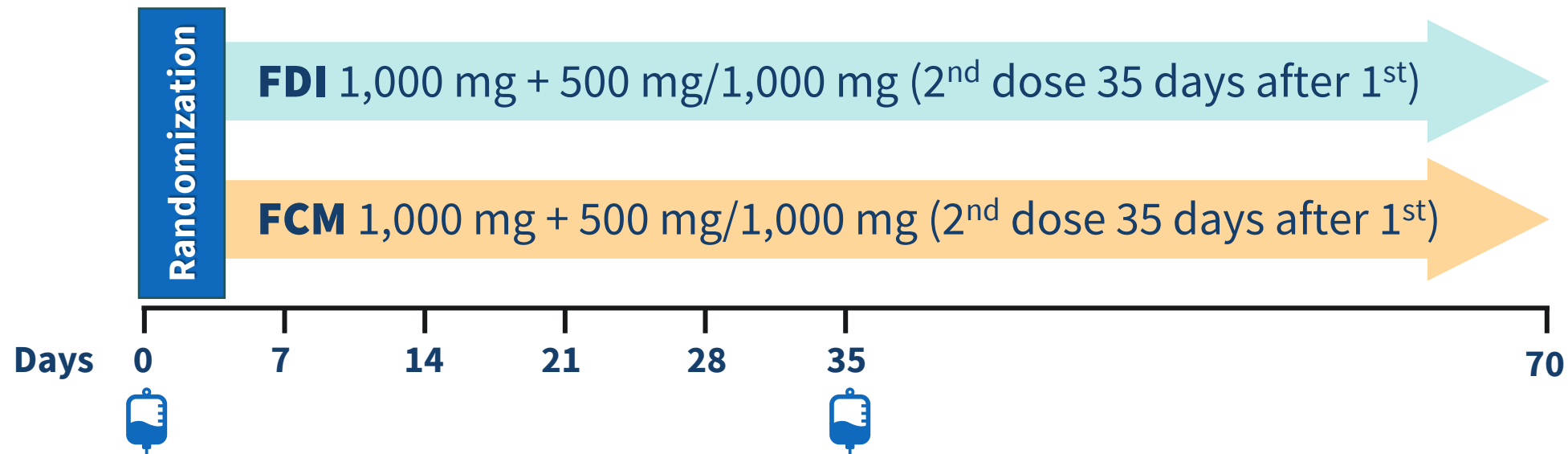
## Urinary Fractional Excretion of Phosphate



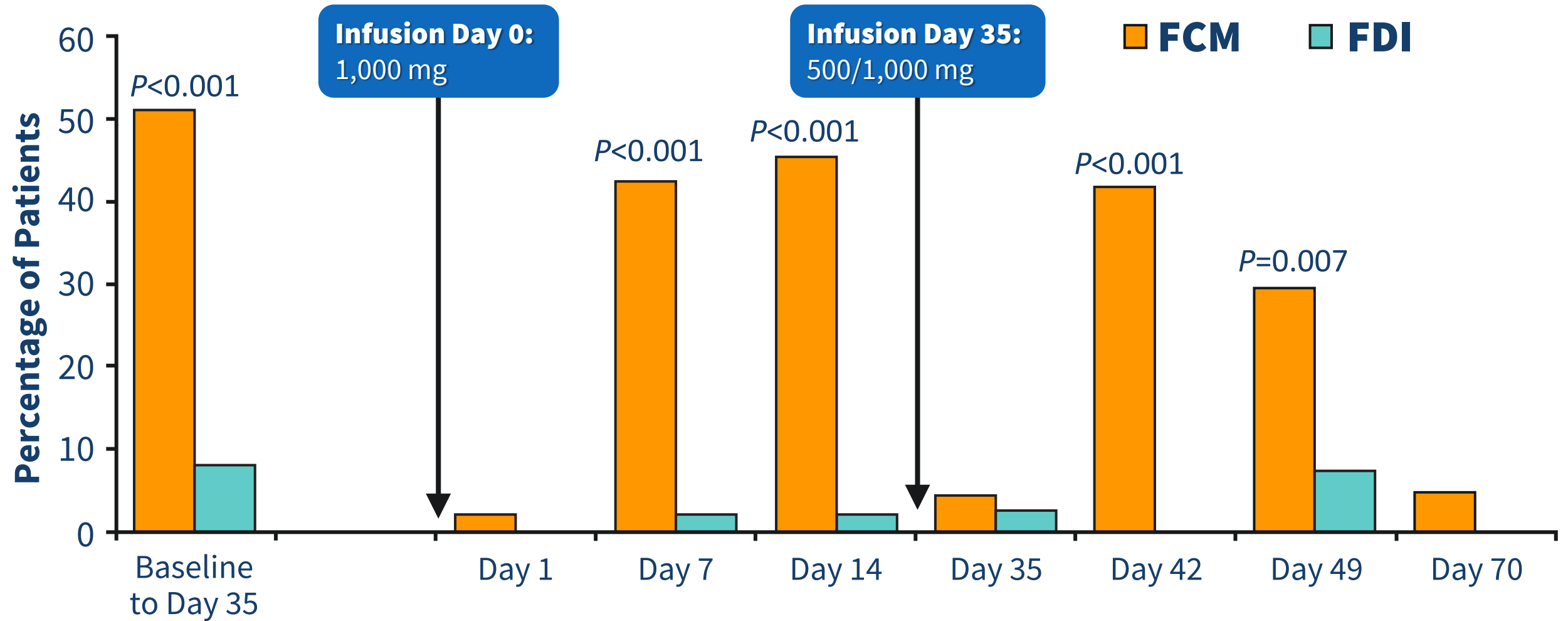
# PHOSPHARE-IBD Trial: Double-Blinded RCT of FDI vs. FCM



- 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



# PHOSPHARE-IBD Trial: Primary Outcome of Incident Hypophosphatemia

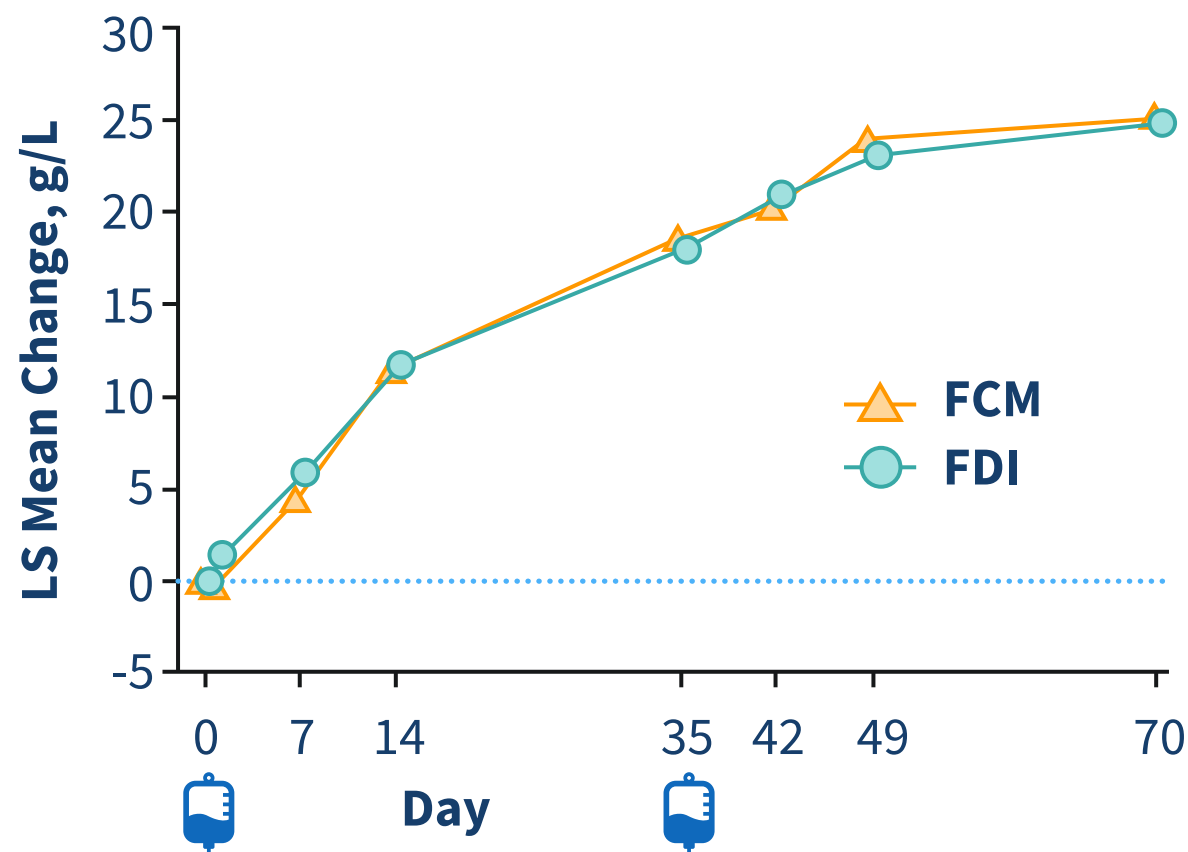


Zoller H, et al. *Gut*. 2023.

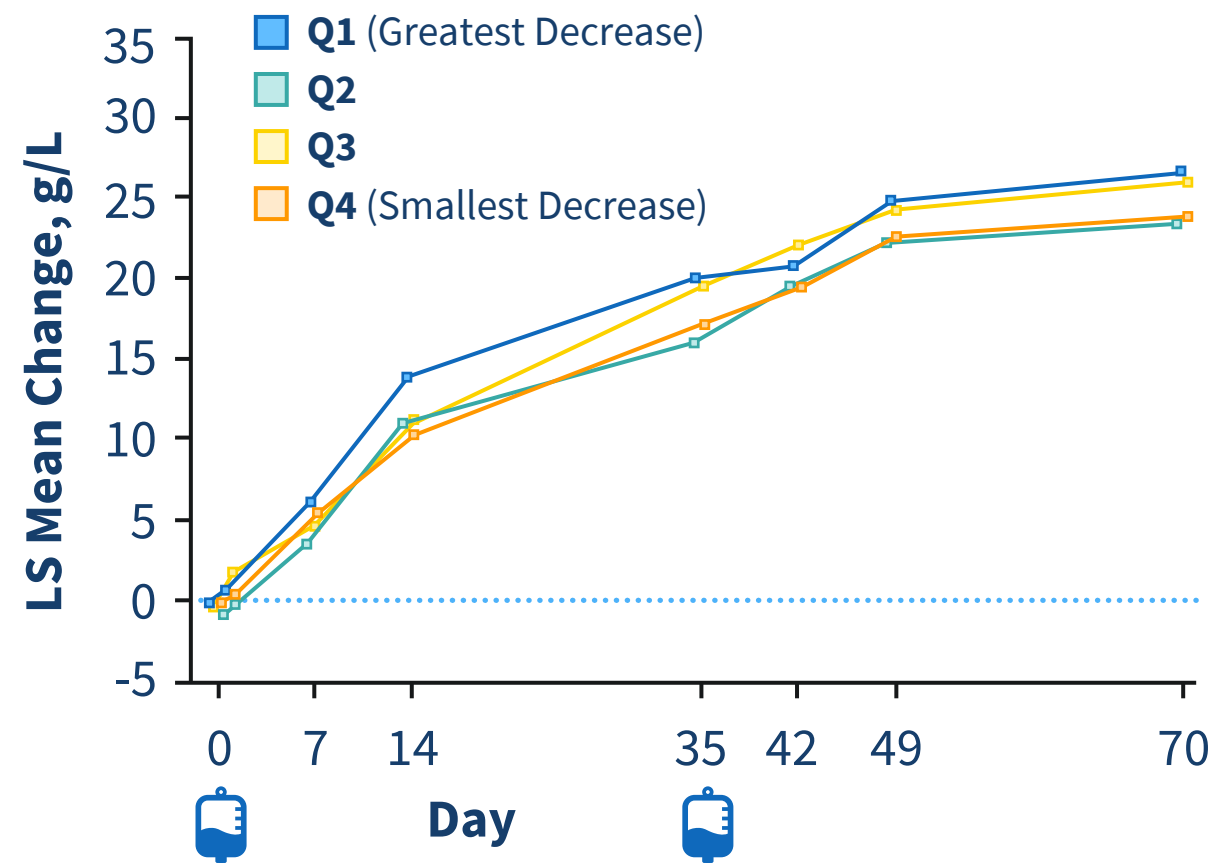


# PHOSPHARE-IBD Trial: Secondary Outcome of Hemoglobin

Hb



Hb Response by Decrease in Phosphate



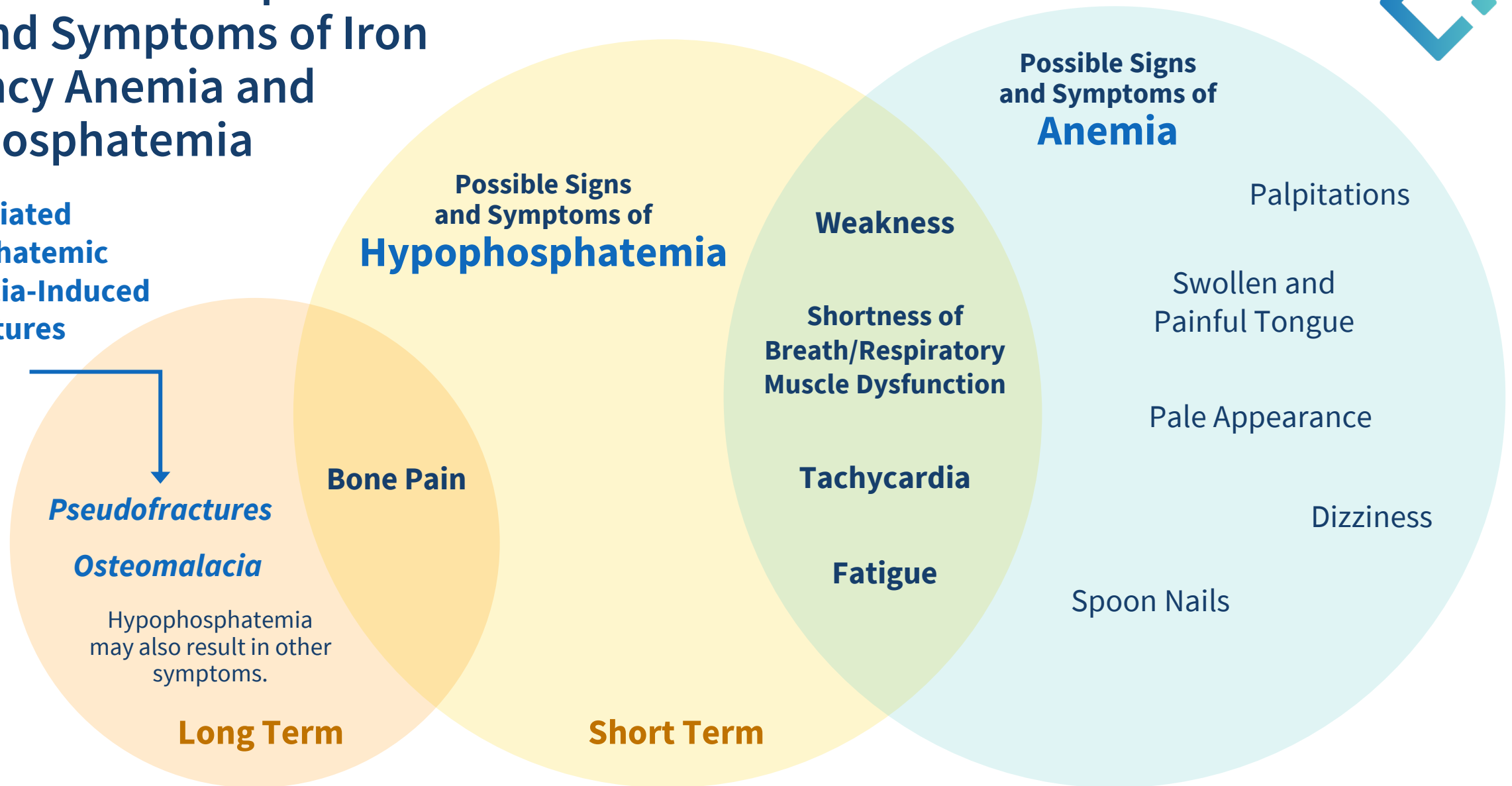
Zoller H, et al. *Gut*. 2023.



# Great Deal of Overlap Between Signs and Symptoms of Iron Deficiency Anemia and Hypophosphatemia

## iFGF23-Mediated Hypophosphatemic Osteomalacia-Induced Pseudofractures

(Insufficiency Fractures, Looser Zones)

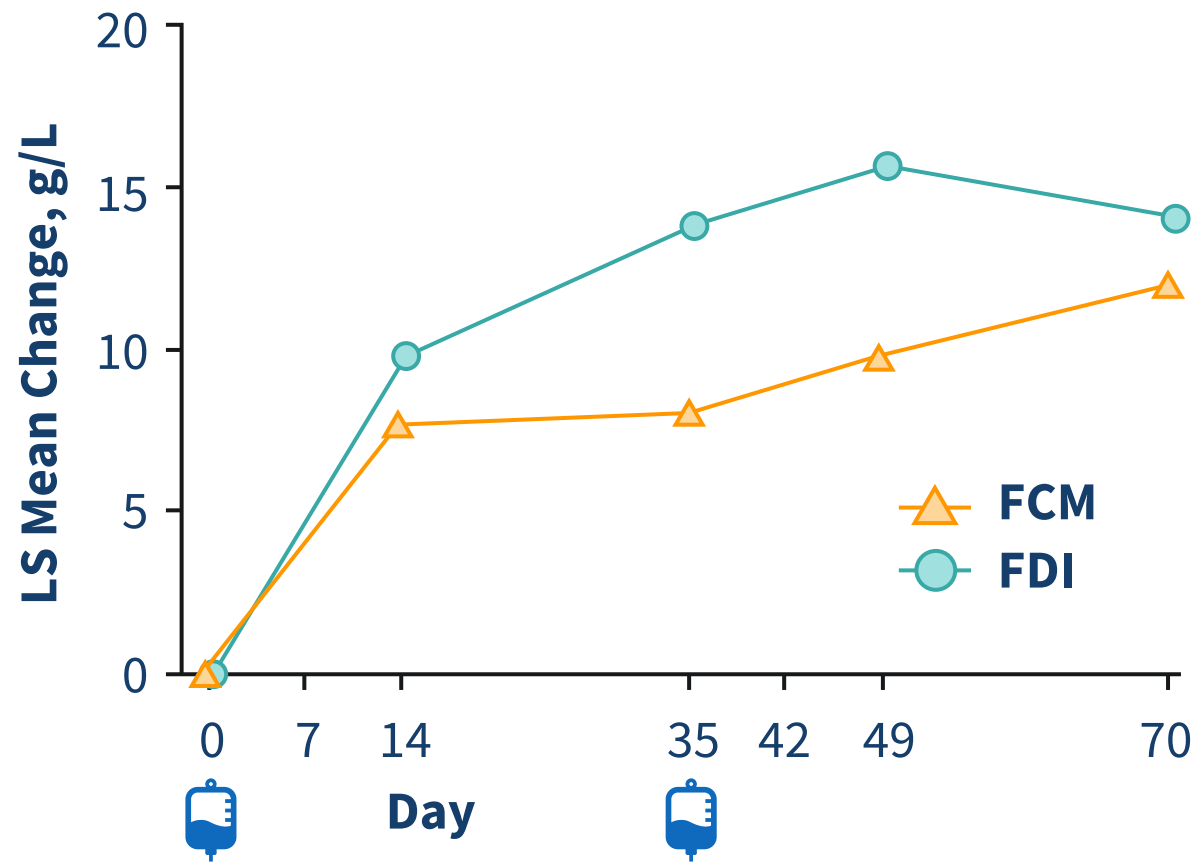


Zoller H, et al. *Curr Opin Nephrol Hypertens*. 2017; BMJ Best Practice. Iron Deficiency Anemia. 2026; Lopez A, et al. *Lancet*. 2016; Auerbach M, et al. *Am J Hematol*. 2016; Geerse D, et al. *Crit Care*. 2010; Gaasbeek A, et al. *Am J Med*. 2005.

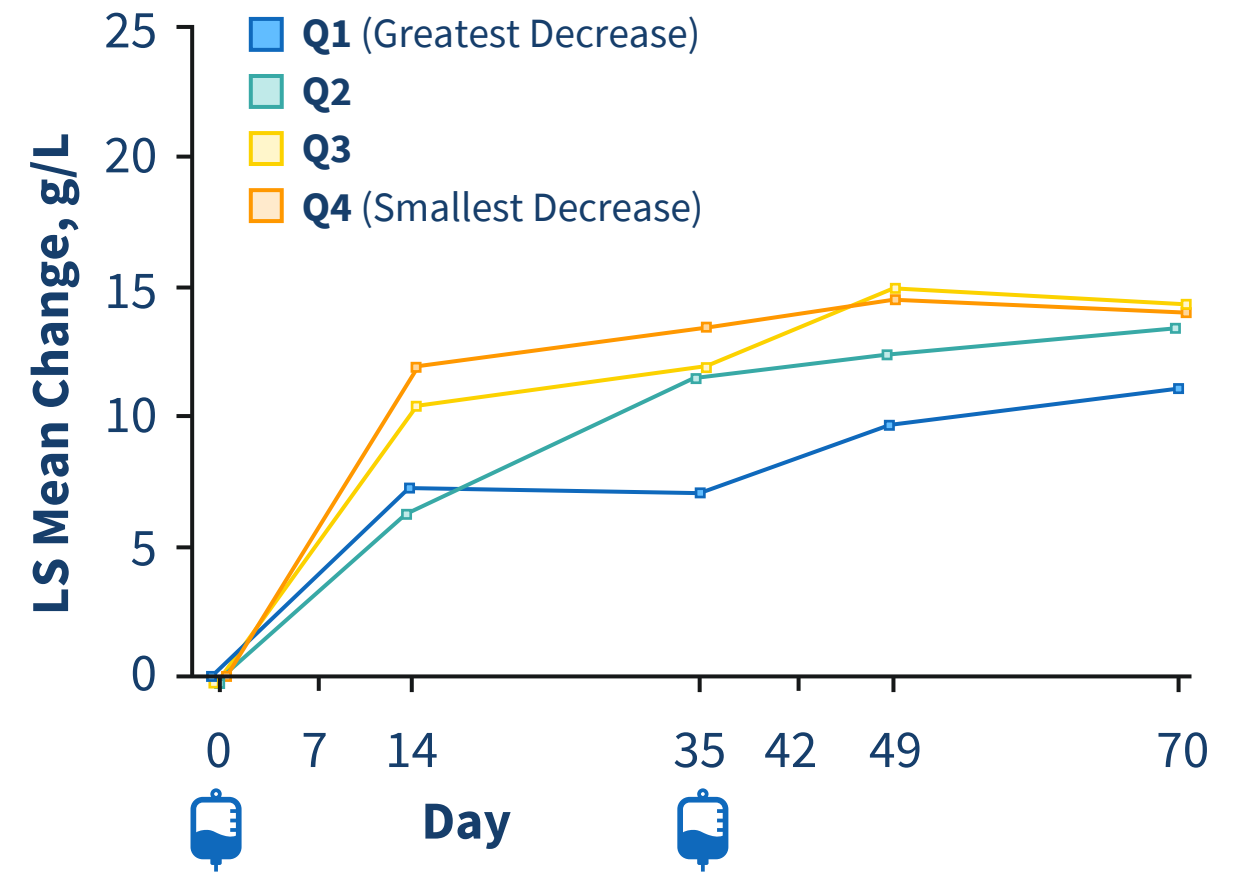
# PHOSPHARE-IBD Trial: Secondary Outcome of Fatigue



## FACIT Fatigue Scale Score



## FACIT Fatigue Scale Score by Decrease in Phosphate

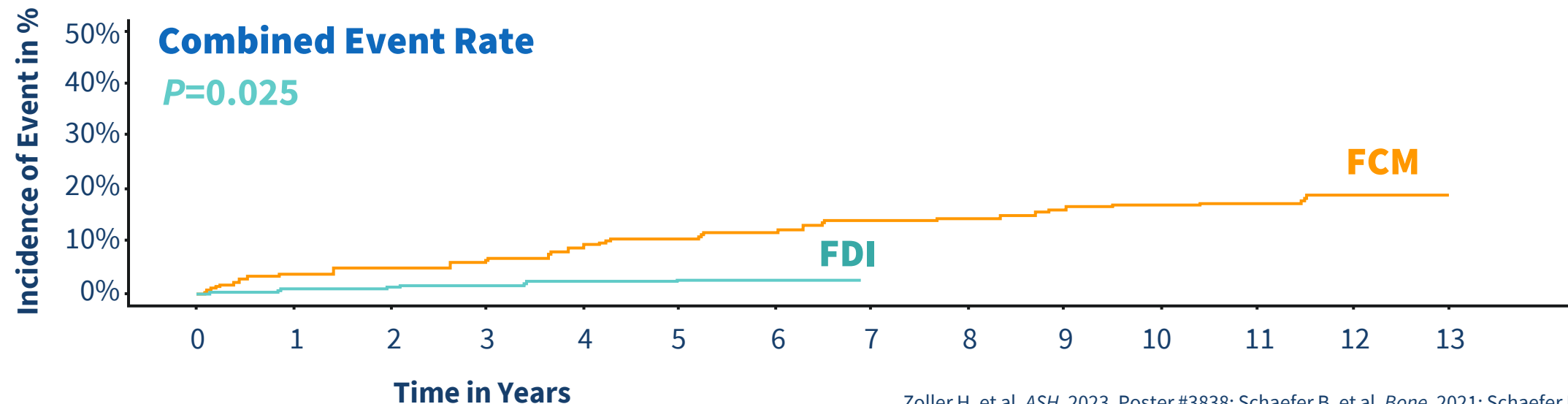


Zoller H, et al. *Gut*. 2023.

# FCM: More Fractures, Osteomalacia, and Kidney Stones



- 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.



# Differentiating IV Iron Products

## Total Dose Infusion (TDI) Capacity by IV Iron Product

| Iron Product                      | TDI on the Label | CB Patient Considerations                                                                                    |
|-----------------------------------|------------------|--------------------------------------------------------------------------------------------------------------|
| Low-Molecular-Weight Iron Dextran | No               | Long infusion times                                                                                          |
| FMX                               | No               | Label does not allow TDI; notable MRI interference                                                           |
| FCM                               | Yes              | <b>Hypophosphatemia risk, especially high in chronic bleeding patients including HHT (see product label)</b> |
| FDI                               | Yes              | None beyond mild, transient side effects listed on label                                                     |

**HHT Guidelines Advise Against\***

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

CB, chronic bleeding FCM, ferric carboxymaltose; FDI, ferric derisomaltose; FMX, ferumoxytol

## TDI is optimal in the Chronically Bleeding (CB) Patient.

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; FDA Prescribing Info.

# FCM Label Update

August 13, 2026



***Symptomatic hypophosphatemia*** added as a **Black Box Warning** to the product label:

*“Can cause **severe, prolonged hypophosphatemia**...associated with serious outcomes, including hospitalization, osteomalacia, and fractures requiring clinical intervention.”*

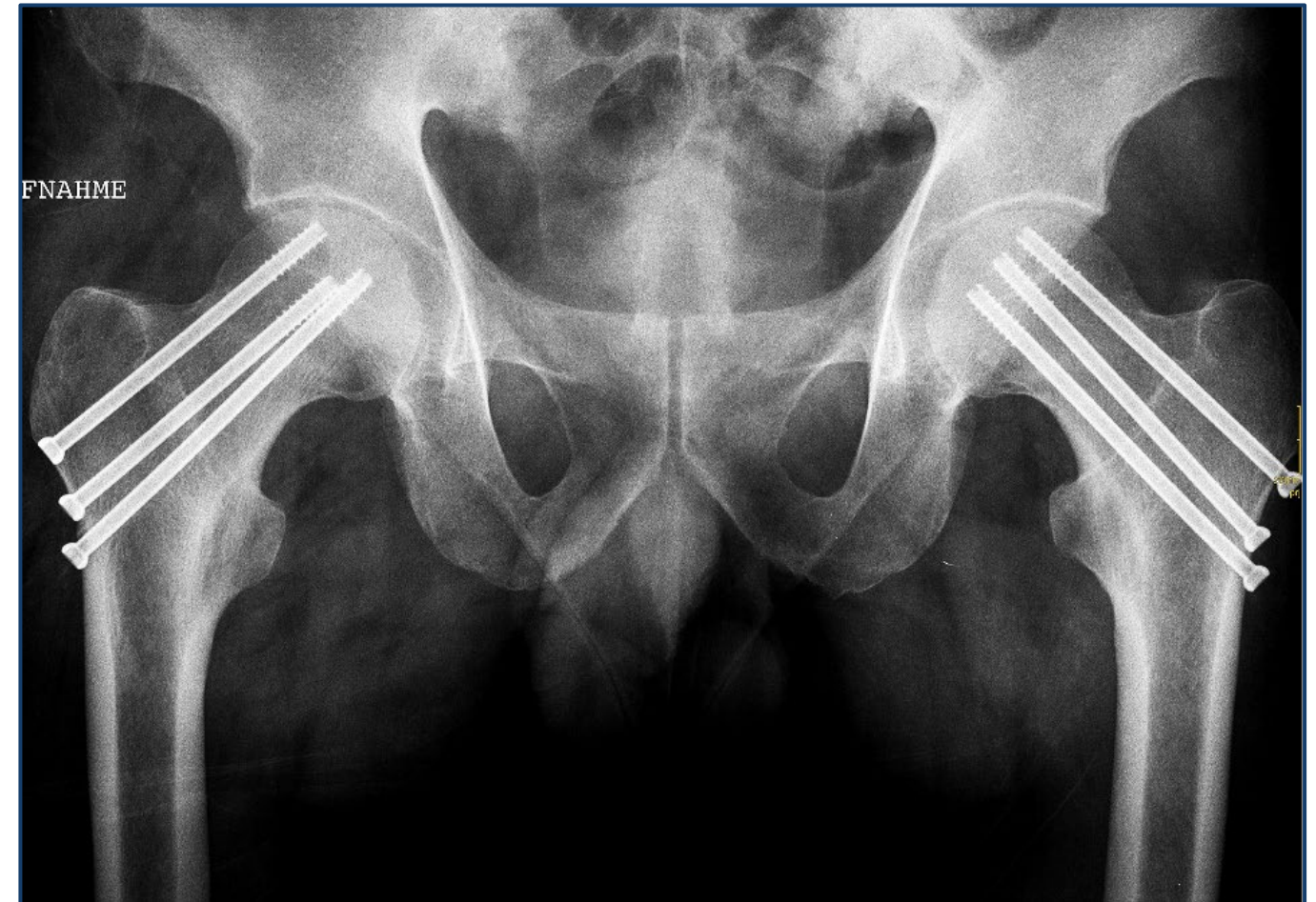
- “Hypophosphatemia has occurred in patients with normal baseline phosphate levels and *without* apparent risk factors”
- “Check serum phosphate levels...correct existing hypo-p prior to administering FCM”
- “***Advise patients about the risk***...and report any signs and symptoms”

FDA Prescribing Information.



# Patient Case 3: Joe's Follow-up

- **45-year-old man with HHT c/b epistaxis, chronic gastrointestinal bleeding presents with weakness, groin pain.**
- Patient seen by orthopedics who determines he requires femoral neck stabilization with intramedullary nails.
- **iFGF23 tested** from archived sample: **173 pg/ml.**
- He stops receiving FCM and is switched to FDI; his hypophosphatemia does not recur and his bones remineralize over time.



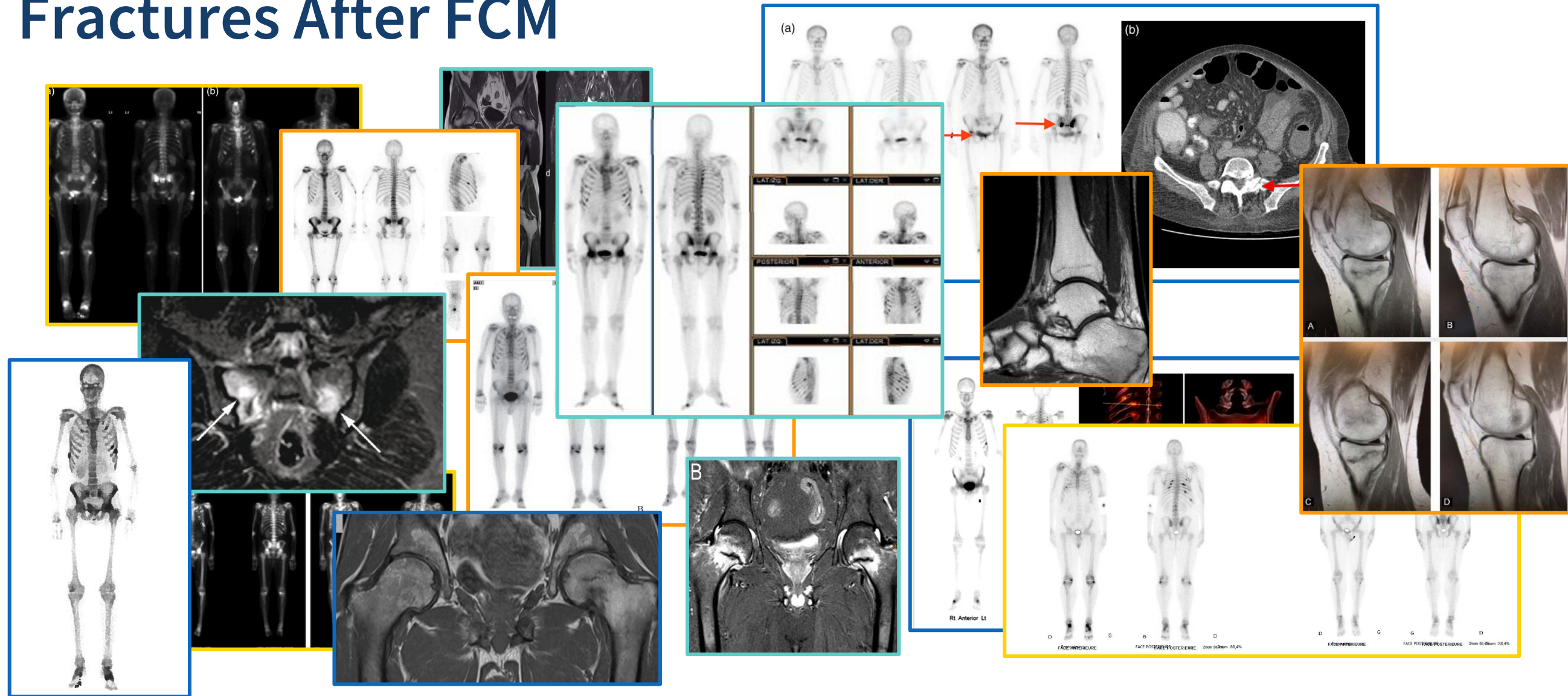
Schaefer B, et al. *Gastroenterology*. 2017.



# Bone Burden and Patient Impact

**Optimizing Efficacy and Minimizing IV Iron-Related Bone Toxicities**

# Hundreds of Published Cases of Osteomalacia and Fractures After FCM



Vilaca T, et al. *J Bone Miner Res.* 2022.



# Patient Case 4: Meet Sam

- **55-Year-Old Man with IBD Causing Chronic GI Blood Loss Presents with Acute Ankle Fracture after Minor Trauma.**
- DEXA scan shows mild osteopenia.
- Received initial ferric carboxymaltose infusions (x2) to replete iron 3 months ago after years on iron sucrose.
- Phosphate levels, after infusion and today, were both normal.

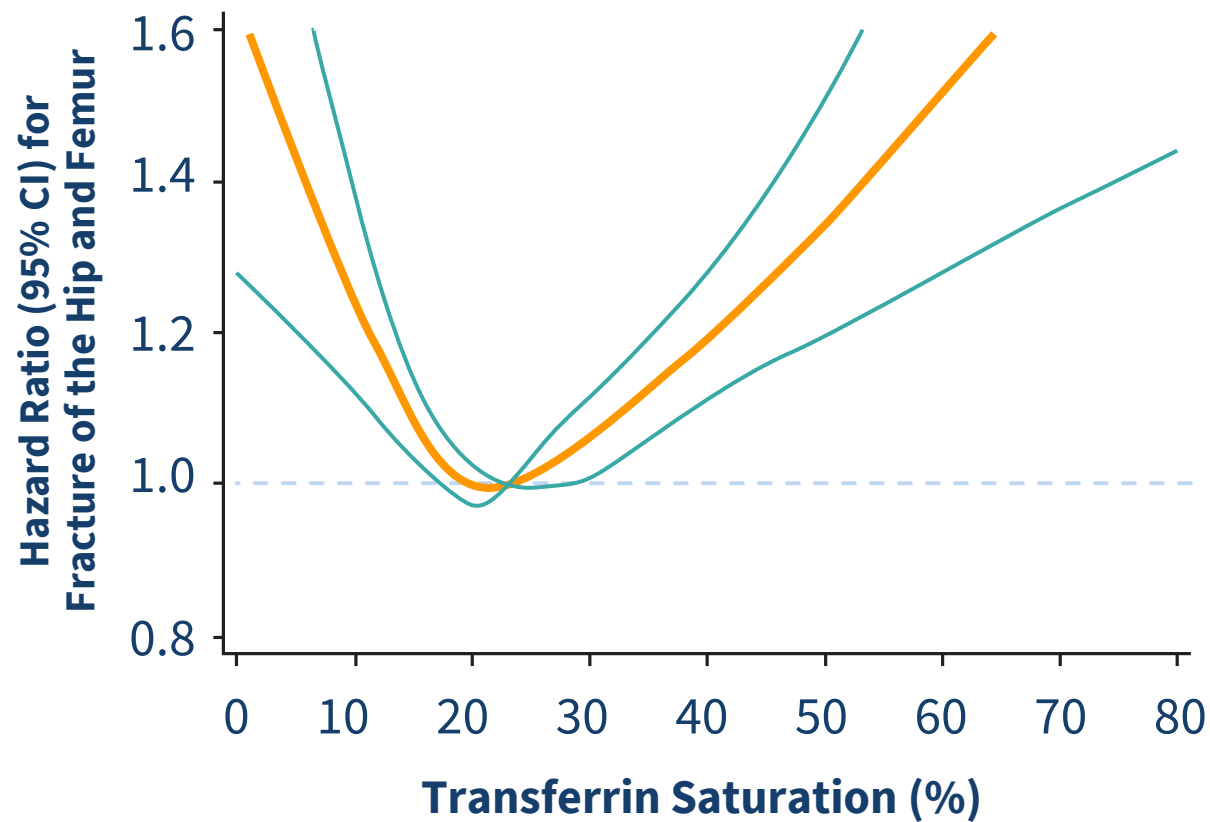


**Did the FCM contribute to his fracture risk in any way?**  
**What about simply being iron deficient *itself*? Does this contribute to fracture risk?**

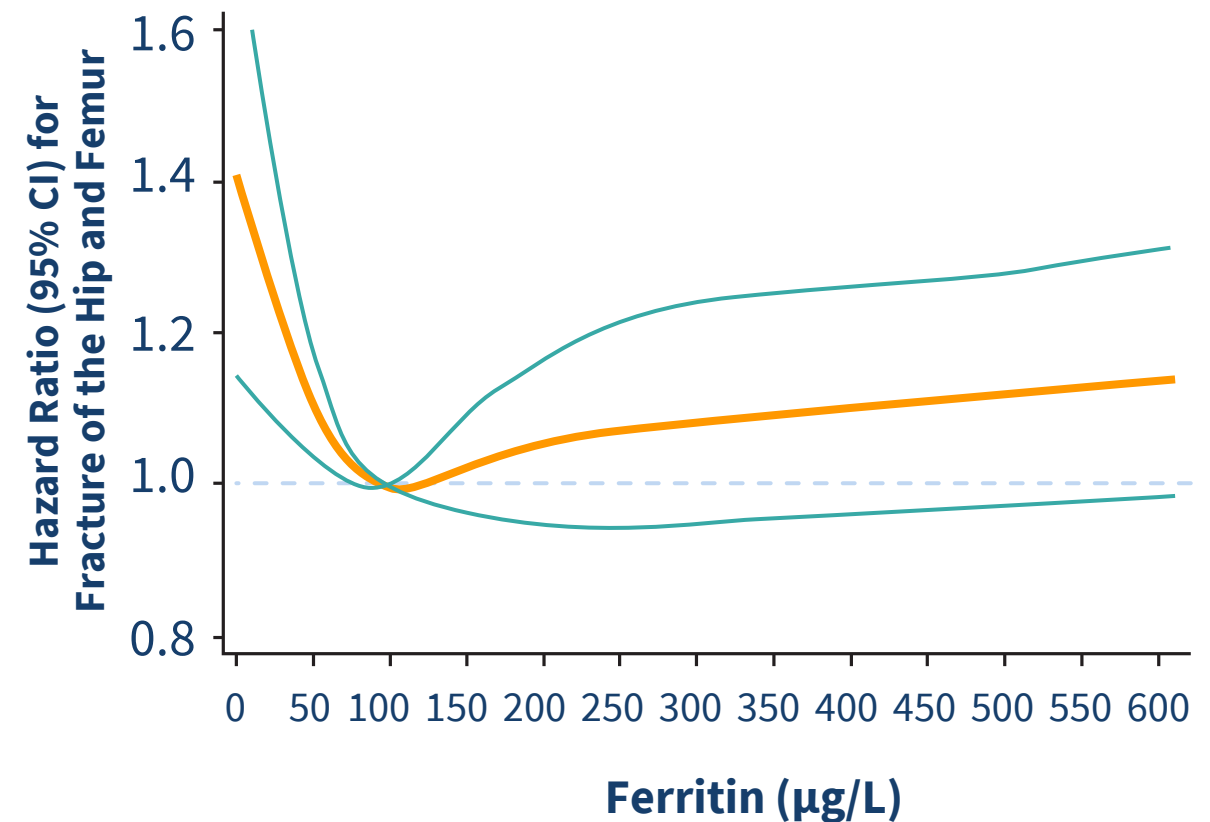


# Iron Deficiency Itself Increases Fracture Risk

## Transferrin Saturation



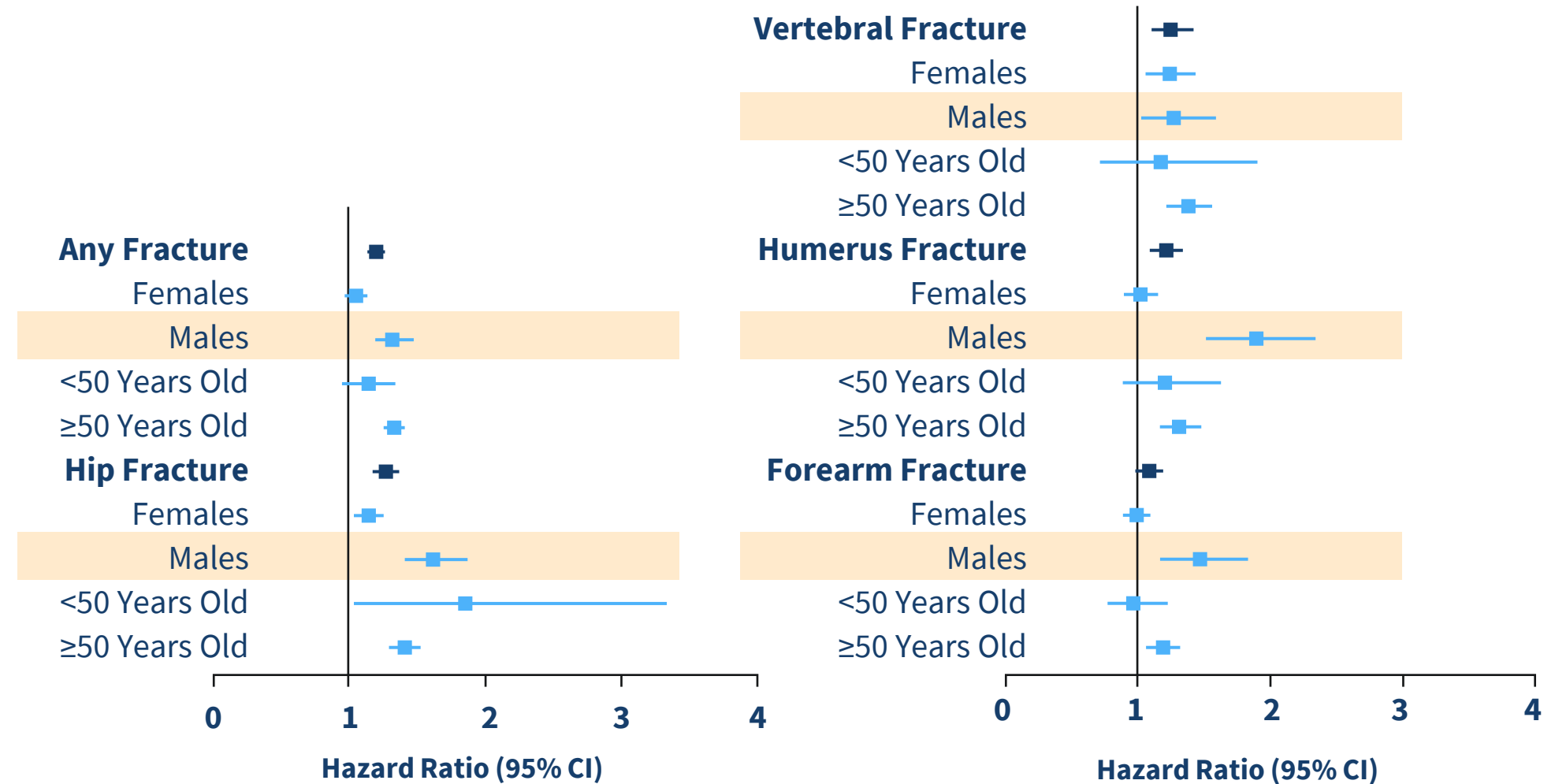
## Ferritin





# Iron Deficiency Itself Increases Fracture Risk, Particularly in Men

- UK IQVIA Medical Research Database (IMRD), incorporating The Health Improvement Network (THIN)
  - 84,932 adults with diagnosis of anemia (<13 g/dL (men) or <12 g/dL (women))
  - 158,731 propensity score matched controls

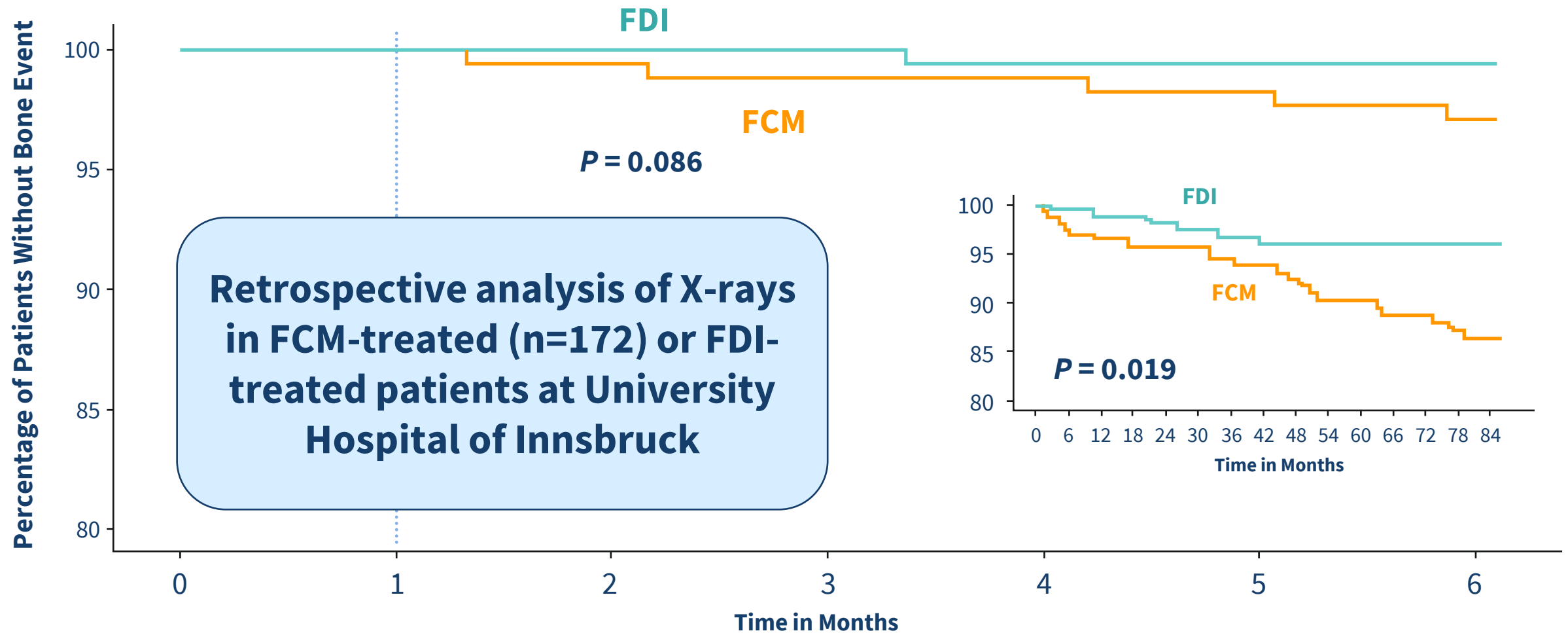


Burden A, et al. *Osteoporos Int.* 2026.



# FCM Itself May be Osteotoxic

FCM deposits in bone immediately after infusion and **increases fracture risk** (not just pseudofractures from hypophosphatemic osteomalacia).



Wagner S, et al. *Blood*. 2026.



# Animated Whiteboard Placeholder

## *Whiteboard-Animated Explainer Video (extended length):*

Audio-visual illustration of the relative influence of IV iron products on bone metabolism, osteoblast/osteocyte activity, the dysregulation of phosphate homeostasis, and all bone-related clinical complications, including significant increases in fracture risk, in all patients with ID/IDA.



# FCM Itself May be Osteotoxic

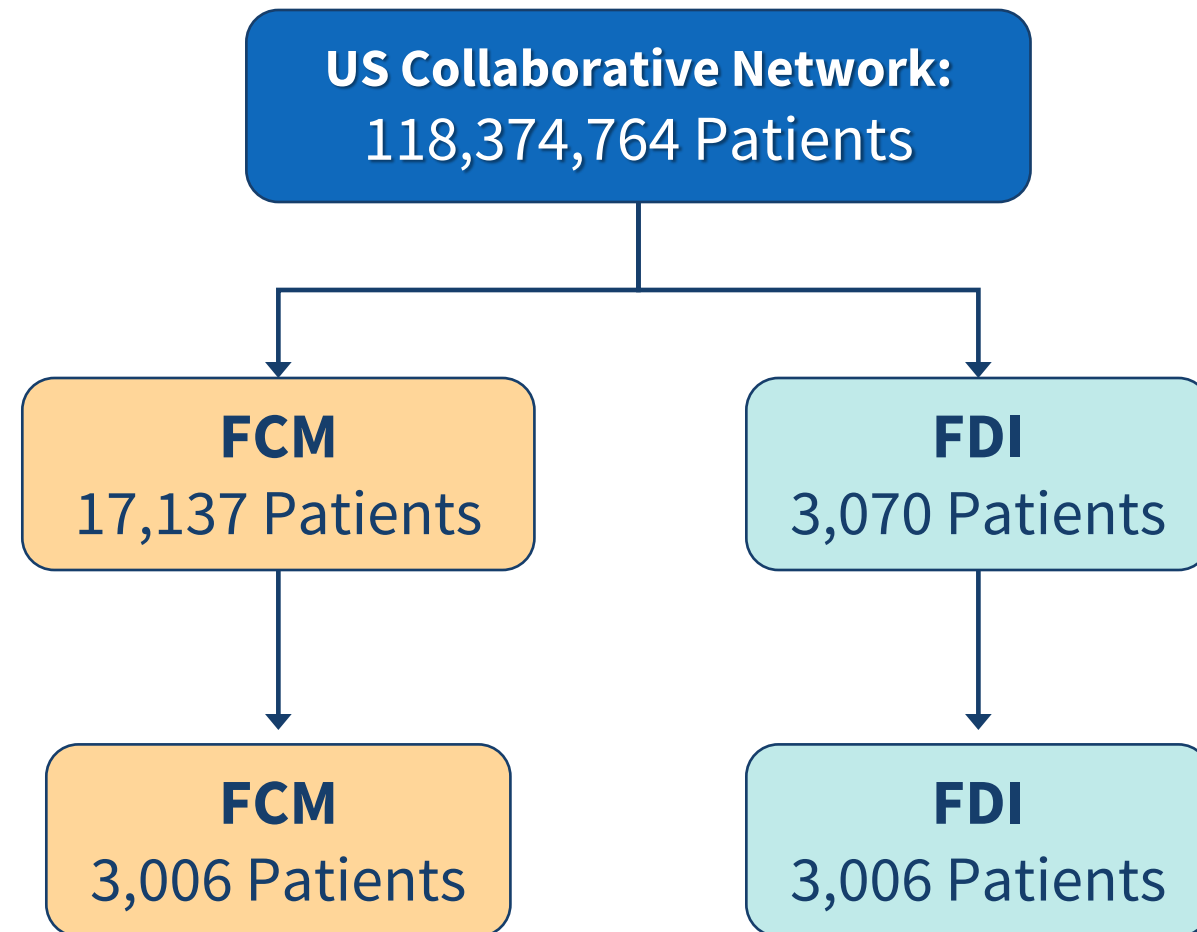
FCM deposits in bone immediately after infusion and **increases fracture risk** (not just pseudofractures from hypophosphatemic osteomalacia).

## Inclusion Criteria, Index Event:

- **IV Iron:** One dosing period.
- **FCM:** Without any other IV iron formulation.
- **FDI:** Without any other IV iron formulation.
- No fracture one year before the index event.

## Outcome:

- Fractures, Stress Fractures
- Pathological Fractures
- $\geq 4$  weeks after the index event



## Time to Event Analysis:

- Adjusted Cox Proportional Hazards Model
- One year after IV iron

## Kaplan Meier Analysis: FCM- vs FDI-Treated Patients

- 1 month to 1 year after IV iron
- 1 month to 10 years after IV iron

Wagner S, et al. *Blood*. 2026.



# FCM Itself May be Osteotoxic

FCM deposits in bone immediately after infusion and ***increases fracture risk*** (not just pseudofractures from hypophosphatemic osteomalacia).

| Results of TriNetX Cox Regression                       | Multivariate HR for Bone Fracture | P-Value          |
|---------------------------------------------------------|-----------------------------------|------------------|
| <b>Sex</b><br>(Male = 0; Female = 1)                    | 0.996 (0.759-1.232)               | 0.784            |
| <b>Age</b>                                              | <b>1.026</b> (1.020-1.032)        | <b>&lt;0.001</b> |
| <b>Treatment Group FDI vs FCM</b><br>(FDI = 0; FCM = 1) | <b>2.029</b> (1.347-3.056)        | <b>0.001</b>     |
| <b>Chronic Kidney Disease</b>                           | <b>1.303</b> (1.017-1.670)        | <b>0.036</b>     |
| <b>Osteoporosis Without Fracture</b>                    | <b>2.351</b> (1.776-3.112)        | <b>&lt;0.001</b> |
| <b>Iron Deficiency</b>                                  | 1.349 (0.991-1.836)               | 0.057            |
| <b>Iron Deficiency Anemia</b>                           | 1.116 (0.890-1.398)               | 0.949            |
| <b>Hemoglobin</b>                                       | <b>0.938</b> (0.884-0.997)        | <b>0.038</b>     |

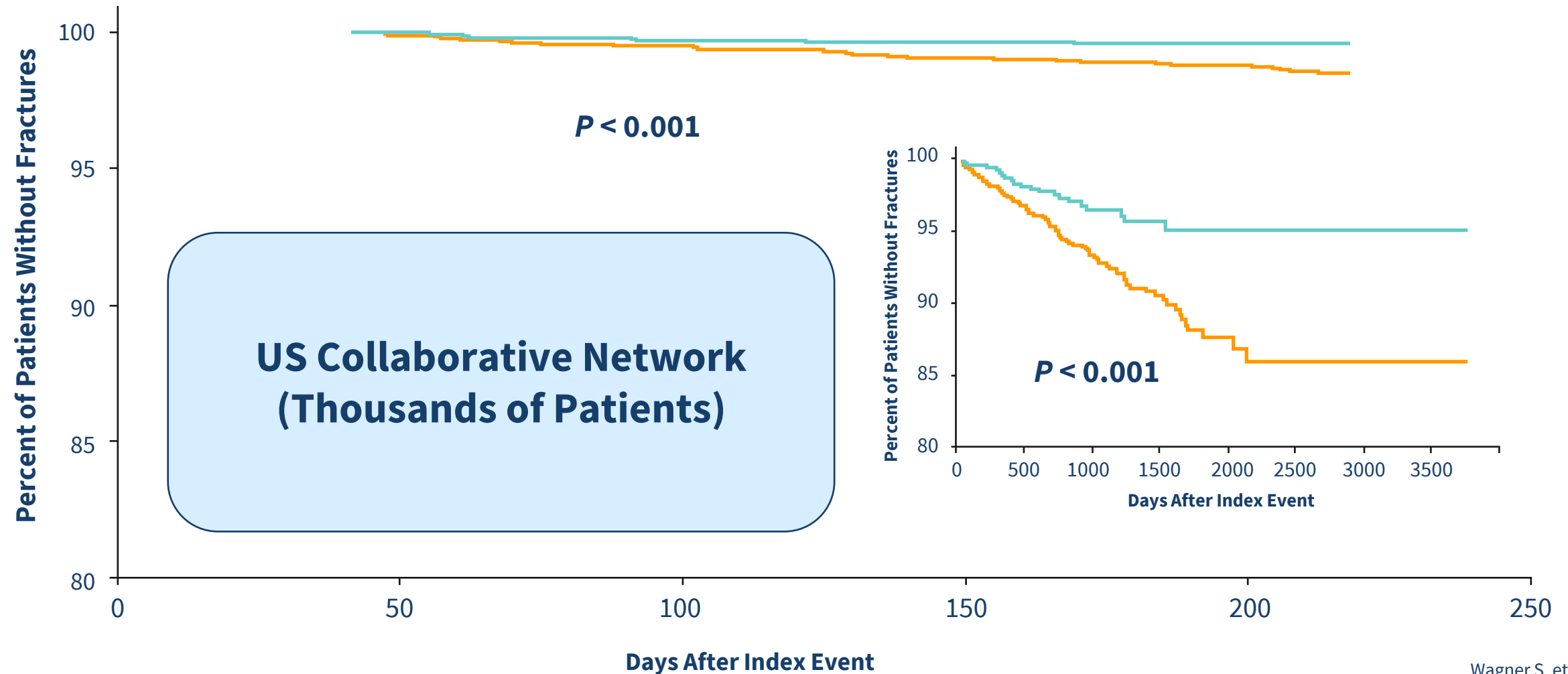
| Results of TriNetX Cox Regression | Multivariate HR for Bone Fracture | P-Value          |
|-----------------------------------|-----------------------------------|------------------|
| <b>Serum/Plasma-Calcium</b>       | <b>0.674</b> (0.596-0.799)        | <b>&lt;0.001</b> |
| <b>Serum/Plasma-Magnesium</b>     | 0.824 (0.509-1.332)               | 0.429            |
| <b>Serum/Plasma-Phosphate</b>     | 1.015 (0.917-1.124)               | 0.771            |
| <b>Serum/Plasma-Ferritin</b>      | 1.001 (0.999-1.002)               | 0.973            |
| <b>Serum/Plasma-Transferrin</b>   | 0.999 (0.996-1.001)               | 0.37             |

Wagner S, et al. *Blood*. 2026.



# FCM Itself May be Osteotoxic

FCM deposits in bone immediately after infusion and **increases fracture risk** (not just pseudofractures from hypophosphatemic osteomalacia).

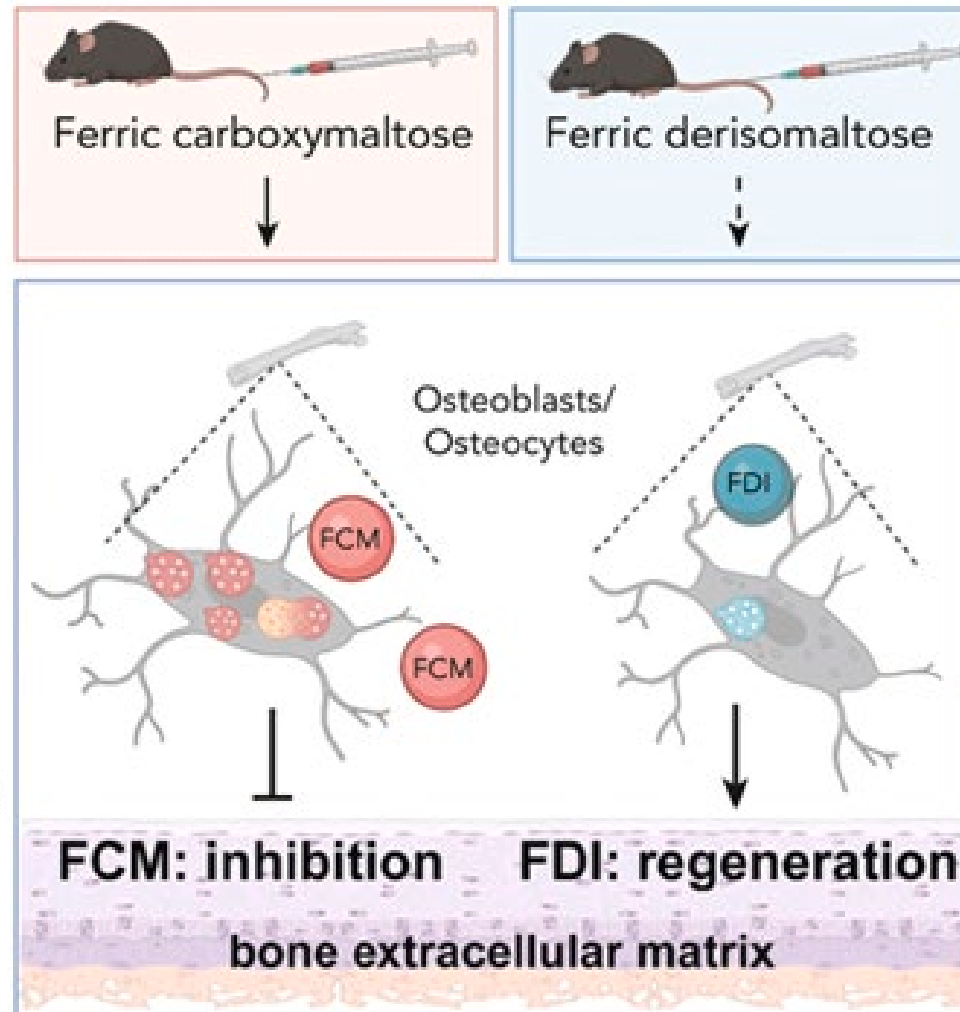
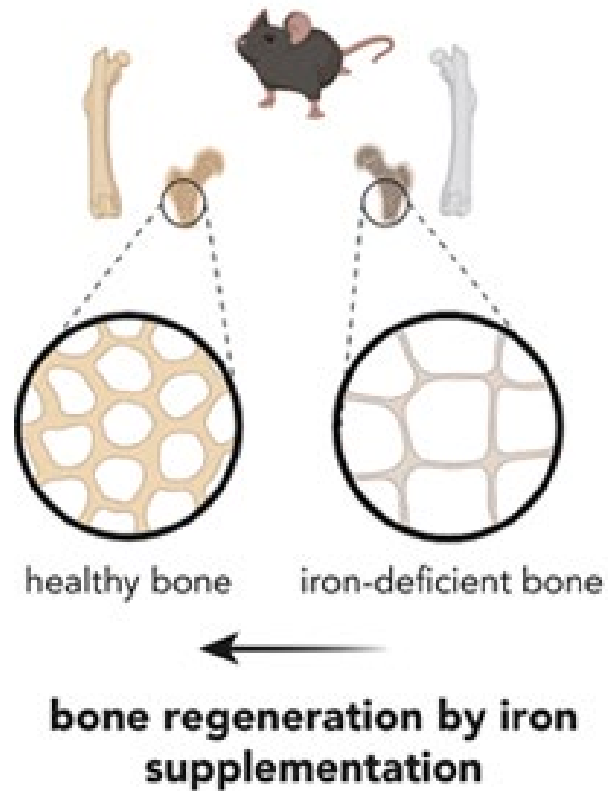


Wagner S, et al. *Blood*. 2026.

# Mouse Studies Demonstrate FCM Deposition in Osteocytes and Negative Impacts



## Animal model of iron deficiency anemia



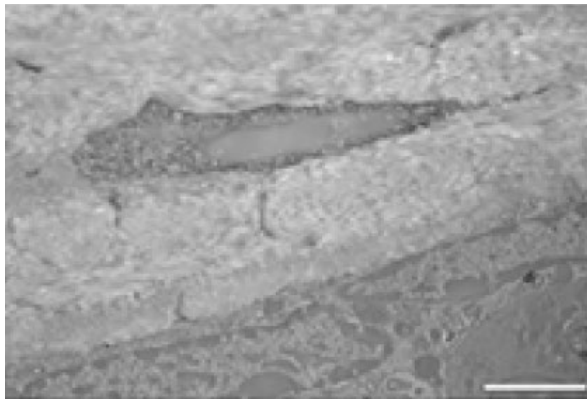
Wagner S, et al. *Blood*. 2026.



# Mouse Studies Demonstrate FCM Deposition in Osteocytes and Negative Impacts

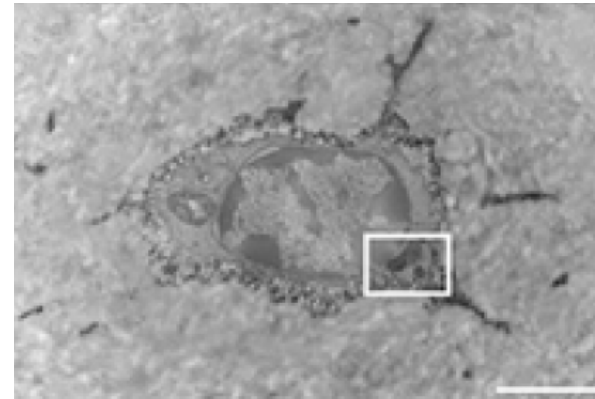
Electron microscopy of early embedding osteocytes with iron-filled endo-lysosomal vesicles

## Control

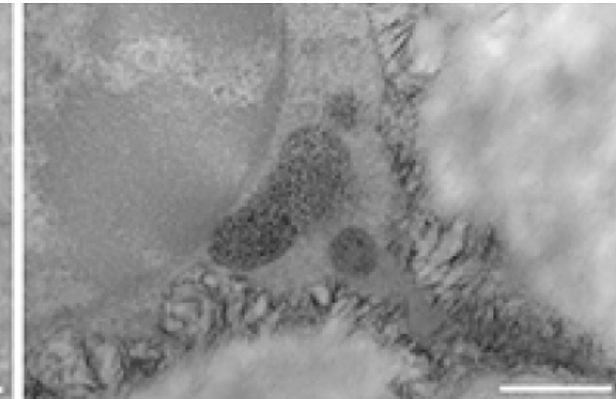


Scale Bar: 2  $\mu$ m

## IDA + FCM



Scale Bar: 2  $\mu$ m

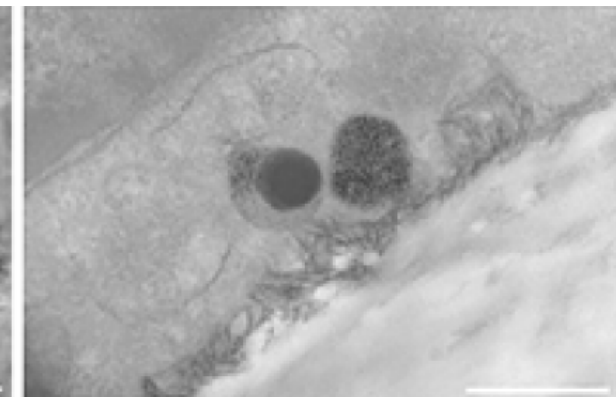
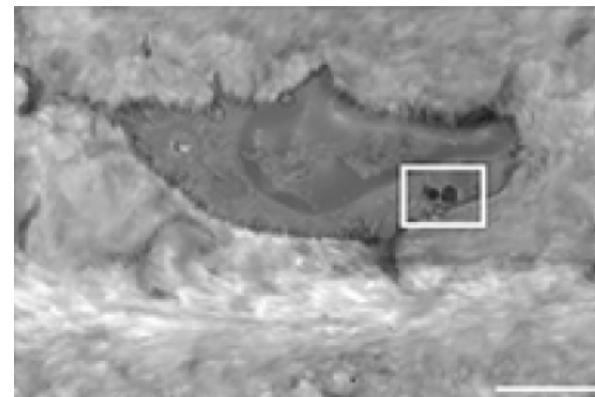


Scale Bar: 500 nm

## IDA



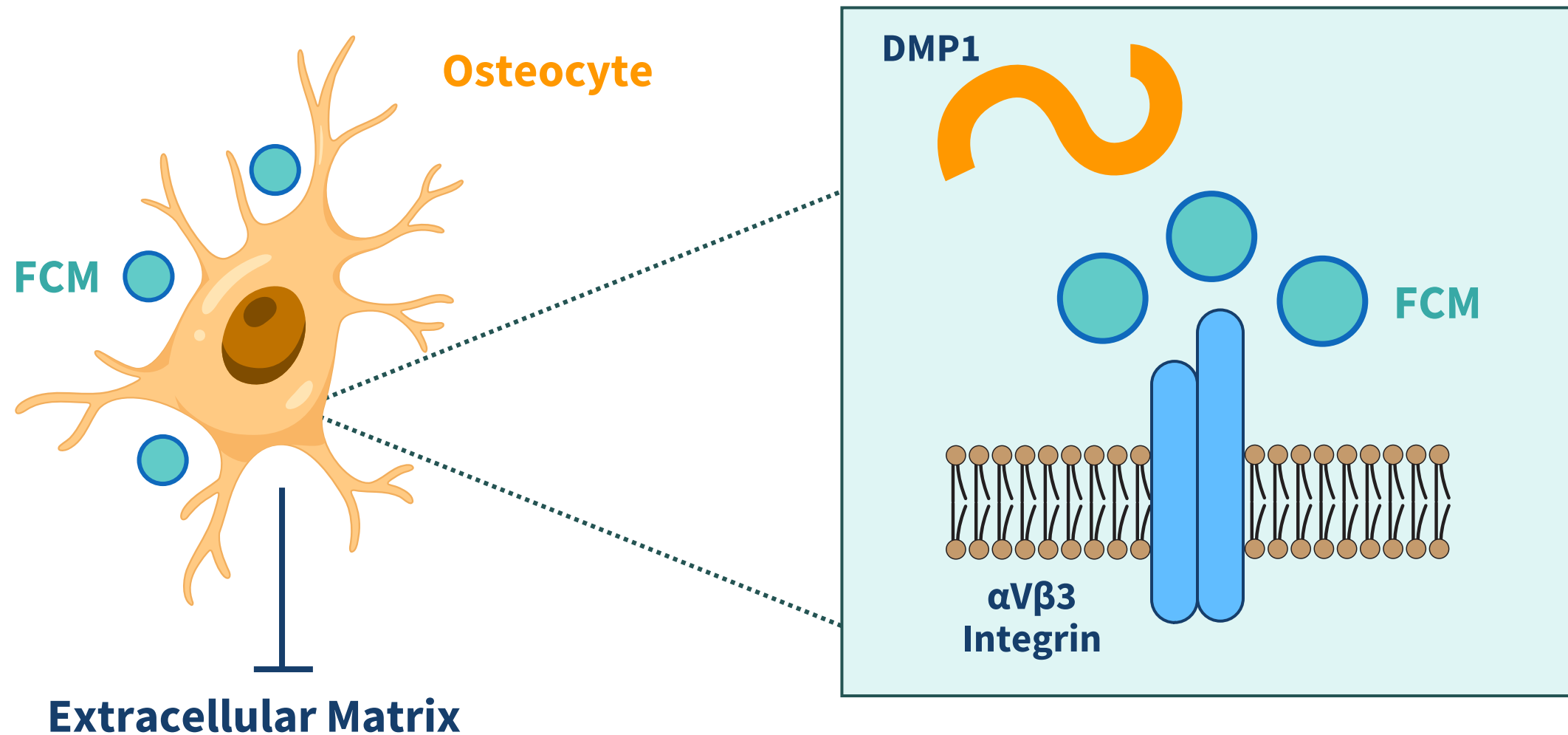
## IDA + FDI



Wagner S, et al.  
*Blood*. 2026.



# Mouse Studies Demonstrate FCM Deposition in Osteocytes and Negative Impacts



Wagner S, et al. *Blood*. 2026; Finberg K, et al. *Blood*. 2026; Martens K, et al. *Hematology Am Soc Hematol Educ Program*. 2023; Auerbach M, et al. *Am J Hematol*. 2025; Auerbach M, et al. *JAMA*. 2025; Martin A. *Curr Opin Nephrol Hypertens*. 2019.

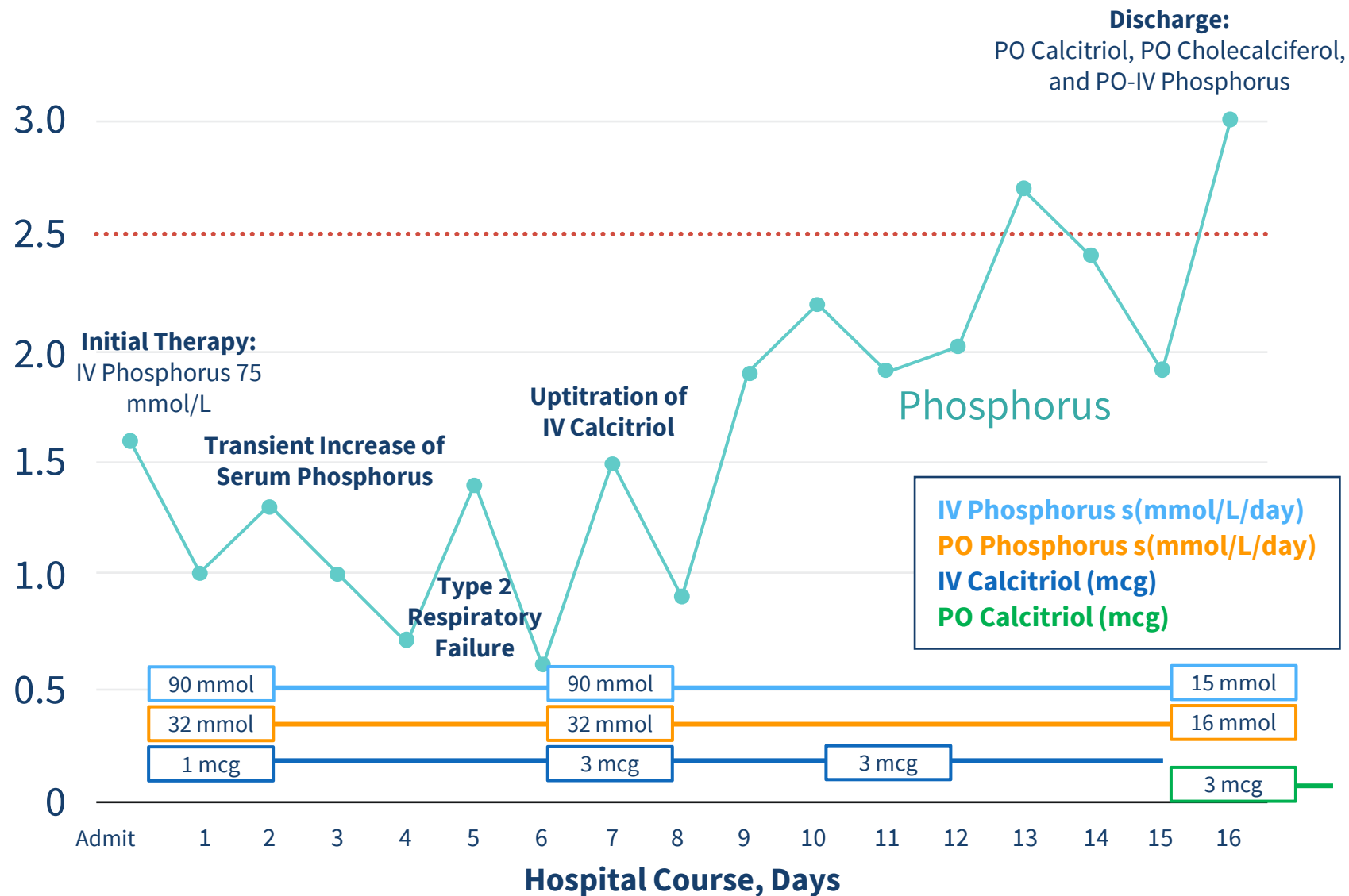


# Patient Case 5: Meet Phoebe

- **28-Year-Old Woman, Healthy, Heavy Menstrual Bleeding.**
- Evaluated for heavy menstrual bleeding, found to have iron deficiency anemia, administered **one course of FCM.**
- **Six weeks later**, presents with fatigue, muscle weakness, palpitations.
- **Two weeks after this**, is admitted for worsening symptoms, found to have phosphate of 1.6 mg/dL (LLN, 2.5 mg/dL) that drops to 1.0 mg/dL within 24 hours.
  - Treated aggressively with PO and IV phosphate, calcitriol, with transient increases in phosphate but continued downward trajectory.
  - **Hospital Day 7: Acute respiratory failure; intubation; phosphate 0.6 mg/dL.**



# Severe Hypophosphatemia Can Happen After Only ONE Course of FCM



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



# Myths Regarding FCM Treatment-Emergent Hypophosphatemia

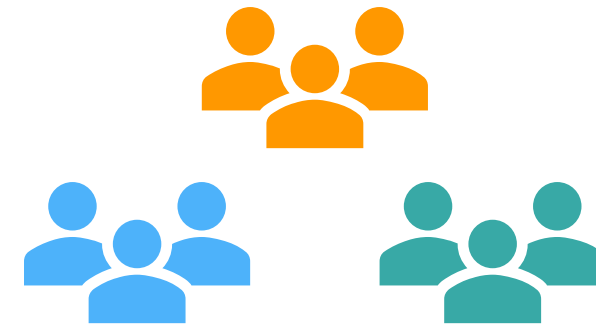
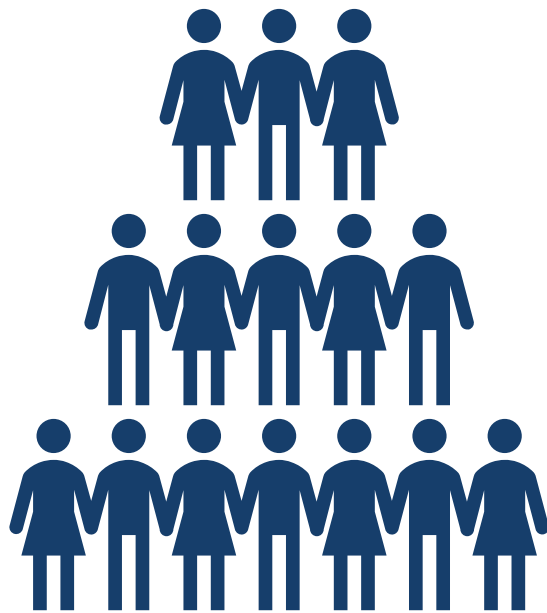
- **Myth #1:** It's common but not clinically relevant and doesn't cause symptoms.
  - **FACT:** The data summarily debunks this statement.
- **Myth #2:** "I don't know, I give FCM all the time and none of my patients are hypophosphatemic."
  - **FACT:** If phosphate is not checked before infusion and weekly for three weeks after each infusion, this is easily missed.
- **Myth #3:** "I know this is a problem in adults, but I'm a pediatrician and this just doesn't happen in kids."
  - **FACT:** Yes, it does. The rate is 33% rather than 50-75%, and can last for weeks to months in children as well.
- **Myth #4:** "I heard pregnant women don't get this complication, and my OB colleagues use FCM all the time, so it must be fine in pregnant women."
  - **FACT:** It absolutely happens in pregnant women (15-45% incidence) and is not currently well-recognized in the OB/Gyn community.

Schaefer B, et al. *Bone*. 2022; Wolf M, et al. *J Bone Miner Res*. 2013; Auerbach M, et al. *Am J Hematol*. 2021; Auerbach M, et al. *Am J Hematol*. 2025; Kirk S, et al. *Am J Hematol*. 2021.

# Risk Factors for FCM Treatment-Emergent Hypophosphatemia: **The Reality**



**Everyone** is at **high risk**.



**Certain groups** are at **very high risk**.

Schaefer B, et al. *Bone*. 2022; Wolf M, et al. *J Bone Miner Res*. 2013; Auerbach M, et al. *Am J Hematol*. 2021; Auerbach M, et al. *Am J Hematol*. 2025; Wolf M, et al. *JAMA*. 2020; Magagnoli J, et al. *Am J Hematol*. 2025.

# Can FCM Treatment-Emergent Hypophosphatemia Be Treated?



- Not really, but **it can be prevented** easily by avoiding FCM.
- You can give PO and IV phosphate, but patient will urinate it out.
- You can give PO and IV calcitriol, but you're increasing the risk for kidney stones.
- You can give burosumab, an antibody directed against FGF23, that is used to treat X-linked hypophosphatemic rickets and the paraneoplastic syndrome tumor-induced osteomalacia, but it **costs tens of thousands of dollars per dose** in the US.



# Remember: ID/IDA Management Takes a Team!

- Diagnosing, evaluating, and treating ID/IDA is a *multidisciplinary and interprofessional effort*
- Iron repletion is a core component
  - IV vs. oral modalities
  - Selection of specific IV iron product
  - Dosing, administration, tolerability
- Communication, collaboration, and clinical coordination
  - With the patient at the center



DeLoughery T, et al. *Clin Gastroenterol Hepatol*. 2024; Batsuli G, et al. *Haemophilia*. 2026.



# Key Educational and Clinical Takeaways

- Expanding evidence now calls the traditional “oral iron first, IV iron if needed” paradigm into question
  - IV iron offers tolerability, efficacy, and even health economic benefits vs. oral iron
- Not all IV iron formulations are created equal
  - FDI and ferumoxitol offer preferable dosing and safety profiles in ID/IDA
  - LMW iron dextran is also a suitable option
  - FCM should be avoided if possible
- FCM has uniquely deleterious effects on bone health
  - Exhibits high rates of treatment-emergent hypophosphatemia
  - Exerts direct osteotoxicity, even independent of hypophosphatemia
    - ***Accumulates in osteocytes and impairs bone formation***
  - Associated with increased risk of fractures and bone complications



# Guided Reflection and Actuation

- *How will you apply what you've learned today?*
- Will this education impact the way you collaborate with your care team in the management of ID/IDA?
- What would you personally consider to be the key takeaways?
- Reflect on any gaps, barriers, or outstanding questions in your practice



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# Interactive Q&A