Hereditary Hemorrhagic Telangiectasia and Other Vascular Bleeding Disorders

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Disclosures

Dr. Al-Samkari is a member of the Second International HHT Guidelines Committee.

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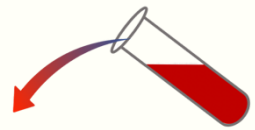
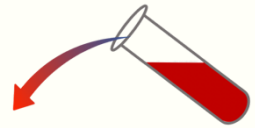


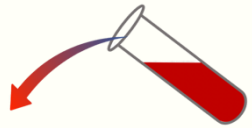
Learning Objectives

- Understand the diagnosis and clinical manifestations of hereditary hemorrhagic telangiectasia.
- Properly treat bleeding in hereditary hemorrhagic telangiectasia with antifibrinolytic and antiangiogenic medications.
- Know how to manage iron deficiency and iron deficiency anemia in HHT.
- Recognize other vascular bleeding disorders, including acquired von Willebrand disease.



The Spectrum of (Non-Platelet) Bleeding Disorders

Coagulation Factor Problem		Vascular Structural 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	**Hereditary Hemorrhagic Telangiectasia** **1 in 5,000 people** No coagulation factor deficiency Disordered angiogenesis



Outline

Diagnosis and Clinical Manifestations of HHT

A Long History

Henry Gawen Sutton, 1837-1861
First identified familial epistaxis (1864)

Henri Jules Louis Marie Rendu, 1844-1902
First distinguished HHT from hemophilia (1896)

Sutton HG, *Med Mirror* 1864
Rendu H, *Bull Mem Soc Med Hop (Paris)* 1896

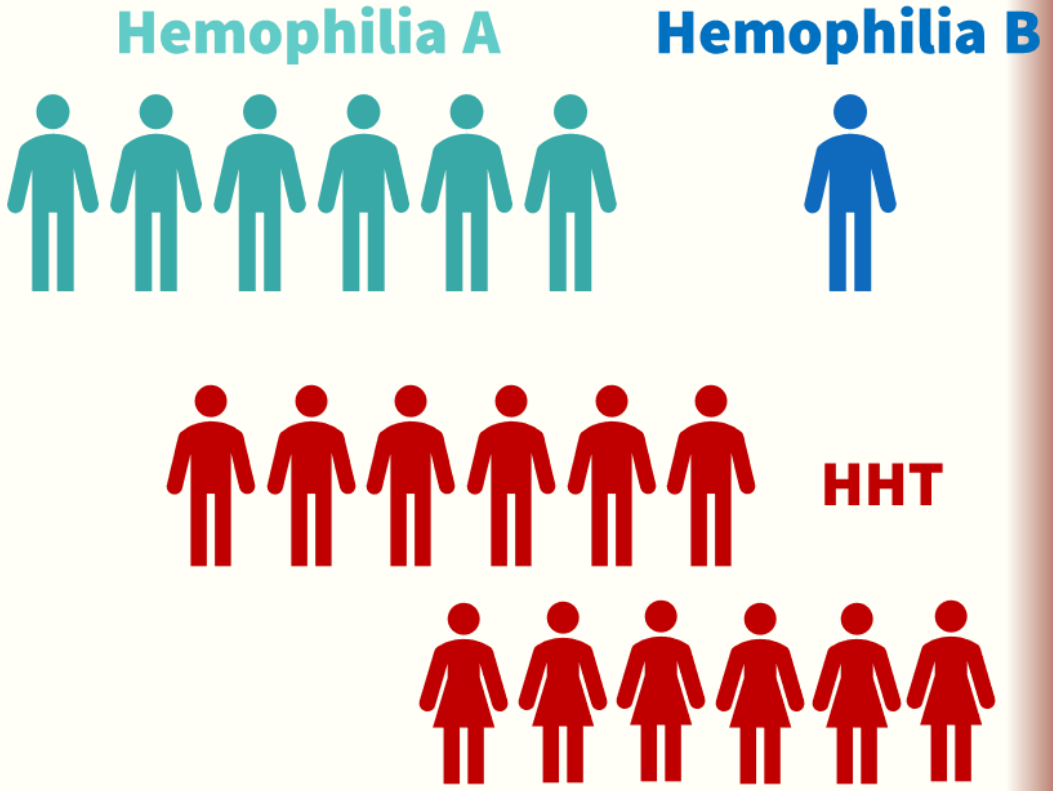
HHT is a Multisystem Hereditary Bleeding Disorder with Numerous Morbid and Potentially Fatal Manifestations

- Progressive, multisystem bleeding disorder due to abnormal vessel formation
  - Mucocutaneous telangiectasias → **chronic gastrointestinal hemorrhage** and **severe recurrent epistaxis**
  - Severe **iron deficiency anemia**, often **iron infusion and RBC transfusion-dependent**
  - Visceral arteriovenous malformations (AVMs) in **lung, liver, brain,** others
    - High output cardiac failure
    - Liver disease and cirrhosis
    - Pulmonary hypertension, pulmonary hemorrhage
    - Hemorrhagic stroke, TIA, epilepsy, sudden death
- Patients rank ***bleeding*** as most important clinical manifestation (by a wide margin)
  - AVMs and anemia tie for second
- ***No licensed therapies worldwide to date***

Al-Samkari H., *Blood* 2021

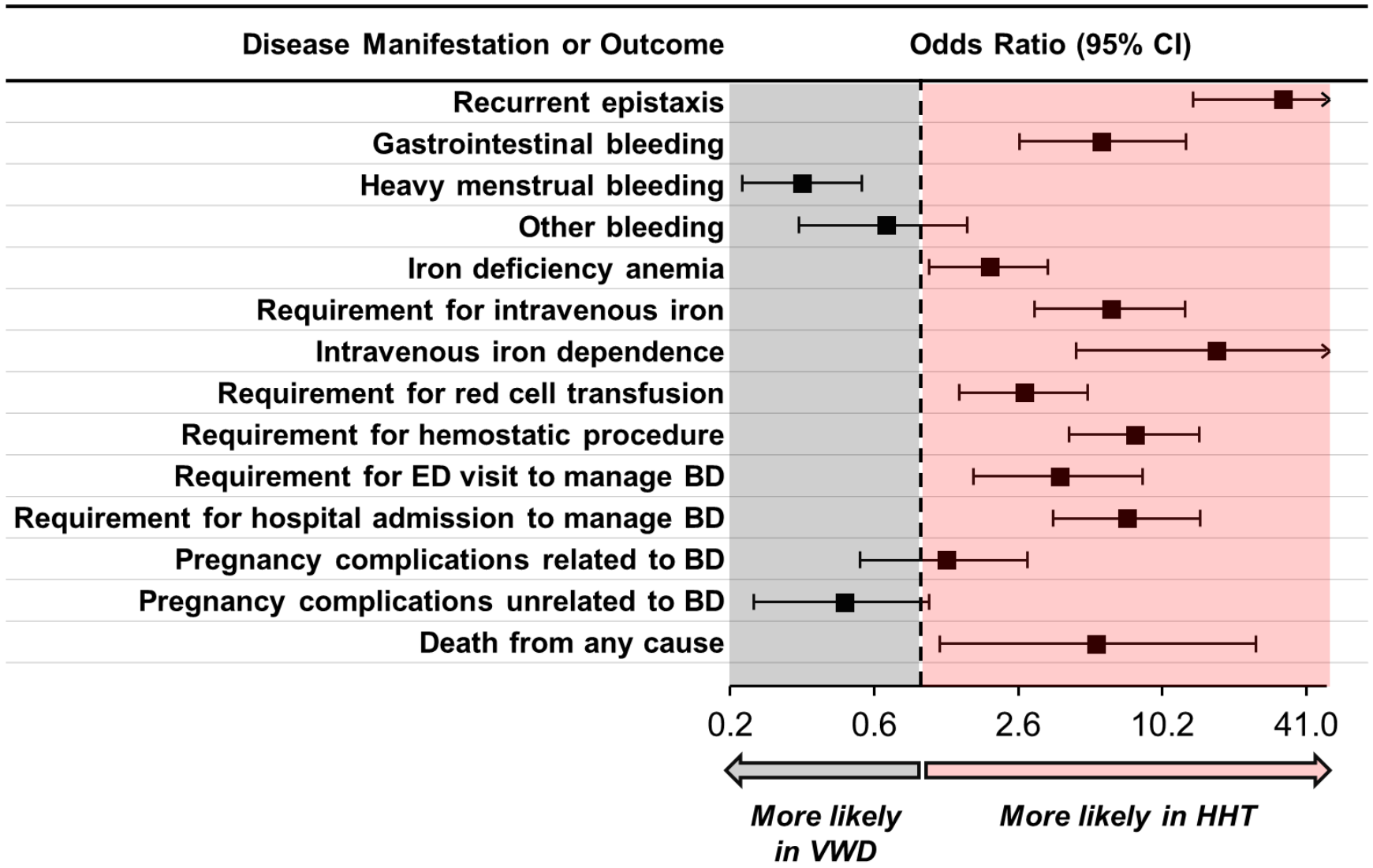
HHT is the Second-Most-Common Inherited Bleeding Disorder

- **Autosomal dominant** inheritance, 1 in 3800 people
- Occurs in all sexes equally
  - Most clinically significant and morbid inherited bleeding disorder of women
- Patients with HHT have **reduced overall survival** compared with healthy controls
- >80,000 people with HHT in US, 1.4M worldwide



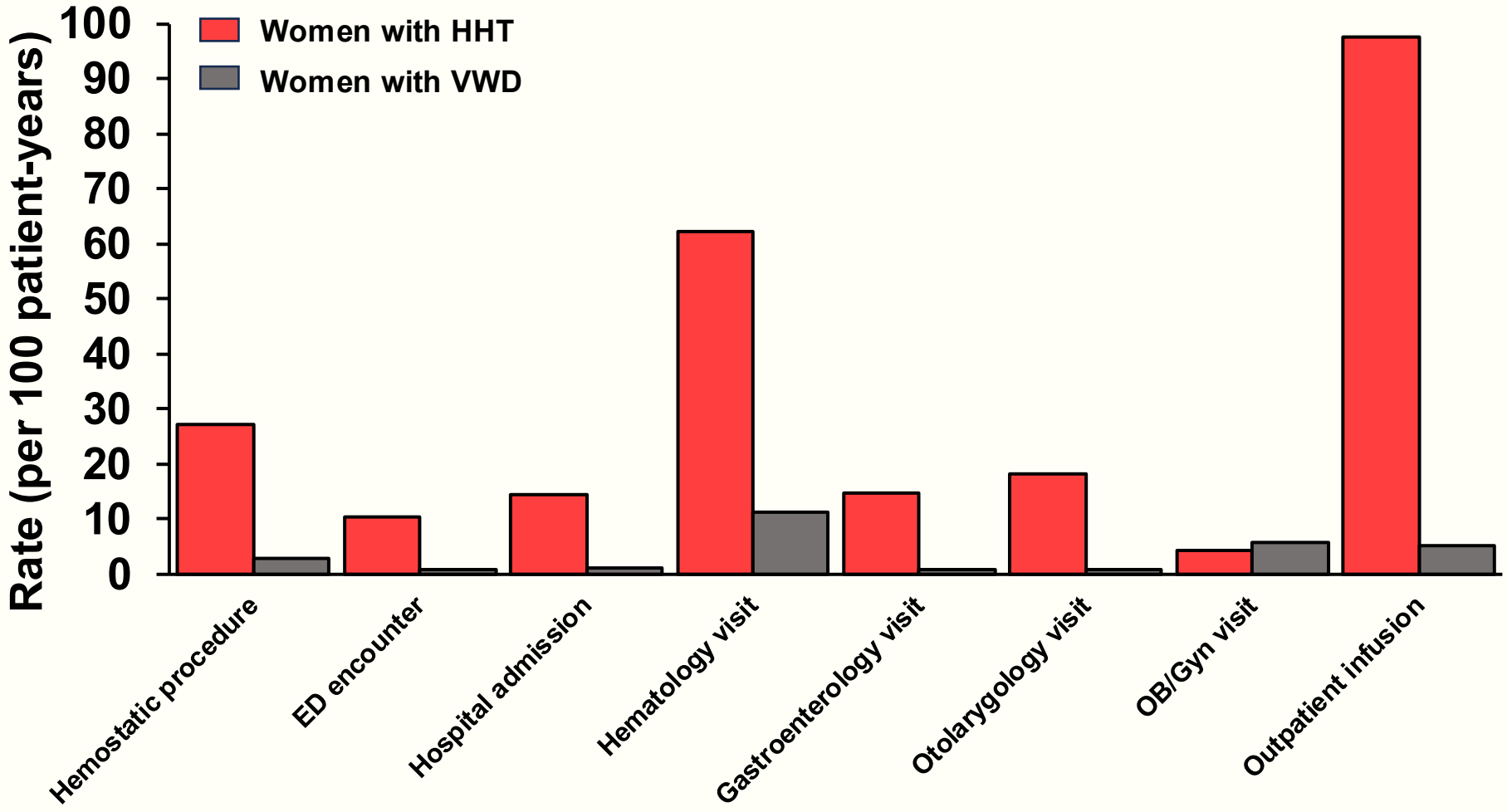
Al-Samkari H., *Blood* 2021; Zhang et al., *Blood Advances* 2024

HHT vs. VWD in Women: Disease Manifestations and Outcomes



Zhang et al., *Blood Advances* 2024

HHT vs. VWD in Women: Healthcare Utilization

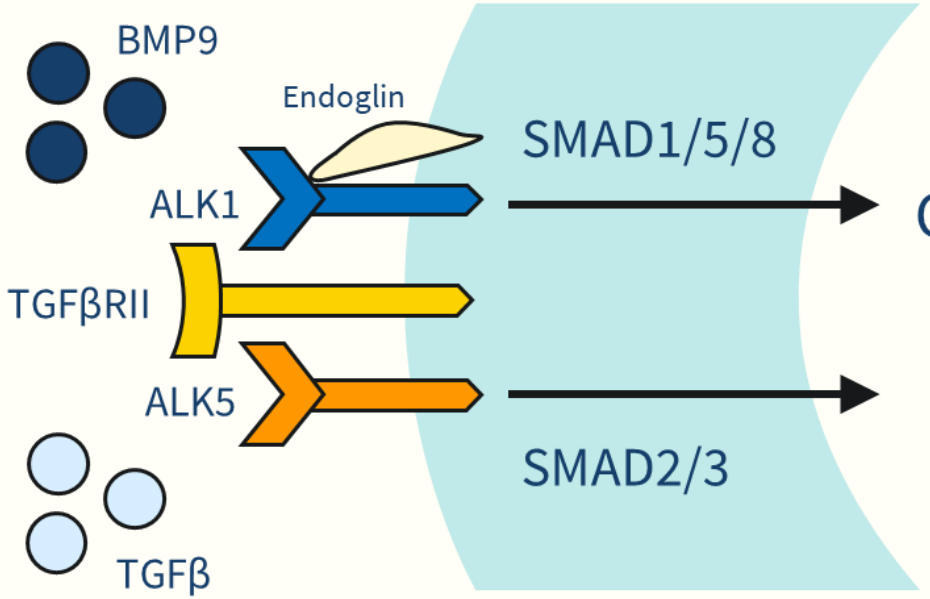


When prevalence-adjusted for relative prevalence of HHT vs. VWD (5x), nearly all healthcare utilization rates remain higher in HHT

Zhang et al., *Blood Advances* 2024

HHT is a Disease of the TGF-β/BMP Signaling Pathway

Normal Signaling Pathway



Promotes endothelial cell proliferation and smooth muscle migration
Inhibits VEGF production

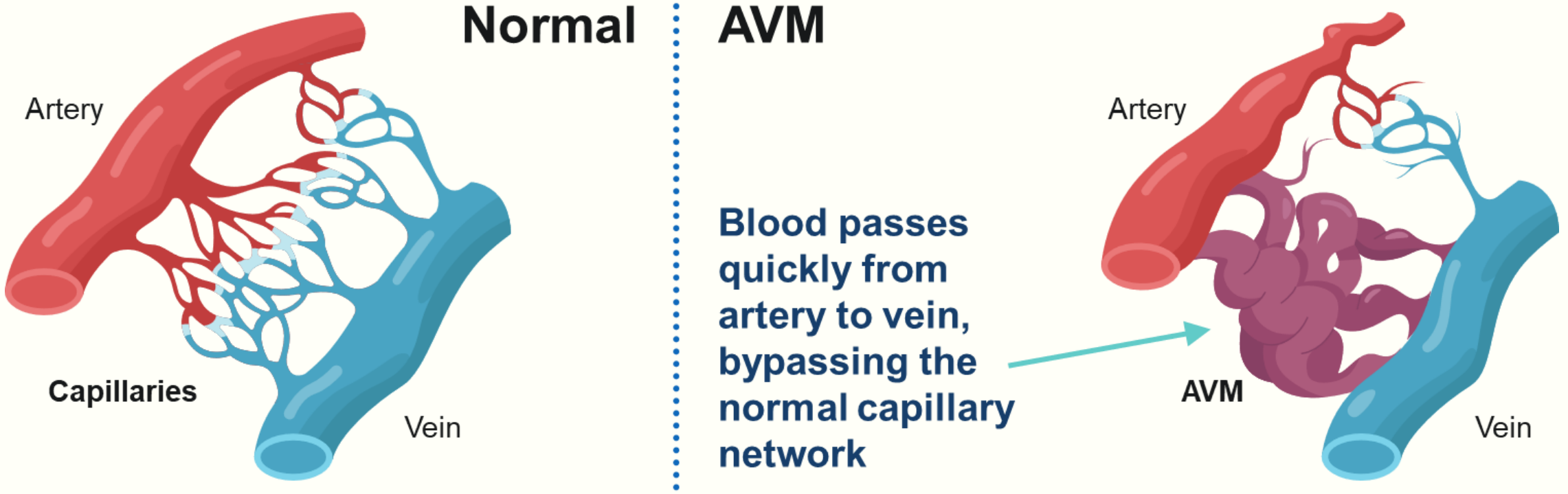
Inhibits endothelial cell proliferation and smooth muscle migration
Promotes VEGF production

In HHT

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

The Pathologic Lesion of HHT is the Arteriovenous Malformation



Telangiectasia is small AVM (<1 millimeter to few millimeters in diameter), usually occur in skin, GI mucosa, upper aerodigestive tract

AVMs are more than a few millimeters in diameter and most commonly occur in lung, liver and brain

Ferry AM, et al. *Am J Rhinol Allergy*. 2020; Viteri-Noel A, et al. *J Clin Med*. 2022; Droege F, et al. *Vasc Med*.

Diagnosis of HHT is Currently Primarily *Clinical* and a *Major Practice Gap*

Curaçao Criteria

- Spontaneous or recurrent **epistaxis**
- **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)

Definite HHT Diagnosis:
3-4 Criteria

Possible HHT: 1-2 Criteria

Can (*Should Ideally*) Confirm with Genetic Testing

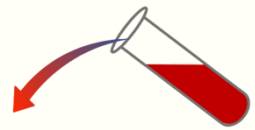
- *ENG* Mutation: HHT Type 1
- *ACVRL1* Mutation: HHT Type 2
- *SMAD4* Mutation: JP-HHT

Average delay in diagnosis is **27 years**

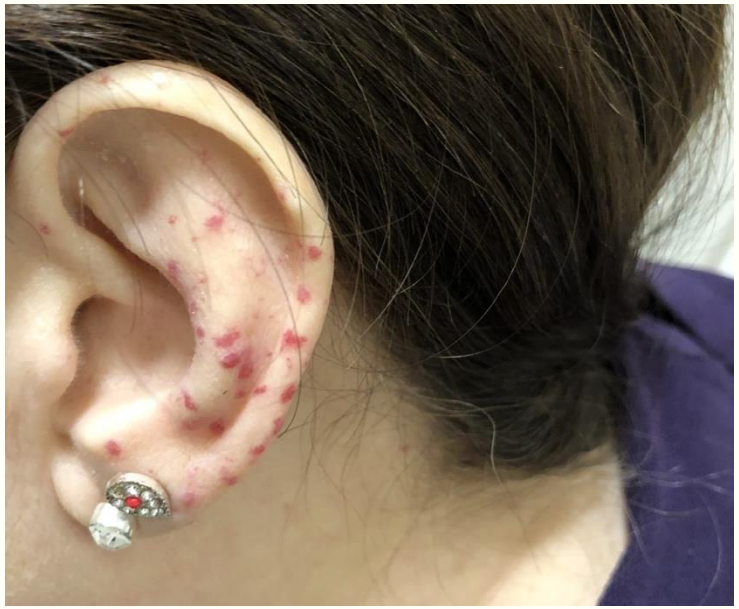
Viteri-Noel A, et al. *J Clin Med*. 2022; Faughnan M, et al. Ann Intern Med. 2020; McDonald J, et al. *Front Genet*. 2015; Garg N, et al. *J Blood Med*. 2014; Shovlin CL, et al. *Am J Med Genet*. 2000.

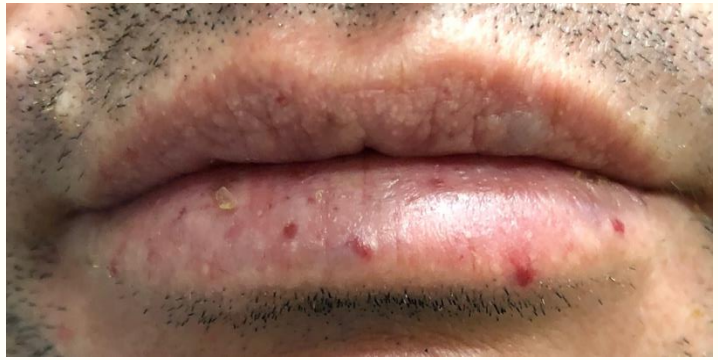
Subtypes of HHT

Disease	Genetic mutation (locus)	Primary visceral manifestations
HHT type 1	*ENG* (9q34.11)	Pulmonary AVMs Brain AVMs
HHT type 2	*ACVRL1* (*ALK1*;12q13.13)	Liver AVMs Pulmonary hypertension Spinal AVMs
Combined syndrome of HHT and juvenile polyposis (JP-HHT)	*MADH4* (*SMAD4*; 18q21.2)	Gastrointestinal polyps Visceral AVMs Pulmonary hypertension



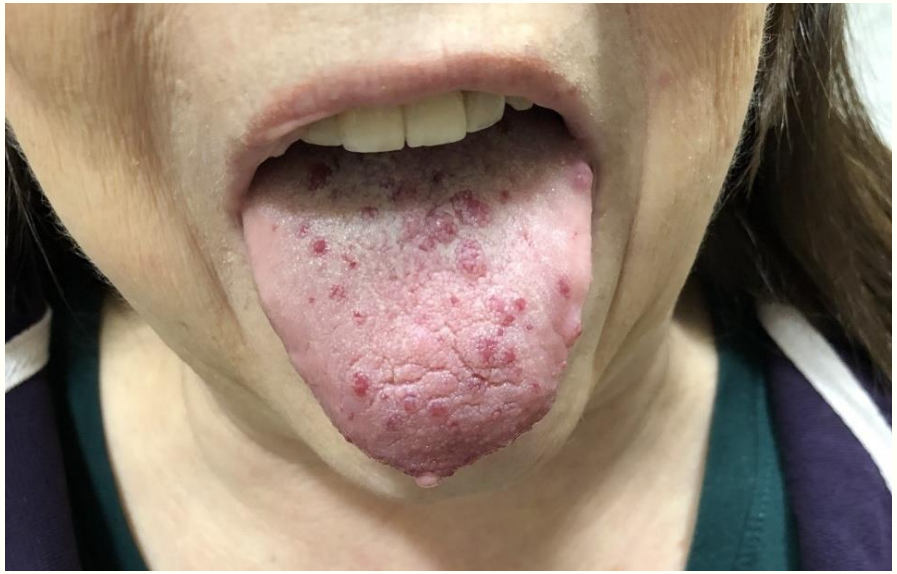
Mucocutaneous Telangiectasias: Skin

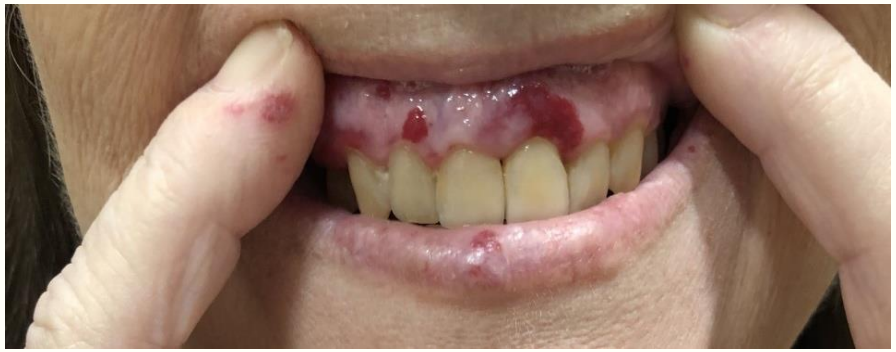


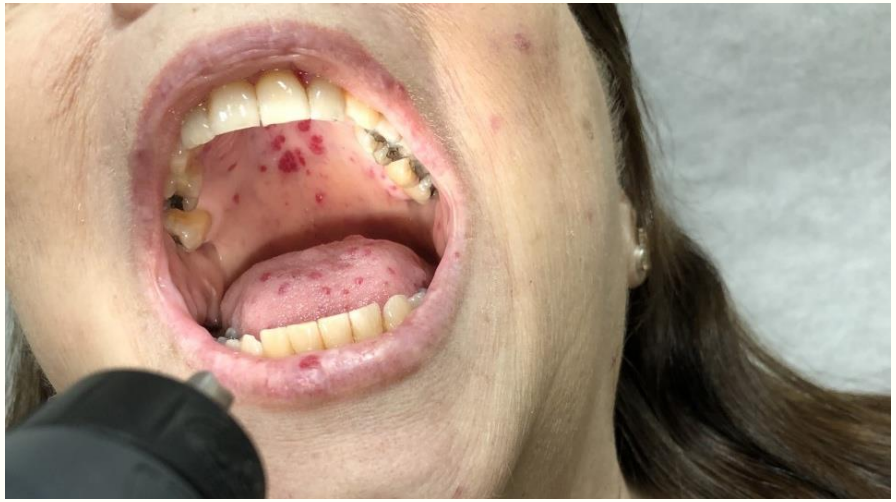


Images from Hanny Al-Samkari, MD

Mucocutaneous Telangiectasias: Oral Cavity

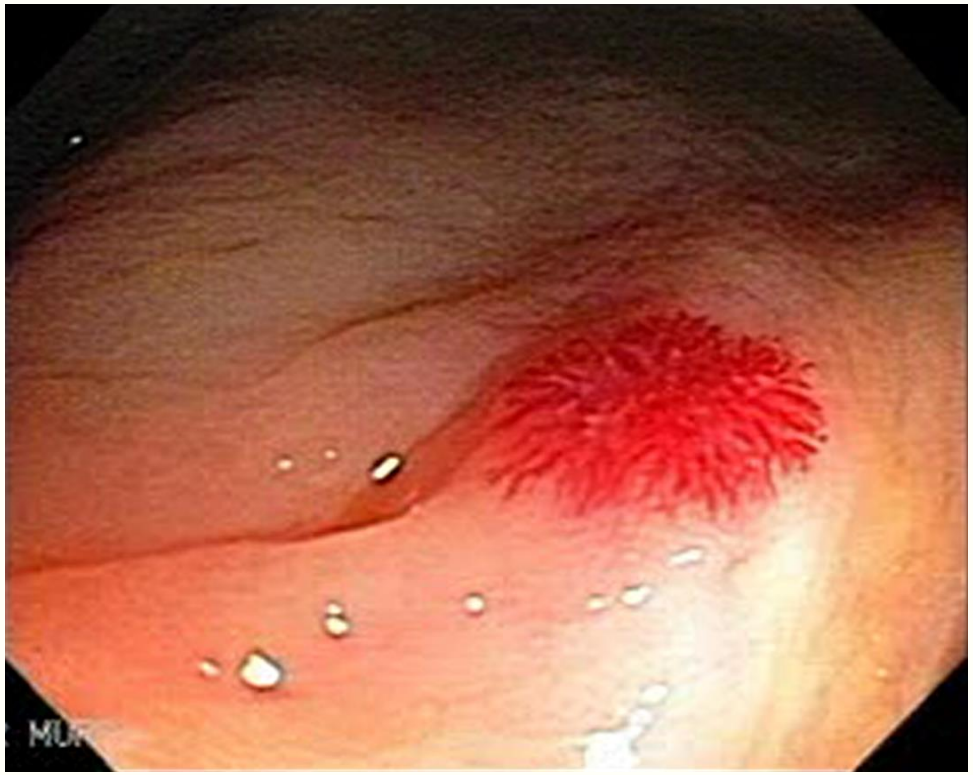


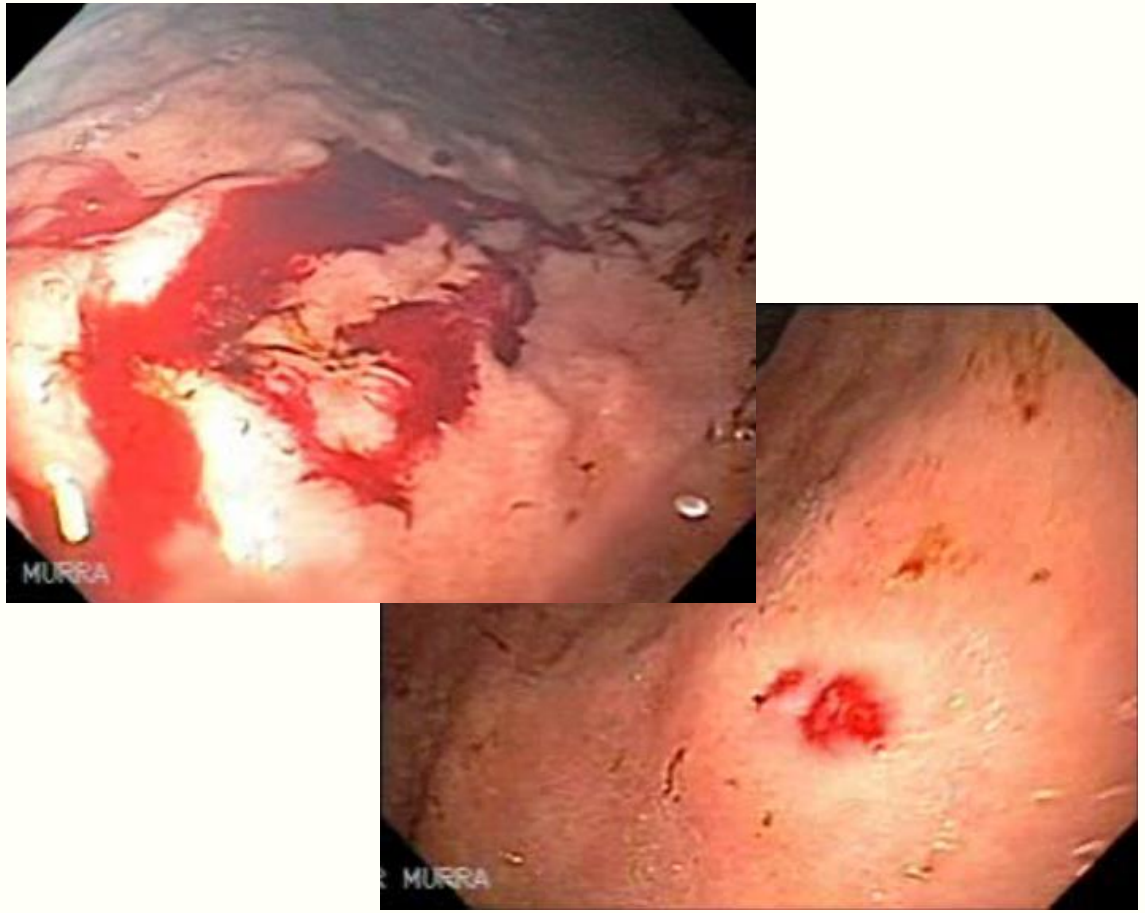




Images from Hanny Al-Samkari, MD

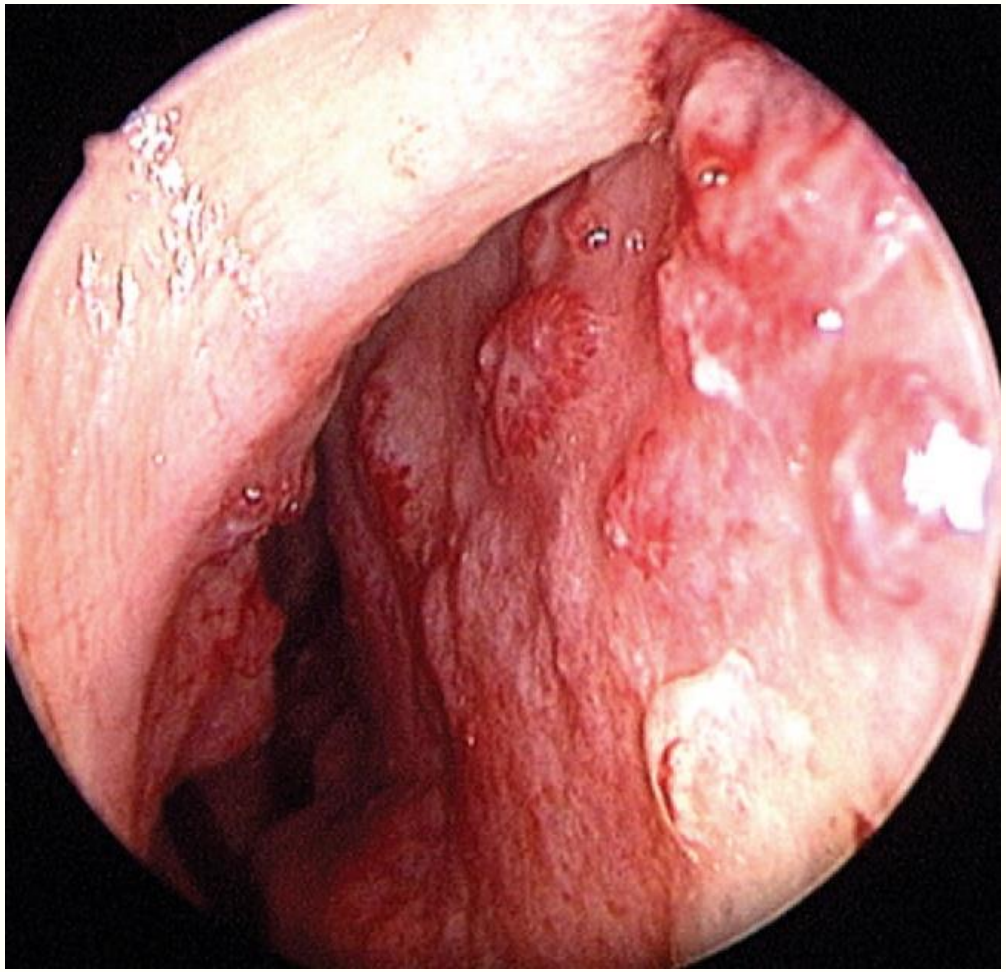
Mucocutaneous Telangiectasias: Gastrointestinal Tract

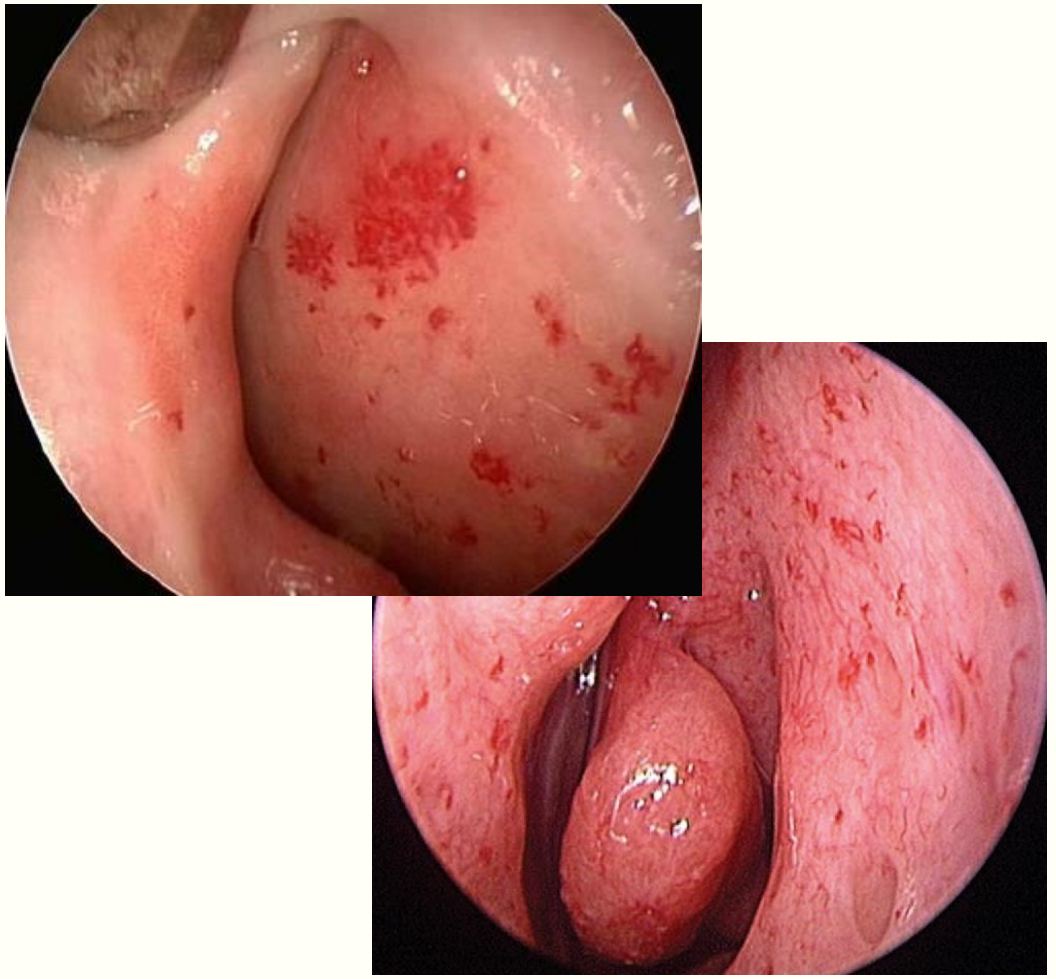




Images from https://gastrointestinalatlas.com/english/hereditary_hemorrhagic_telangi.html

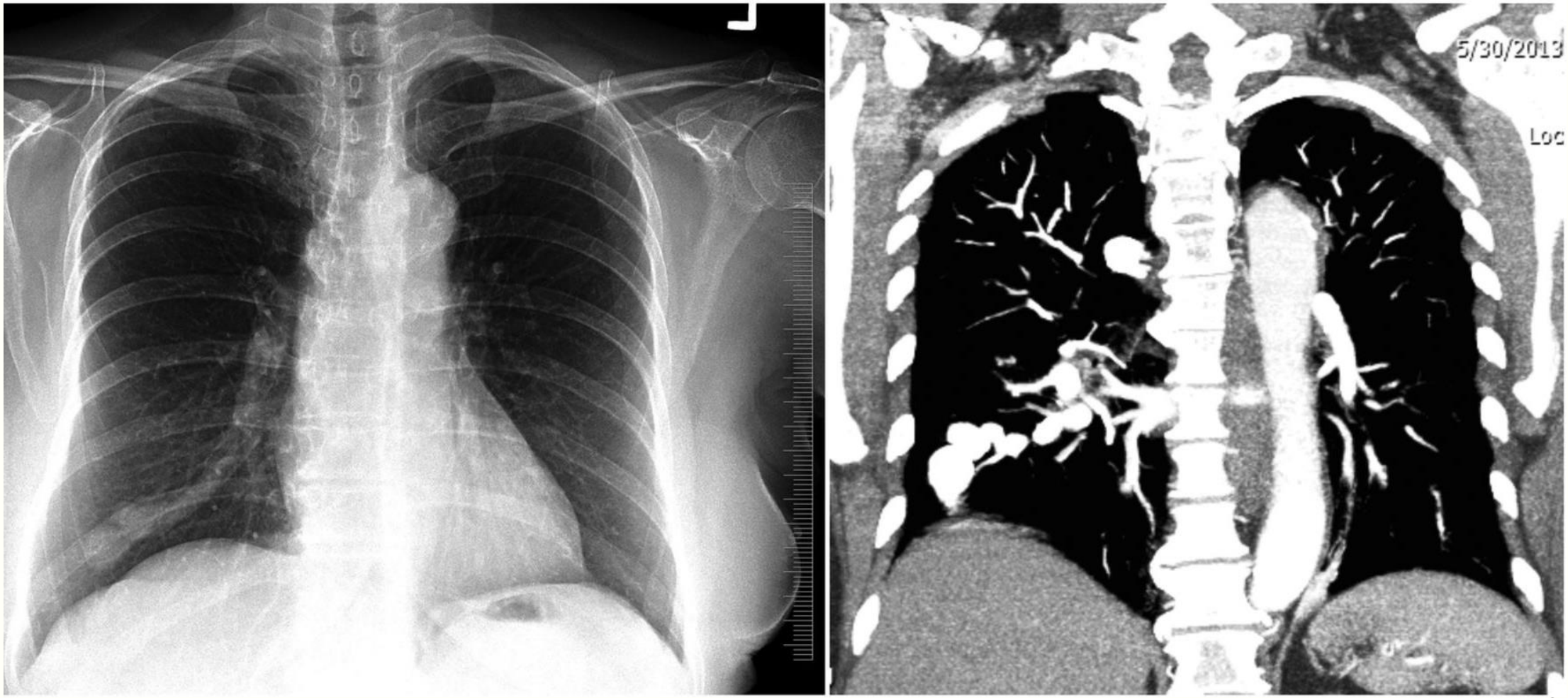
Mucocutaneous Telangiectasias: Nasal Cavity





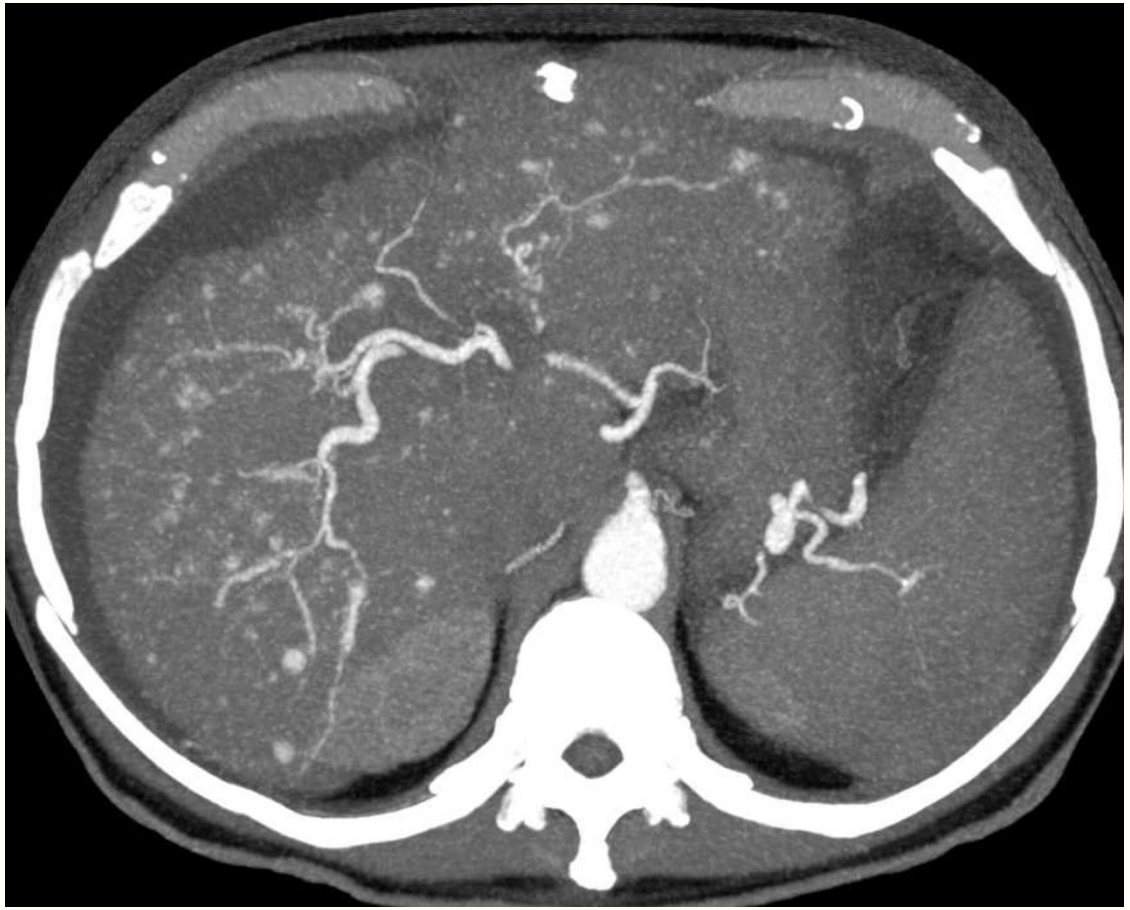
Pagiella et al. *Amer J Rhinol Allergy* 2009, Folz et al. *Eur Arch Otorhinolaryngology* 2006

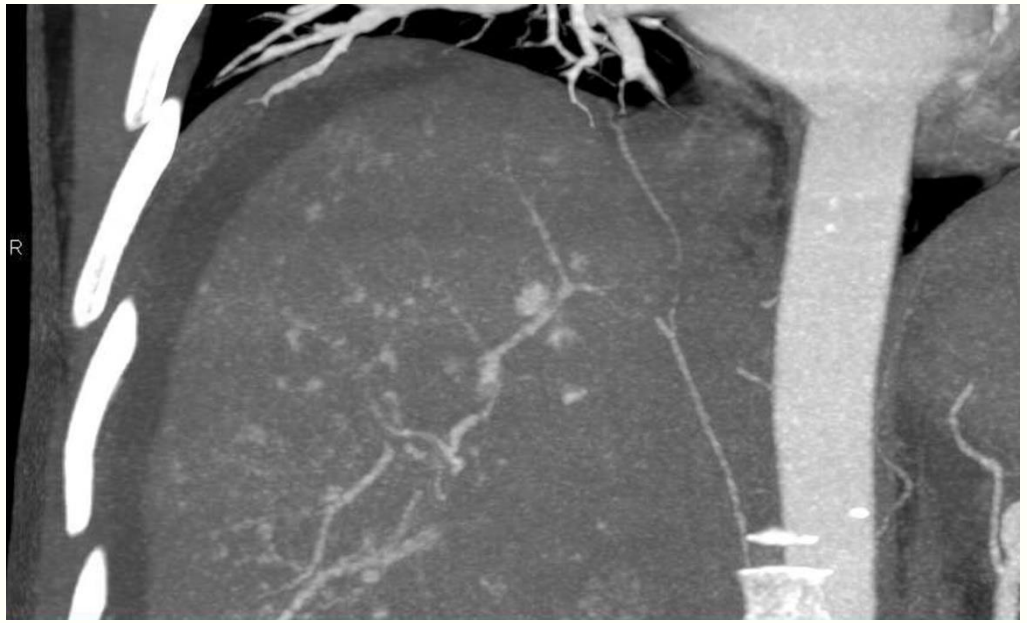
Pulmonary Arteriovenous Malformations (>50%)



Mangla et al. *BMJ Case Rep* 2014

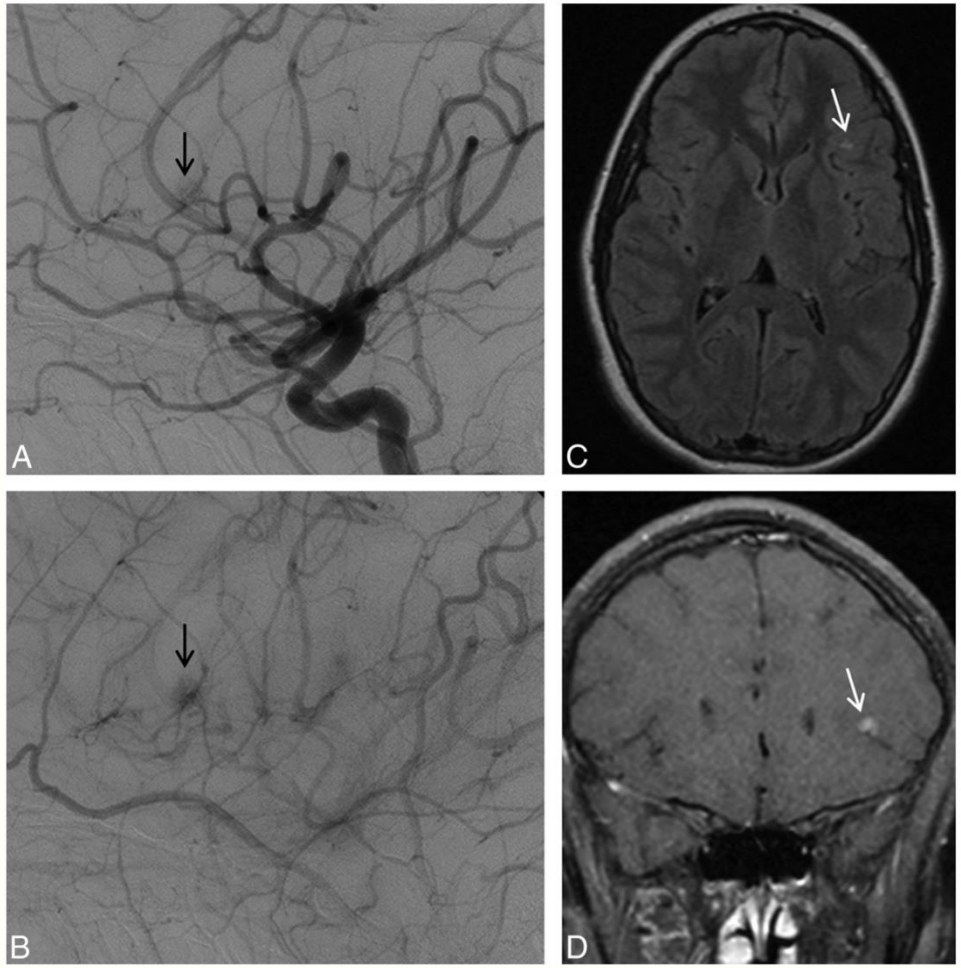
Hepatic Arteriovenous Malformations (~70%)





Images from https://ctisus.com/teachingfiles/liver/349556

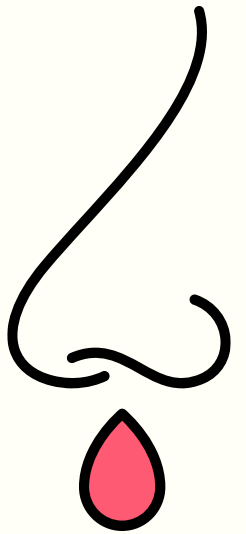
Brain Arteriovenous Malformations (~10-20%)

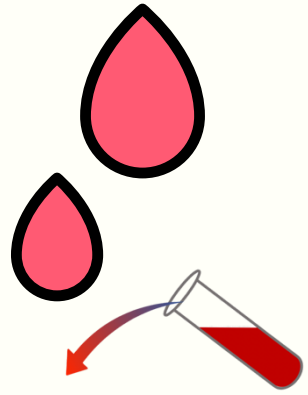


Krings et al. *Amer J Neuroradiol* 2015

Telangiectasias are Fragile and they Bleed, Acutely and Chronically

- Recurrent, severe epistaxis occurs in **50% of children, >95% of adults**
  - Common to have **multiple nosebleeds daily**
  - Not uncommon to have **an hour or more** of nosebleeding daily
  - Result: Iron deficiency anemia, social isolation, unemployment, no travel, depression, anxiety, PTSD
  - Diagnosable DSM-V psychiatric comorbidity (major depression, anxiety, PTSD) in **~40-50% of patients with HHT due to *epistaxis***
- GI telangiectasias are present in 75%, half of which chronically bleed
  - May result in severe anemia, **RBC transfusion and iron infusion dependence**
- **Heavy menstrual bleeding reported by 72%** of women with HHT
- >50% of patients with HHT have **chronic iron deficiency anemia**
  - May be an underestimate due to lack of screening

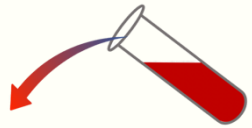




Chaturvedi et al. *Thromb Res* 2017; Youkhana et al., *Angiogenesis* 2023

Recommended AVM Workup

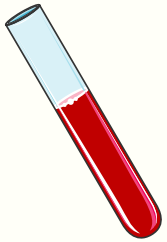
- All patients should have a echocardiogram with agitated saline contrast ("echo bubble study") to screen for pAVMs
  - Repetition necessary every few years
- All patients should have brain MRI to screen for bAVMs
  - If negative, probably do not need to repeat unless develops concerning symptoms
- Liver imaging (i.e. doppler ultrasound) to screen for hAVMs is controversial but currently recommended



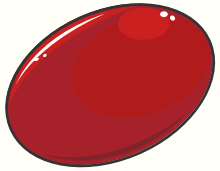
Outline

Treatment of HHT

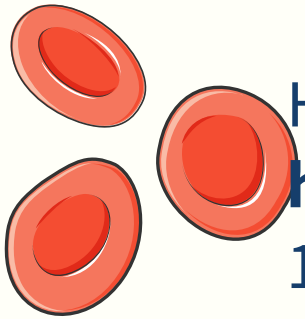
Need for Iron Supplementation is Nearly Universal in HHT



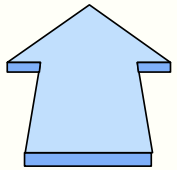
Monitor CBC, Ferritin, Transferrin Saturation (Interval **patient-dependent**)



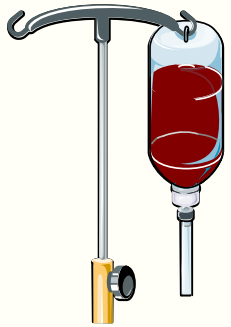
Oral iron **usually inadequate** (except mild bleeding)
Do not "tread water"



Hgb goal for >90%: **Normal hemoglobin**; give 1000-1500 mg IV iron per repletion



Goal (HHT Guidelines):
Ferritin >50 ng/mL ***and***
Transferrin Saturation >20%



Most will need IV iron and will need repeat infusions
Do not hesitate if non-anemic

My trigger for iron infusion:
Ferritin <50 ng/mL ***or***
Transferrin Saturation <20%

Al-Samkari H. How I Treat Bleeding in Hereditary Hemorrhagic Telangiectasia. *Blood* 2024

Choose Wisely Your Intravenous Iron Formulation in HHT

Formulation	Dose	Time	Suitability	Clinical Considerations
LMW Iron Dextran	Hgb-based (label) 1000 mg (off-label)	1-4 H	*Good*	High quantity in single infusion, long infusion time
Iron Sucrose	200-400 mg (label)	1.5-4 H	*Suboptimal*	Inconvenient: 3-5 infusions to give 1000 mg, long infusion time
Ferric Gluconate	125 mg (label) 250 mg (off-label)	1-2 H	*Suboptimal*	Inconvenient: 4-8 infusions to give 1000 mg, long infusion time Contains **benzyl alcohol** (hypersensitivity reactions, local irritation, skin reaction); contraindicated in infants ("gasping syndrome"); avoid in pregnant patients (?crosses the placenta)
Ferumoxytol	510 mg (label) 1020 mg (off-label)	15-30 min	*Ideal*	High quantity in single infusion **Avoid if MRI is planned** within 3 months of infusion
Ferric Carboxymaltose	750 mg (label)	15 min	***Avoid***	**50-75% risk of treatment-emergent hypophosphatemia** (may last up to 3+ months after one infusion; no treatment) Repeat infusions may result in **serious decline in bone density, bone demineralization, osteomalacia, and pseudofractures** Newer formulation, more expensive
Ferric Derisomaltose	1000 mg if ≥50 kg, 20 mg/kg if <50 kg (label)	20 min	*Ideal*	High quantity in single infusion Newer formulation, more expensive

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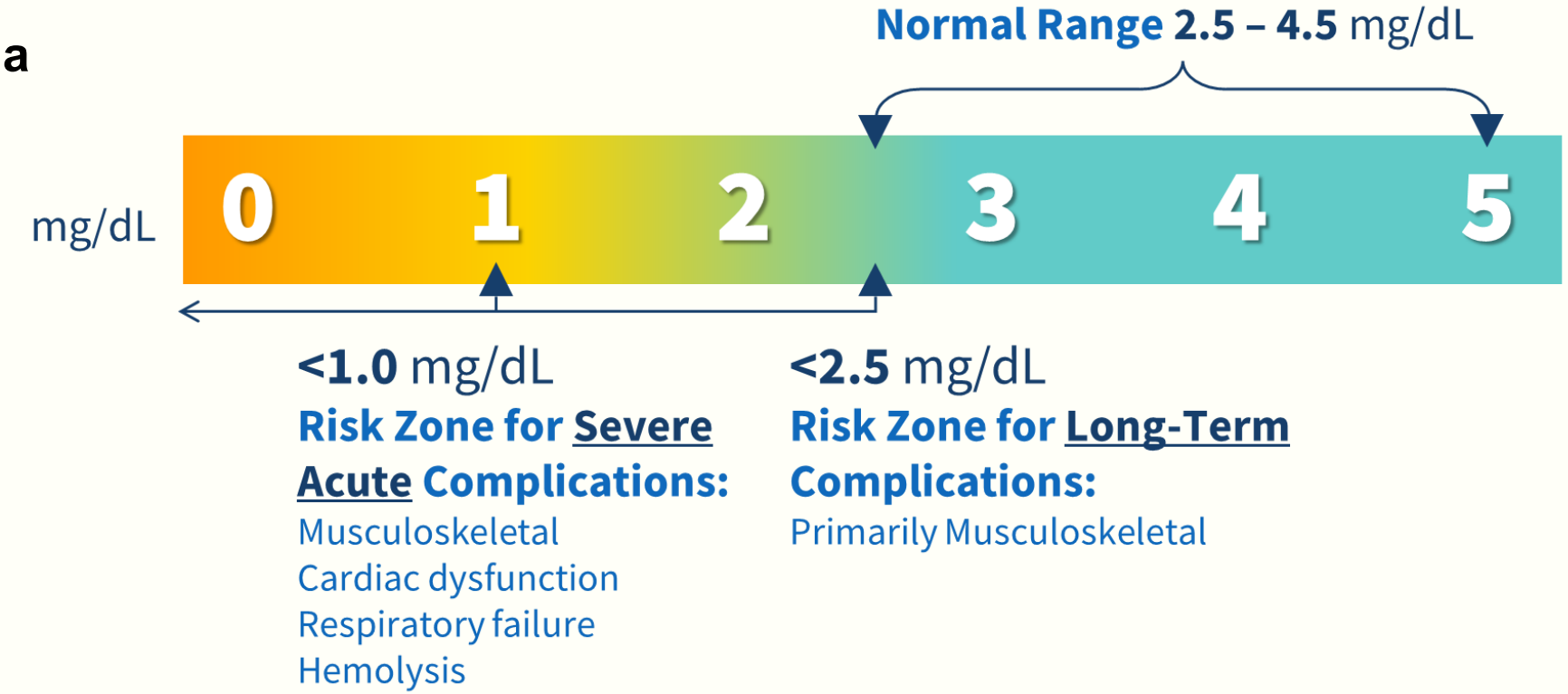
Treatment-Emergent Hypophosphatemia May Be Serious and is AVOIDABLE By Choosing Wisely Your Iron Formulation

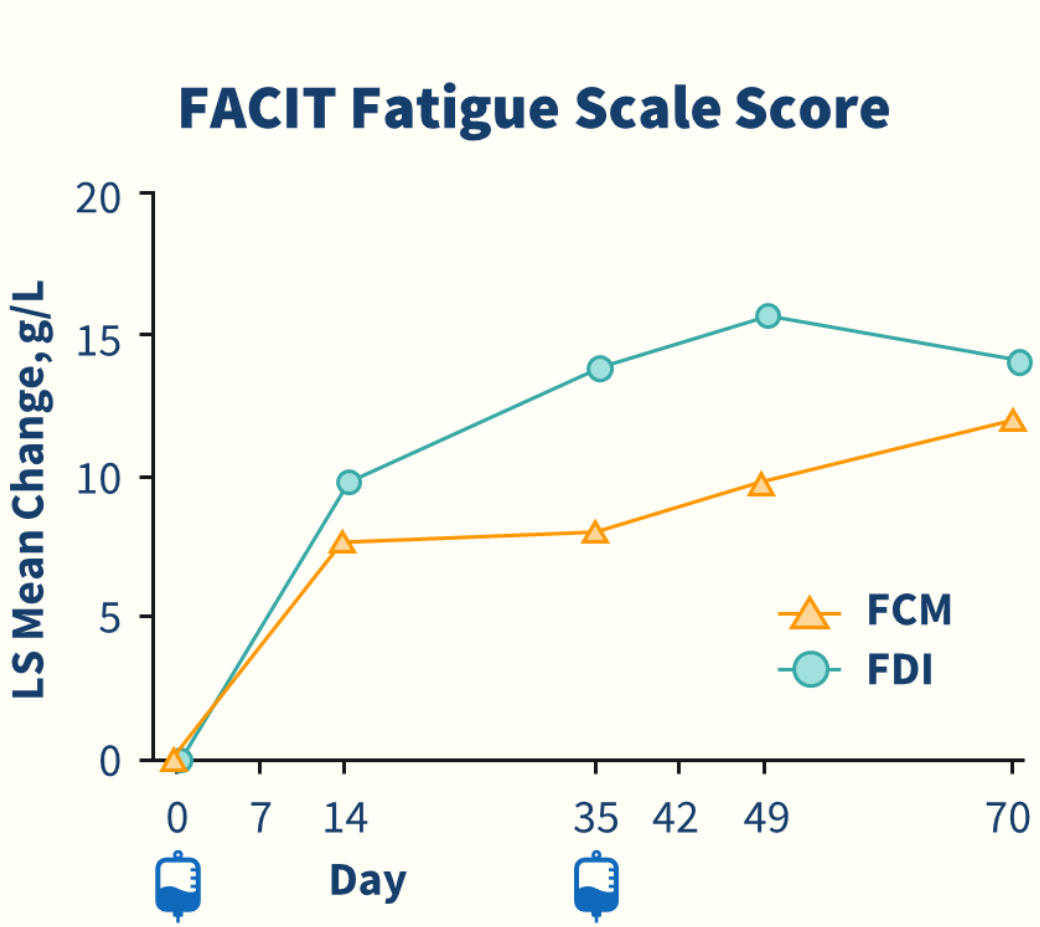
FCM causes massively increased levels of intact FGF23 (iFGF23), which **induce hypophosphatemia** via:

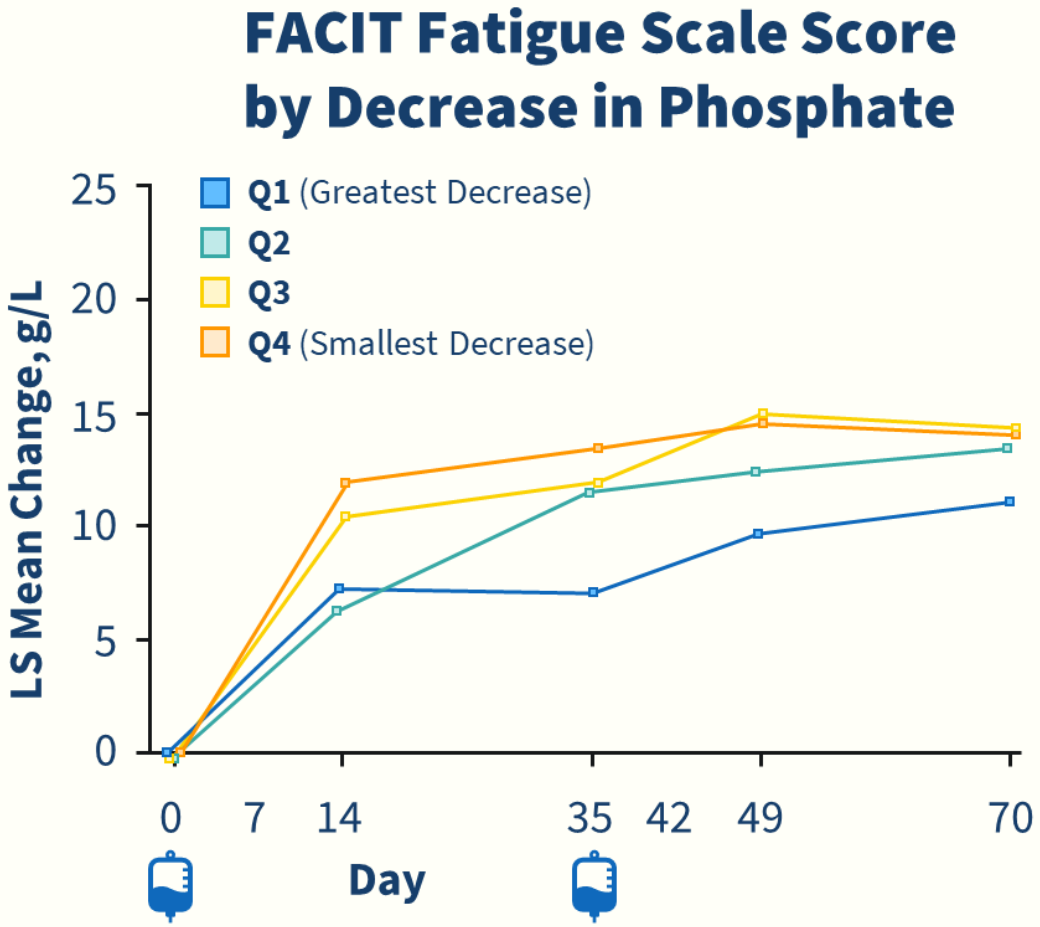
- Urinary phosphate wasting
- Reduced dietary absorption of phosphate in the gut
- Reductions in biologically active vitamin D



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.

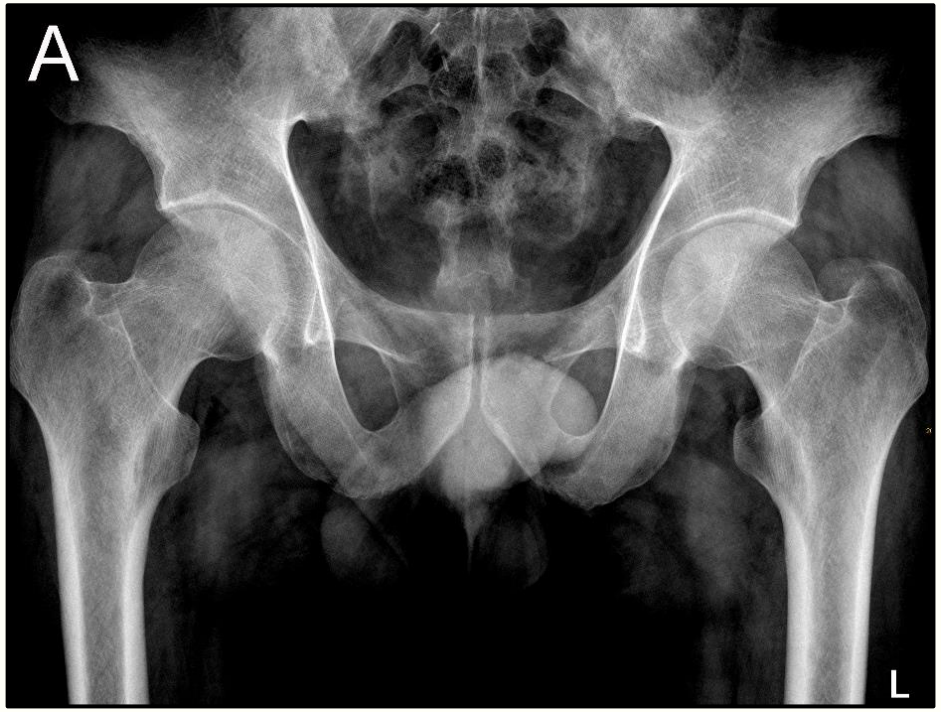
Make Your Patients Feel Much Better, Not Sort of Better

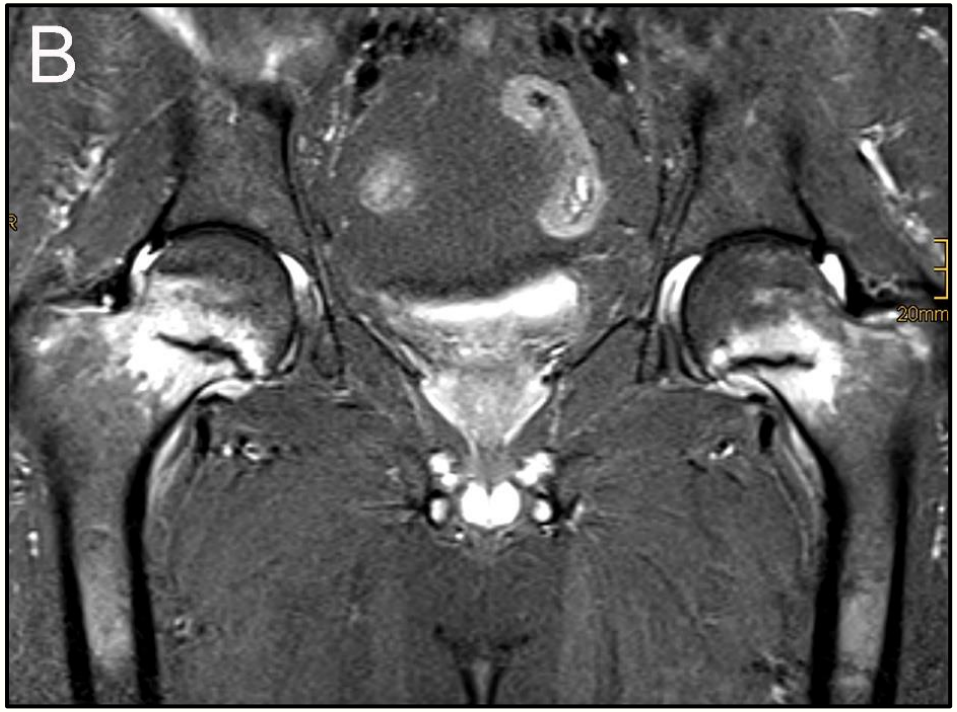




Zoller H, et al. *Gut*. 2023.

iFGF23-Mediated Hypophosphatemic Osteomalacia Pseudofractures (Insufficiency Fractures, Looser's Zones)





Schaefer B, et al, *Gastroenterology*. 2017

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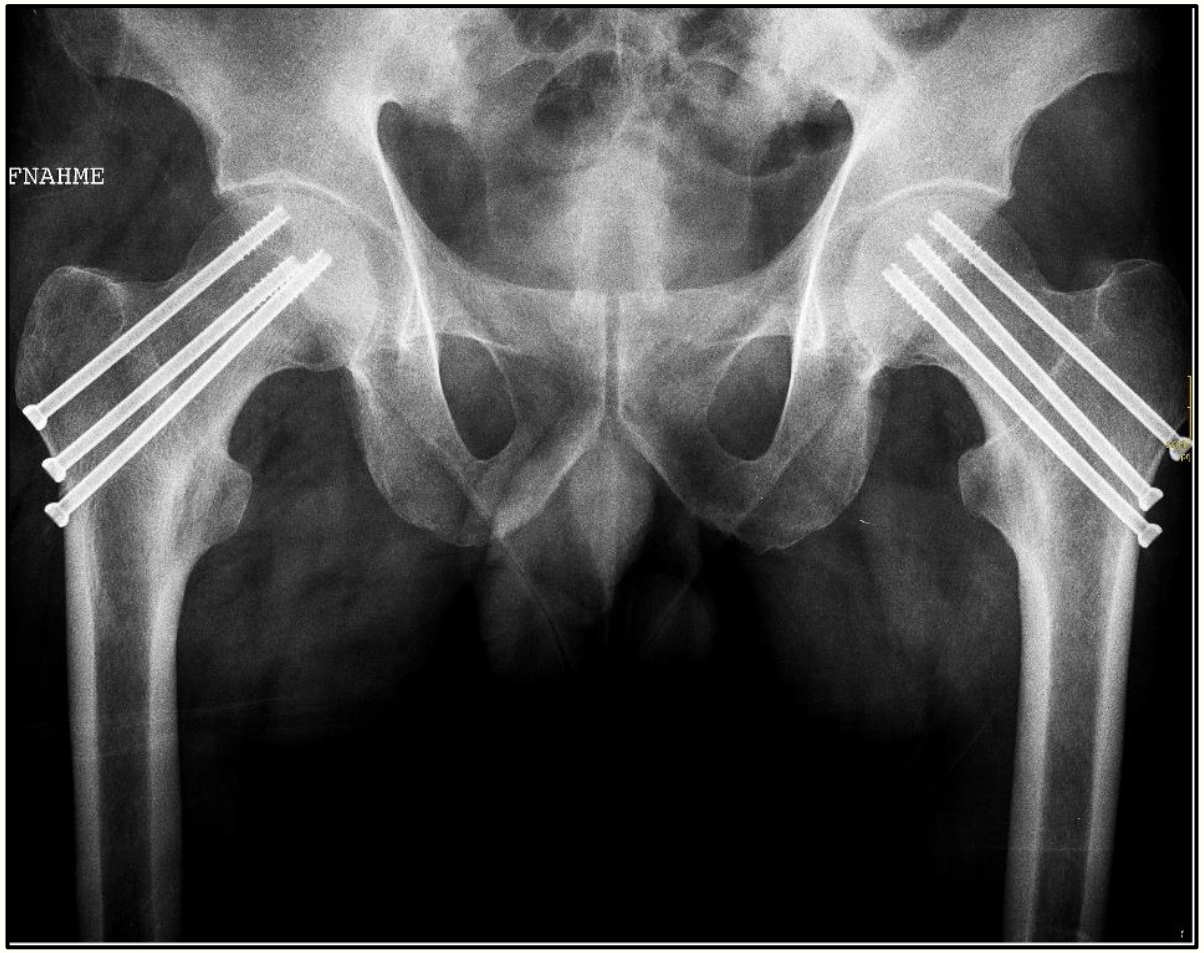

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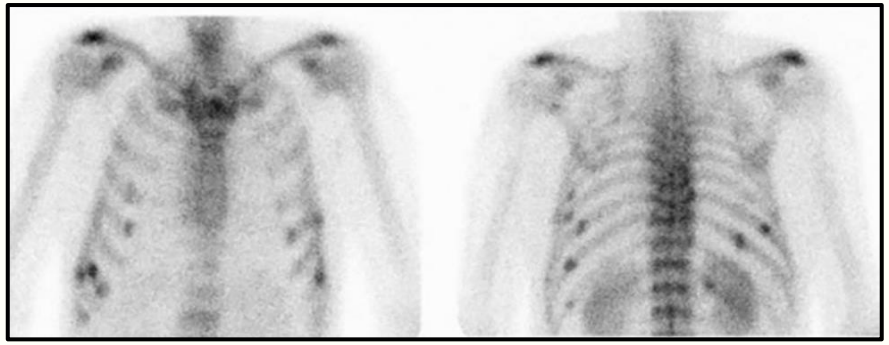
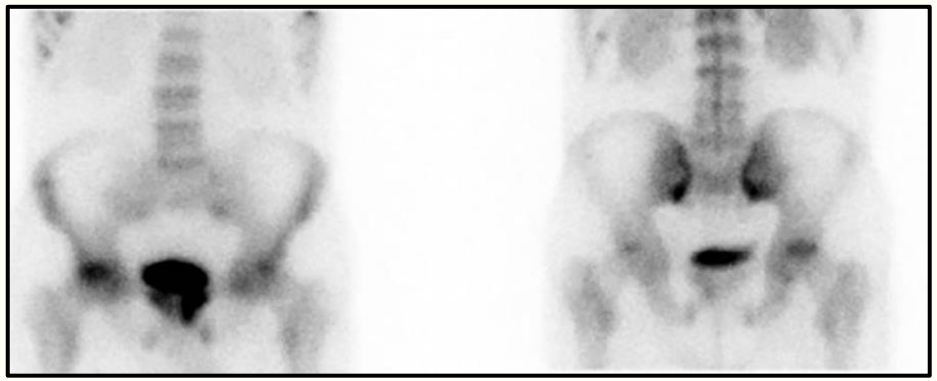
iFGF23-Mediated Hypophosphatemic Osteomalacia Pseudofractures (Insufficiency Fractures, Looser's Zones)

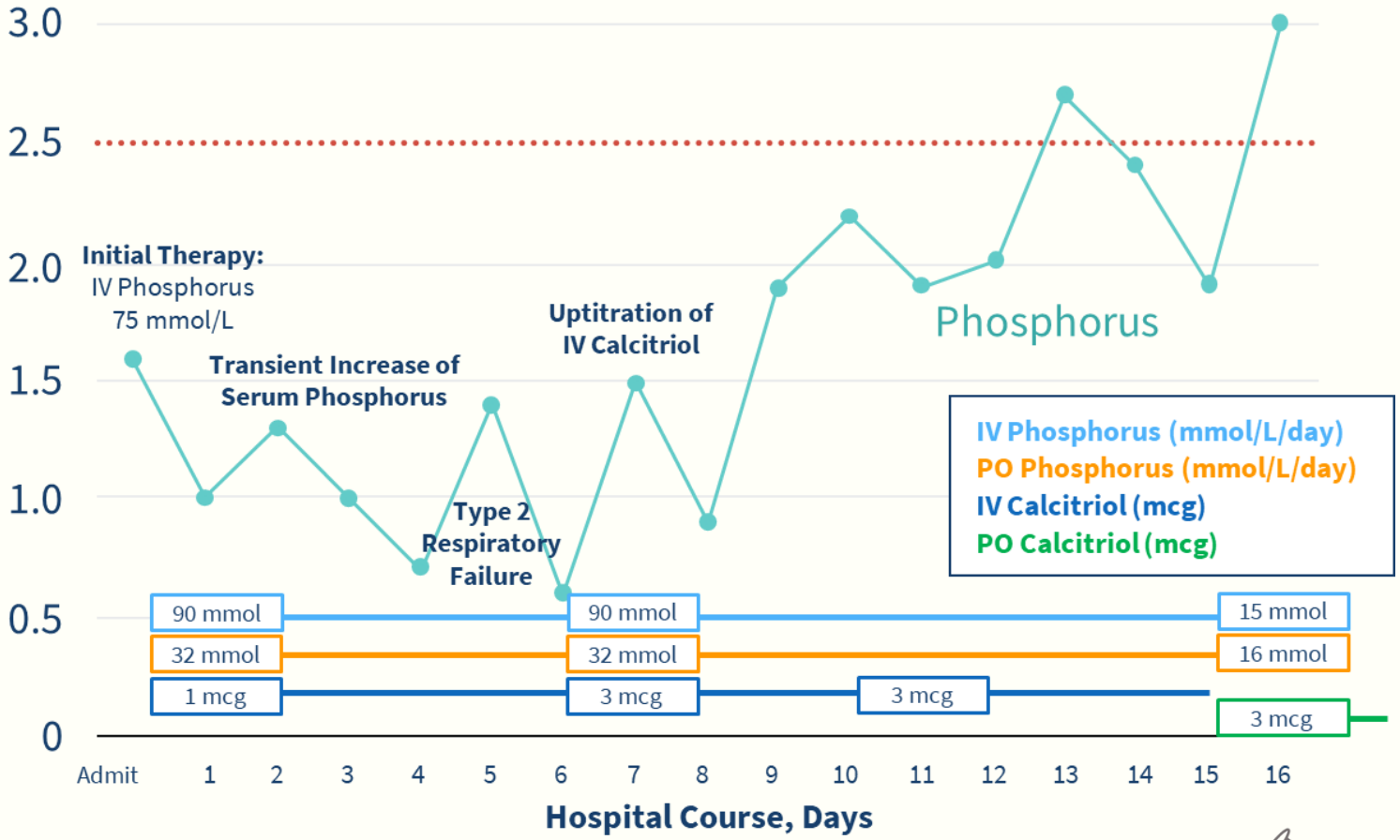




Callejas-Moraga EL, et al. *Bone Rep*. 2020.

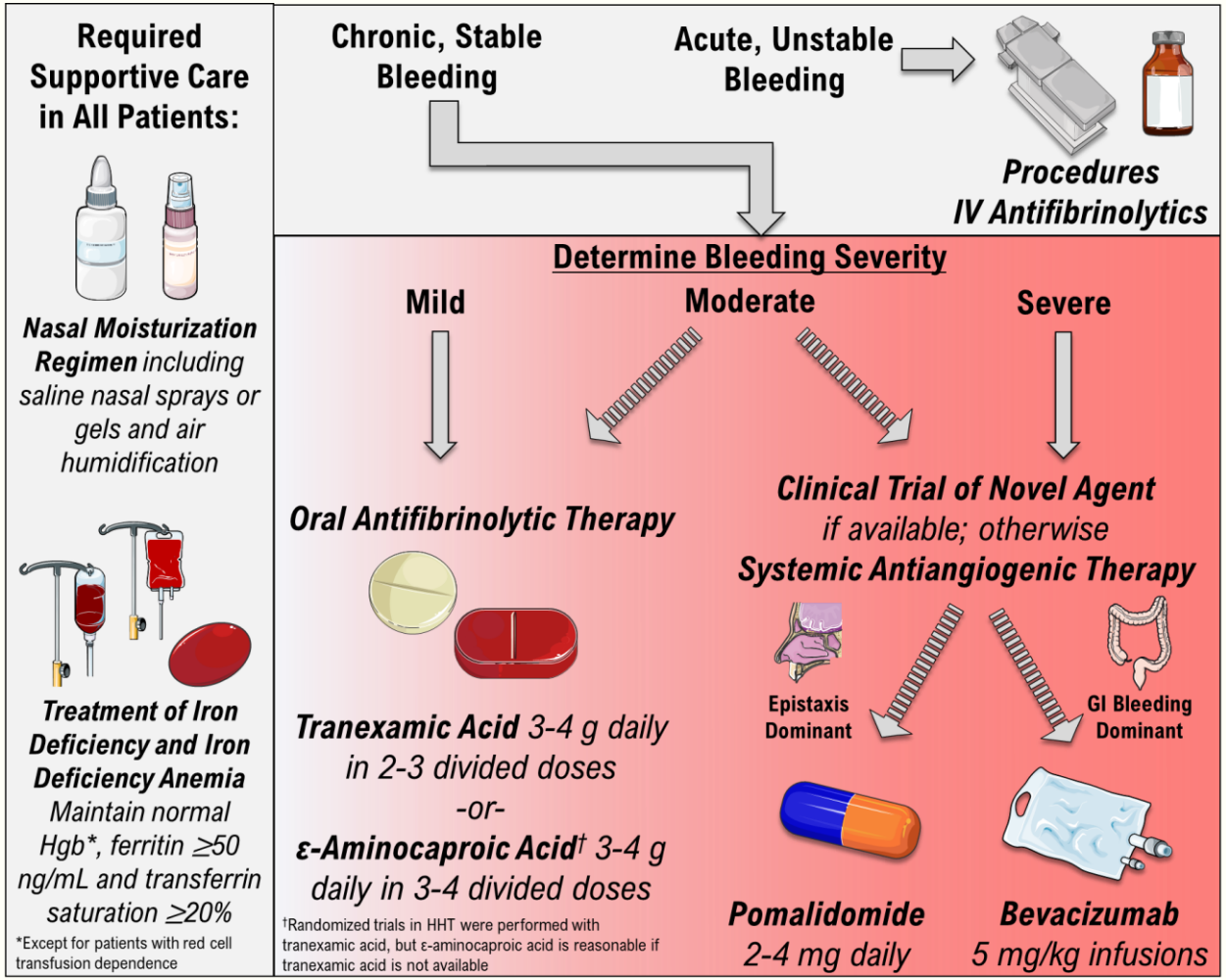
Severe Hypophosphatemia Can Happen After ONE Course of FCM

- 28-year-old woman with HMB
- FCM, 750mg x 2 doses 8 weeks prior to admission
- **Acute respiratory failure on day 7, intubated, serum phosphate 0.6**



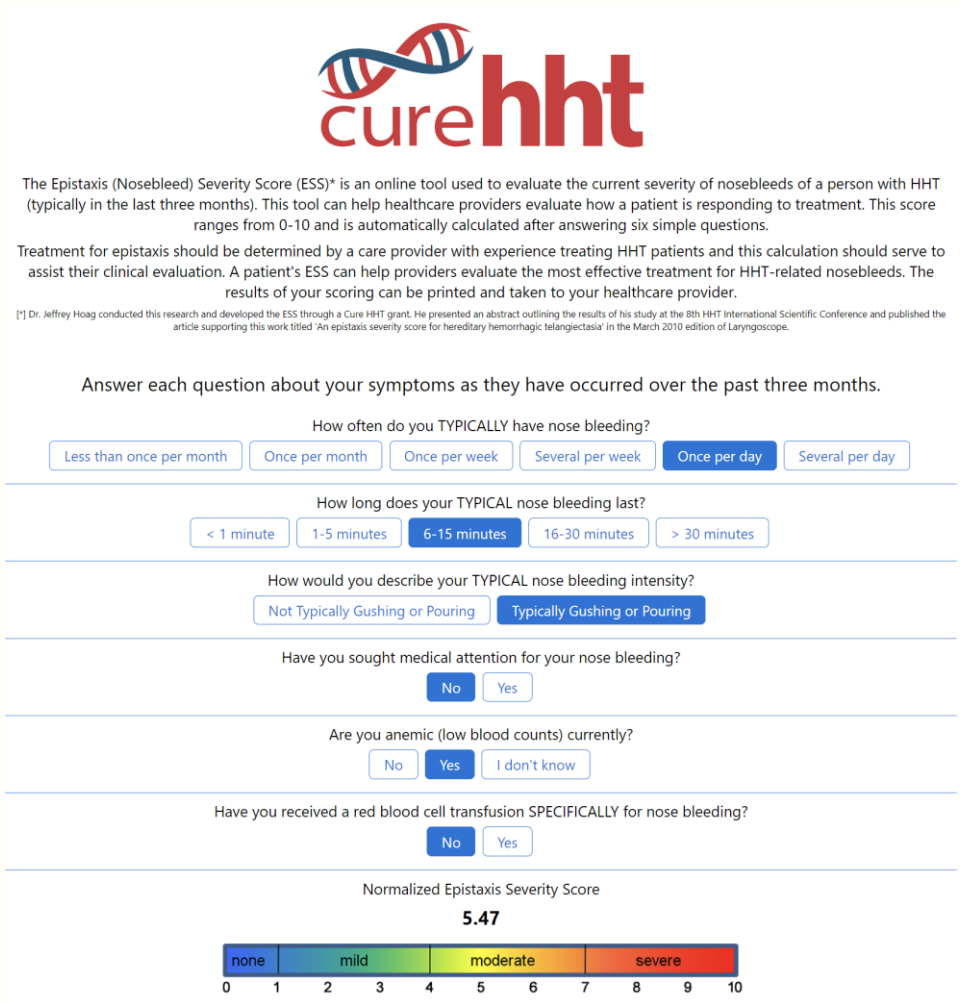
Vasquez-Rios G, et al. *Nefrologia.* 2021.

How I Treat Bleeding in Hereditary Hemorrhagic Telangiectasia



Al-Samkari H. How I Treat Bleeding in Hereditary Hemorrhagic Telangiectasia. *Blood* 2024

Epistaxis Severity Score



Free Calculator at
hhtess.com

Epistaxis Severity Score (ESS)

Systemic Antifibrinolytics for Bleeding in HHT

- Two randomized, controlled trials of oral tranexamic acid (TXA) for HHT
  - In trial of 118 patients, reduction in epistaxis duration of 17.3%
  - In crossover trial of 22 patients, reduction in composite epistaxis endpoint (factoring both duration and intensity) of 54%
  - No significant improvement in Hgb in either trial (but patients not severely anemic at baseline)
- Retrospective series suggesting modest effectiveness in improvement of GI bleeding
- No increase in thrombotic events in any study
  - Recent retrospective series of 24 patients treated for longer durations w/o any VTE

Gaillard S et al., *J Thromb Haemost 2014*
Geisthoff U et al., *Thromb Res* 2014

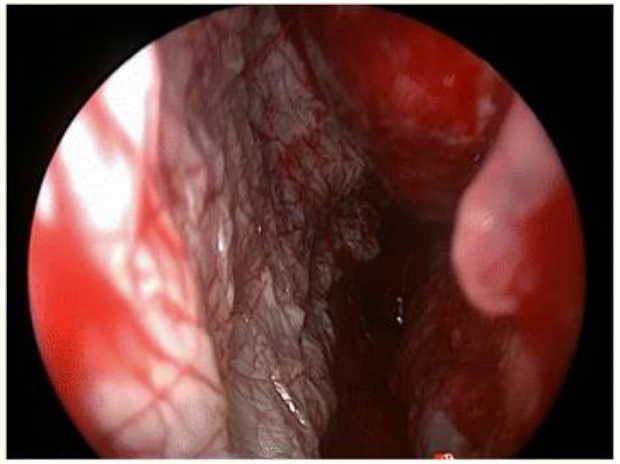
Systemic Hormonal Agents for Bleeding in HHT?

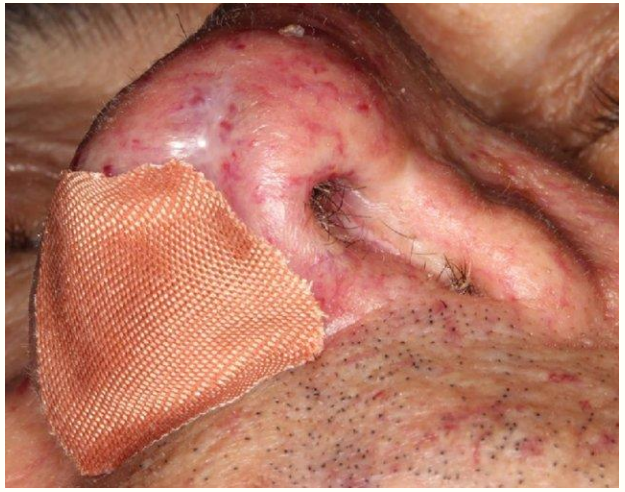
- Very old randomized trial showing no benefit of estrogen (4 mg estradiol valerate daily) on bleeding
- Some studies/case series showing (variable) benefit of SERMs on epistaxis
- All of these agents have clear, proven thrombotic risks
- Male patients do not like hormonal side-effects (agents must be used indefinitely)

Vase P., *Acta Med Scand 1981*

Local Ablative Therapies and Surgical Management

- Local ablative therapies
  - Laser, electrical, or chemical cautery
  - Nasal sclerotherapy
  - Nasal embolization
- Nasal septodermoplasty
- Nasal closure (Young's Procedure)
- Argon plasma coagulation (APC) for GI telangiectasias





Bastianelli et al. *J Otolaryngol* 2015, Malthiery et al. *J Oral Med Oral Surg* 2018

Systemic Bevacizumab for Bleeding in HHT

Bevacizumab

Utility:

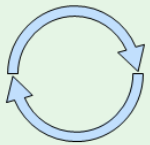
Epistaxis

Gastrointestinal bleeding

Induction

- Administer 4-6 bevacizumab 5 mg/kg infusions every 2 weeks.
- If anemic, administer 1000-2000 mg IV iron during induction.
- Following induction, assess response. If significant improvement in bleeding, proceed to maintenance. If not, discontinue treatment.

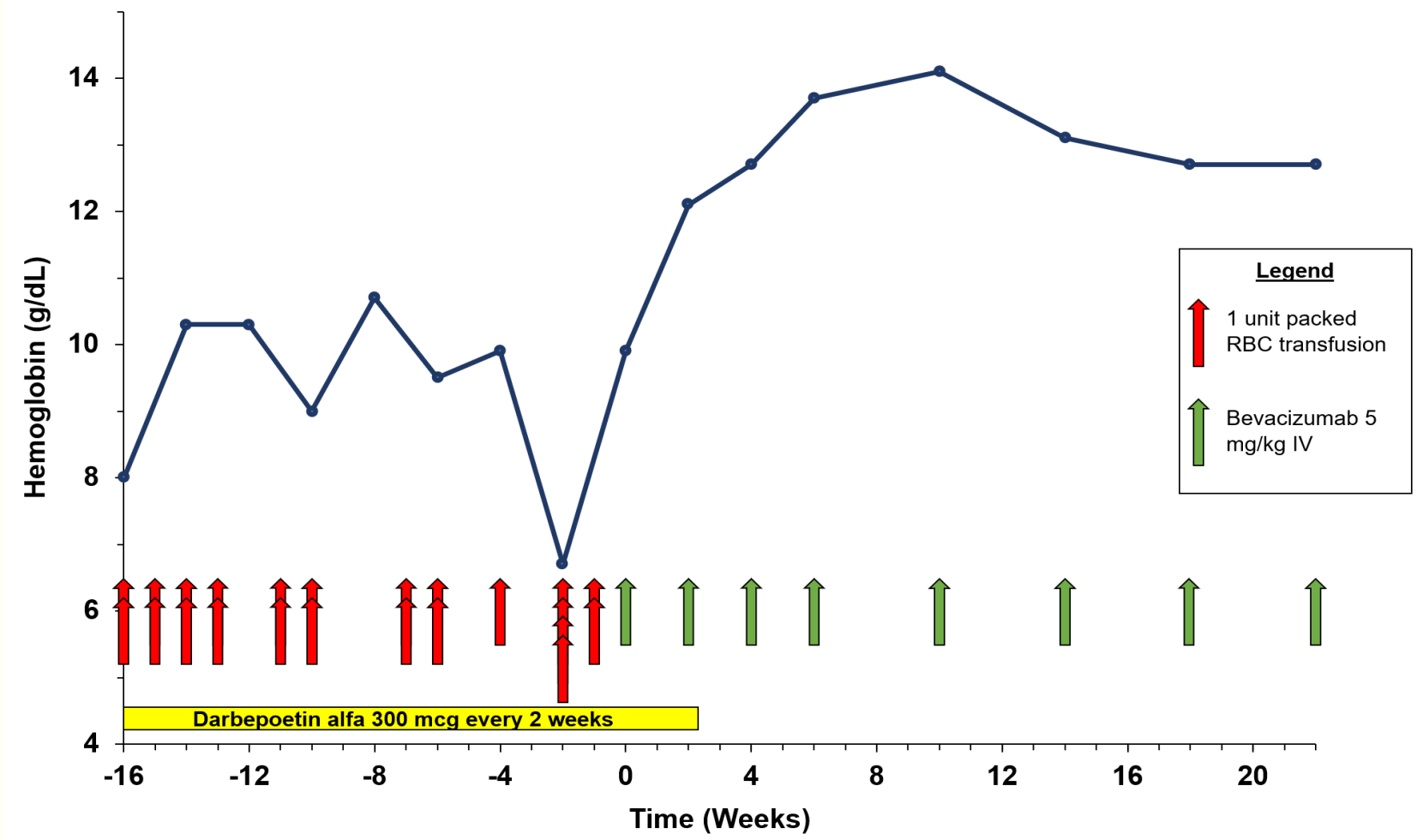
Maintenance



- Bevacizumab 5 mg/kg every 4 weeks, as long as response maintains.
- After 4 maintenance infusions, can consider increasing interval between infusions in willing patients; few patients will tolerate intervals >8 weeks without loss of effect.

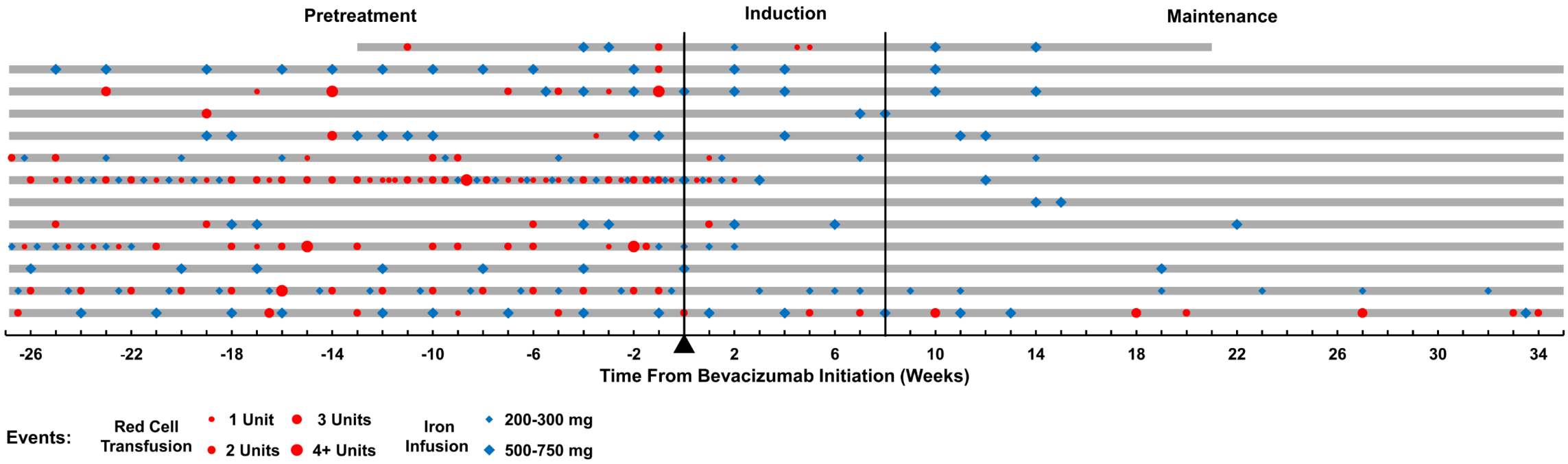
Al-Samkari H. How I Treat Bleeding in Hereditary Hemorrhagic Telangiectasia. *Blood* 2024

Antiangiogenic Therapy Can Be Life-Changing



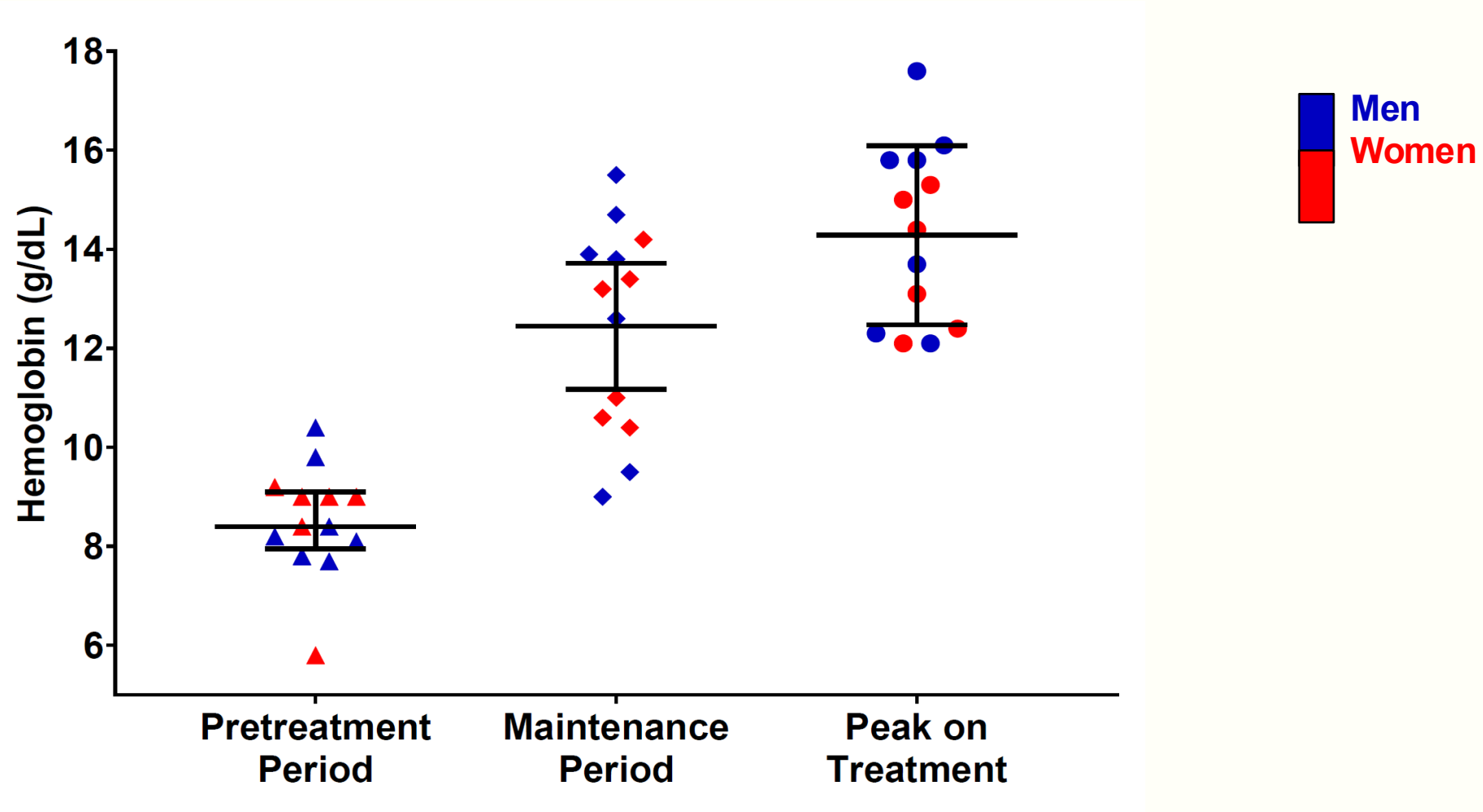
Kritharis et al. *Haematologica 2018*

Impact of Bevacizumab on RBC Transfusions and Iron Infusions: Early Case Series



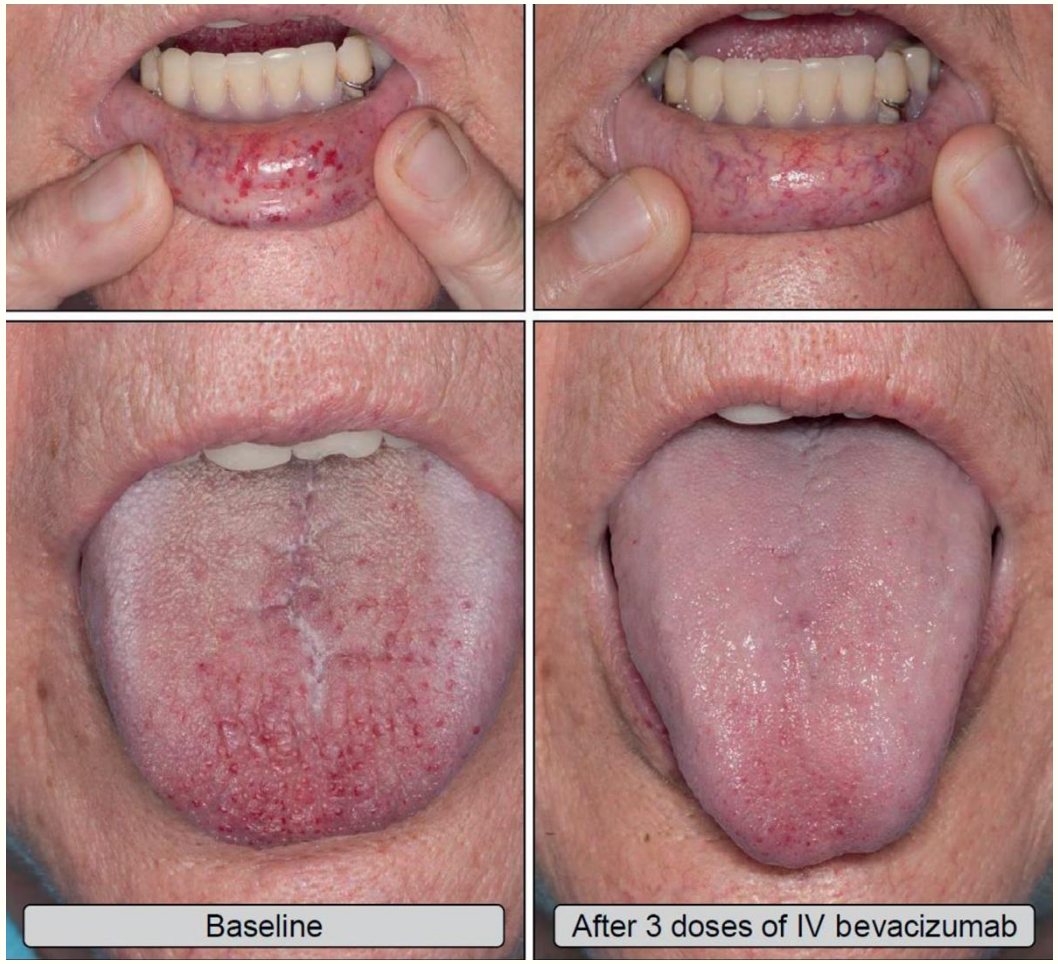
Al-Samkari et al., *J Intern Med* 2018

Impact of Bevacizumab on Hemoglobin: Early Case Series



Al-Samkari et al., *J Intern Med* 2018

Seeing is Believing



Iyer et al., *Mayo Clin Proc* 2018

InHIBIT-Bleed Study

- International, 12-center retrospective study of HHT patients receiving bevacizumab
- Effectiveness measures: Hemoglobin, epistaxis severity score (ESS), red cell transfusion requirement, and iron infusion requirement before and after bevacizumab initiation
- Safety: All bevacizumab-related treatment-emergent adverse events (TEAEs) collected

Epistaxis Severity Score (ESS)

Al-Samkari et al., *Haematologica* 2020

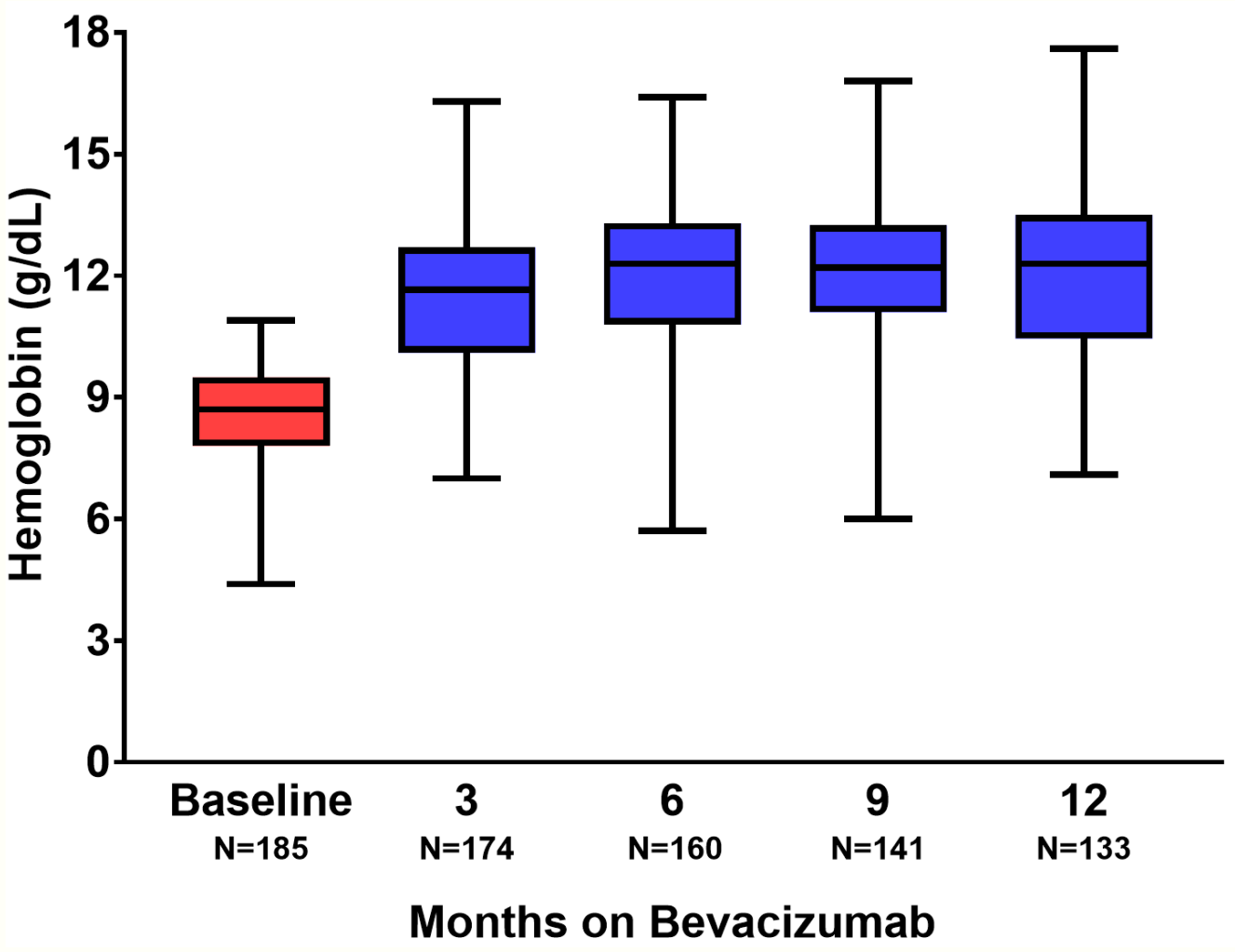
InHIBIT-Bleed Patient Population

- 238 patients treated with bevacizumab for a median of 12 months
  - Received median of 11 infusions
  - Total of 343.9 patient-years of bevacizumab treatment
- 181 patients received maintenance treatment
  - 136 received continuous maintenance
  - 45 received intermittent maintenance

Characteristic	Value
Age (years), mean (range)	63 (29-91)
% Female	62
% Definite HHT by Curaçao criteria	97
Genetic mutation (HHT subtype)	ENG (HHT-1): 52 (22%) ALK1 (HHT-2): 92 (39%) SMAD4 (HHT-JPS): 4 (2%) Genetic testing not done: 80 (34%)
Prior procedural treatments	For epistaxis: 182 (77%) For GI bleeding: 119 (50%)

Al-Samkari et al., *Haematologica* 2020

InHIBIT-Bleed: Effect of Bevacizumab on Hemoglobin



Change in Mean Hgb:

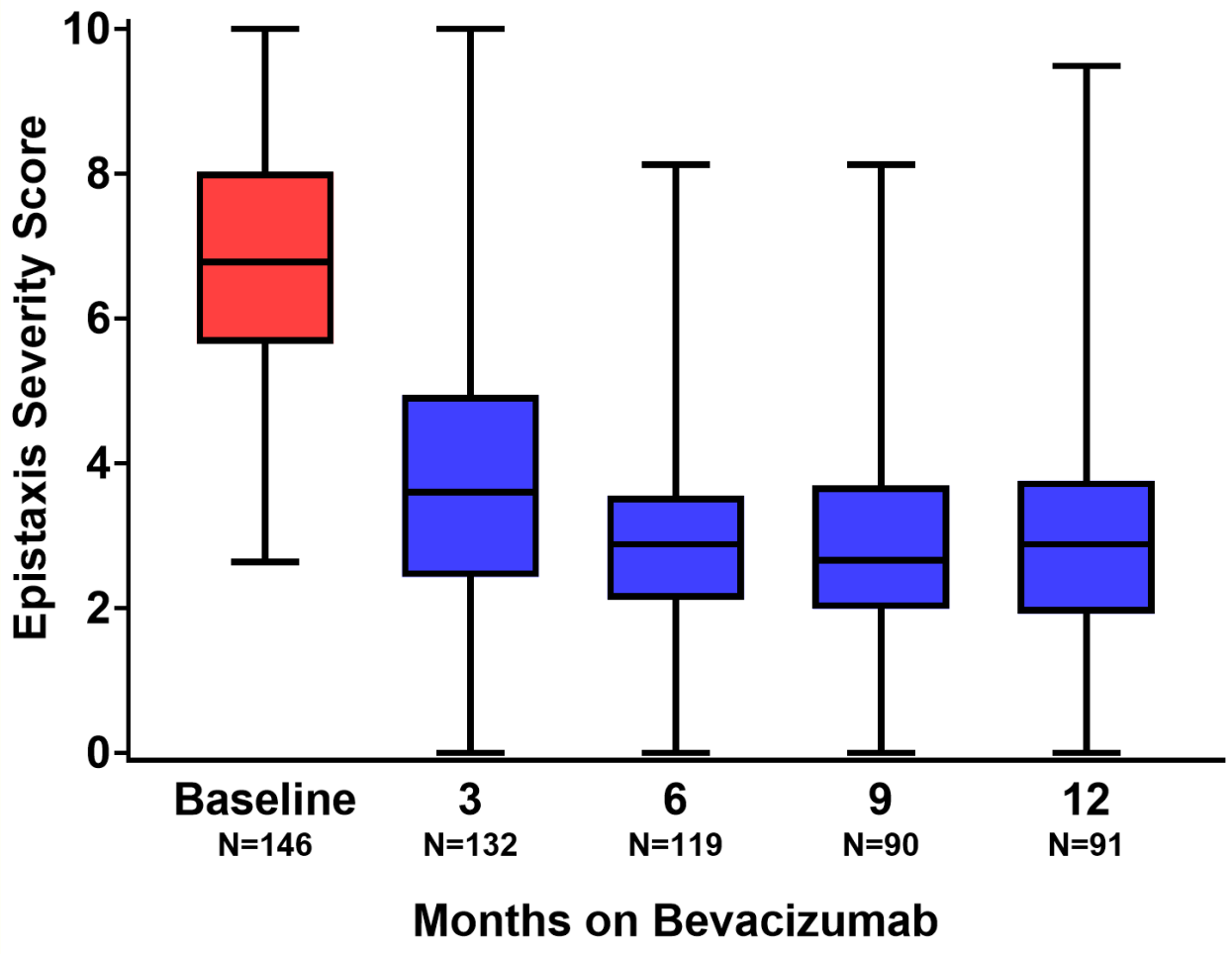
Baseline: **8.6 g/dL** (95% CI, 8.5 to 8.8)

On-Treatment: **11.8 g/dL** (95% CI, 11.5 to 12.1)

Difference: **+3.2 g/dL** (95% CI, 2.9 to 3.4), ***P*<0.0001**

Al-Samkari et al., *Haematologica* 2020

InHIBIT-Bleed: Effect of Bevacizumab on Epistaxis Severity Score



Change in Mean ESS:

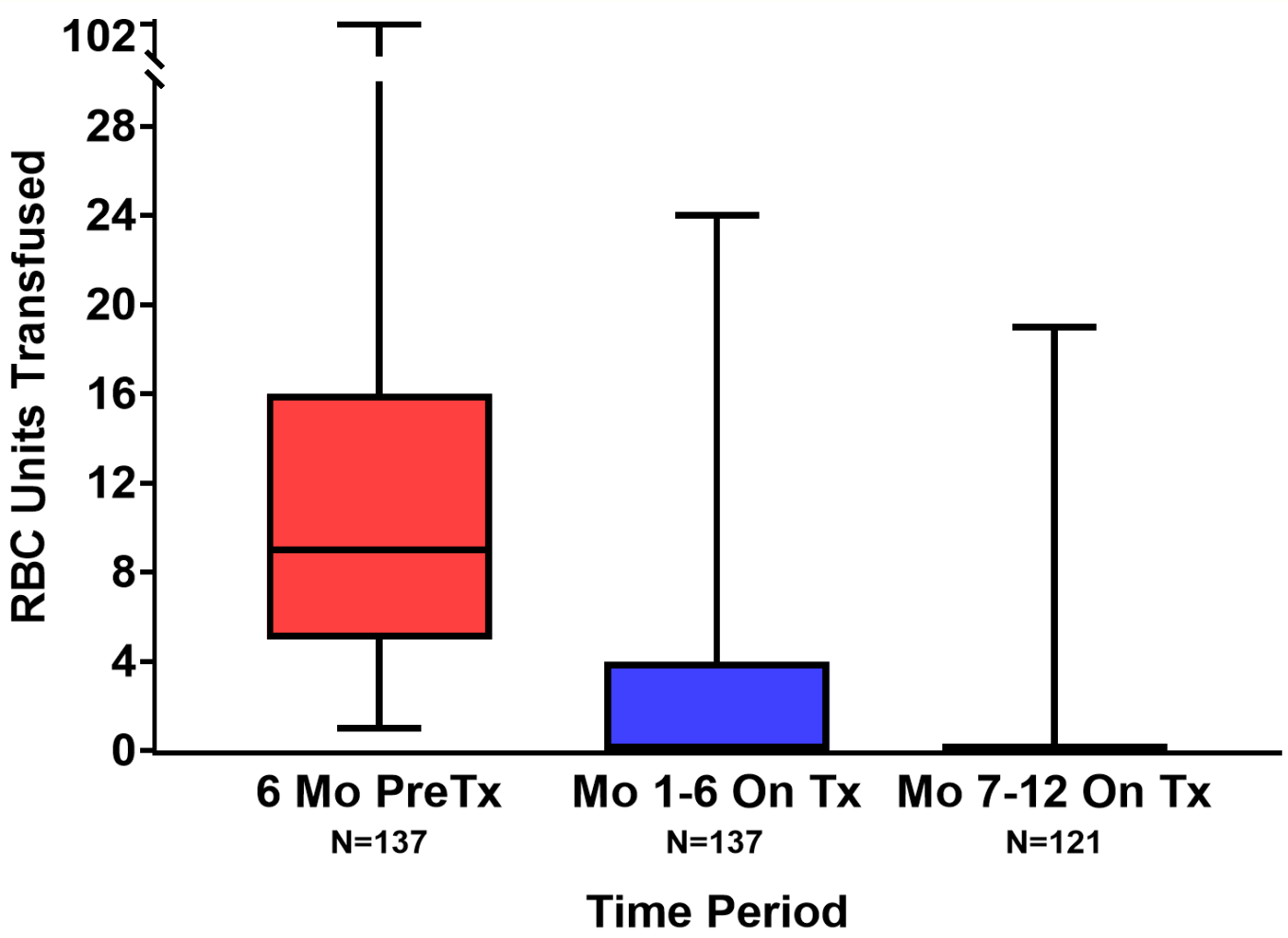
Baseline: **6.81** (95% CI, 6.56 to 7.06)

On-Treatment: **3.44** (95% CI, 3.17 to 3.71)

Difference: **-3.37 g/dL** (95% CI, -3.69 to -3.05), ***P*<0.0001**

Al-Samkari et al., *Haematologica* 2020

InHIBIT-Bleed: Effect of Bevacizumab on Red Cell Transfusions



<u>Change in Median RBC Units Transfused:</u>

6 Mo PreTx: **9 units** (IQR, 5 to 16 units)

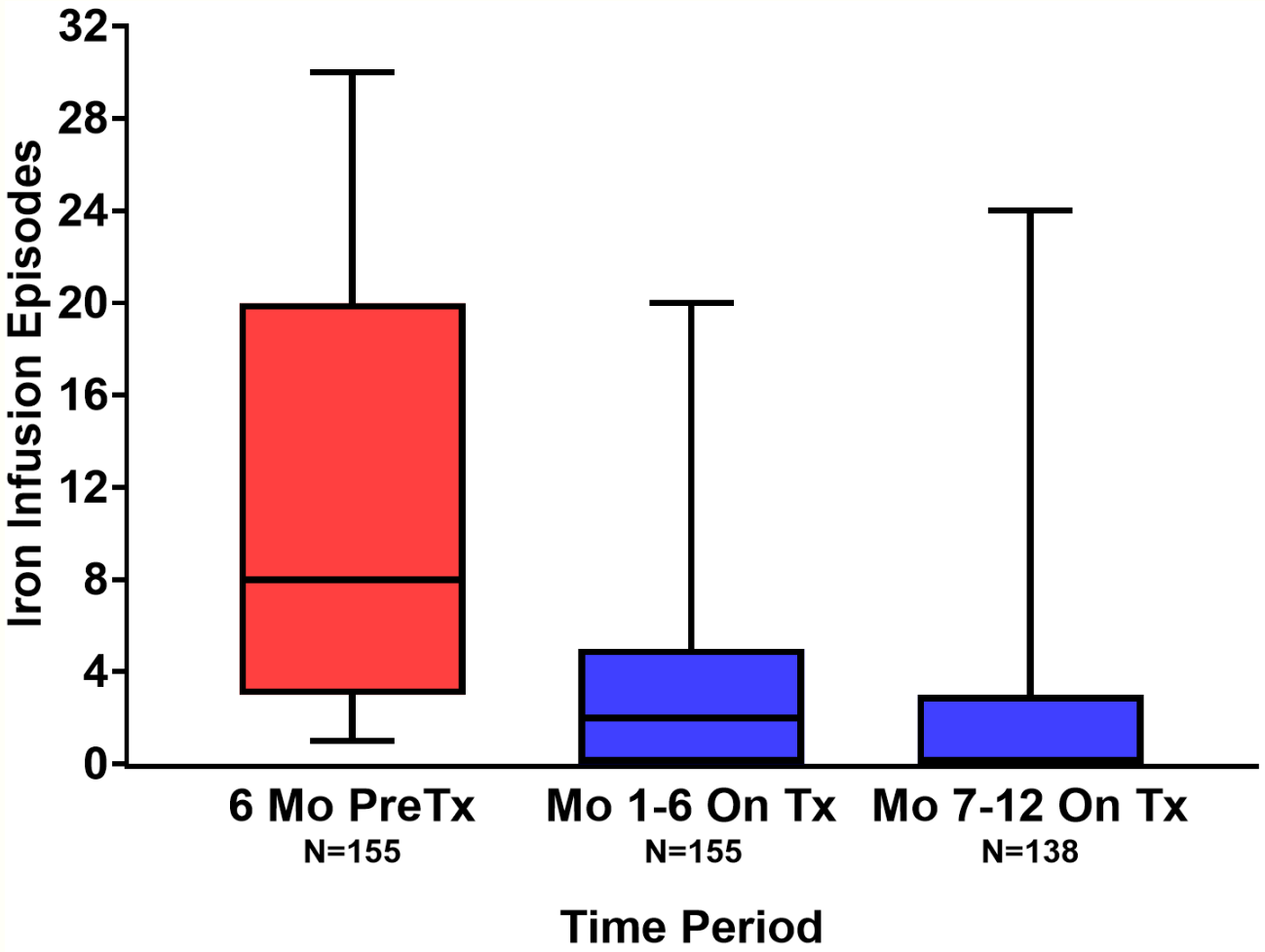
Mo 1-6 OnTx: **0 units** (IQR, 0 to 4 units)

Mo 1-6 OnTx: **0 units** (IQR, 0 to 0 units)

Difference: **-9 units *P*<0.0001**

Al-Samkari et al., *Haematologica* 2020

InHIBIT-Bleed: Effect of Bevacizumab on Iron Infusions



<u>Change in Median Iron Infusion Episodes:</u>

6 Mo PreTx: **8**
(IQR, 3 to 20)

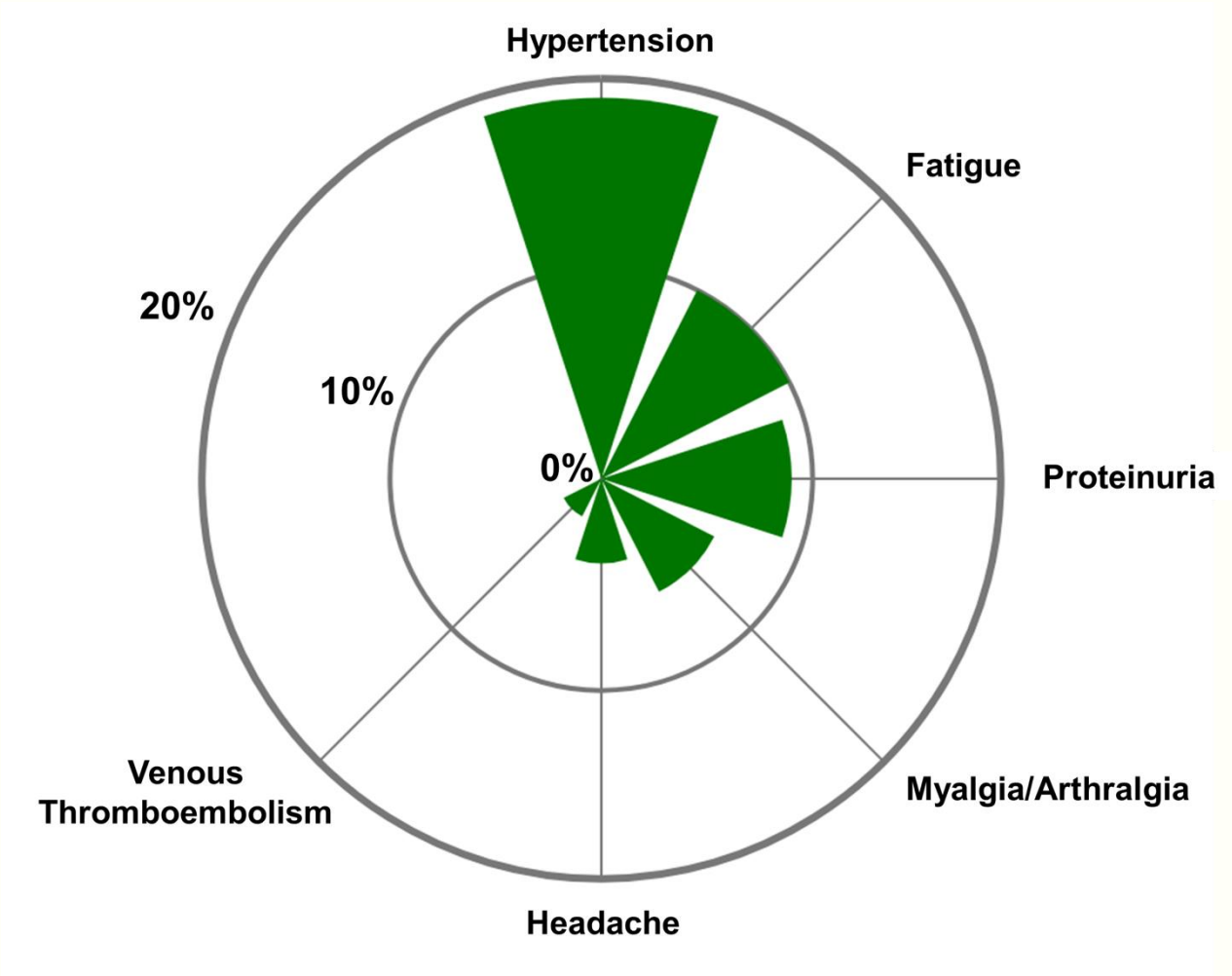
Mo 1-6 OnTx: **2**
(IQR, 0 to 5)

Mo 1-6 OnTx: **0**
(IQR, 0 to 2)

Difference: **-8 infusions**
***P*<0.0001**

Al-Samkari et al., *Haematologica* 2020

InHIBIT-Bleed: Treatment-Emergent Adverse Events



TEAEs with >1% Incidence:

Any (38%)
Hypertension (18%)
Fatigue (10%)
Proteinuria (9%)
Myalgia/arthralgia (6%)
Headache (4%)
VTE (2%)

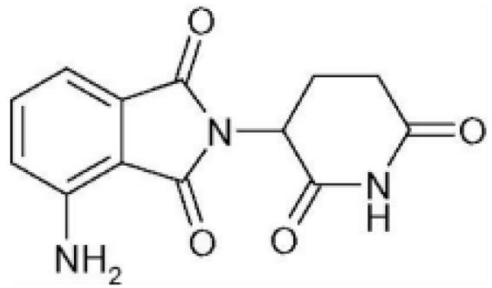
No Fatal TEAEs

No increase in TEAE rates for those treated for longer durations

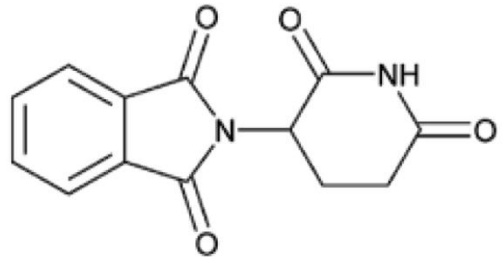
Al-Samkari et al., *Haematologica* 2020

Thalidomide: An Immunomodulatory Imide Drug in HHT

- IMiD with antiangiogenic properties
- Downregulates VEGF and improves vessel wall integrity
- Multiple small studies including ~60 total patients
- Clear improvements in Hgb, epistaxis severity, RBC transfusion requirements, and/or HRQOL
- Problem is AEs—primarily neuropathy that develops in many with long-term use
- Pomalidomide, a newer thalidomide derivative without neuropathy concerns and less toxicity, was then selected to evaluate in a large NIH-funded study



Pomalidomide

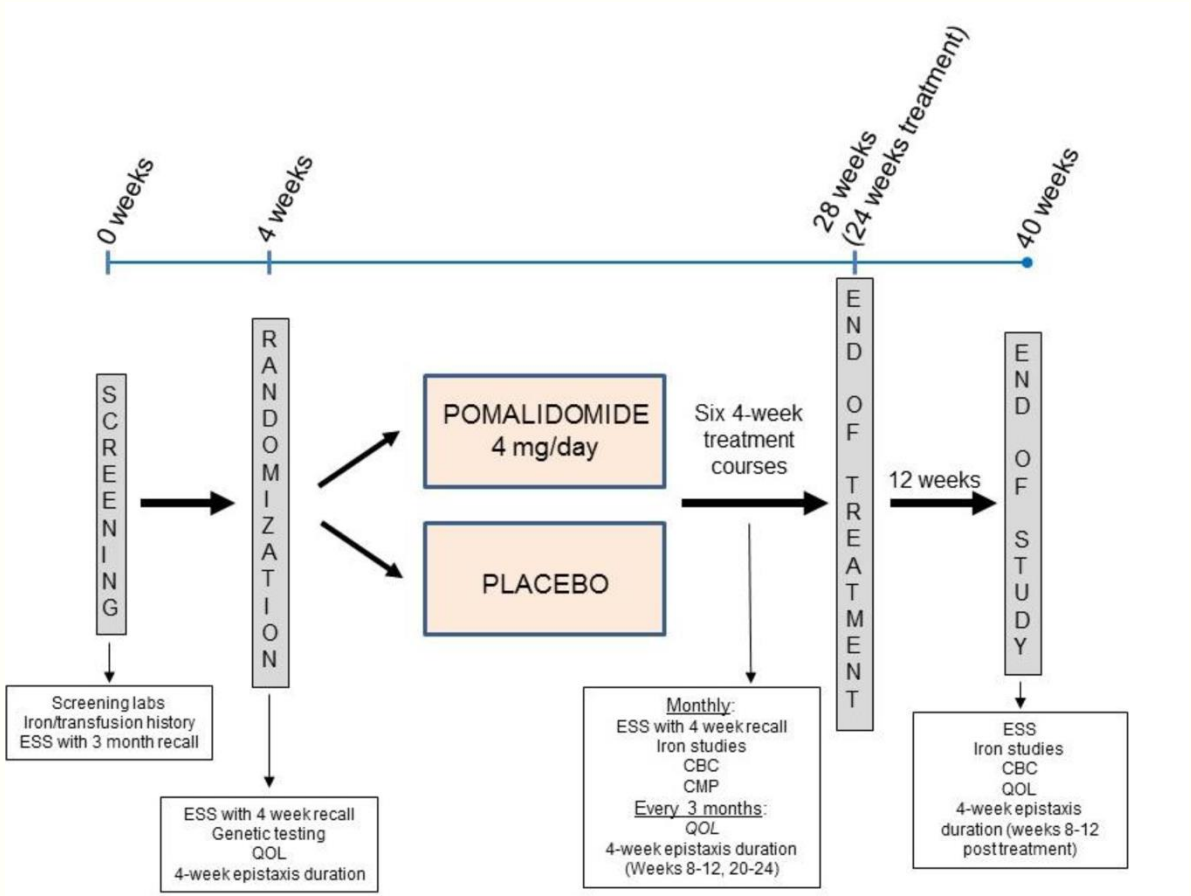


Thalidomide

Lebrin et al., *Nat Med* 2010; Invernizzi et al. *Lancet Haematol* 2015

Pomalidomide: Multicenter U.S. Randomized, Controlled PATH-HHT Study

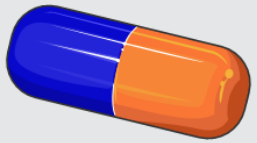
PATH
Pomalidomide for the Treatment of Bleeding in HHT



Al-Samkari et al., ASH 2023 (ASH Late-Breaking Abstract LBA-3)

Pomalidomide in HHT

Pomalidomide

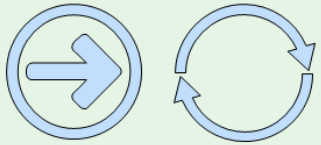


Utility:

Epistaxis

Gastrointestinal bleeding

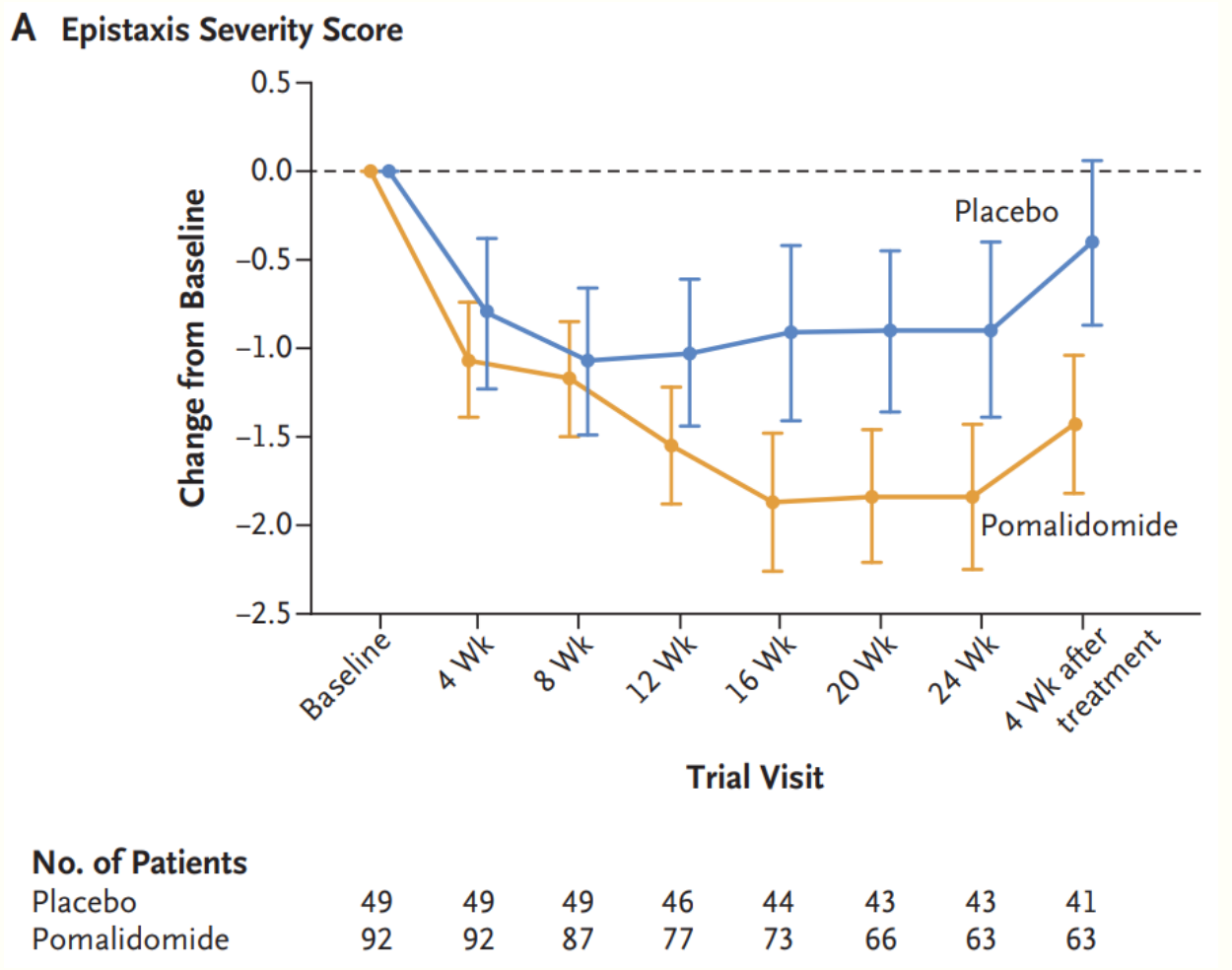
Dosing



- For most patients, initiate at 4 mg daily (without off weeks).
- For older adults (age ≥65), mild neutropenia (ANC 1000-2000 cells/μL), chronic constipation, IBS, or IBD, initiate at 2 mg daily.
  - If 2 mg well-tolerated, increase dose at 1 mg intervals up to 4 mg daily maximum dose.
- Continue therapy as long as response is maintained.

Al-Samkari H. How I Treat Bleeding in Hereditary Hemorrhagic Telangiectasia. *Blood* 2024

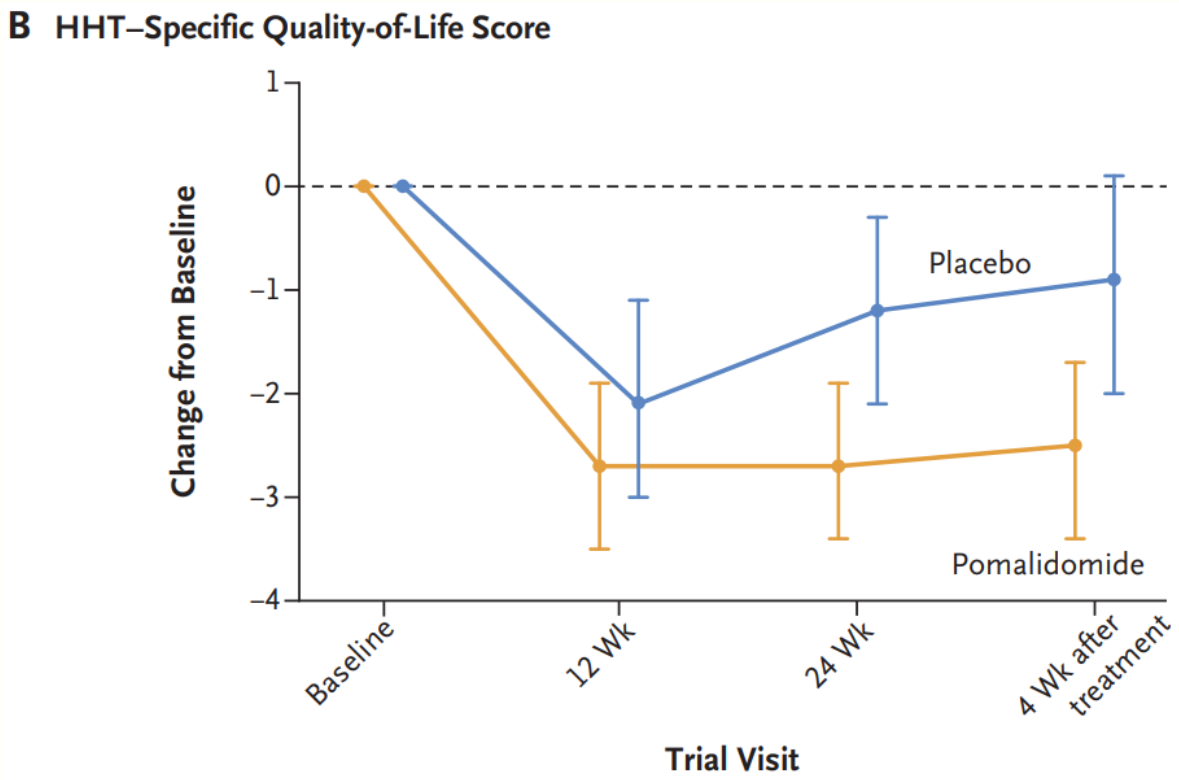
Pomalidomide Significantly Improved ESS versus Placebo



No. of Patients								
Placebo	49	49	49	46	44	43	43	41
Pomalidomide	92	92	87	77	73	66	63	63

Al-Samkari et al., *New Engl J Med* 2024

Substantial Improvement in HHT-Specific HR-QOL with Pomalidomide versus Placebo



No. of Patients				
Placebo	48	44	42	37
Pomalidomide	90	70	59	61

Al-Samkari et al., *New Engl J Med* 2024

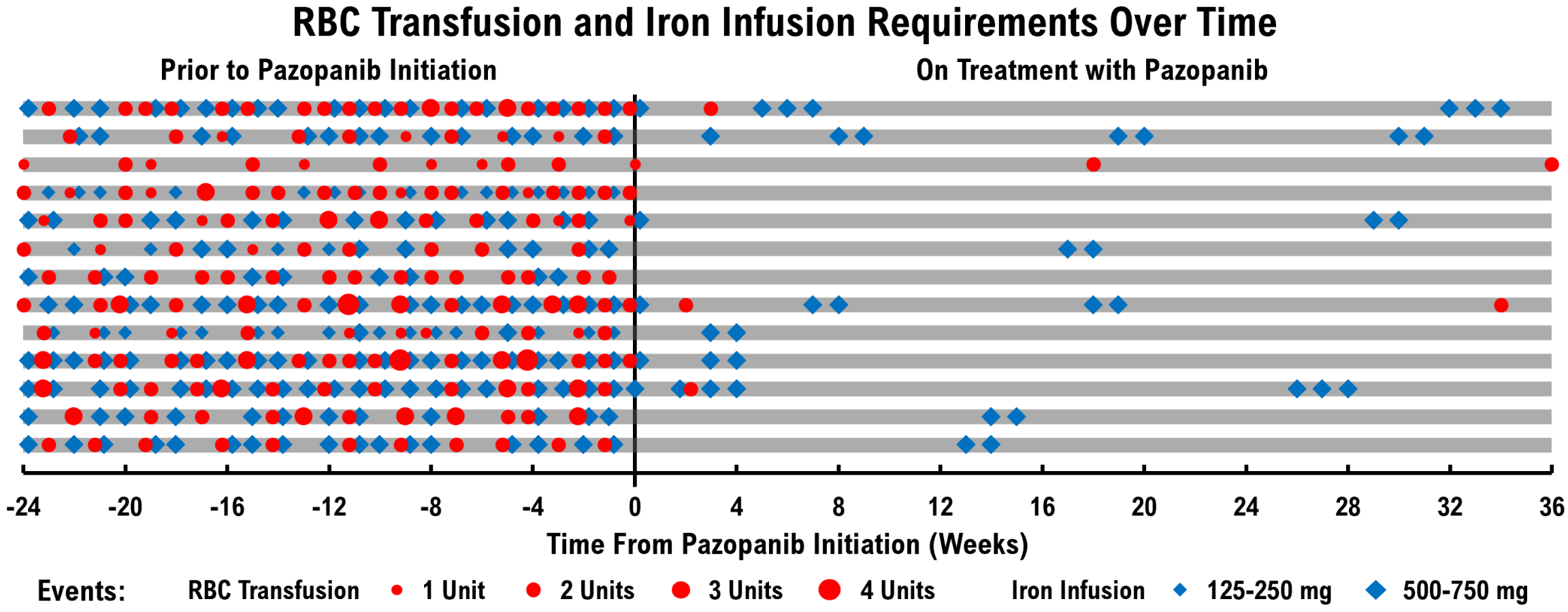
Multicenter U.S. Randomized, Controlled PATH-HHT Study

Table 3. Safety Outcomes.*

Outcome	Pomalidomide (N=95)	Placebo (N=49)	P Value
Adverse events of special interest — no. of patients (%)			
Constipation	45 (47)	9 (18)	<0.001
Fatigue	42 (44)	17 (35)	0.27
Neutropenia	42 (44)	5 (10)	<0.001
Rash†	33 (35)	5 (10)	0.002
Tremor‡	8 (8)	0	0.04
Venous thromboembolism§	4 (4)	1 (2)	0.50
Thrombocytopenia	4 (4)	0	0.15
Peripheral neuropathy¶	3 (3)	0	0.21
Arterial thromboembolism	0	0	1.00

Al-Samkari et al., *New Engl J Med* 2024

Pazopanib: A VEGF-Receptor Blocking Tyrosine Kinase Inhibitor



Parambil et al., *Angiogenesis* 2021

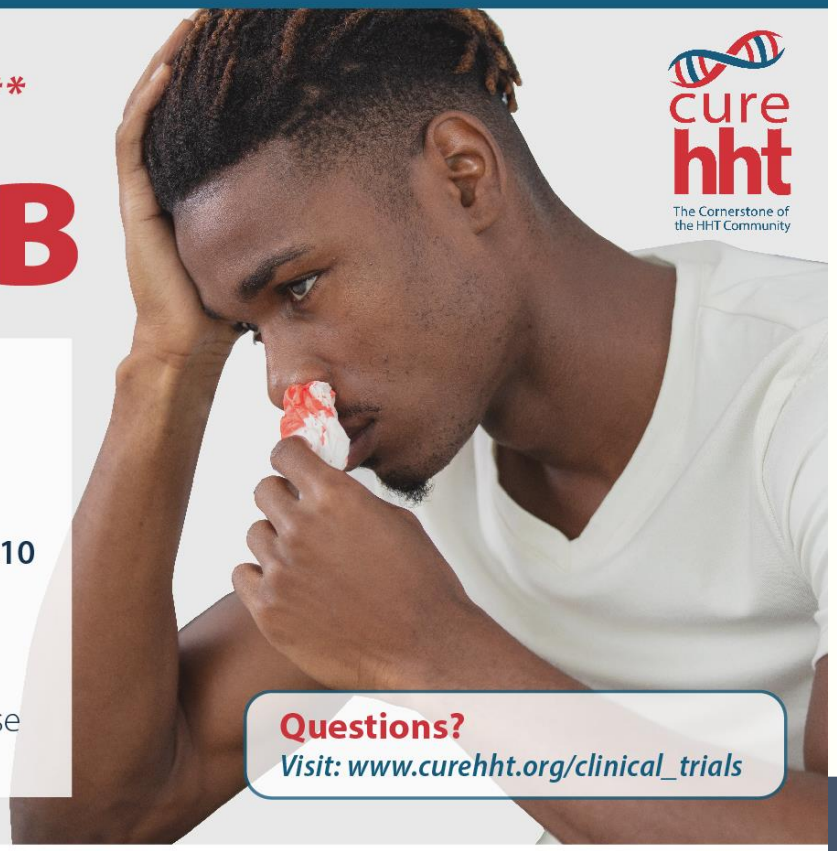
Multicenter U.S. Randomized, Controlled Pazopanib Study

NEW CLINICAL TRIAL

*** UPDATED REQUIREMENTS ***

YOU MAY NOW BE ELIGIBLE!

PAZOPANIB



***NEW* ELIGIBILITY REQUIREMENTS**

- **Age 18-85**
- **Definite or probable diagnosis of HHT**
- **Nosebleeds at least 20 min per week with mild anemia *OR* average hemoglobin <10**
- Ability to complete daily blood pressure and nosebleed monitoring
- Willing to forego other treatments, e.g. laser
- Women of childbearing age potential must use birth control

Her

NOW RECRUITING!

Recommended AVM Screening

Pulmonary AVMs
(pAVMs)

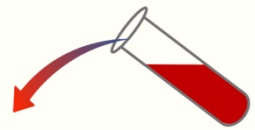
- All patients should have an **echocardiogram with agitated saline contrast ("echo bubble study")** to screen for pAVMs
- **Repetition necessary** every few years

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)

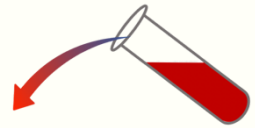
- **Liver imaging** (i.e., doppler ultrasound) to screen for hAVMs is controversial but currently recommended



Faughnan M, et al. *Ann Intern Med*. 2020

Visceral AVM Management

- Pulmonary AVMs: Should always be intervened upon if large enough
  - Standard management is IR embolization
  - In rare cases lung resection if problematic and not amenable to IR embolization
- Brain AVMs: Case-by-case basis
  - Endovascular embolization, stereotactic radiation, and/or microsurgery
- Liver AVMs: Challenging problem
  - Hepatic artery embolization unsafe, associated with high mortality (10-15%)
  - Liver transplant is “definitive” but scarce resource (difficult for HHT patients to get)
  - Emerging role for antiangiogenic therapy



Additional Resources: Second International HHT Guidelines

Annals of Internal Medicine

CLINICAL GUIDELINE

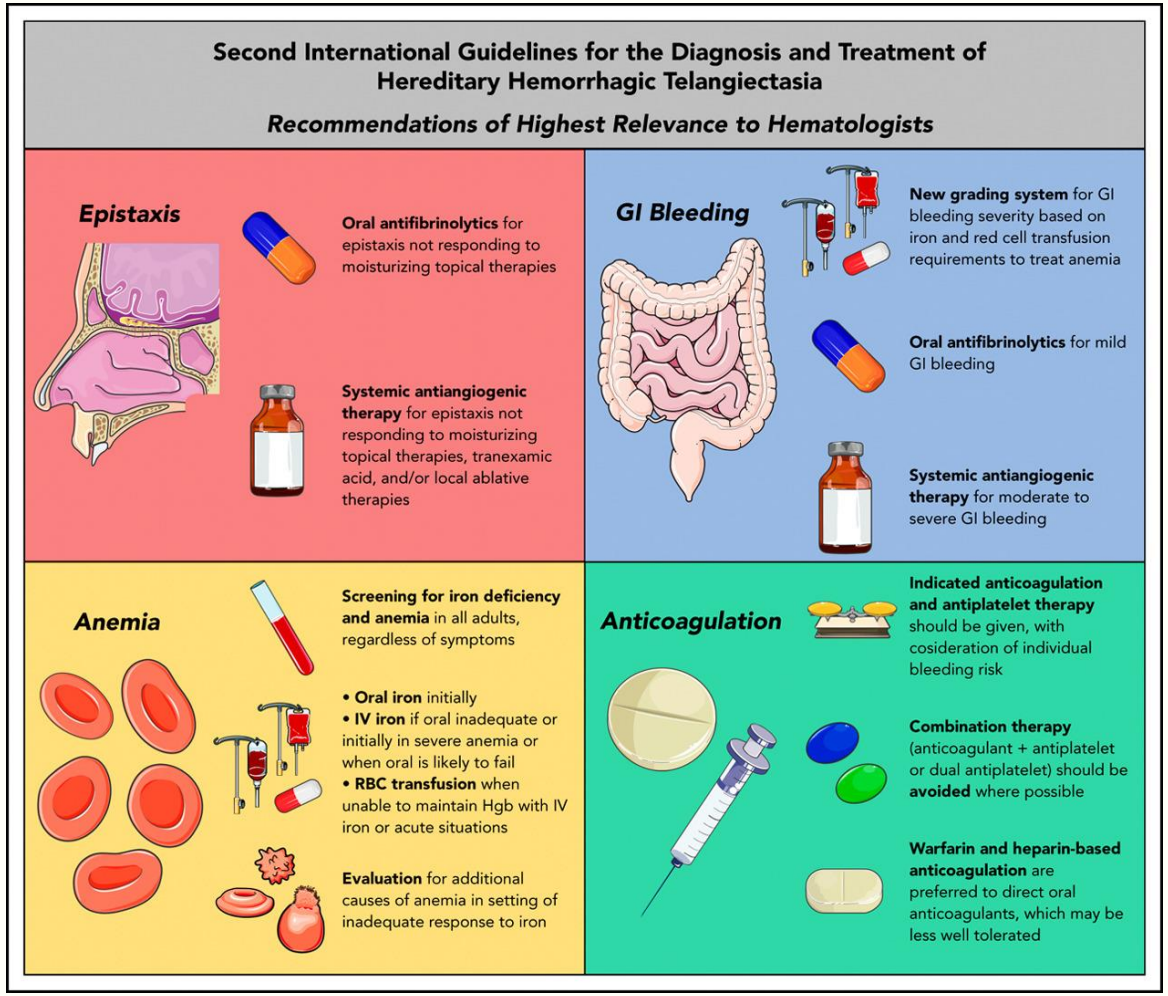
Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

Marie E. Faughnan, MD, MSc; Johannes J. Mager, MD, PhD; Steven W. Hetts, MD; Valerie A. Palda, MD, MSc; Kelly Lang-Robertson; Elisabetta Buscarini, MD; Erik Deslandres, MD; Raj S. Kasthuri, MD; Andrea Lausman, MD; David Poetker, MD, MA; Felix Ratjen, MD; Mark S. Chesnutt, MD; Marianne Clancy, RDH, MPA; Kevin J. Whitehead, MD; Hanny Al-Samkari, MD; Murali Chakinala, MD; Miles Conrad, MD; Daniel Cortes, BscPhm; Claudia Crocione; Jama Darling, MD; Els de Gussem, MD; Carol Derksen; Sophie Dupuis-Girod, MD, PhD; Patrick Foy, MD; Urban Geisthoff, MD; James R. Gossage, MD; Adrienne Hammill, MD; Ketil Heimdal, MD; Katharine Henderson, MS, CGC; Vivek N. Iyer, MD, MPH; Anette D. Kjeldsen, MD; Masaki Komiyama, MD; Kevin Korenblatt, MD; Jamie McDonald, MS, CGC; Jack McMahon; Justin McWilliams, MD; Mary E. Meek, MD; Meir Mei-Zahav, MD; Scott Olitsky, MD, MBA; Sara Palmer, PhD; Rose Pantalone, RN; Jay F. Piccirillo, MD; Beth Plahn, RN, MHA; Mary E.M. Porteous, MD; Marco C. Post, MD, PhD; Ivan Radovanovic, MD; Paul J. Rochon, MD; Josanna Rodriguez-Lopez, MD; Carlo Sabba, MD; Marcelo Serra, MD; Claire Shovlin, PhD, MA; Dennis Sprecher, MD; Andrew J. White, MD; Ingrid Winship, MBChB, MD; and Roberto Zarrabeitia, MD

hhtguidelines.org

Faughnan et al., *Annals of Internal Medicine* 2020.

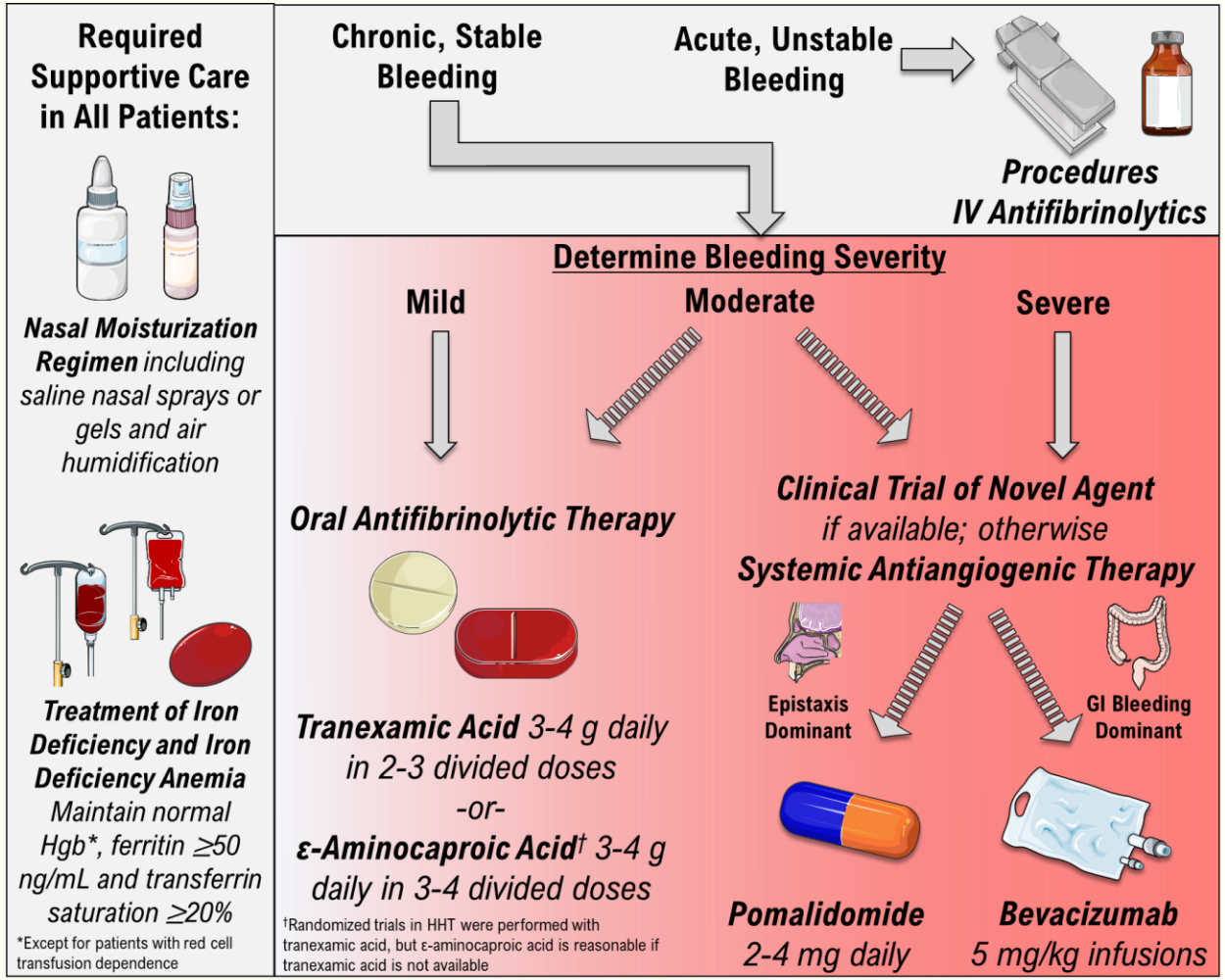
Additional Resources: HHT Guidelines For the Hematologist



Guidelines Highlights for the Hematologist published in *Blood* December 2020 Available Open Access

Al-Samkari H., *Blood* 2021

Additional Resources: How I Treat Bleeding in HHT



How I Treat Bleeding in HHT Published in *Blood* June 2024

Al-Samkari H., *Blood* 2024

Other Vascular Bleeding Disorders

Angiodysplasias in Von Willebrand Disease

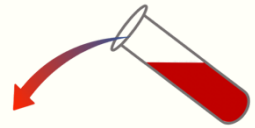
- Von Willebrand Factor itself is antiangiogenic
- Patients with VWD can develop GI angiodysplasias (and also AVMs in other organs/locations)
- Classically associated with type 2A VWD but can occur in any patient with VWD
- Most VWD patients have clearly abnormal nailfold capillaroscopy (dilation, dysplasia, and/or microscopic bleeding)

- Treatment: Regular VWF replacement is usually not feasible (and doesn't resolve established vascular lesions); current standard is supportive (antifibrinolytics, octreotide, etc.)

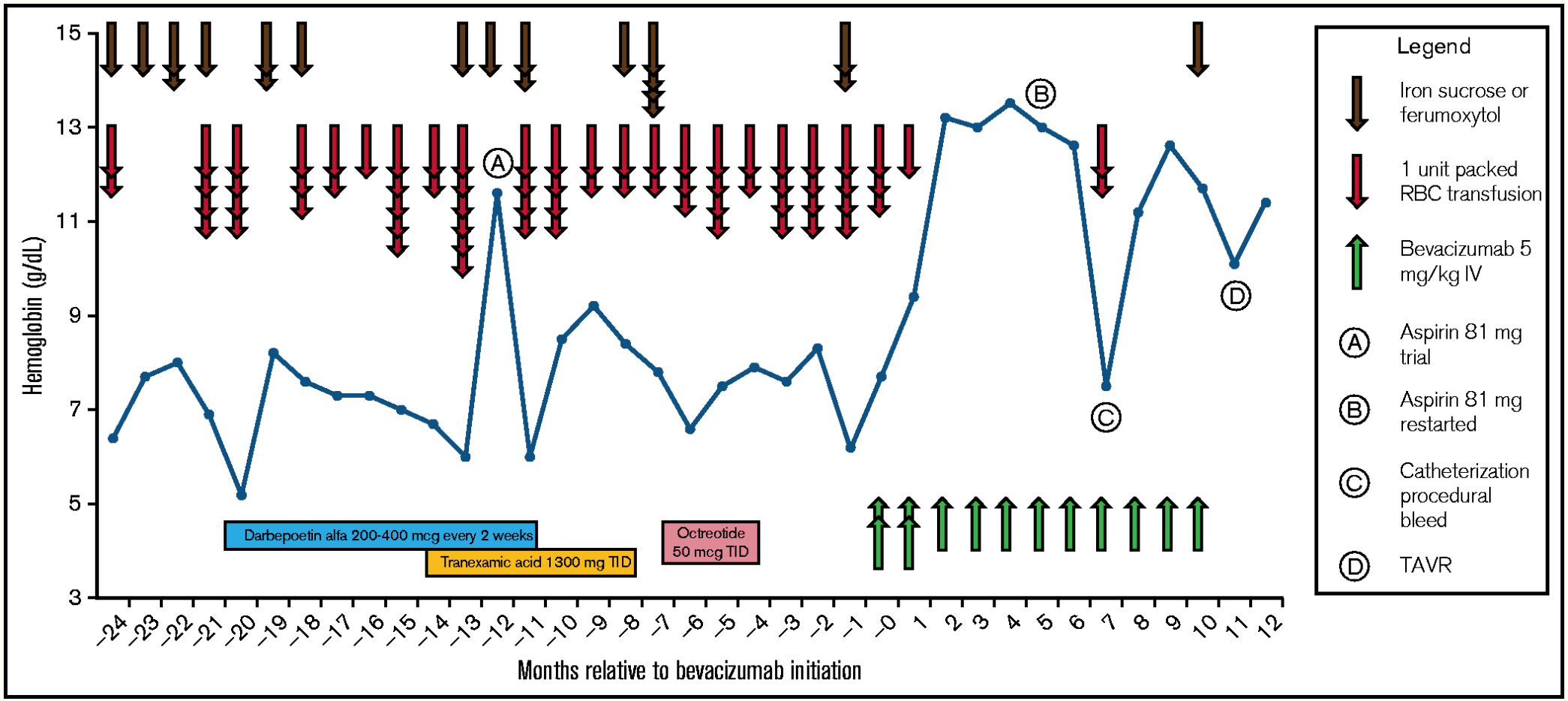
Al-Samkari H. *JTH* 2021

Heyde Syndrome

- Constellation of aortic stenosis, bleeding GI vascular lesions, and acquired von Willebrand syndrome
  - Suspect based on clinical history (remember AS may not be known)
  - AVR often, but not always, fixes bleeding
  - Standard for bleeding still supportive (antifibrinolytics, octreotide)
  - May be a role for bridging antiangiogenic therapies in patients with Heyde syndrome unable to undergo valve replacement due to inability to tolerate anticoagulation



Bevacizumab in Heyde Syndrome



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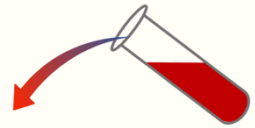
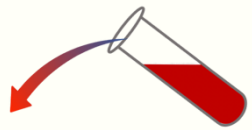
Conclusions

- HHT is a common hereditary bleeding disorder with significant morbidity and no approved therapies
- Systemic therapies to reduce bleeding and telangiectasias, in particular antiangiogenic treatments, are now standard-of-care
- Bevacizumab is highly effective and safe to manage bleeding in HHT; studies are ongoing
- Remember vascular abnormalities in von Willebrand disease and Heyde syndrome

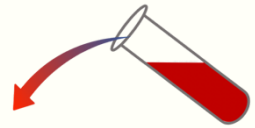


Questions?



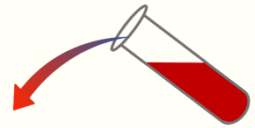
CME Question 1

- A 45-year-old man with HHT (*ENG* mutated) presents to clinic for evaluation. He complains of worsening nosebleeding over the past 6 months. His Epistaxis Severity Score in clinic today is 4.35. His hemoglobin is 14.5 g/dL, ferritin is 51 ng/mL, and transferrin saturation is 25%.
- Which of the following is the next best step in the management of this patient?
  - A) Prescribe intravenous bevacizumab
  - B) Prescribe ferric derisomaltose, 1000 mg x1
  - C) Prescribe oral tamoxifen
  - D) Prescribe oral tranexamic acid



CME Question 2

- A 65-year-old woman with HHT (*ACVRL1* mutated) presents to clinic for evaluation. She complains of worsening fatigue and reduced energy over the past 6 months. Her Epistaxis Severity Score in clinic today is 3.35. Her hemoglobin is 7.5 g/dL, ferritin is 9 ng/mL, and transferrin saturation is 4%. A recent endoscopy showed several non-bleeding telangiectatic lesions in her stomach and duodenum.
- Which of the following is the next best step in the management of this patient?
  - A) Prescribe intravenous bevacizumab
  - B) Prescribe intravenous bevacizumab and ferumoxytol
  - C) Prescribe ferumoxytol
  - D) Prescribe oral tranexamic acid and ferumoxytol



CME Question 3

- Which of the following is contraindicated for use in HHT?
  - A) Ferric gluconate
  - B) Ferric carboxymaltose
  - C) Ferric derisomaltose
  - D) Iron dextran