CORNERSTONE CLINICAL TOOL

Challenging the Status Quo in Hereditary Hemorrhagic Telangiectasia: *A Comprehensive Review of IV Iron Best Practices at the Hematology-Primary Care Interface*

Second International HHT Guidelines

At-A-Glance Summary of Anemia Recommendations

Adapted from:
Faughnan M, et al.
Ann Intern Med. 2020.

C1

QoE: **HIGH**

SoR: **STRONG**

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.

C2

QoE: **MOD.**

SoR: **STRONG**

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

C3

QoE: **LOW**

SoR: **STRONG**

RBC transfusions in the following settings:

- Hemodynamic instability/shock
- Comorbidities that require a higher hemoglobin (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

C4

QoE: **LOW**

SoR: **STRONG**

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

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

MOD: Moderate, QoE: Quality of Evidence, SoR: Strength of Recommendation

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IV Iron Products and Use in HHT

Adapted from: **FDA Prescribing Information, Auerbach M, et al. Lancet Haematol. 2020;7(4):e342-e350; Faughnan M, et al. Ann Intern Med. 2020; Magagnoli J, et al. Am J Hematol. 2025; Auerbach M, Wolf M. Am J Hematol. 2025.**

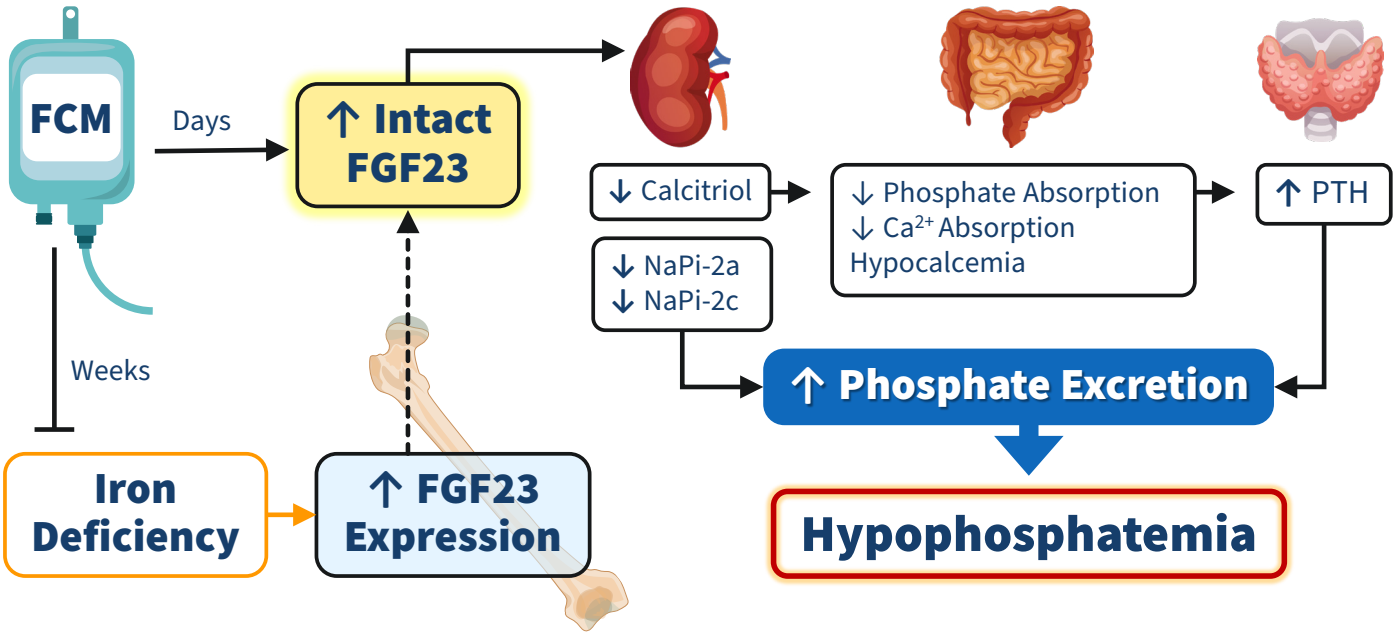
*IV iron formulations that allow for **total dose infusions (TDI)** – that is, **full dose iron repletion in a single infusion** – are preferred in HHT, as they **mitigate the already immense infusion burden for these patients who typically require repeated infusions**.*

Iron Product	TDI on Label	Infusion Time	Patients	Common Adverse Events	Warnings & Precautions
FCM AVOID in HHT	Yes	≥15 minutes	Adults, Peds (≥1y)	Nausea, hypertension, **hypophosphatemia**, flushing	Hypersensitivity reactions, **symptomatic hypophosphatemia**, hypertension
FDI	Yes	≥20 minutes	Adults	Nausea, injection site reactions, rash, hypotension	Hypersensitivity reactions, iron overload
FMX	No	≥15 minutes	Adults	Dizziness, hypotension, constipation, nausea, **MRI interference**	**Black box:** fatal and serious hypersensitivity reactions, including anaphylaxis
Iron Sucrose	No	≥15 minutes	Adults, Peds (≥2y)	Diarrhea, nausea, vomiting, headache, hypotension, pruritus	Hypersensitivity reactions, hypotension, iron overload
Low-Molecular-Weight Iron Dextran	No	1 hour (not to exceed 50 mg/min)	Adults, Peds (≥4 months)	Pruritis, abdominal pain, nausea, vomiting, diarrhea	**Black box:** risk for anaphylactic-type reactions, including fatalities
Sodium Ferric Gluconate	No	1 hour	Adults, Peds (≥6y)	Chest pain, leg cramps, dizziness, dyspnea, nausea, vomiting, diarrhea	Hypersensitivity reactions, hypotension, iron overload, benzyl alcohol toxicity

FCM: ferric carboxymaltose, FDI: ferric derisomaltose, FMX: ferumoxytol, Peds: pediatric patients

Mechanism of FCM-Induced Hypophosphatemia

Adapted from: **Schaefer B, et al. Bone. 2022 Jan:154:116202.**



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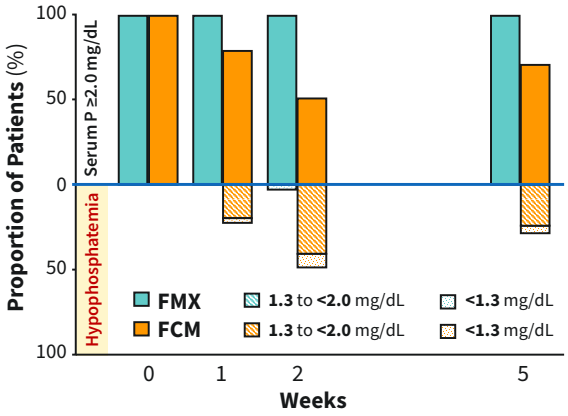
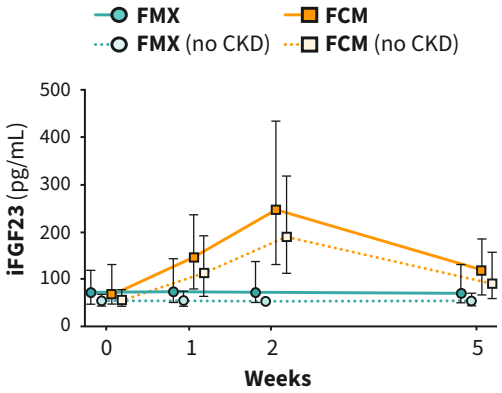
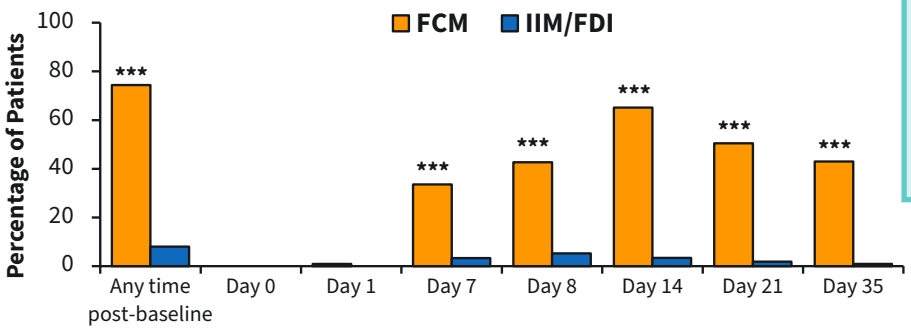
Key Trial Evidence of FCM-Induced Hypophosphatemia

The FIRM Trial
Primary End Point: Serum Phosphate After IV Iron
N = 1997
Adapted from: Wolf et al. JCI Insight 2018 Dec 6;3(23):e124486.





Conclusion: FCM rapidly increases biologically active FGF23 in patients with IDA.



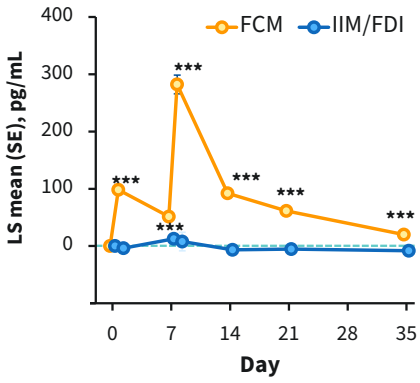
The PHOSPHARE IDA Trials (A&B)
Primary End Point: Incidence of hypophosphatemia up to 35 days
N = 123
Adapted from: Wolf et al. JAMA. 2020;323(5):432-443

Conclusion: IIM/FDI resulted in lower incidence of hypophosphatemia vs FCM.

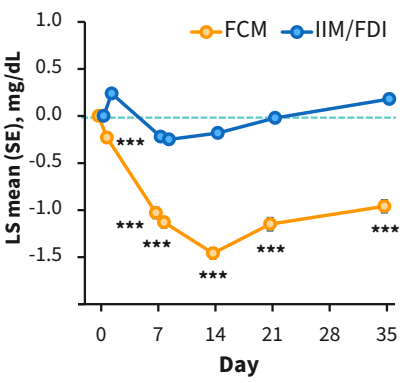
Incidence of **hypophosphatemia** <2 mg/dL: **IIM/FDI:** 8.0% vs **FCM:** 74.4%, p<0.001

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

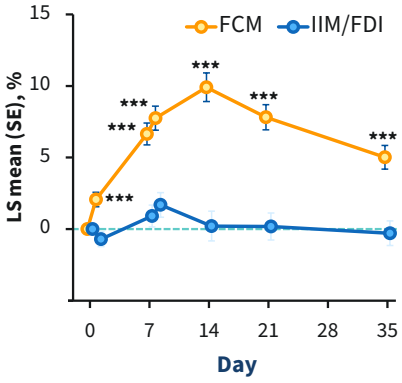
Intact FGF23



Serum Phosphate



Urinary Fractional Excretion of Phosphate



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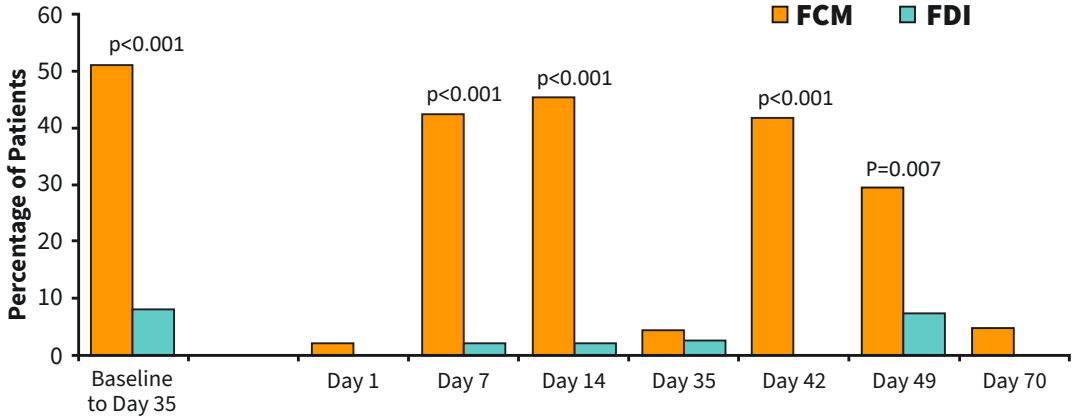
Key Trial Evidence of FCM-Induced Hypophosphatemia

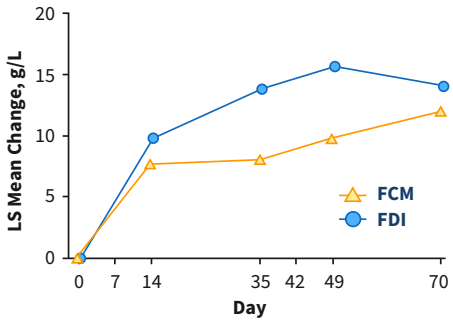
The PHOSPHARE-IBD Trial
Primary End Point: Incidence of hypophosphatemia up to 35 days
N = 156
Adapted from:
Zoller et al. Gut. 2023 Apr;72(4):644-653.



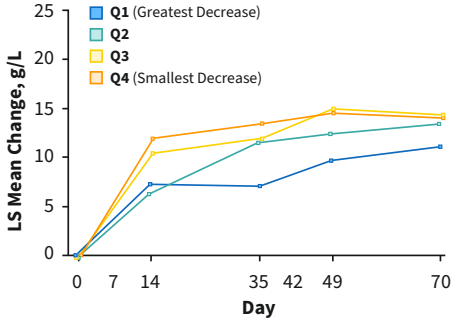
Conclusion: FCM caused a significantly higher rate of hypophosphatemia than FDI.

Secondary Outcome: **Fatigue**

FACIT Fatigue Scale Score

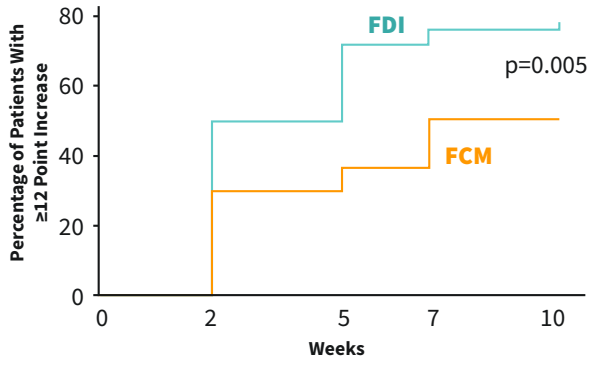


FACIT Fatigue Scale Score by Decrease in Phosphate



The PHOSPHARE-IBD Trial: Fatigue Subanalysis
Primary End Point: Percent of patients achieving a FACIT Fatigue Scale improvement of >12 points at any time during study period
N = 97
Adapted from:
Mehta AR, et al. Blood. 2022; 140(Supplement 1):2469–2470.

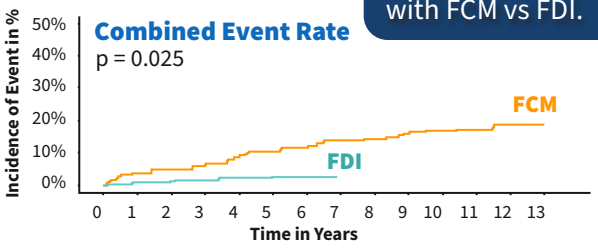
FACIT Fatigue Scale Improvement of ≥12 Points



Conclusion: Patients on FDI were significantly more likely to achieve fatigue improvement vs those on FCM.

Retrospective Analysis of Fractures, Osteomalacia, and Kidney Stones
Primary End Point: Combined event rate of fractures, osteomalacia, and kidney stones in FDI vs FCM
N = 289
Adapted from:
Zoller H, et al. Blood. 2023; 142(Supplement 1):3838.

Conclusion: Combined event rate was significantly higher with FCM vs FDI.



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