Hereditary Hemorrhagic Telangiectasia

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Disclosures

- I have no actual or potential conflict of interest to disclose in relation to this presentation.

Outline

- HHT refresher
- Clinical manifestations, screening, and treatment
- How does this impact your practice?
- What's new in HHT

Refresher: what is HHT?

- Osler-Weber-Rendu
- Inherited disorder of blood vessel formation
- Mucocutaneous telangiectasias and visceral arteriovenous malformations
- Manifestations depend on tissue distribution

HHT is NOT…

- A coagulopathy
- Von Willebrand Disease
- Platelet disorder
- Other multi-eponymous diseases
- … as rare as you might think

Genetics

- Autosomal dominant inheritance
- Affects up to 1:5000 worldwide
- More prevalent than most realize
  - Fragile X (1:5000)
  - Marfan (1:5,000 to 10,000)
  - Myasthenia gravis (1:4000)

Diagnostic criteria

Level of Diagnostic Certainty	Number of Criteria Present
Unlikely	**≤ 1**
Possible	**2**
Definite	**≥ 3**

1. Recurrent spontaneous epistaxis
2. Multiple characteristic telangiectasias
3. Visceral arteriovenous malformations
4. Family history meeting above criteria

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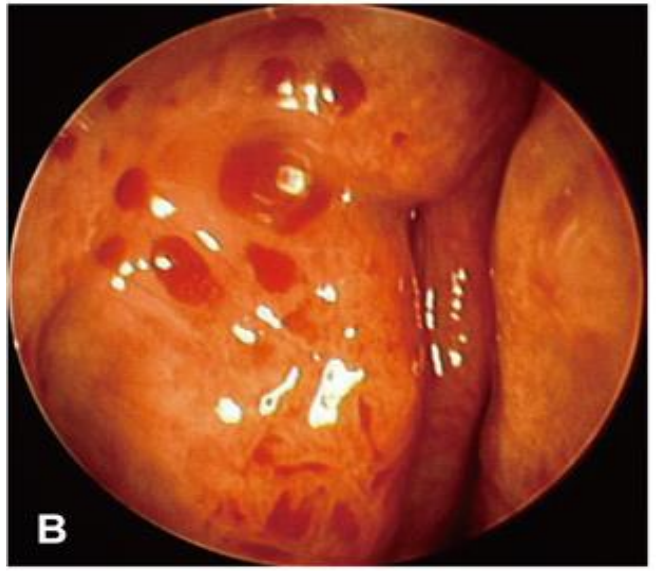
Clinical manifestations

- Mucocutaneous telangiectasis
  - Face, lips, ears, finger tips
  - Nasal and GI mucosa
- Visceral AVMs
  - Lungs, brain, liver, elsewhere

Clinical manifestations
Epistaxis

- Affects almost all patients
  - Nearly 100% by age 40
- Average onset age 12
- Symptoms range from occasional epistaxis to life-threatening hemorrhage
- Anemia is common



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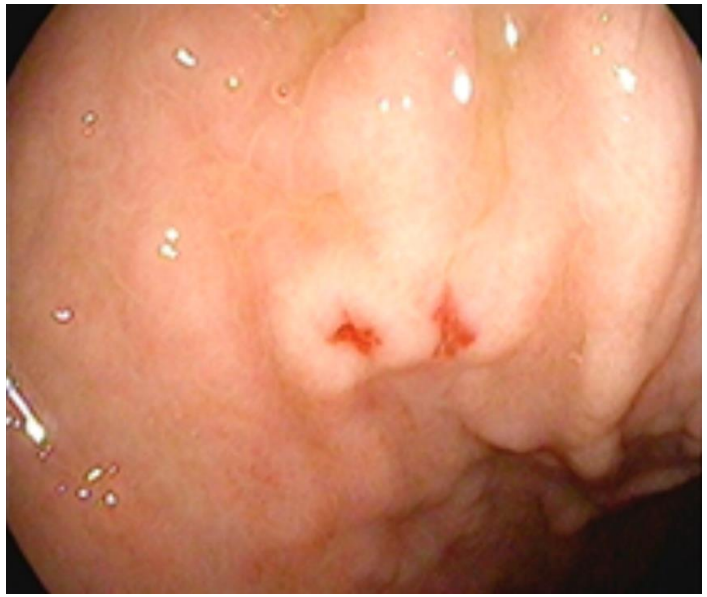
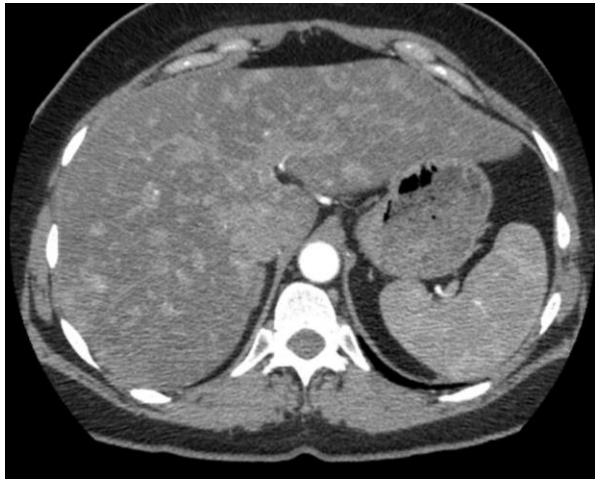
Clinical manifestations
GI telangiectasias

- Present in most patients with HHT
- Clinically significant GI bleeding in 10%
- Most common in stomach and small bowel



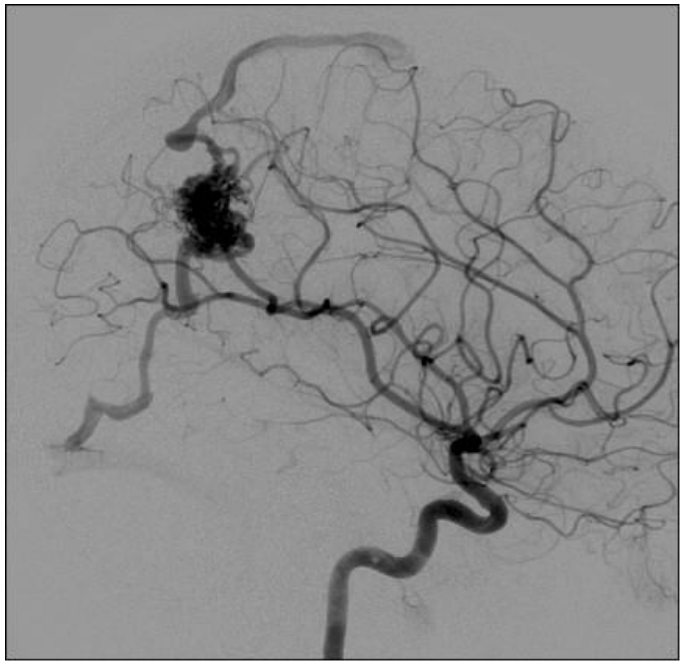
Clinical manifestations
Hepatic vascular malformations

- Common in patients with HHT
- Typically cause no symptoms (10%)
- Manifestations depend on predominant shunting
  - HA -> HV (arteriovenous)
  - HA -> PV (arterioportal)
  - PV -> HV (portovenous)
- High output heart failure, portal hypertension, biliary ischemia, encephalopathy



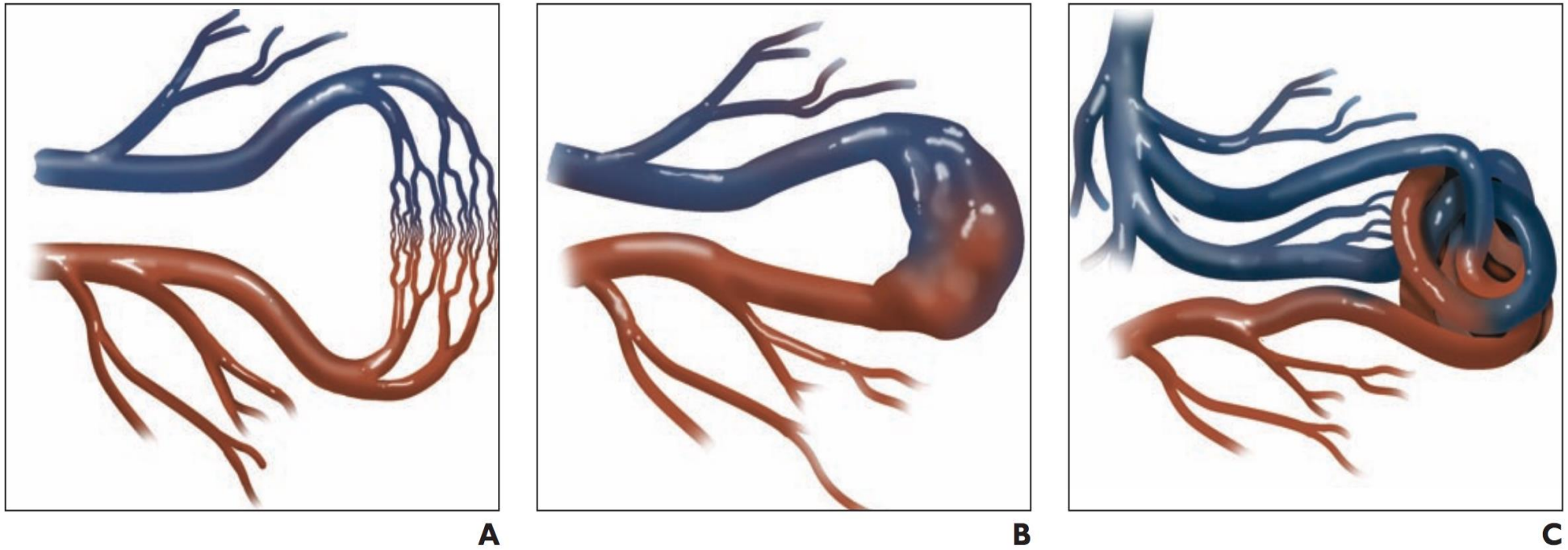
Clinical manifestations
Cerebral Vascular Malformations

- Affect up to 10% with HHT
- AVMs and pial fistulae at highest risk bleeding
  - 0.5% per year
- Small AVMs, capillary telangiectasias, venous anomalies less likely to bleed



of

Pulmonary AVMs

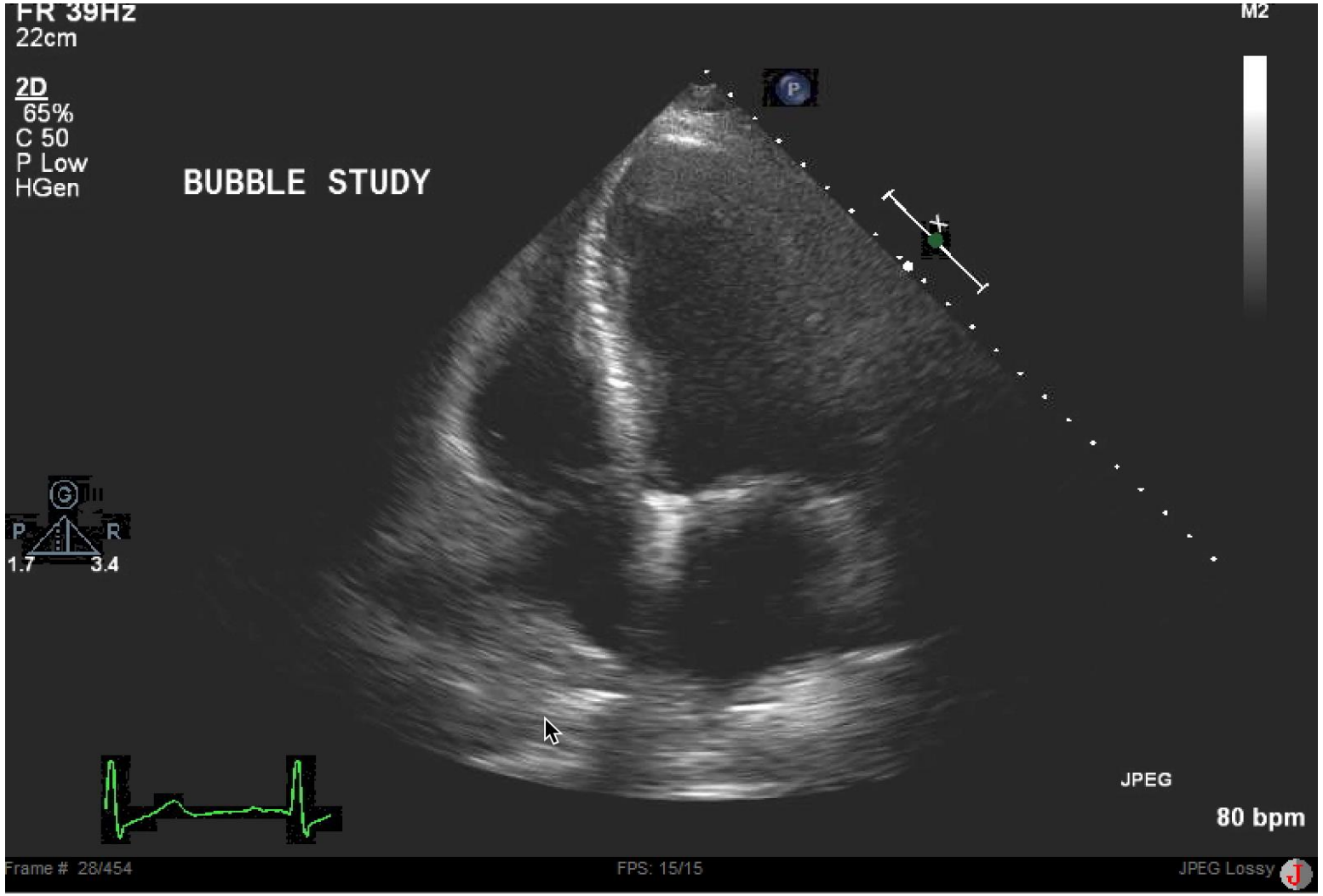


Diffuse (A), simple (B), and complex (C) pulmonary AVM morphologies, from Trerotola et al., *AJR* 2010; 195:383.[13]

Pulmonary AVMs:
Clinical consequences and complications

- Right-to-left intrapulmonary shunt
  - Hypoxemia
  - Paradoxical embolic complications
    - Embolic stroke; brain abscess
- Hemorrhage

Pulmonary AVMs:
Right to left shunt



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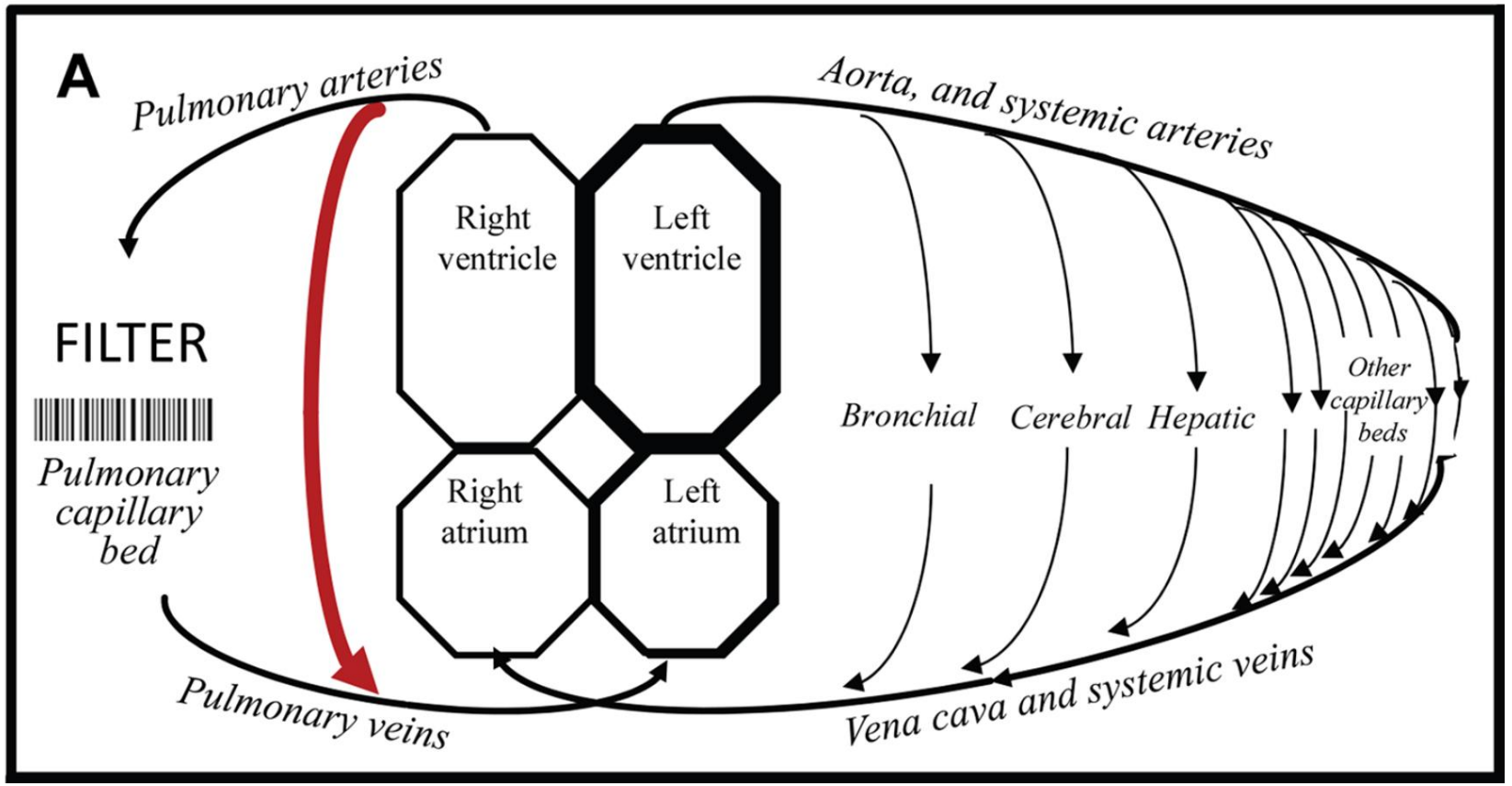
Pulmonary AVMs

Pulmonary capillary filtration



from Shovlin CL, et al. PLoS One. 2014 Feb 19; 9(2):e88812

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Pulmonary AVMs:
Embolic complications

Embolic stroke and transient ischemic attacks

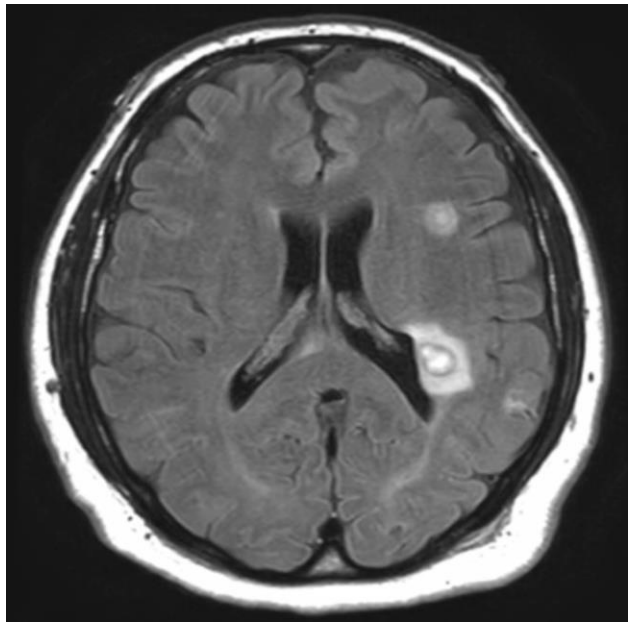
- Clinical stroke diagnosed in 25% with PAVMs
- 50% will show infarcts on brain imaging

Brain abscess

- 400-fold more likely with PAVM (10%)
- Often occur before HHT / PAVM diagnosis
- Periodontal microbes

Other

- Coronary embolus, vertebral abscess, others



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Relevance to your practice
Overlap with common IM conditions

- Unexplained anemia
- GI bleeding
    - Melena may triggers search for colon cancer
    - Angioectasias from other conditions
- Stroke
- Heart failure
- Pulmonary hypertension

Interim Summary

- HHT is not very rare
- Manifestations are often easily recognizable
- Recognition allows effective treatment
- Overlap with common medical conditions

Updates…

1. Better understanding of molecular pathogenesis
2. Advances in treating epistaxis
3. Advances in embolotherapy for lung AVMs
4. Inhibitors of angiogenesis

Update #1
Advances in understanding pathogenesis

Gene	Name	Phenotype	Frequency
Endoglin	HHT-1	Epistaxis, lung, brain AVMs	45%
ACVRL1	HHT-2	Epistaxis, liver and GI AVMs	40%
Smad4	HHT-Juvenile polyposis syndrome	HHT plus juvenile polyposis	2%
Unknown gene, chromosome 5	HHT-3	Same as HHT-1	< 8%
Unknown gene, chromosome 7	HHT-4	Epistaxis, CVMs, PAVMs	
GDF2	HHT-5	Similar to HHT-2	< 5%
RASA1	Capillary malformation-AVM syndrome; Parkes Weber	Cutaneous telangiectasia, visceral AVMs (muscle, bone, spine, brain)	NA
EPHB4	CM-AVM2	Cutaneous telangiectasia, CNS AVMs, epistaxis	NA

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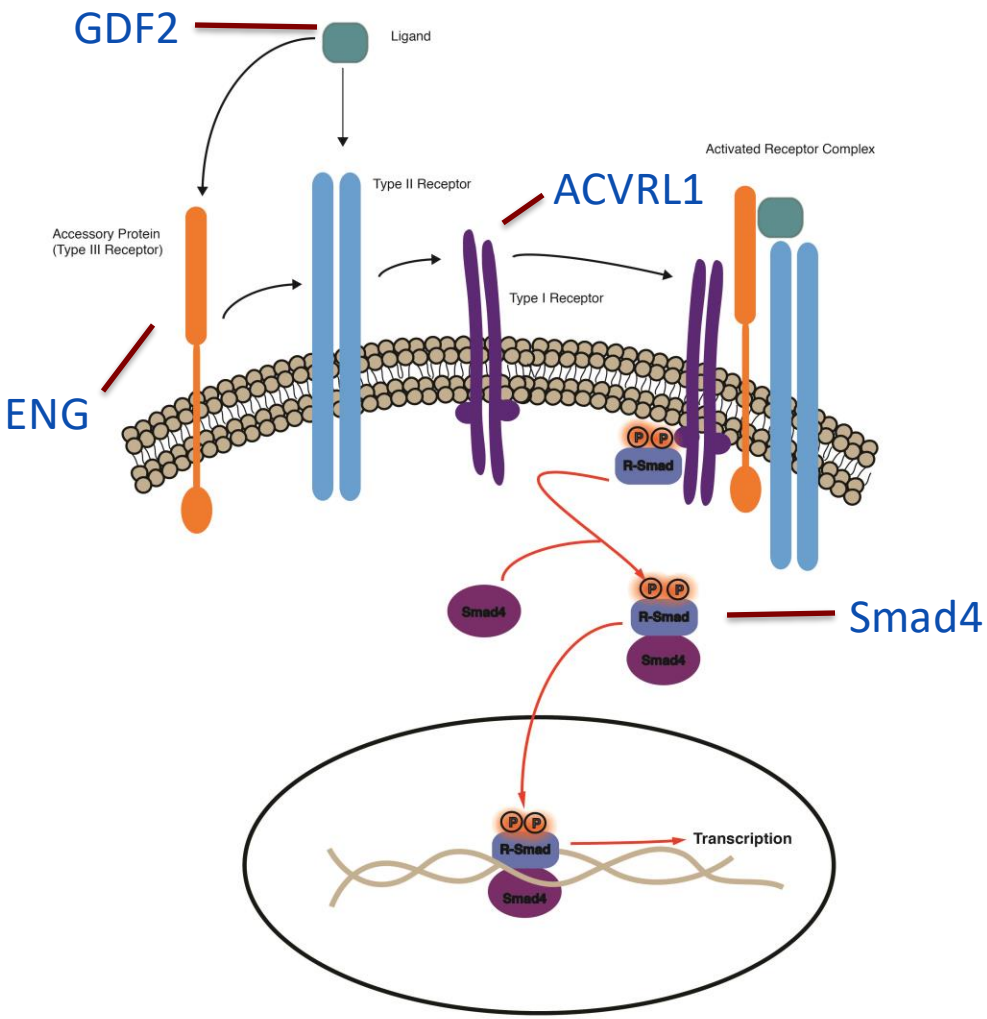
Endothelial TGF-beta signaling



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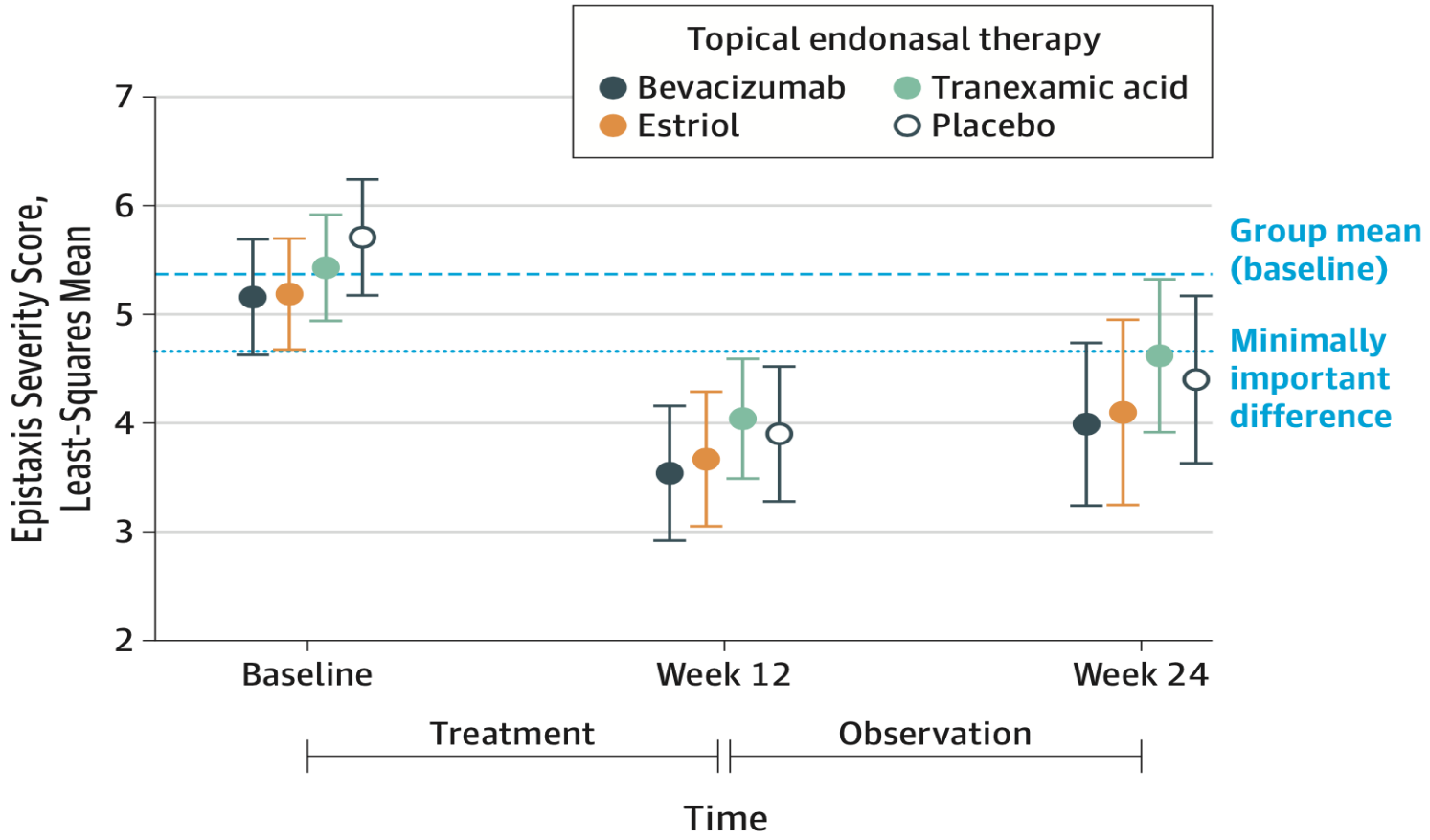
Advances in treating epistaxis
NOSE Study

Figure 2. Change in Epistaxis Severity Score With Topical Endonasal Therapy in the North American Study of Epistaxis in HHT



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Whitehead KJ, et al. *JAMA*. 2016; 316(6): 943-951

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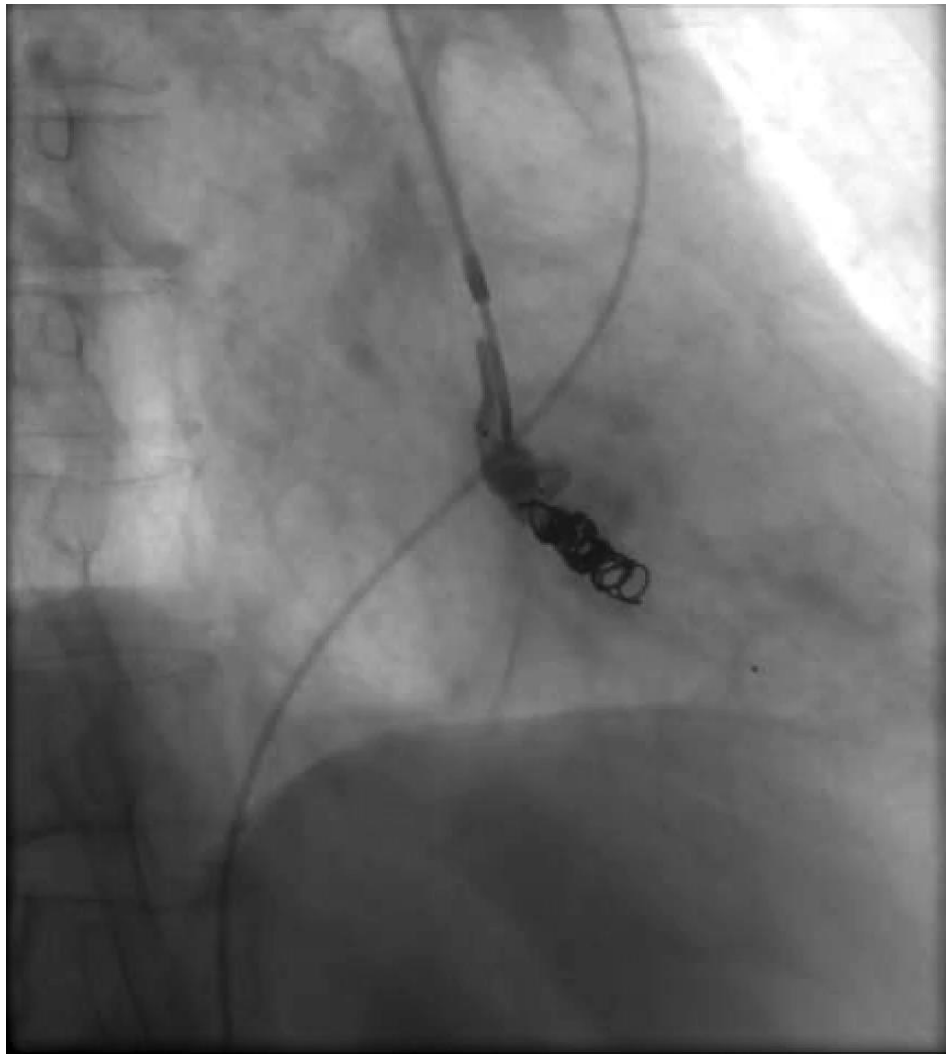
Advances in treating epistaxis
Coblation

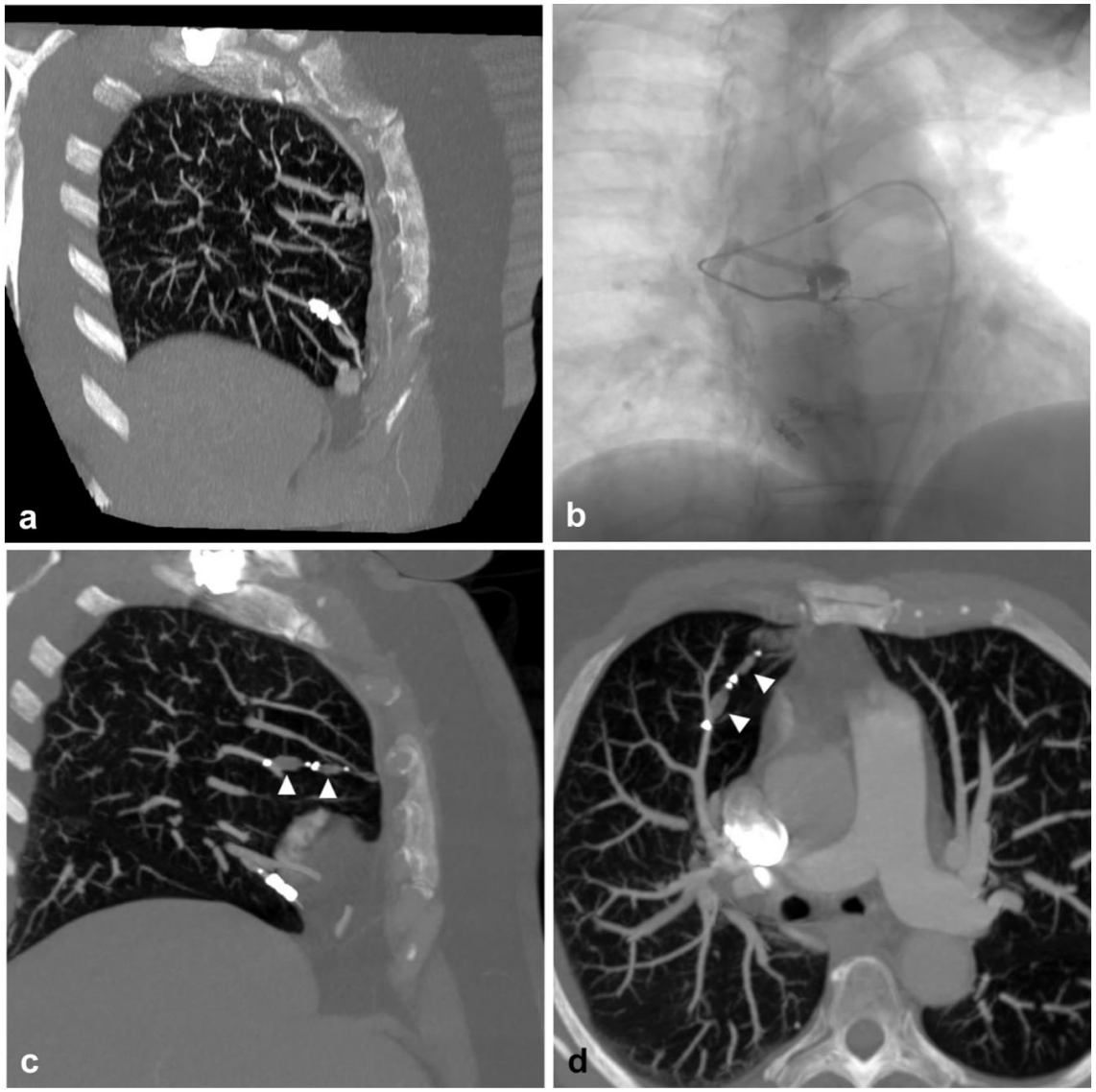
- Ablation of nasal telangiectasis
  - Electrocautery -> laser -> coblation
- Less thermal injury (70˚C vs 600˚C)
- More sustained control of epistaxis
  - 24+ months sustained response
  - No difference with bevacizumab injection

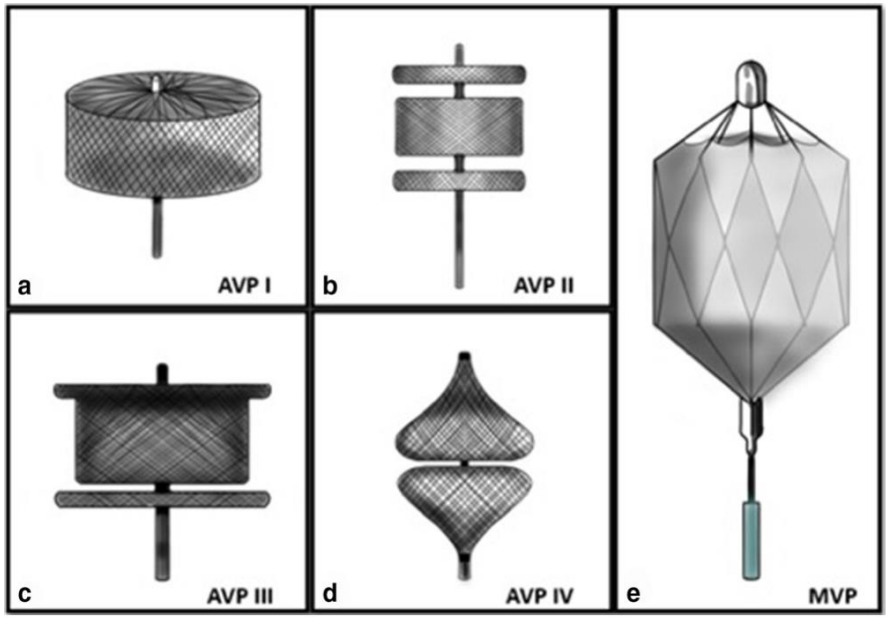
Feller CN, et al. *Am J Otolarngol*. 2022. Online ahead of print.

Advances in embolotherapy



Advances in embolotherapy





Br J Radio. 2021; 94(1123): https://doi.org/10.1259/bjr.20200695

Ratnani R, et al. *J Vasc Interv Radiol* 2019; 30: 1089-1097

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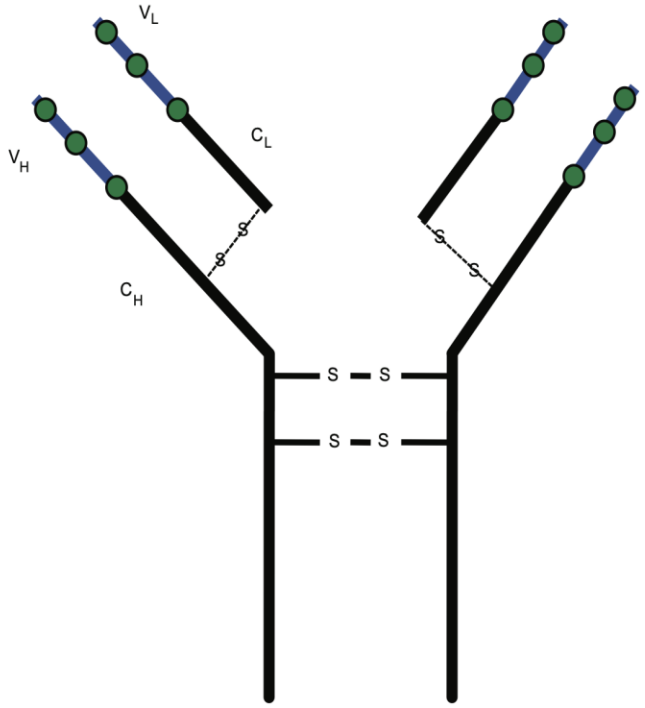
Inhibitors of angiogenesis

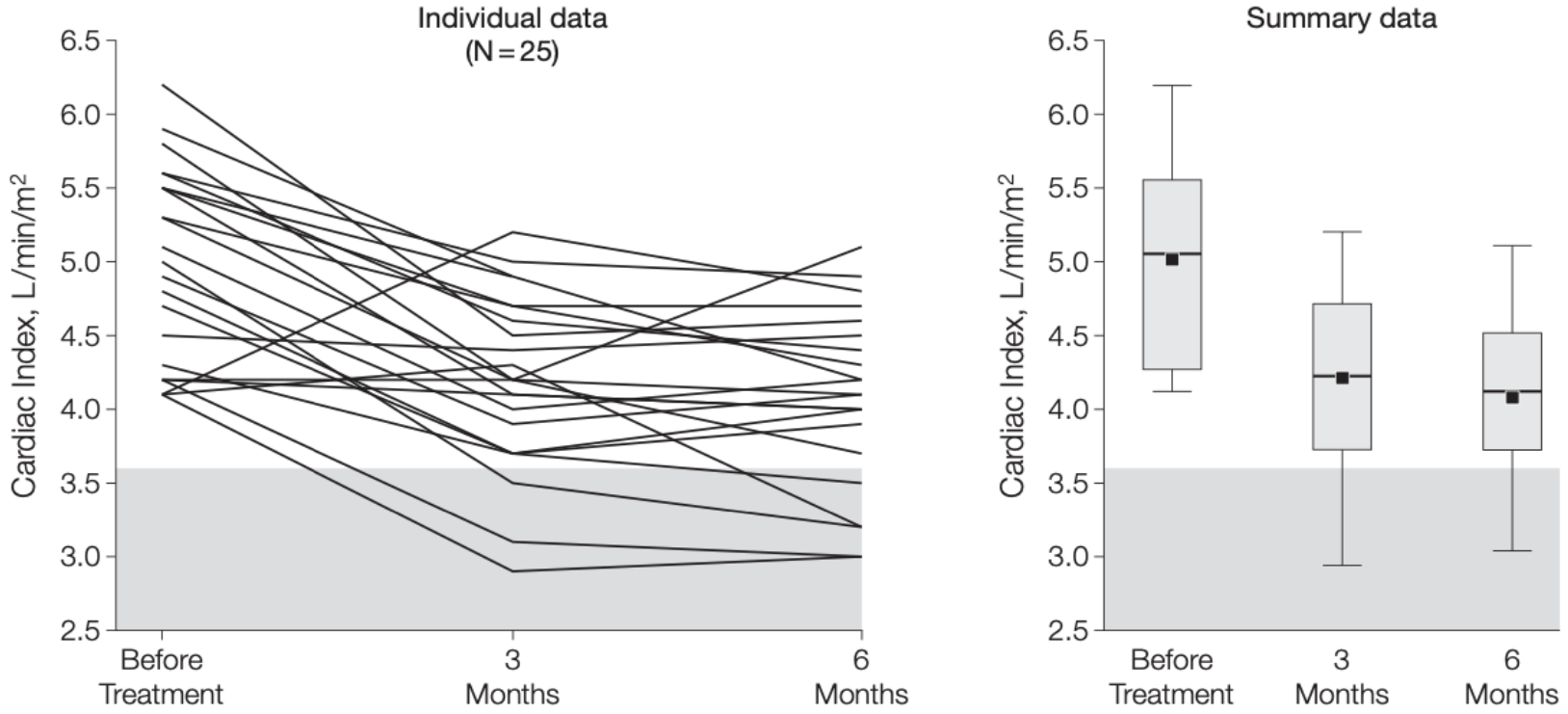
Bevacizumab

- Monoclonal Ab vs vascular endothelial growth factor (VEGF)
- Developed for treatment of advanced solid tumors
  - Colorectal, lung, others
- Function
  - Promotes angiogenesis
  - Stabilizes vascular endothelial cell
  - Cross talk with TGF-beta pathway



Bevacizumab in patients with HHT and severe hepatic vascular malformations and high cardiac output

Figure 1. Blinded Cardiac Index Before Treatment and 3 and 6 Months After the Beginning of Treatment With Bevacizumab



Cardiac index significantly declined in response to bevacizumab treatment. Squares indicate mean values; error bars, 95% CIs; boxes, median and interquartile range; shaded area, reference value range.

JAMA, 2012: 307(9):950-955

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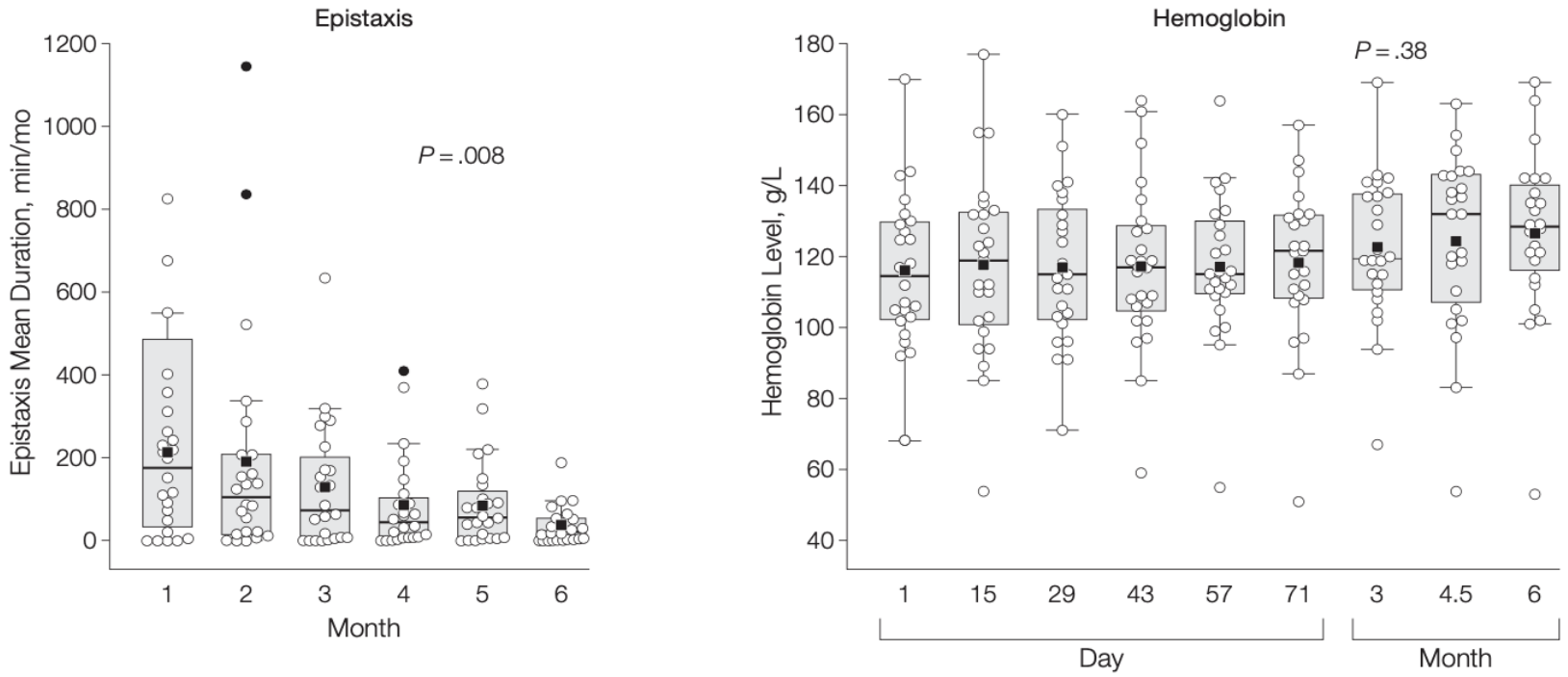
Bevacizumab in patients with HHT and severe hepatic vascular malformations and high cardiac output

Figure 3. Epistaxis and Hemoglobin Levels After Treatment With Bevacizumab



The mean duration of epistaxis episodes (measured as minutes per month) significantly declined; the mean number of epistaxis episodes was 26 episodes per month before treatment and 20 per month after treatment. Hemoglobin levels remained stable throughout the course of the study. Squares indicate mean values; open circles, individual values; error bars, 95% CI; and filled circles, outliers (either an outside value, defined as a value smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range; or a far-out value, defined as a value that is smaller than the lower quartile minus 3 times the interquartile range, or larger than the upper quartile plus 3 times the interquartile range). *P* values are for mixed model.

Intravenous bevacizumab for refractory HHT-related epistaxis and GI bleeding

TABLE 3. ESS Scores in Patients With Significant Epistaxis (n = 30)

Variable	Baseline	During the initial bevacizumab treatment cycle			After the completion of the initial treatment cycle			
		1 mo	3 mo	End of cycle	1-3 mo	4-6 mo	7-9 mo	10-12 mo
n	30	21	14	10	17	15	9	5
ESS score								
Mean ± SD	6.6±2.2	3.9±2.1	4.4±1.8	2.9±2.1	2.4±1.5	3.5±2.2	3.4±3.7	3.0±1.4
Median (25th, 75th)	6.5 (5.2, 8.2)	3.3 (2.4, 5.4)	4.0 (3.2, 6.0)	2.3 (1.5, 5.1)	2.0 (1.8, 2.9)	3.2 (2.4, 5.0)	2.8 (0.7, 3.3)	2.8 (1.9, 4.5)
Change from baseline								
Mean ± SD		−2.9±2.9	−2.4±3.0	−3.8±2.8	−4.3±2.3	−3.7±3.0	−3.5±3.1	−3.4±3.4
Median (25th, 75th)		−3.3 (−4.2, −1.5)	−2.8 (−5.4, −0.8)	−3.6 (−7.0, −1.8)	−4.2 (−5.4, −2.3)	−4.0 (−5.8, −1.8)	−3.5 (−4.8, −1.4)	−2.8 (−4.2, −1.4)
P value (signed-rank test)		<.001	.013	.004	<.001	.001	.016	.125

ESS = Epistaxis Severity Score.

TABLE 4. Blood Transfusion Data Before and After Bevacizumab Treatments[a]

Variable	Before bevacizumab treatment		After the initiation of bevacizumab treatment			
	Lifetime	6 mo[b]	1-3 mo	4-6 mo	7-9 mo[b]	9-12 mo[b]
All patients (N=34)						
Number followed	34	34	34	28	25	23
Any transfusion, n (%)	28 (82)	18 (53)	5 (15)	4 (14)	2 (8)	2 (9)
RBC units, median (min, max)[c]	9.5 (1, >500)	9 (1, 96)	8 (2, 18)	12 (2, 20)	11.5 (5, 18)	1.5 (1, 2)
Non—transfusion-dependent patients (n=18)						
Number followed	18	18	18	14	11	10
Any transfusion, n (%)	12 (67)	2 (11)	0 (0)	0 (0)	0 (0)	1 (10)
RBC units, median (min, max)[c]	2.5 (1, 10)	1 (1, 1)				2 (2, 2)
Transfusion-dependent patients (n=16)						
Number followed	16	16	16	14	14	13
Any transfusion, n (%)	16 (100)	14 (88)	5 (31)	4 (29)	2 (14)	1 (8)
RBC units, median (min, max)[c]	75 (4, >500)	12 (1, 96)	8 (2, 18)	12 (2, 20)	11.5 (5, 18)	1 (1, 1)

[a]RBC = red blood cell.
[b]P=.007 (McNemar's test) comparing the 6-mo interval before bevacizumab treatment with a similar 6-mo interval after the completion of the initial bevacizumab treatment (7-12 mo after the initiation of bevacizumab) for the overall cohort as well as transfusion-dependent cohort.
[c]The median (min, max) number of RBC units transfused is presented for the subset of patients who received transfusions.

Mayo Clin Proc, 2018; 93(2):155-166

Intravenous bevacizumab for refractory HHT-related epistaxis and GI bleeding

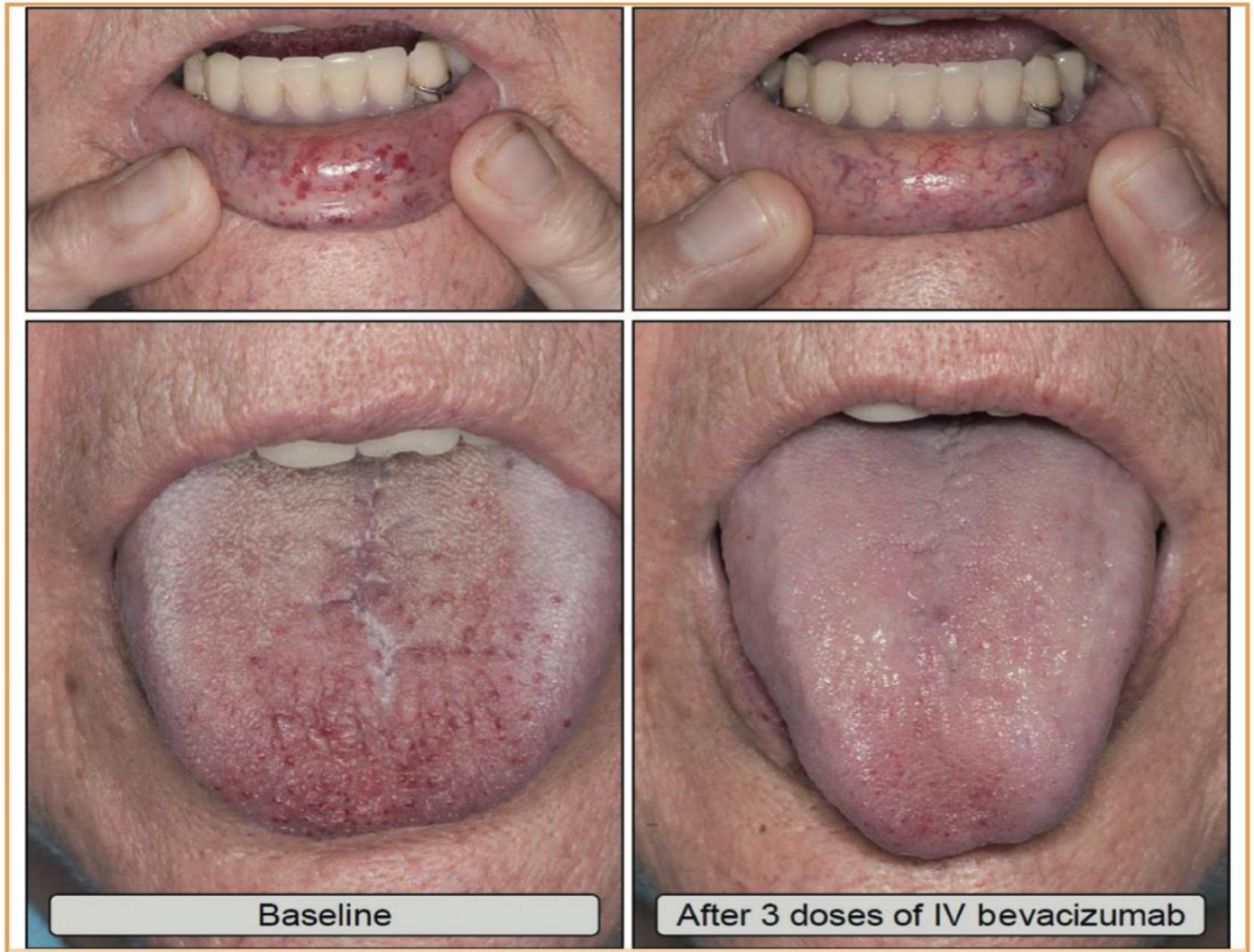


FIGURE 2. Improved mucocutaneous telangiectasias after IV bevacizumab treatment. IV = intravenous.

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Intravenous bevacizumab for refractory HHT-related epistaxis and GI bleeding

Unanswered questions:

- Length/frequency of treatment
- Adverse effects, especially after decades of use
- Precise mechanism?
- Alternatives

What does the future hold?

- Increased awareness will prevent complications
- Improvements in existing screening and treatment
- Expanding role of inhibitors of angiogenesis
- Alternates to bevacizumab
    - Thalidomide, Pomalidomide, Pazopinib, others

Thank You

- HHT is not so rare
- Clinical manifestations are easily recognizable
- Complications can be effectively prevented
- Defects in genes in endothelial TGF-beta signaling
- Recent improvements in treating epistaxis, PAVMs
- Inhibitors of angiogenesis have revolutionized HHT treatment