POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

Difetti acquisiti della coagulazione
A. TOSETTO

Novità dal Meeting della Società Americana di Ematologia

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COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO
Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

Disclosures of Alberto Tosetto

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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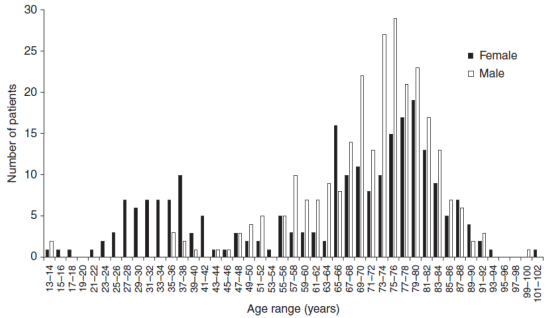
CLS-Behring					√		

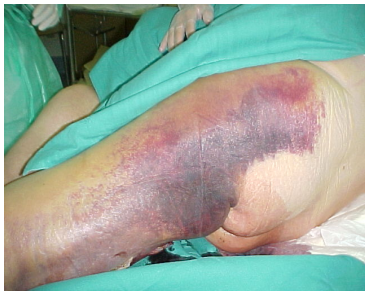
Difetti acquisiti della coagulazione

- Difetti acquisiti “rari” dell’emostasi
  - Emofilia acquisita
  - VWD acquisito
  - Altri difetti
- Sicurezza delle terapie antitrombotiche
- HHT

Acquired hemophilia (AHA): clinical & epidemiologic data

- Età mediana di diagnosi 78 anni
- Incidenza 1.48/milione/anno
- Mortalità per emorragia: 15-22%



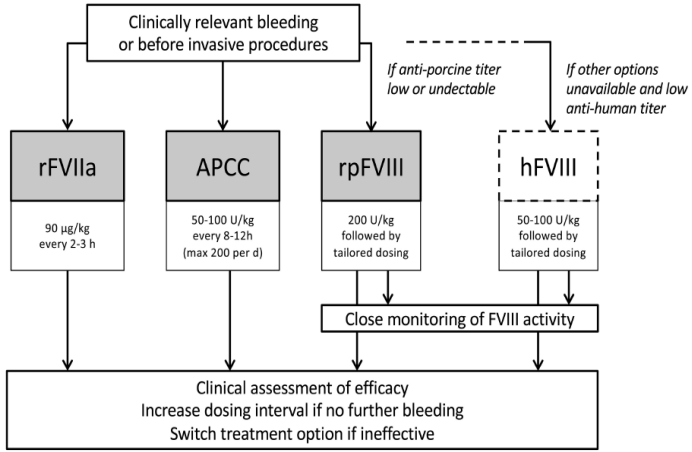


- Diagnosi in seguito a emorragia 467/501 (93.2 %)
- Vaste ecchimosi, Ematomi muscolari (ileo-psoas)
- Emorragie retroperitoneali
- *Emartri rari*

Collins et al, Blood 2007; Knoebl et al, JTH 2012; Baudo et al, Blood 2012

AHA Therapeutic approach

Bleeding control



Immunosuppresion

FVIII ≥1 IU/dL & low-titer inhibitor (≤20 BU):

- Oral prednisone 1 mg/kg or Prednisolone e.v. 0.8 mg/kg) for three weeks

FVIII <1 IU/dL, or high-titer inhibitor or refractoryness:

- Rituximab 375 mg/m^2 weekly *or*
- Cyclophosphamide 1.5−2 mg/kg/day PO, for six weeks

Tiede, et al., Haematologica, 2020

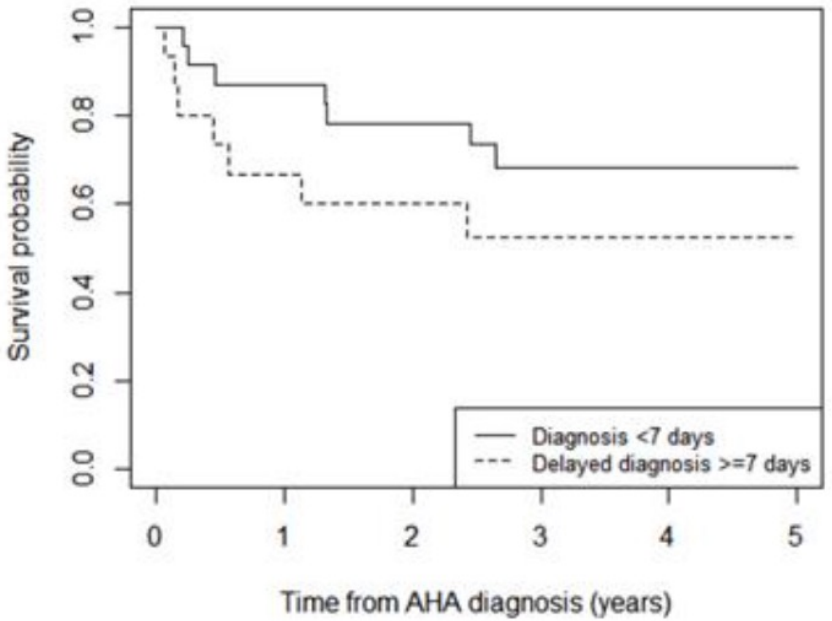
Prevalence and Risk Factors of Diagnostic Delays in Acquired Hemophilia A (Rutherford, Poster 2627)

- 38 patients diagnosed with AHA from January 2000-December 2021) in Alberta, Canada: 4.34 cases/million/year
- Median time from bleeding symptom and prolonged aPTT to diagnosis was 3.5 days (IQR 0-11.0)
- Diagnosis was delayed ≥7 days in 17 (45%) patients.
- Top reasons for delays ≥7 days:
  - Delayed ordering of aPTT from 7-62 days after bleeding (6/15; 40%),
  - Delayed ordering of mixing study following first abnormal aPTT from 7 days to >1 year (9/15; 60%)
  - Attribution of bleeding to antiplatelets/anticoagulants (5/15; 33%).

Rutherford B, Cusano E, Goodyear MD, Sun H (2023) Prevalence and Risk Factors of Diagnostic Delays in Acquired Hemophilia A. Blood 142 (Supplement 1):2627-2627.

Prevalence and Risk Factors of Diagnostic Delays in Acquired Hemophilia A (Rutherford, Poster 2627)

- 18 patients (47%) died at a median of 7 months, the most common causes being infection (4), malignancy (3), bleeding (2), and thrombosis (2)
- Delayed diagnosis ≥7 days was associated with a trend towards worse 3-month OS (80% vs 91%) and 1-year OS (67% vs 87%, log-rank P=0.40).
- On Cox proportional hazards analysis, male sex (HR 4.0, 95% CI 1.5-10.5) and CCI 4-5 vs 0-3 (HR 7.0, 95% CI 1.5-32.3), but not delayed diagnosis (HR 1.5, 95% CI 0.6-3.9) were associated with increased hazard of death.



Rutherford B, Cusano E, Goodyear MD, Sun H (2023) Prevalence and Risk Factors of Diagnostic Delays in Acquired Hemophilia A. Blood 142 (Supplement 1):2627-2627.

Epidemiology, Outcomes, and 30-Day Readmissions in Acquired Hemophilia (Sharma, Oral 26)

- A retrospective study based on the US Nationwide Readmissions Database (2016-2019) identified 1450 hospital admissions with acquired hemophilia
- Out of 1349 patients who were discharged alive, 371 were readmitted within 30 days, with a 30-day readmission rate of 27%

Characteristics (N=1450)	N (%)
Males	803 (55.4%)
Age group of 61-80 years	857 (59.1%)
Underlying solid malignancy	(20.9%)
Autoimmune disorder	13.5%
Charlson comorbidity index of >3	28.5%
Reason for readmission (N=371)	
Infections	114 (30.8%)
Bleeding events	105 (28.2%)

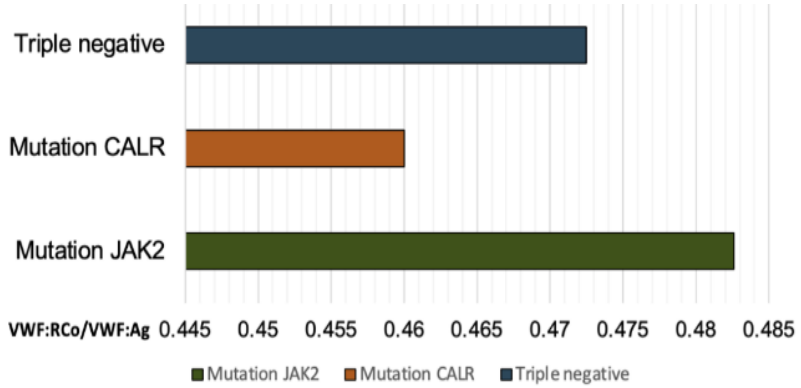
Sharma A, Sharma A, Singh V (2023) Epidemiology, Outcomes, and 30-Day Readmissions in Acquired Hemophilia. Blood 142 (Supplement 1):26-26.

Acquired Von Willebrand Syndrome associated with MPN (Moreno, Poster 1253)

- Data from 184 Ph- MPN patients diagnoses and followed between 01/01/2000 to 05/31/2022 at a large Mexican Hospital
- Thirty patients were identified as having AvWS based on a VWF:RCo/VWF:Ag < 0.7

Characteristics (N=30)	N or value
Female (%)	20 (66.6)
Median age	57
PV (%)	12 (40)
ET (%)	4 (13.3)
PMF (%)	14 (46.7)
Median platelet count (IQR)	998 (441-2307)

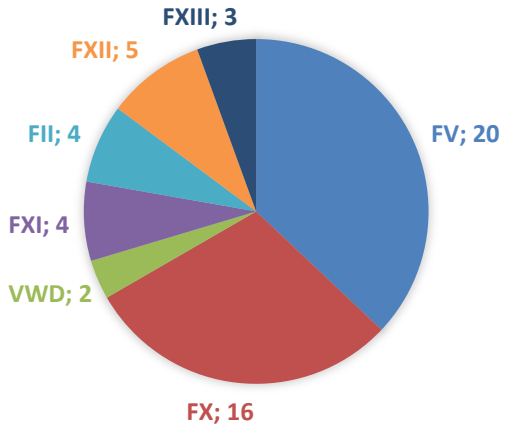
- At diagnosis, bleeding episodes occurred in 13.3%.
- 96.7% of the AvWS patients were treated with hydroxyurea, which corrected cellular alterations and laboratory abnormalities found in AvWS.



Moreno Garcia OJJ, et al (2023) Acquired Von Willebrand Syndrome, Epidemiology, Laboratory Findings and Molecular Alterations on Classic Myeloproliferative Neoplasms in Mexican Population. Blood 142:1253.

Isolated Acquired Clotting Factor Deficiency (ACFD): Clinical Features, Treatments, and Prognosis (Dandan, Poster 3995)

- Retrospective analysis of isolated ACFD other than AHA admitted to the Blood Disease Hospital, Chinese Academy of Medical Sciences, from July 1997 to December 2021
- 20 and 33 patients received PCC and FFP, respectively
- Thirty-seven (68.5%) received immunosuppressive therapy
- Nine patients died (4 because of major bleeding)



Characteristics (N=54)	N or value
Males (%)	28 (52%)
Bleeding at presentation (%)	44 (82%)
Underlying malignancy (%)	19 (35%)
Autoimmunity (%)	12 (22%)
Infection	4 (7.4%)
Neutralizing antibodies	24 (44%)

Yu D, Xue F, Liu X, Chen Y, Fu R, Sun T, Dai X, Ju M, Dong H, Yang R, Liu W, Zhang L (2023) A Single-Center Study of Patients with Isolated Acquired Clotting Factor Deficiency: Clinical Features, Treatments, and Prognosis. Blood 142:3995.

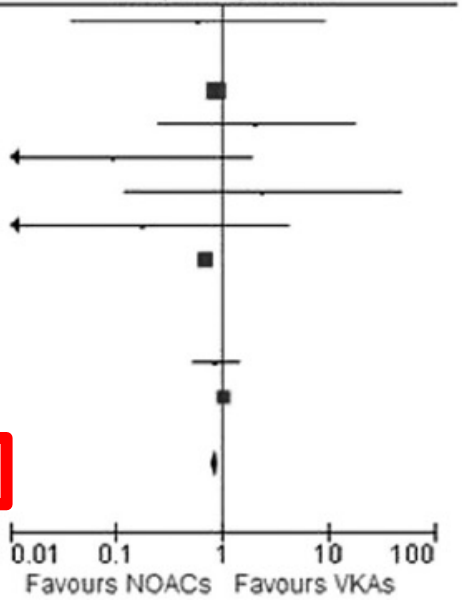
Relative risk of major bleeding in DOAC clinical trials

Major bleeding

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01136408 (D)	1	104	1	62	0.1%	0.60 [0.04, 9.36]
PETRO	0	166	0	70		Not estimable
RE-LY	741	12091	421	6022	38.8%	0.88 [0.78, 0.98]
WEITZ	6	713	1	250	0.1%	2.10 [0.25, 17.39]
CHUNG	0	159	2	75	0.2%	0.10 [0.00, 1.95]
YAMASHITA	2	260	0	125	0.0%	2.41 [0.12, 49.90]
ARISTOTLE-J	0	143	1	75	0.1%	0.18 [0.01, 4.27]
ARISTOTLE	327	9088	462	9052	31.9%	0.70 [0.61, 0.81]
NCT00973245 (R1)	0	75	0	27		Not estimable
NCT00973323 (R2)	0	50	0	26		Not estimable
J-ROCKET-AF	26	639	30	639	2.1%	0.87 [0.52, 1.45]
ROCKET-AF	395	7111	386	7125	26.6%	1.03 [0.89, 1.18]
Total (95% CI)		30599		23548	100.0%	0.86 [0.80, 0.93]
Total events	1498		1304			

Heterogeneity: Chi² = 18.58, df = 8 (P = 0.02); I² = 57%

Test for overall effect: Z = 4.03 (P < 0.0001)



Dentali et al, Circulation 2013

Safety of Apixaban, Rivaroxaban, and Warfarin in AF and VTE patients (Schaefer, Oral 135)

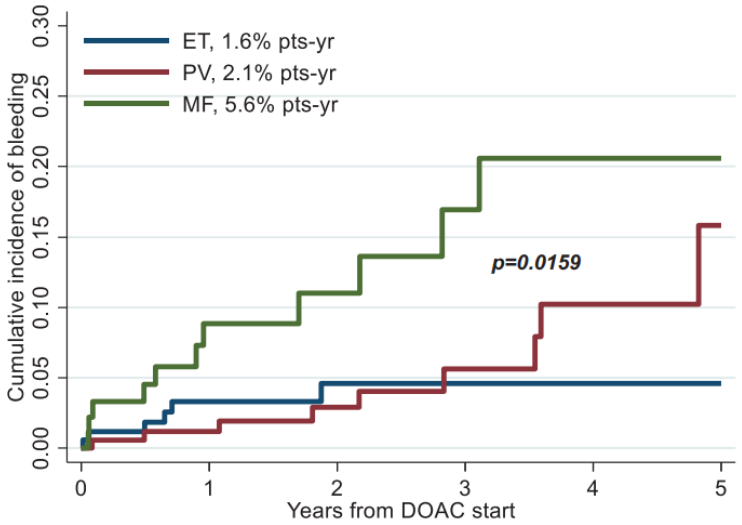
- Retrospective registry-based cohort of adults starting apixaban, rivaroxaban, or warfarin therapy for the indications of VTE and/or non-valvular AF.
- Six anticoagulation clinics in Michigan, from January 2009 to June 2023
- 13,435 propensity-matched patients on OAC (3,536 on apixaban, 1,395 on rivaroxaban, and 8,504 on warfarin)

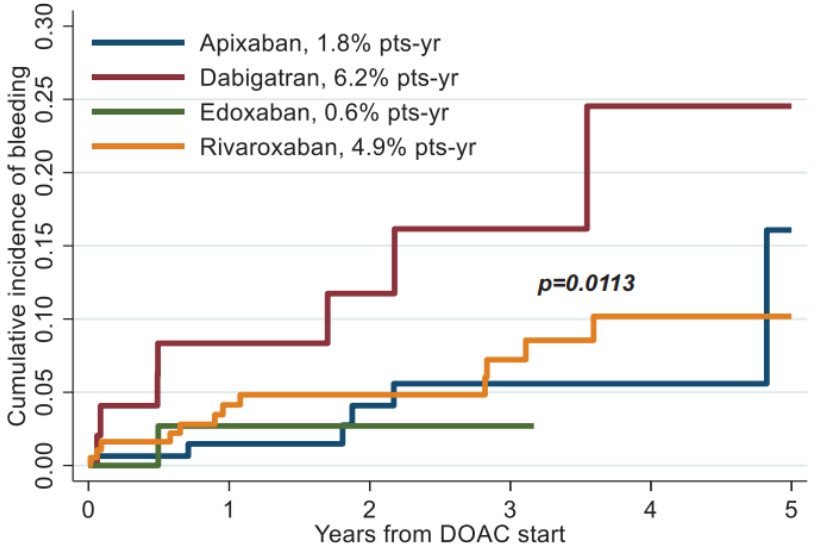
Event rate	Apixaban N=3527	VKA N=3527	Rivaroxaban N=1395	VKA N=4185	Apixaban N=1395	Rivaroxaban N=1395
Major bleeding %-year	3.4	4.7 **	4.7	3.6 *	2.6	4.7 **
Thrombosis %-year	2.6	2.1 *	NR	NR	NR	NR
Mortality %-year	3.7	4.4 *	NR	NR	2.6	3.5 *

* $p < 0.05$; ** $p < 0.001$

Schaefer JK, Errickson J, Kong X, Ali MA, Chipalkatti N, Haymart B, Kaatz S, Krol GD, Sood SL, Froehlich J, Barnes GD (2023) A Comparison of Bleeding Events Among Patients on Apixaban, Rivaroxaban, and Warfarin for Atrial Fibrillation and/or Venous Thromboembolism. Blood 142:135.

Major bleeding events during DOAC therapy in Ph- MPN patients



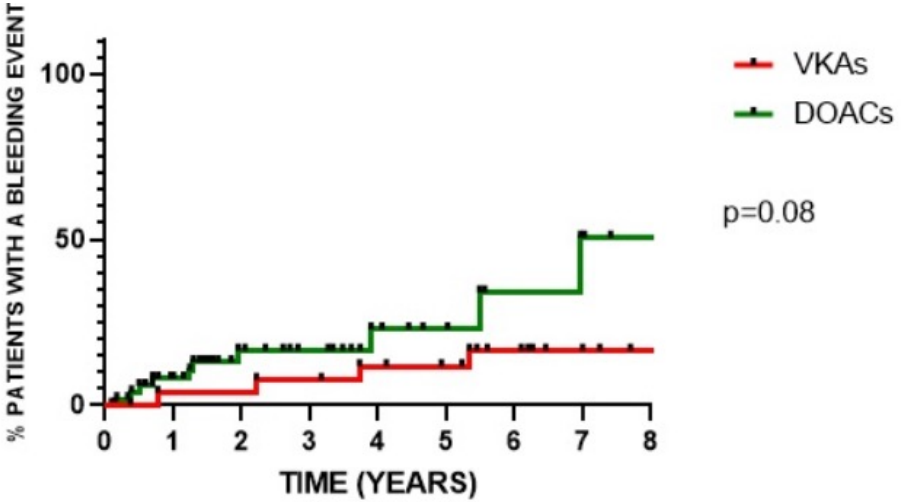


- Observational, multicenter, international study in 442 Ph- MPN patients
- Annual rate of MB: 3% and 2.3% in AF and VTE, respectively

Barbui et al. Leukemia, 2021.

Oral Anticoagulant Therapy in Patients with Ph- MPN (Cavalca, Poster 1838)

Characteristics (N=156)	N or value
Females (%)	89 (57%)
Median age, years	69
PVE	35
ET	48
MF	61
VKA	64 (41%)
DOAC	92 (59%)

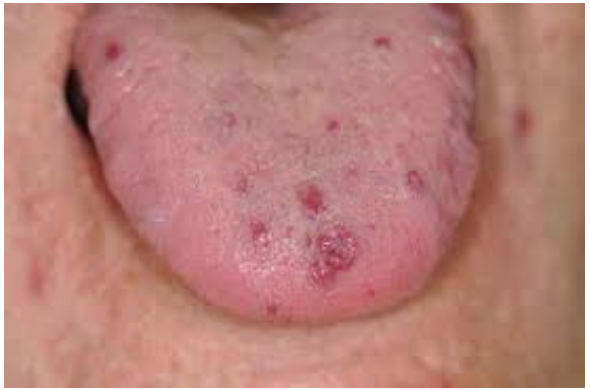


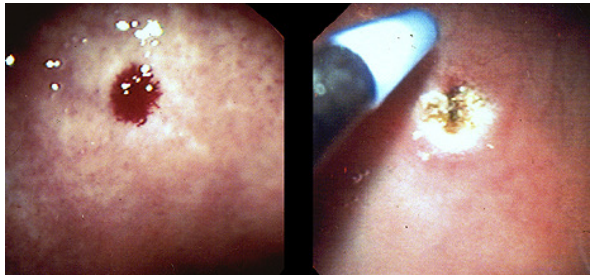
The incidence rate of MB/CRNMB was 5.6/pts/year in the DOACs group and 3.3/pts/year in the VKAs group.

Cavalca F, Civettini I, Bonfanti S, Gambacorti-Passerini C, Elli EM (2023) Oral Anticoagulant Therapy in Patients with Philadelphia-Negative Myeloproliferative Neoplasms: A Real-Life Comparison between Vitamin K Antagonists and Direct Oral Anticoagulants. Blood 142:1838

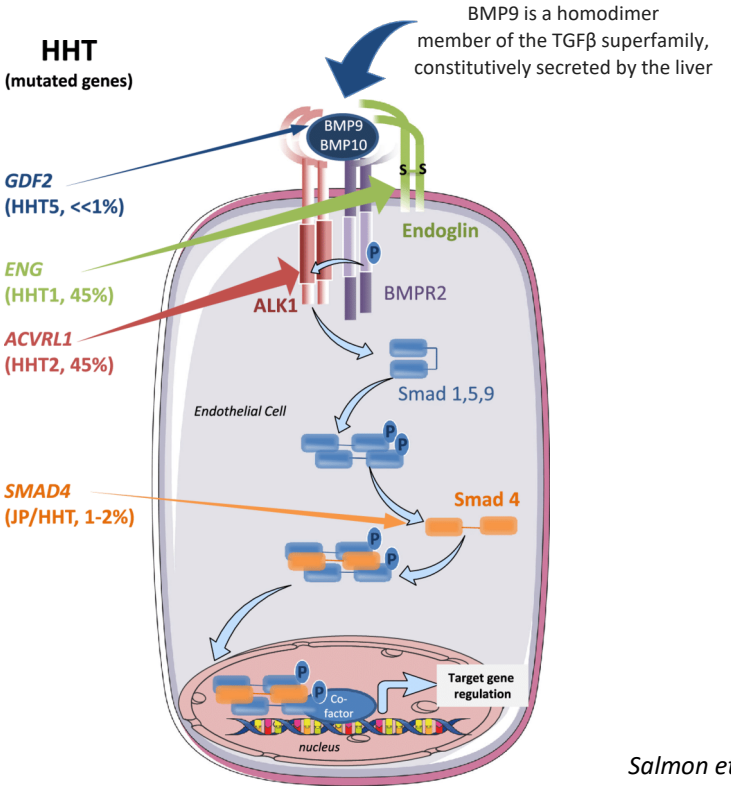
Hereditary Hemorrhagic Telangiectasia (HHT; Osler-Weber-Rendu syndrome)

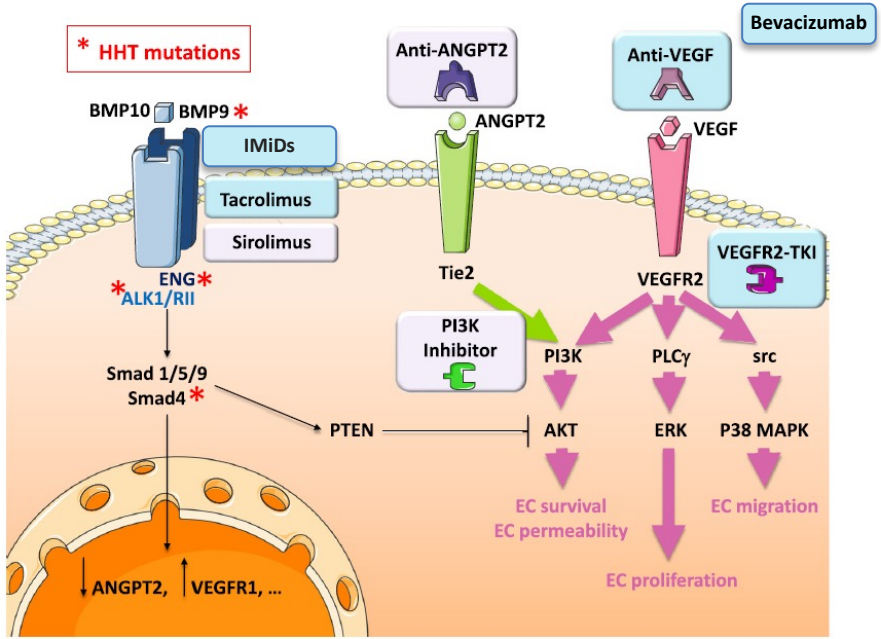
- An autosomal dominant vascular disorder
- Associated with mucocutaneous telangiectasia, epistaxis, gastrointestinal bleeding, and iron deficiency anemia
- Arteriovenous malformations (AVMs) commonly occur in the pulmonary, hepatic, and cerebral circulation
- Estimated prevalence 1:5000





Mutations in the BMP9-10 activated ALK1/Endoglin pathway are associated with HHT





Salmon et al. Nat Commun, 2020; Robert et al. Orphanet Journal of Rare Diseases, 2020 (modified)

HHT May be the Most Clinically Significant and Morbid Inherited Bleeding Disorder of Women (Zhang, Oral 28)

- Observational, single-center cohort study of 100 randomly selected women with HHT and 100 age-matched women with VWD
- Bleeding and healthcare utilization outcomes
- Comparisons should be taken with some caution, as VWD prevalence may be higher than HHT, and VWD is a very heterogeneous disorder

Table 1. Table 1. Bleeding outcomes of women with HHT versus VWD. IQR, interquartile range. 95% CI, 95% confidence interval.

	Hereditary hemorrhagic telangiectasia N = 100	Von Willebrand disease N = 100	Odds ratio (95% CI) for incidence in HHT group relative to VWD group	*P* value
Incidence of Bleeding by Site				
Recurrent epistaxis, n (%)	92 (92)	26 (26)	32.73 (13.81-71.80)	<0.0001†
Gastrointestinal bleeding, n (%)	36 (36)	9 (9)	5.69 (2.59-12.89)	<0.0001†
Heavy menstrual bleeding, n (%)	35 (35)	63 (63)	0.32 (0.18-0.57)	<0.0001†
Other bleeding, n (%)	12 (12)	16 (16)	0.72 (0.31-1.57)	0.42†
Hemoglobin, Hematologic Support Requirements, and Interventions				
Lowest measured hemoglobin, median (IQR)	10.7 (7.9-12.6)	11.4 (9.9-12.5)	n/a	0.02^
Iron deficiency anemia, n (%)	66 (66)	50 (50)	1.94 (1.09-3.41)	0.02†
Requirement for intravenous iron, n (%)	41 (41)	10 (10)	6.25 (2.99-12.78)	<0.0001†
Intravenous iron dependence*, n (%)	26 (26)	2 (2)	17.22 (4.49-74.77)	<0.0001‡
Requirement for red cell transfusion, n (%)	42 (42)	21 (21)	2.72 (1.45-4.99)	0.001†
Requirement for hemostatic procedure**, n (%)	78 (78)	31 (31)	7.89 (4.16-14.60)	<0.0001†
Hemostatic procedures, per 100 patient-years	27.2	3.0	n/a	<0.0001ᵛ
Death due to bleeding complications, n (%)	3 (3)	0 (0)	n/a	0.25‡

*Defined as a requirement for ≥2000 mg elemental iron infused over any contiguous 12-month period.
**Included surgical or other interventional procedures in the uterus to manage heavy menstrual bleeding (e.g., hysterectomy), nasal cavity to manage epistaxis (e.g., nasal cautery), GI tract to manage GI bleeding (e.g., endoscopy), or other interventional procedures done to manage bleeding at any site.
†Per Chi-square test.
‡Per Fisher's exact test.
^Per two-tailed *t*-test (parametric data).
ᵛPer Wilcoxon rank sum test (non-parametric data).

Zhang E, Virk Z, Rodriguez-Lopez J, Al-Samkari H (2023) Hereditary Hemorrhagic Telangiectasia May be the Most Clinically Significant and Morbid Inherited Bleeding Disorder of Women. Blood 142:28.

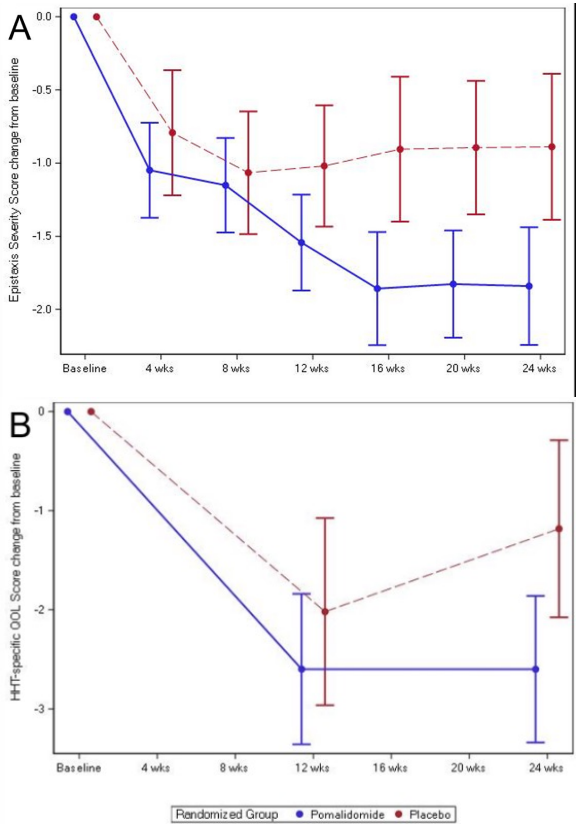
Treatment options in HHT

Phase	Intervention	Comparator	Outcomes	Ref
III crossover	Tranexamic acid	Placebo	17.3% (15.7 min) in the duration of epistaxis per month	*Gaillard et al. J Thromb Haemost, 2014*
II	Thalidomide up to 200 mg/d	None	3/31 complete response (no bleedings) 28/31 partial response	*Invernizzi et al. Lancet Haematol, 2015*
IIb	Bevacizumab 5mg/kg every 14days	Placebo	7/11 (63%) in the bevacizumab group vs 4/12 (33.3%) n the placebo group decreased the number of RBC transfusions by at least 50%	*Dupuis-Girod et al. J Intern Med, 2023*
Retrospective cohort	Bevacizumab 5mg/kg every 14days	Pre-treatment	238 HHT patients. Increase of mean Hb by 3.2 g/dL and decrease of the epistaxis severity score (ESS) by 3.4 points	*Al-Samkari et al. Haematologica, 2021*

Al-Samkari H et al., Haematologica 106 (8):2161-2169, 2021. Dupuis-Girod S et al. Journal of internal medicine 294 (6):761-774., 2023
Gaillard S et al. J Thromb Haemost 12 (9):1494-1502, 2014. Invernizzi R et al., The Lancet Haematology 2 (11):e465-473, 2015

Pomalidomide Reduces Epistaxis and Improves Quality of Life in HHT (Al-Samkari, LBA3)

- RCT that enrolled 144 HHT patients, randomized in a 2:1 ratio to receive pomalidomide 4 mg daily or matching placebo for 6 months
- 95 patients received pomalidomide, and 49 patients received placebo
- At 24 weeks, the ESS in patients treated with pomalidomide decreased by a mean of -1.84 [-2.24, -1.44] and in the placebo group decreased by -0.89
  [-1.39, -0.39]
- The HHT-specific QOL score, which ranges from 0 to 16 with higher scores indicating more limitations, also decreased more in the pomalidomide (mean -2.6, 95% CI [-3.3, -1.9]) vs the placebo group at 24 weeks (mean -1.2, 95% CI [-2.1, -0.3], p = 0.015)
- Adverse events that occurred more in the pomalidomide group included mild to moderate neutropenia (45% vs. 10%), constipation/diarrhea (60% vs. 37%), and rash (36% vs. 10%). Venous thrombosis occurred in 2% of patients in each group.



Al-Samkari H et al, (2023) PATH-HHT, a Double-Blind, Randomized, Placebo-Controlled Trial in Hereditary Hemorrhagic Telangiectasia Demonstrates That Pomalidomide Reduces Epistaxis and Improves Quality of Life. Blood 142:LBA-3

Grazie!

alberto.tosetto@aulss8.veneto.it