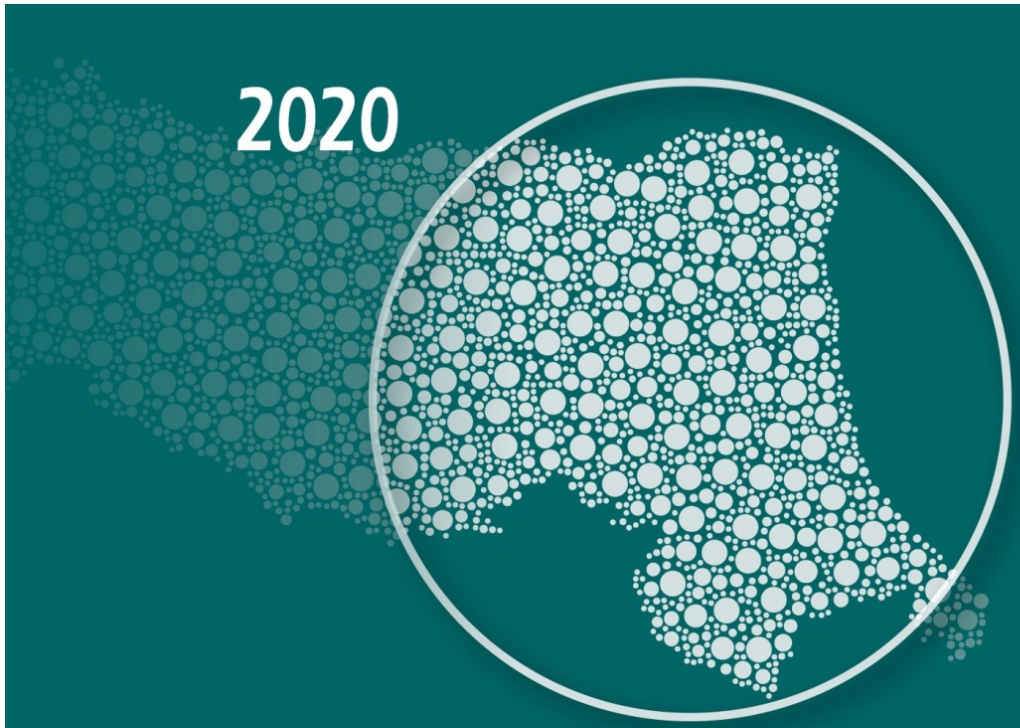


Progetto
Ematologia
Romagna

La Sindrome di Von Willebrand Acquisita (AVWS)

Augusto Bramante Federici

Disclosures

A.B. Federici

Employment	*NONE*
Research support	*NONE*
Scientific advisory board	*CSL-BEHRING, GRIFOLS, KEDRION-LFB, OCTAPHARMA, TAKEDA, WERFEN-IL*
Consultancy	*NONE*
Speakers bureau	*NONE*
Major stockholder	*NONE*
Patents	*NONE*
Honoraria	*CSL-BEHRING, GRIFOLS, KEDRION-LFB, OCTAPHARMA, TAKEDA, WERFEN-IL*
Travel support	*NONE*
Other	*NONE*

Is AVWS a bleeding disorder: just a lab VWF abnormality?

- **Definition of AVWS**
- **Mechanisms of AVWS**
- **Prevalence of AVWS**
- **Conditions associated with AVWS**
  - *Cardiovascular disorders*
  - *Hematologic disorders*

Acquired VWS

Definition

- **Acquired VWS (AVWS) is a rare acquired bleeding disorder similar to inherited VWD in terms of lab findings**
  - *Prolonged Platelet Function (PFA), defects of VWF activities*
- **But it is different from inherited VWD**
  - *Occurs later in life in subjects without personal and family history of bleeding*

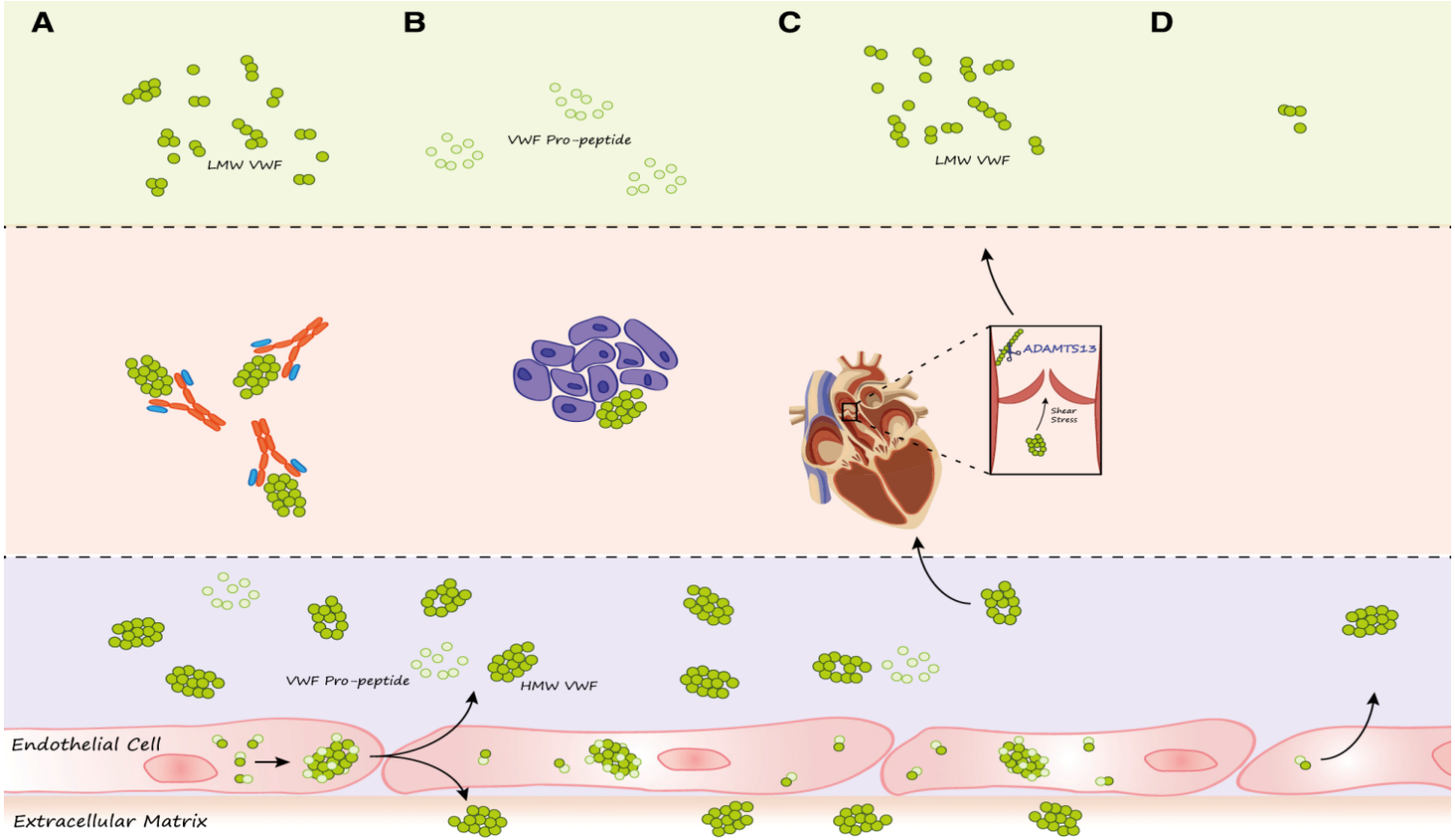
AVWS reported in the literature

1968-2020

- **1160 Pub Med citations** *to December 2019*
- **722 scientific reports** *including:*
  - ***9*** *national or expert recommendations*
  - ***1*** *prospective +* ***4*** *retrospective studies*
  - ***2*** *"How I Treat" in Blood*
- **Cochrane database:** *no reports*

Main mechanisms causing AVWS

Not only autoantibodies to VWF



Callaghan MU et al. Blood. 2013;122:2019-22.

Prevalence of AVWS

- **No large prospective studies available**
- **Only one single-institution study**
  - ***25/260 patients*** *with hematologic disorders showed a form of acquired VWS.*

Mohri H et al. Blood. 1998;91:3623-9.

Retrospective studies on AVWS

1968-2000

Scientific and Standardization Committee Communication

Acquired von Willebrand Syndrome: Data from an International Registry

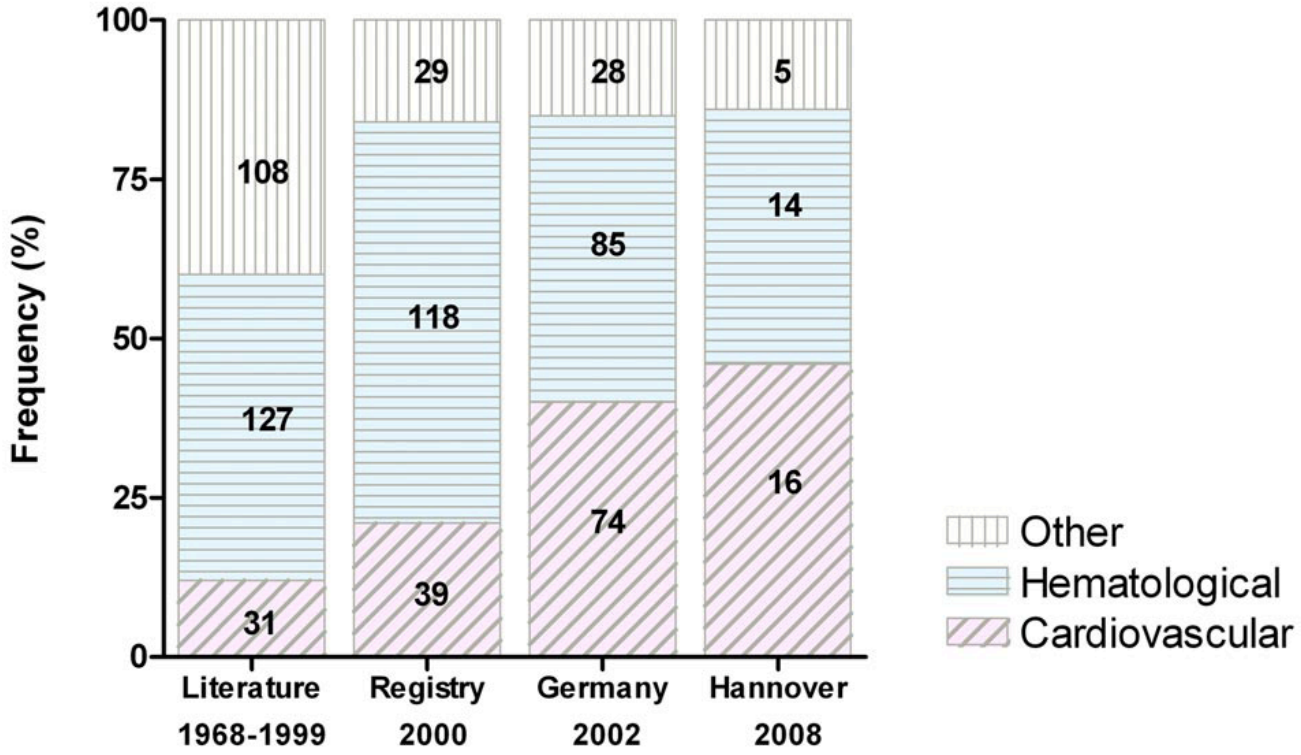
On behalf of the Subcommittee on von Willebrand Factor

Augusto B. Federici[1*], Jacob H. Rand[2], Paolo Bucciarelli[1], Ulrich Budde[3], Perry J. J. van Genderen[4], Hiroshi Mohri[5], Dominique Meyer[6], Francesco Rodeghiero[7], J. Evan Sadler[8]

- **266** *cases of acquired vWS in the literature (1968-1999)*
- **186** *cases reported by the ISTH-SSC Registry*

ISTH-SCC, International Society on Thrombosis and Haemostasis-Scientific and Standardization Committee. Federici AB et al. Thromb Haemost. 2000;84:345-9.

The current changing spectrum of AVWS-associated disorders



Tiede A et al. Blood. 2011;117:6777-85.

Differential diagnosis between AVWS and VWD

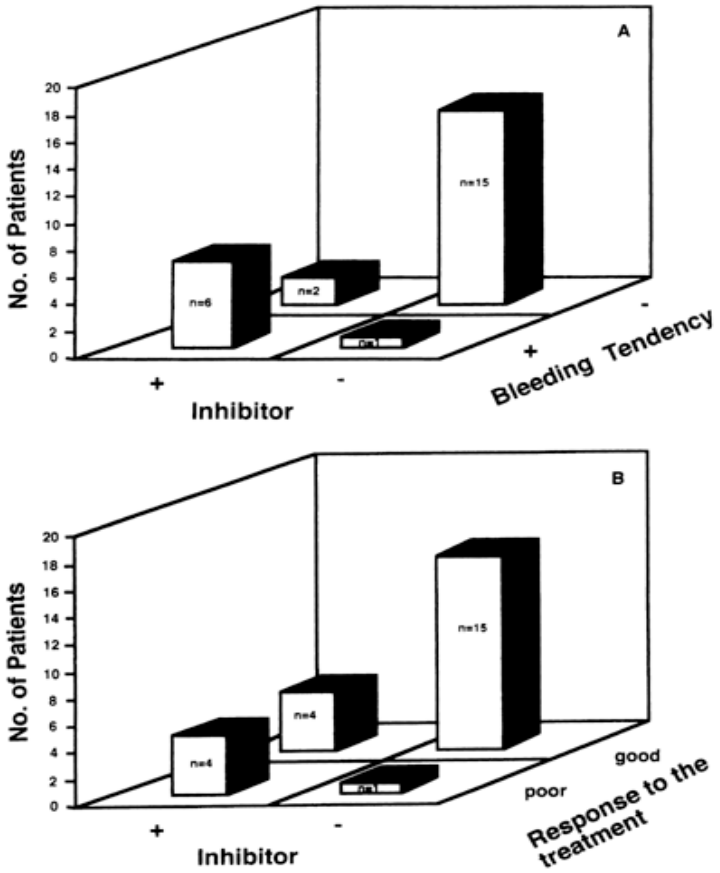
Tiede A et al. Blood. 2011;117:6777-85.

Autoantibodies in AVWS

Neutralizing vs non-neutralizing antibodies

- **Neutralizing autoantibodies** interact with the functional portions of VWF: they are associated with loss of specific VWF activities;
- **Non-neutralizing autoantibodies** can remove VWF from circulation without interaction with functional portions of VWF.

Clinical significance of the presence of autoantibodies against VWF



Mohri H et al. Blood. 1998;91:3623-9.

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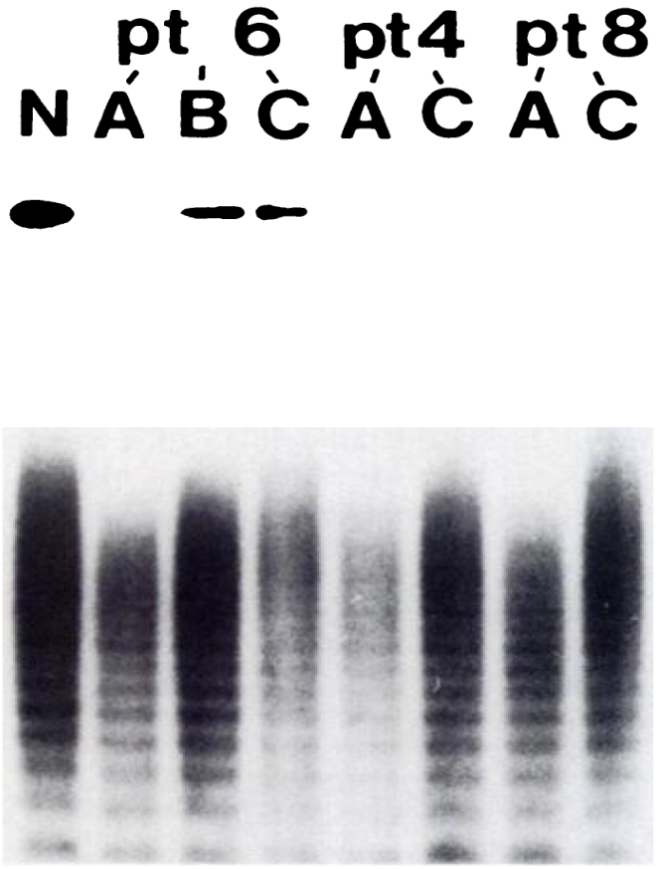
Loss of the Largest von Willebrand Factor Multimers From the Plasma of Patients With Congenital Cardiac Defects

By Joan C. Gill, Allen D. Wilson, Janet Endres-Brooks, and Robert R. Montgomery

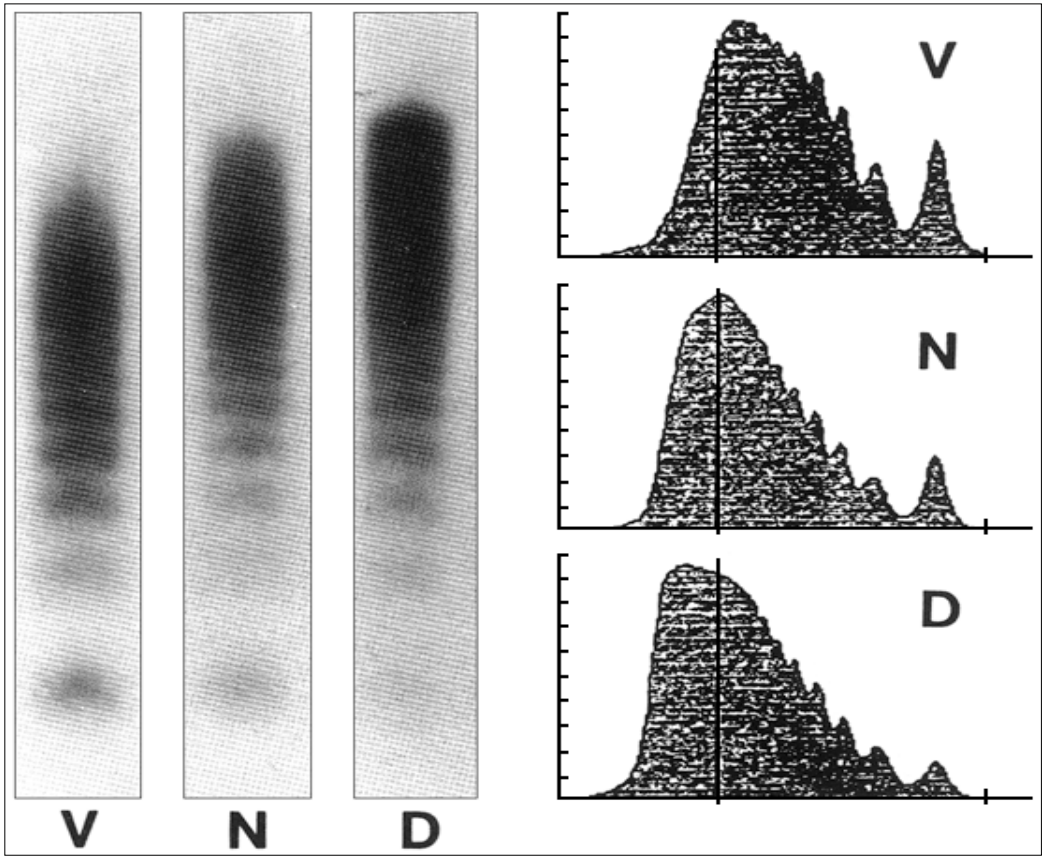
Table 1. Factor VIII Molecular Complex in Congenital Cardiac Defects

Patient	Cardiac Defect	Bleeding Symptoms	F VIII:C (U/dL)	vW:A (U/dL)	vW:rist (U/dL)	vWF Subunits
1	VSD	Yes*	73	27	23	Abnormal
2	VSD	Yes*	132	140	118	Abnormal
3	VSD, tetralogy of Fallot	Yes†‡	82	65	70	Abnormal
4	VSD	No	83	36	22	Abnormal
5	VSD, coarct (both repaired)	Yes§	145	106	98	Abnormal
6	VSD	Yes*‡‖	49	37	22	Abnormal
7	ASD primum	No	94	45	47	Abnormal
8	VSD	Yes†‡‖	81	43	41	Abnormal
9	VSD	No	54	208	170	Abnormal
10	VSD, coarct (coarct repaired)	No	118	82	62	Abnormal
11	Supravalvular aortic stenosis	Yes†‡¶	101	100	42	Abnormal
12	Aortic stenosis	No	47	42	32	Abnormal



Blood 1986;67(3):758-61.

Loss of HMW VWF multimers in aortic stenosis



Weinstein M et al. Blood. 1988;71:1648-55.

Valvular disease (V); **Normal pool plasma (N)**;
and from a patient **90' after infusion** of **Desmopressin (D)**.

Changes in HMW VWF multimers in aortic stenosis after cardiac surgery

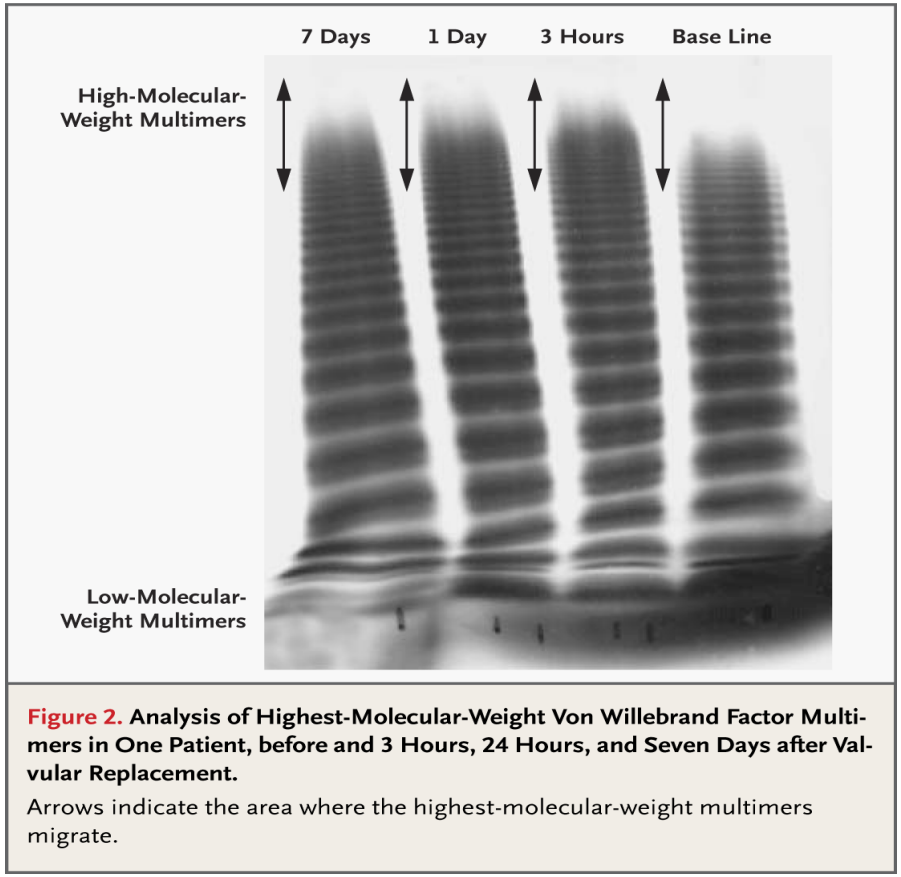


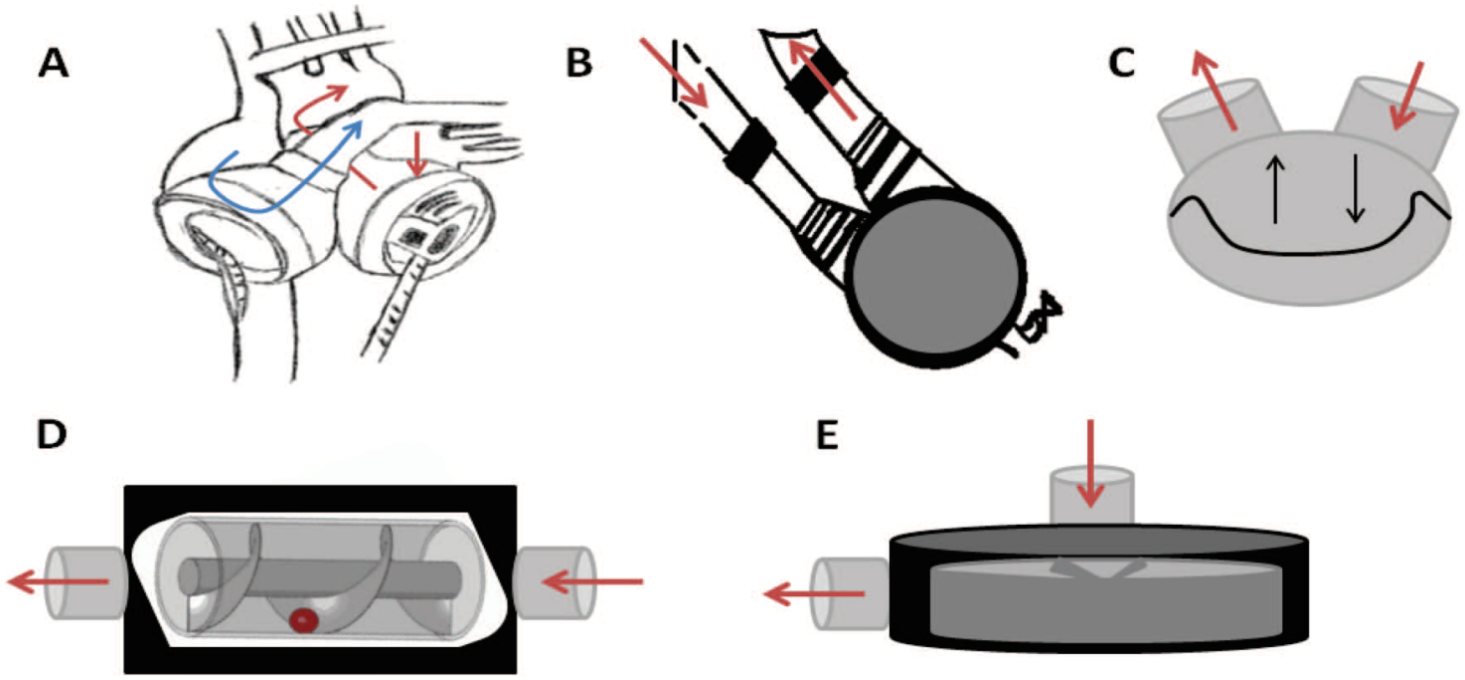
Figure 2. Analysis of Highest-Molecular-Weight Von Willebrand Factor Multimers in One Patient, before and 3 Hours, 24 Hours, and Seven Days after Valvular Replacement.

Arrows indicate the area where the highest-molecular-weight multimers migrate.

Vincentelli A et al. N Engl J Med. 2003;349:343-9.

Mechanical circulatory support: balancing bleeding and clotting in high-risk patients

Lisa Baumann Kreuziger[1] and M. Patricia Massicotte[2]

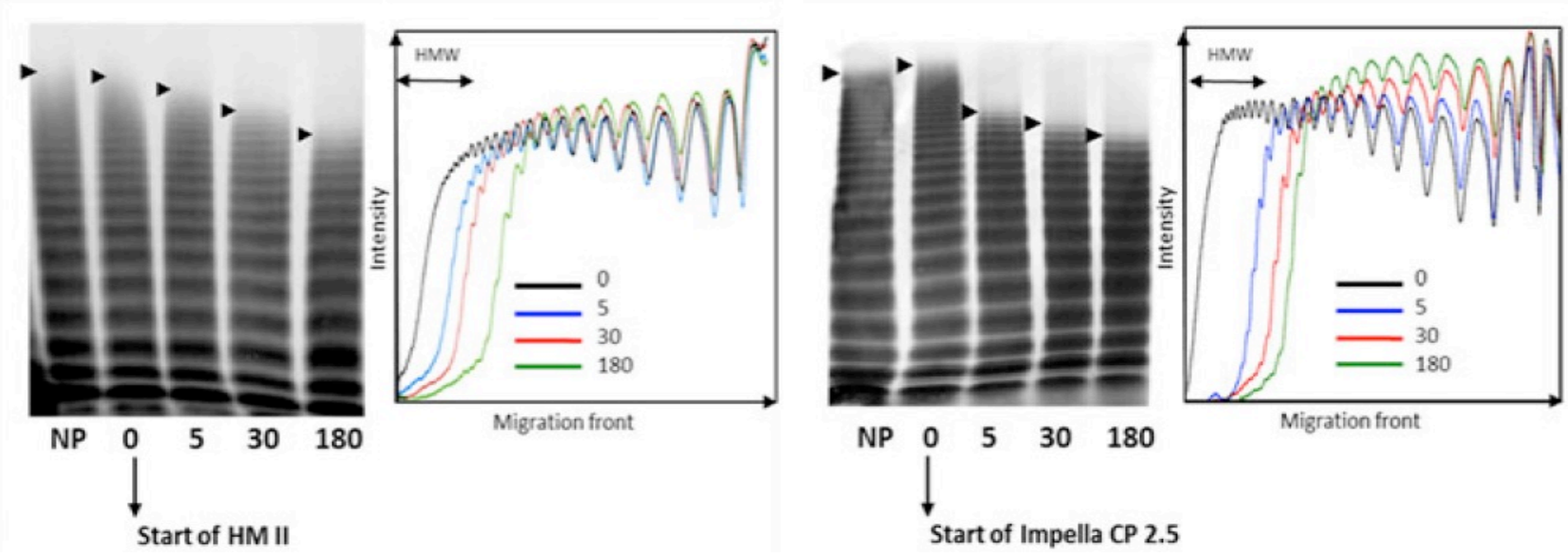


Hematology, 2015.

A) Total artificial heart. *Blue arrow represents the path of deoxygenated blood and red arrows represent the path of oxygenated blood.*
B) Pulsatile LVAD.
C) Oscillating membrane of pulsatile devices.
D) Continuous flow of axial LVAD.
E) Continuous flow of centrifugal LVAD.

Circulatory support devices: fundamental aspects and clinical management of bleeding and thrombosis

S. SUSEN,*† A. RAUCH,*† E. VAN BELLE,†‡ A. VINCENTELLI†‡§ and P. J. LENTING¶



Susen S et al. J Thromb Haemost. 2015;13:1757-67.

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  - *Hematologic disorders*

Current Diagnostic and Therapeutic Approaches to Patients with Acquired von Willebrand Syndrome: A 2013 Update

Augusto B. Federici, MD[1] Ulrich Budde, MD[2] Giancarlo Castaman, MD[3] Jacob H. Rand, MD[4] Andreas Tiede, MD[5]

Main diseases that are associated with acquired von Willebrand syndrome.

Underlying disorders	ISTH-SSC registry 2000 (*n* = 186)	Previous literature 1968–1998 (*n* = 266)	German registry 2006–2011 (*n* = 840)
Lymphoproliferative	89 (48)	79 (30)	153 (18)
Monoclonal gammopathy of undetermined significance	43 (23)	37(14)	113 (14)
Multiple myeloma	16 (9)	19 (7)	17 (2)
Waldenström macroglobulinemia	8 (4)	5 (2)	15 (2)
Non-Hodgkin lymphoma	8 (4)	10 (4)	5
Hairy cell leukemia	0	1	1
Acute lymphocytic leukemia	1	0	2
Myeloproliferative	29 (15)	48 (18)	287 (34)
Essential thrombocythemia	21 (11)	17 (6)	174 (21)
Polycythemia vera	1	9 (3)	78 (9)
Chronic myeloid leukemia	5 (3)	22 (8)	3
Myelofibrosis	2 (1)	0	32 (4)

Semin Thromb Hemost 2013;39:191-201.

Treatment of Acquired von Willebrand Syndrome in Patients With Monoclonal Gammopathy of Uncertain Significance: Comparison of Three Different Therapeutic Approaches

By Augusto B. Federici, Federica Stabile, Giancarlo Castaman, Maria Teresa Canciani, and Pier Mannuccio Mannucci

Patient No.	Age*/ Sex	MGUS Type	Acquired Bleeding Symptoms
1	43/F	IgGλ	Menorrhagia
2	28/F	IgGκ	Hemoperitoneum for corpus luteum hemorrhage
3	57/F	IgGλ	Spontaneous and posttraumatic hematomas, epistaxis, menorrhagia, melena
4	36/F	IgGκ	Menorrhagia
5	66/M	IgGλ	Melena
6	72/M	IgGλ	Epistaxis
7	56/M	IgGκ	Epistaxis, bleeding after dental extraction
8	78/M	IgGλ	Epistaxis, posttraumatic hematoma
9	43/F	IgMκ	Gum bleeding
10	54/M	IgMκ	Epistaxis, gum bleeding

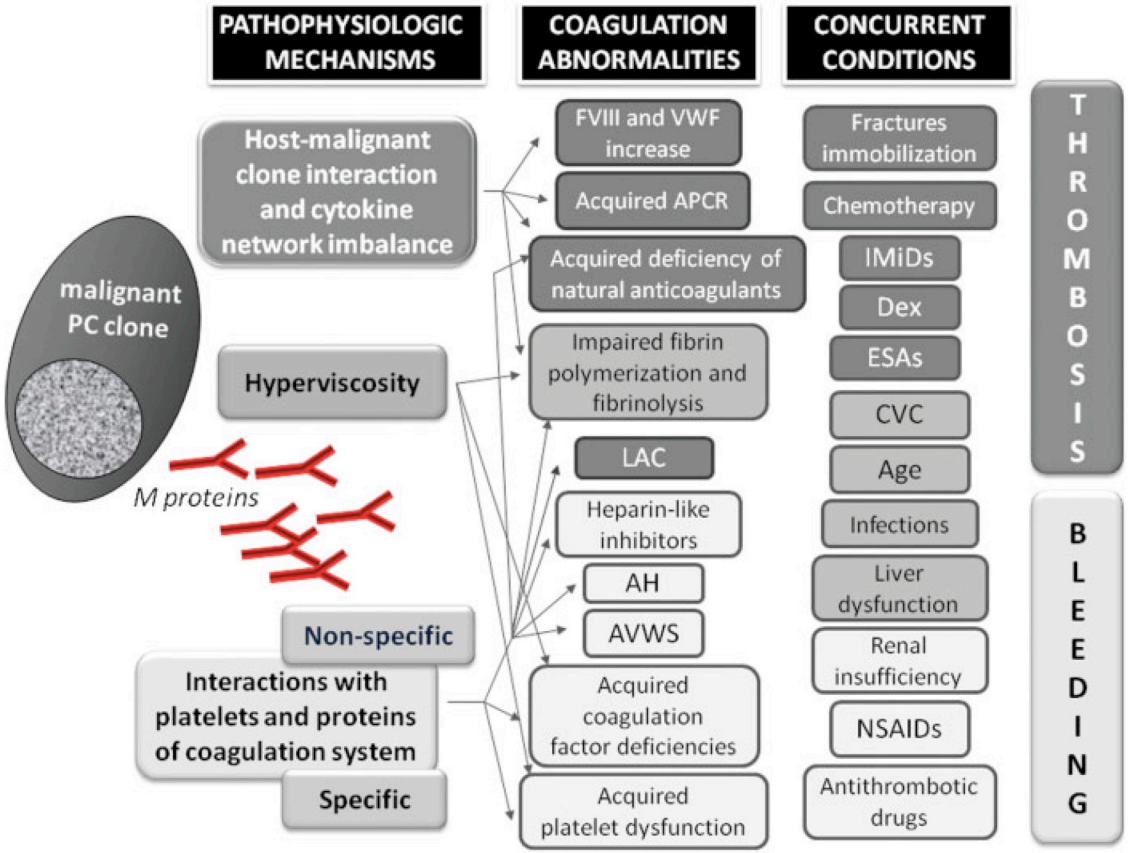
Ig, immunoglobulin.

Laboratory Measurements	IgG-MGUS (n = 8)	IgM-MGUS (n = 2)	Normal Controls (n = 20)
BT (min)	10-21	18-23	3-7
Factor VIII:C (U/dL)	9-36	20-36	62-156
vWF:Ag (U/dL)	3-16	26-37	52-148
vWF:RCo (U/dL)	<6	<6	49-151
vWF:propeptide (U/dL)	54-216	49-53	49-158
vWF (propeptide/Ag) ratio	7-51	1.3-2	0.7-1.9
High molecular weight multimers			
in plasma	Present	Absent	Present
in platelets	Present	Present	Present

Blood. 1998;92:2707-11.

Multiple Hemostatic Defects occurring in

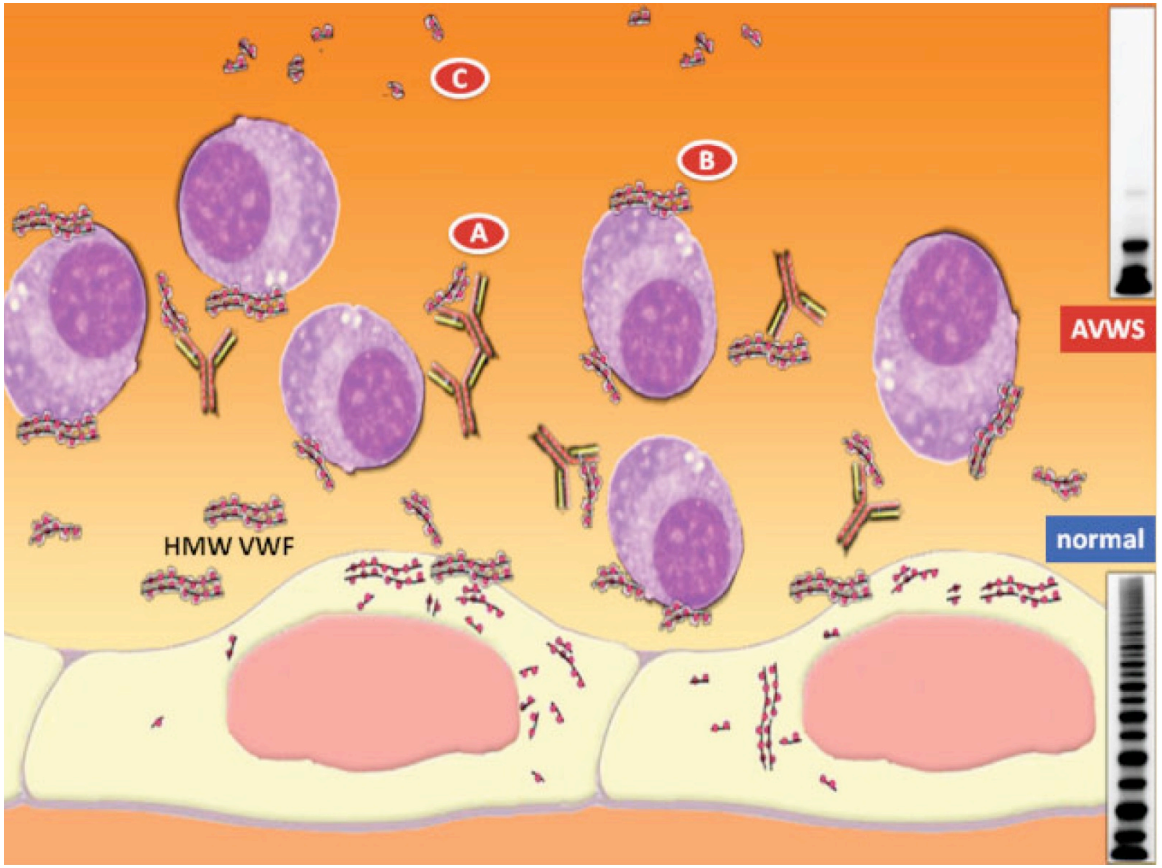
In Myeloma and other Plasma Cell Disorders



Coppola A et al. Semin Thromb Hemost. 2011 Nov;37(8):929-45.

Mechanisms of Acquired Defects of VWF (AVWS)

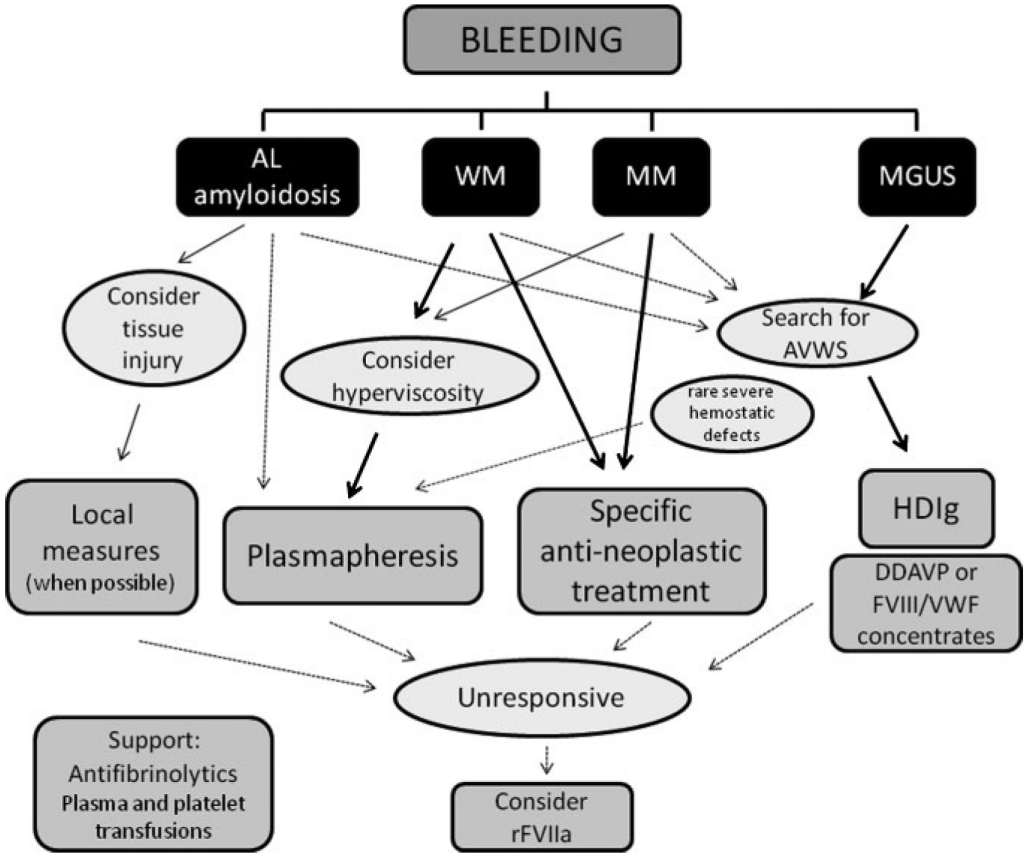
in Myeloma and other Plasma Cell Disorders



Coppola A et al. Semin Thromb Hemost. 2011 Nov;37(8):929-45.

Management of Bleeding Episodes

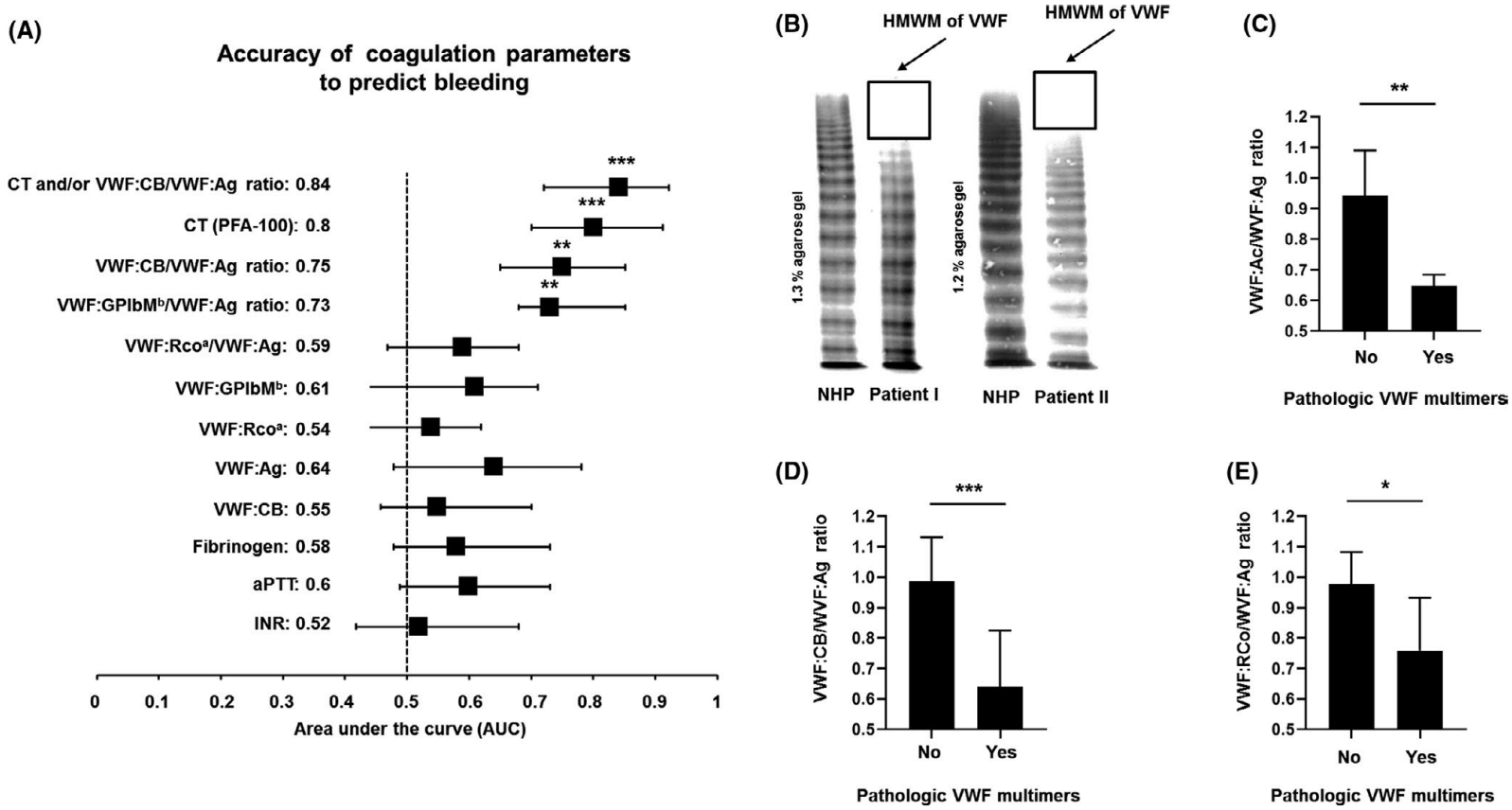
In Plasma Cell Disorders



Coppola A et al. Semin Thromb Hemost. 2011 Nov;37(8):929-45.

Disease progression and defects in primary hemostasis as major cause of bleeding in multiple myeloma

Clemens Hinterleitner[1] | Ann-Christin Pecher[1] | Klaus-Peter Kreißelmeier[1] | Ulrich Budde[2] | Lothar Kanz[1] | Hans-Georg Kopp[1] | Karl Jaschonek[1]



Eur J Haematol. 2020 Jan;104(1):26-35.

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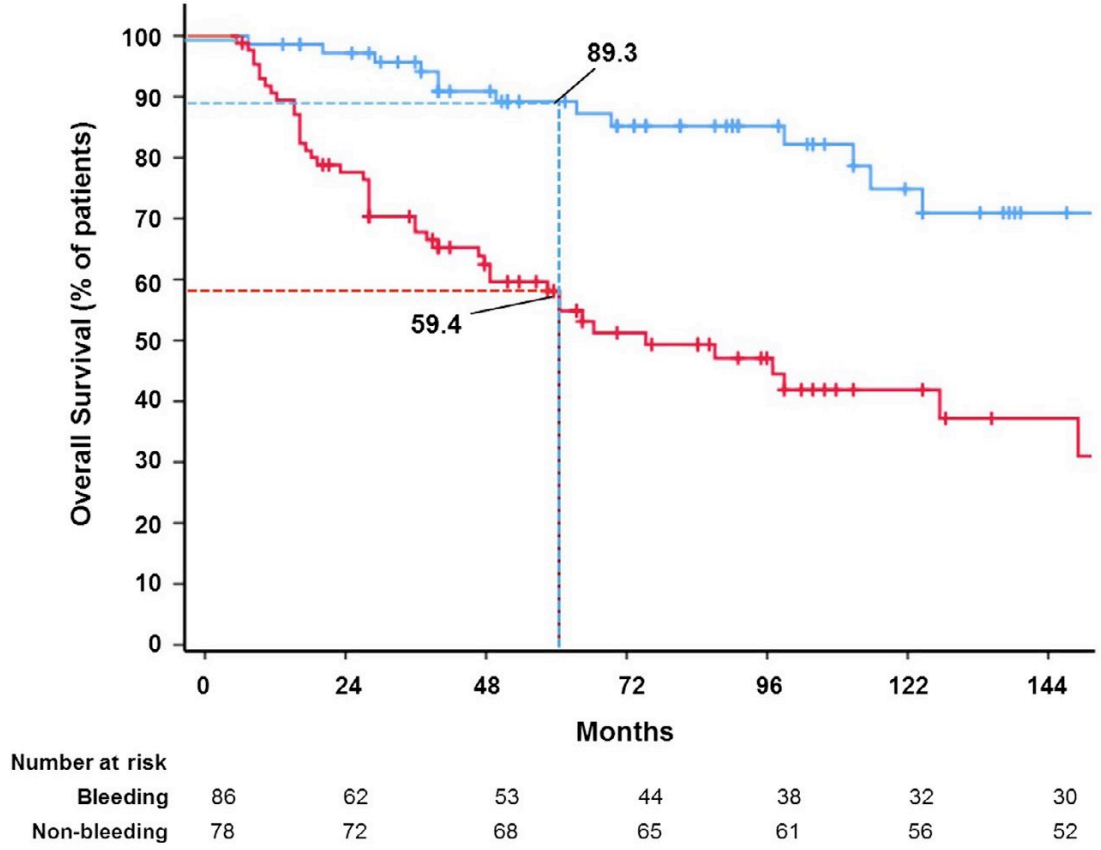


	No. of deaths/ total No. of patients	Median overall survival (95% CI) mo	5-y overall survival rate %
Bleeding	56/86	74 (38.5 -105.5)	59.4
Non-bleeding	26/78	nr	89.3

Hazard Ratio for death 4.2 (95%CI: 2.3 – 7.8)

P < .001

Pts. with bleeding

Pts. without bleeding

Eur J Haematol. 2020 Jan;104(1):26-35.

Acquired von Willebrand's Disease in the Myeloproliferative Syndrome

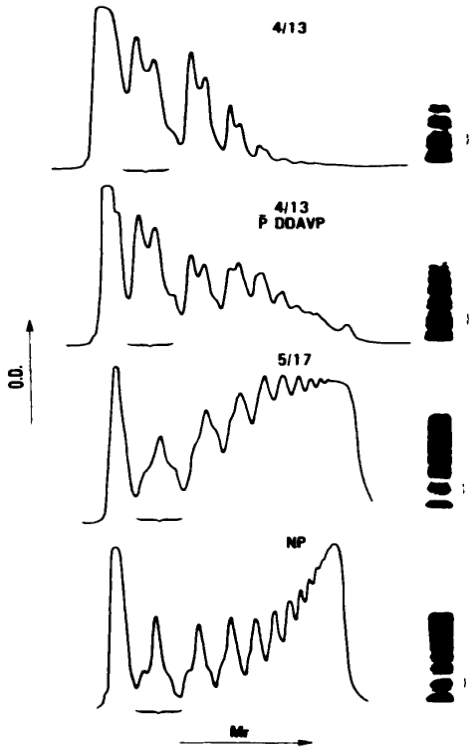
By Ulrich Budde, Gerd Schaefer, Norbert Mueller, Hans Egli, Judith Dent, Zaverio Ruggeri, and Theodore Zimmerman

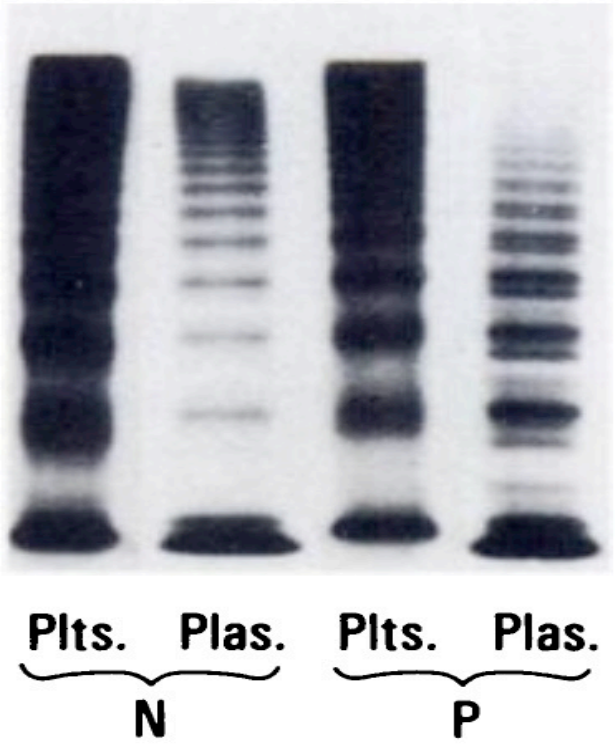
Patient No.	Date	Platelet Count (per μL)	WBC (per μL)	VIII:C (U/dL)	vWF:Ag (U/dL)	vWF:RCo (U/dL)	Bleeding Time	Comments
1	6/21/79	716,000	10,900	61	130	57	6 min	
	3/28/82	450,000	—	—	—	—	—	Splenectomy
	4/13/82	5,860,000	—	160	90	9	—	Bleeding from surgical wound
	4/13/82*	5,930,000	—	260	190	35	—	DDAVP response insufficient for hemostasis; Cohn fraction I given, bleeding stopped
	4/14/82	6,900,000	—	—	—			
	4/15/82	5,000,000	—	—	110	14	> 15 min	
	4/19/82	4,944,000	86,400	120	157	11	> 15 min	Busulfan and thrombocytophoresis begun
	5/17/82	1,005,000	7,800	130	140	86	2 min, 30 sec	
	9/20/83	1,057,000	19,300	97	80	49	—	Large multimers present but relatively diminished (similar to the patient shown in Fig 3); asymptomatic
2	1981							Splenectomy
	9/10/82	2,570,000	23,000	95	76	10	> 15 min	Bleeding after dental extraction
	9/10/82*	2,480,000	28,000	350	145	158	—	DDAVP given, bleeding stopped
	9/11/82	2,260,000	26,000	195	105	33	—	Bleeding recurred, Cohn fraction I given, bleeding stopped
	10/4/82	1,860,000	19,600	92	85	27	> 15 min	
	10/8/82	1,640,000	21,500	95	140	39	—	
	11/10/83	507,000	10,600	185	190	133	—	Large multimers present but relatively diminished (similar to the patient shown in Fig 3); asymptomatic

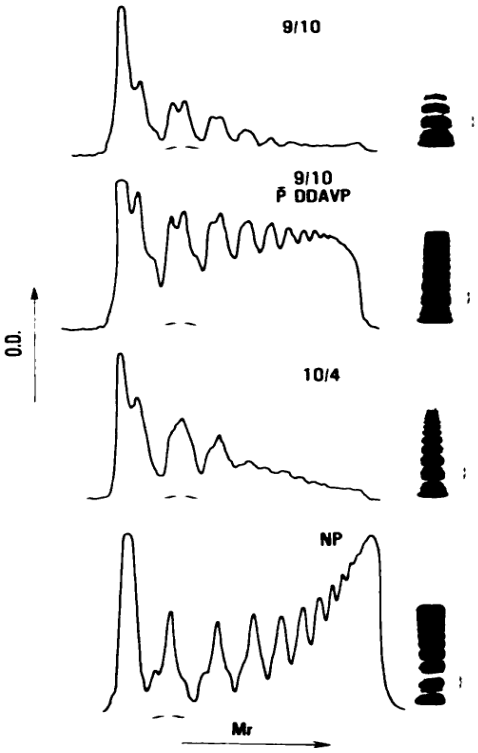
Blood. 1984;64:981-5.

AVWS in patients with ET

Multimeric analysis of VWF

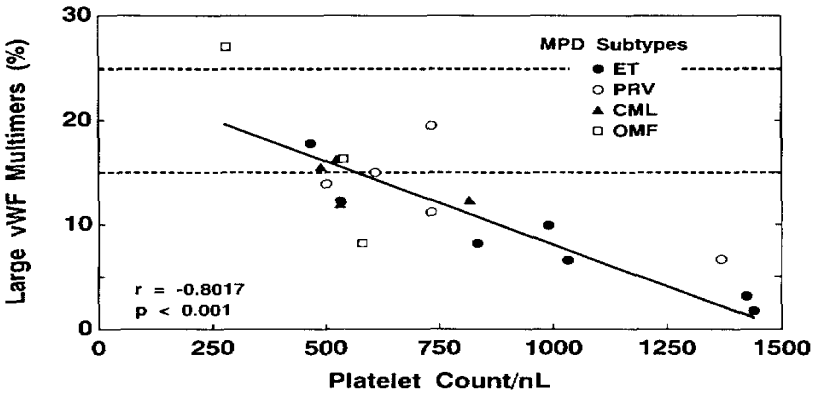


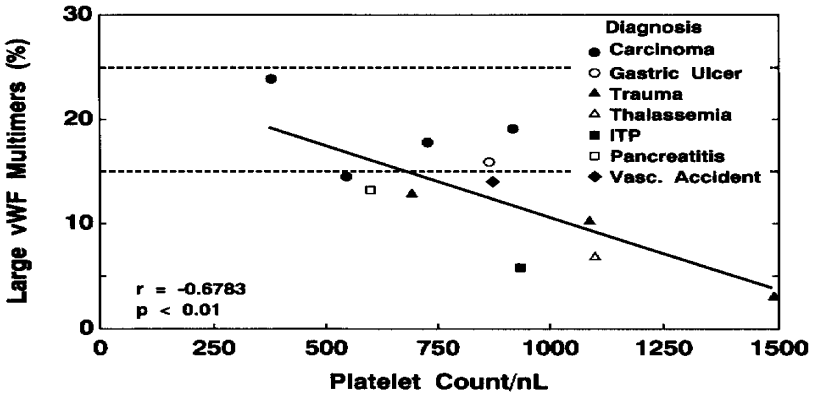


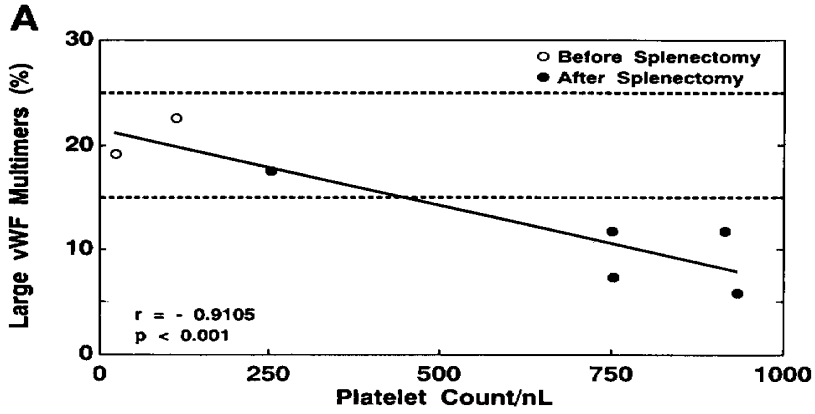


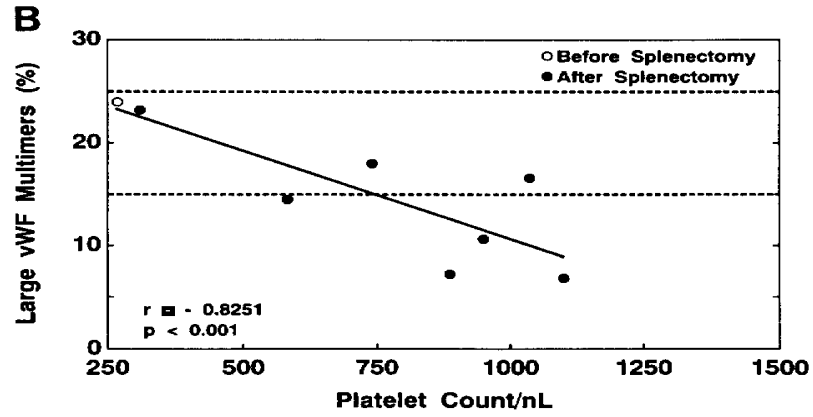
Budde U et al. Blood. 1984;64:981-5.

AVWS in patients with increased platelet counts









Budde U et al. Blood. 1993;82:1749-57.

Essential Thrombocythemia and Acquired von Willebrand Syndrome: The Shadowlands between Thrombosis and Bleeding

Hassan Awada [1,*], Maria Teresa Voso [2,3], Paola Guglielmelli [4] and Carmelo Gurnari [1,2]

Risk factors for bleeding in patients with essential thrombocythemia.

Risk Factors
Advanced age (>60 years)
Extreme thrombocytosis (platelet count > 1000×10^9/L)
Leukocytosis (leukocyte count ≥ 11×10^9/L)
Driving mutation: *JAK2* V617F is associated with higher risk of bleeding (*CALR* unclear)
History of bleeding/thrombosis
Acquired von Willebrand syndrome
Splenomegaly and portal hypertension
Medication induced (antiplatelet therapy and anticoagulation therapies)

Cancers (Basel). 2020 Jun 30;12(7):1746.

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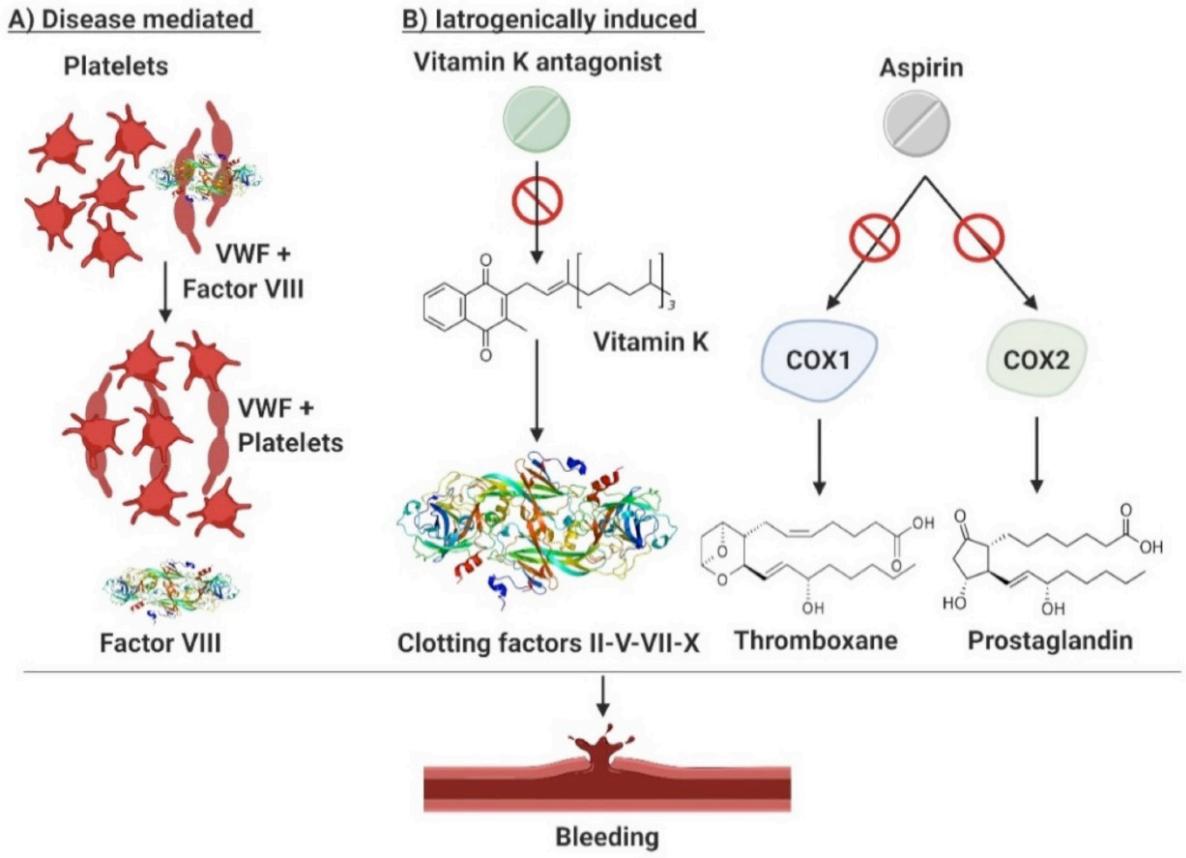

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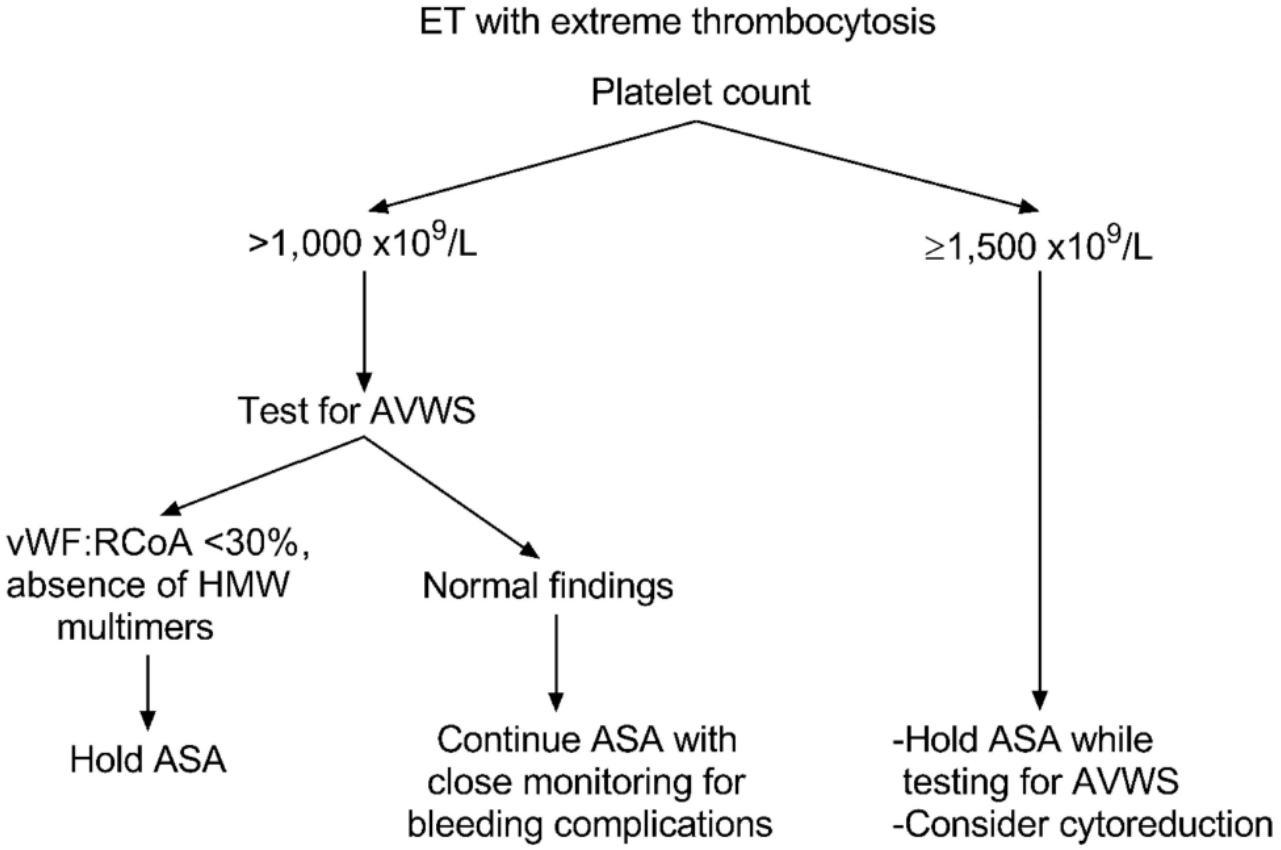


Cancers (Basel). 2020 Jun 30;12(7):1746.

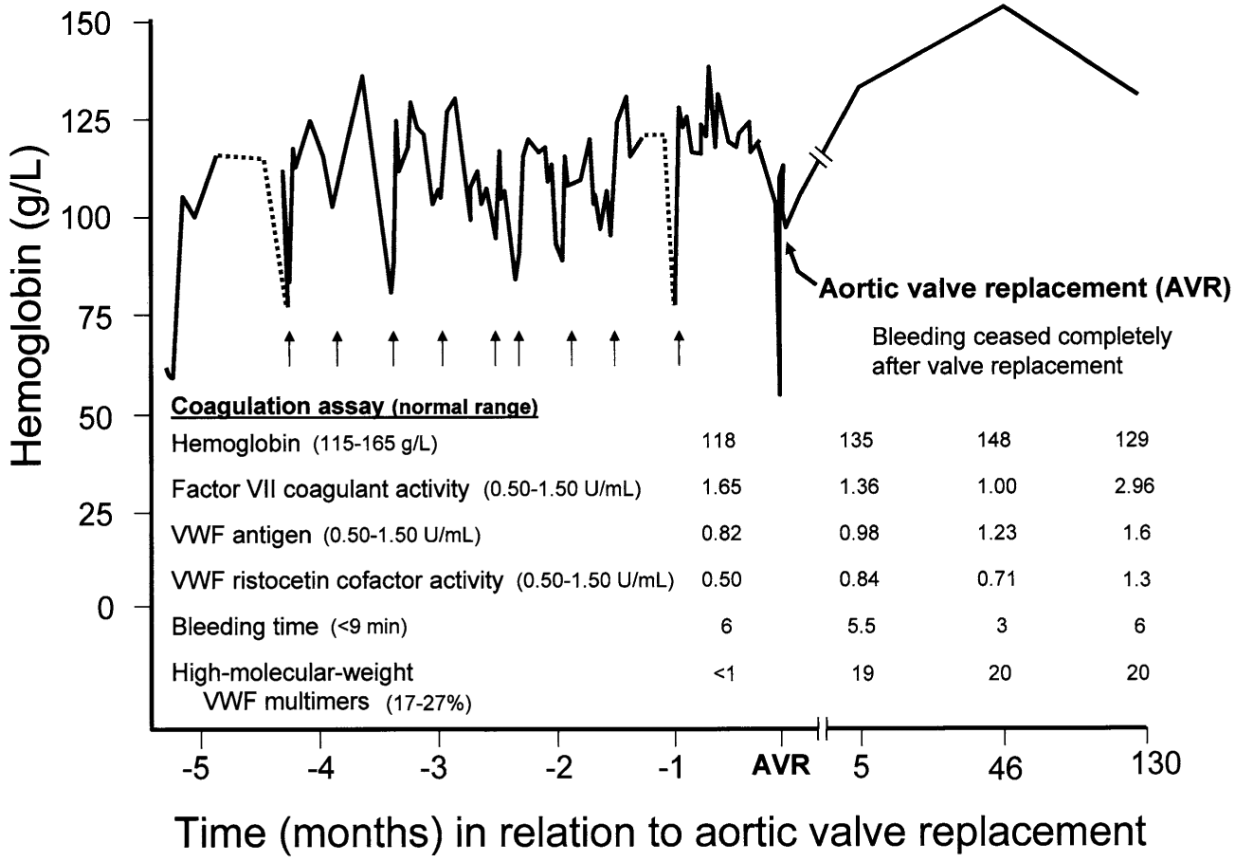
Acquired AVWS

Aims of Treatment

- **Treat the underlying disorder**
  - Chemotherapy, radiotherapy or surgery
- **Manage acute bleeding**

AVWS associated with aortic stenosis

Case report

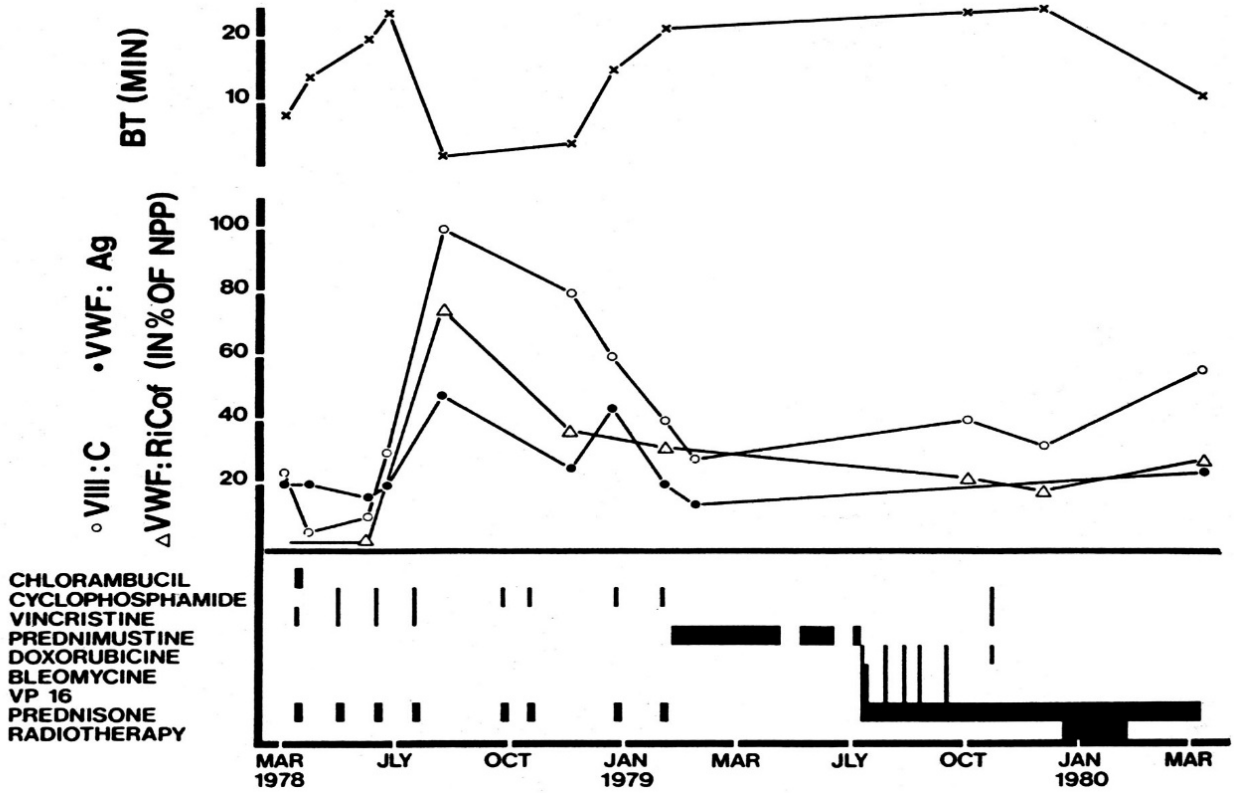


Warkentin TE et al. Transfus Med Rev. 2003;17:272-86.

AVWS in non-Hodgkin lymphoma

VWF activities during remission and relapse of NHL

Ag, antigen;
BT, bleeding time;
NPP, normal pool plasma;
RiCof, ristocetin cofactor.



Tran TC et al. Br J Haematatol. 1985;61:307-14.

Acquired VWS

Therapeutic Approaches

- **DDAVP** *(desmopressin acetate)*
- **VWF concentrates with** *or* **without FVIII**
- **High-dose IVIG** *(intravenous immunoglobulin)*
- **Plasmapheresis**
- **Immunosuppressive drugs**
- **rFVIIa** ***(recombinant activated factor VIIa)***
- **Retuximab?**

Therapeutic options according to underlying disorders

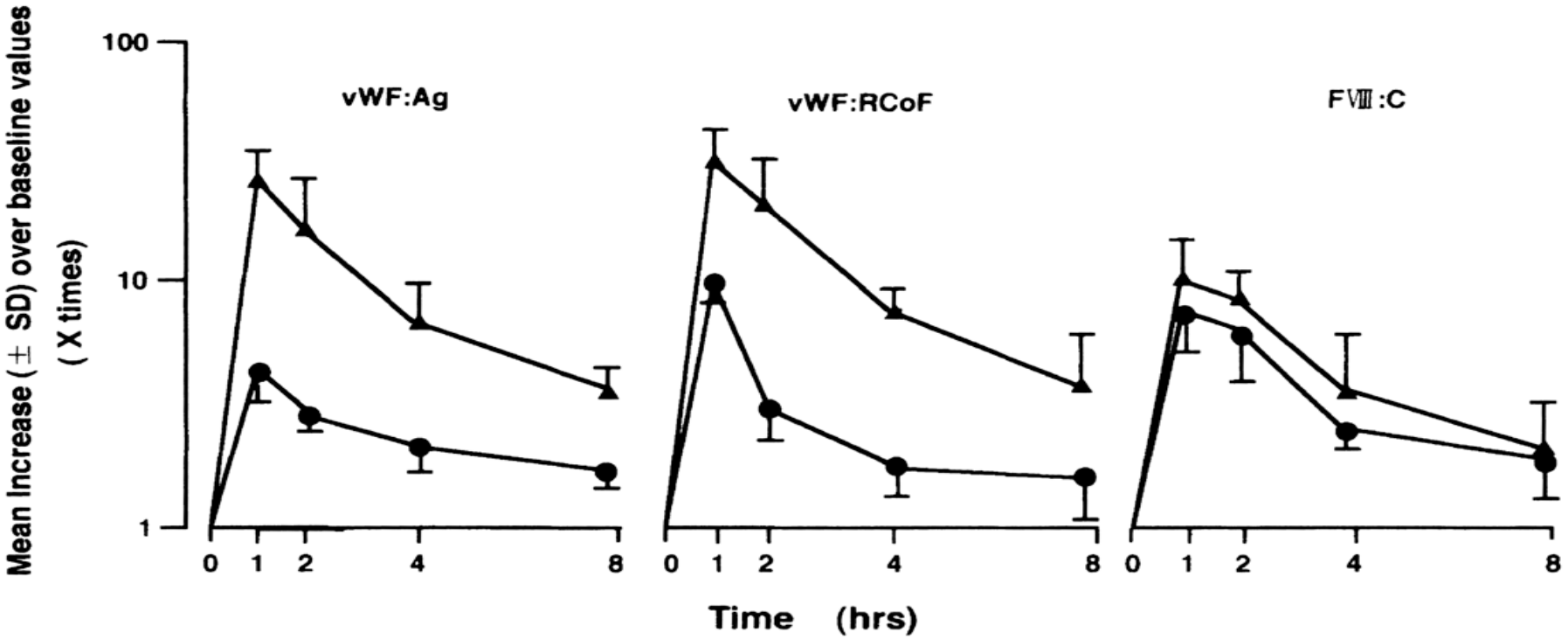
Underlying disorder	Causal treatment	Additional treatment options
Autoimmune disorders		
Systemic lupus erythematosus	Steroids, cyclophosphamide	IVIG (only IgG-MGUS or anti-VWF IgG), plasmapheresis, antifibrinolytics, VWF-containing concentrate, rFVIIa
Lymphoproliferative disorders		
MGUS	Usually untreated	
Lymphoma, multiple myeloma	Chemotherapy according to entity	
Cardiovascular		
Aortic valve stenosis and other anomalies with increased shear stress	Corrective surgery	VWF-containing concentrate, antifibrinolytics
Dysfunctional heart valve prosthesis, LVAD	Corrective surgery if applicable	Reduce or withdraw anticoagulation, VWF-containing concentrate
Myeloproliferative neoplasia		
Essential thrombocythemia	Cytoreductive therapy, chemotherapy, or stem cell transplantation in case of progression	
Polycythemia vera	Phlebotomy, cytoreductive therapy, chemotherapy, or stem cell transplantation in case of progression	Withdraw aspirin (if applicable), desmopressin, antifibrinolytics, VWF-containing concentrate
Chronic myeloid leukemia	Tyrosine kinase inhibitors, stem cell transplantation	

VWF indicates von Willebrand factor.

Tiede A et al. Blood. 2011;117:6777-85.

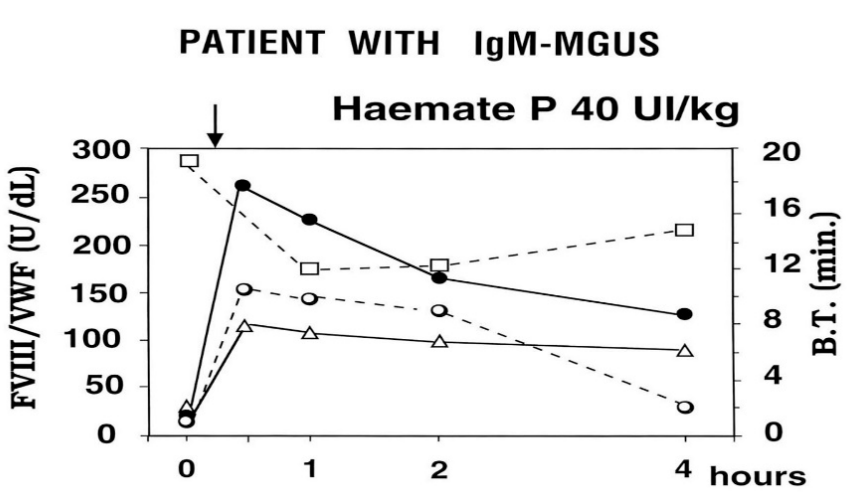
IgG, immunoglobulin G; **LVAD**, left ventricular assist device;
MGUS, monoclonal gammopathy of undetermined significance.

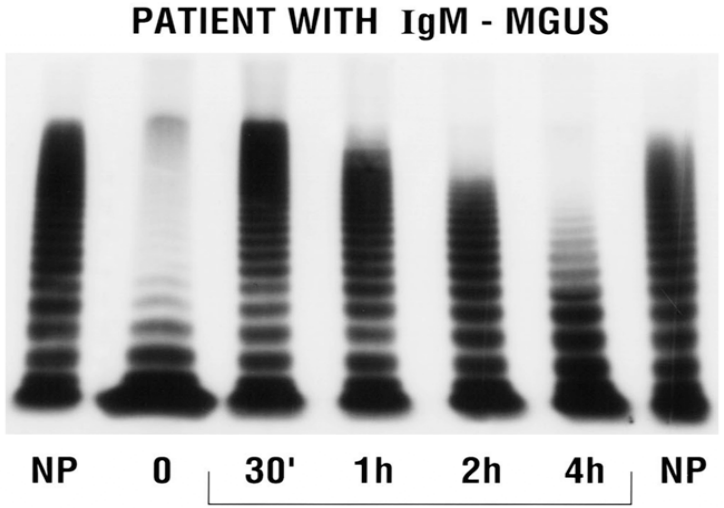
Biological response to DDAVP in inherited VWD *vs* AVWS



RCoF, ristocetin cofactor.

VWF/FVIII concentrates in AVWS associated with IgM-MGUS

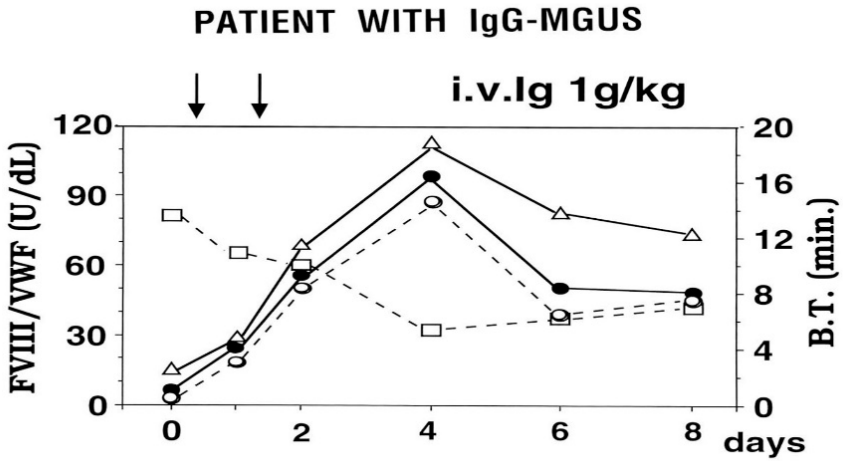


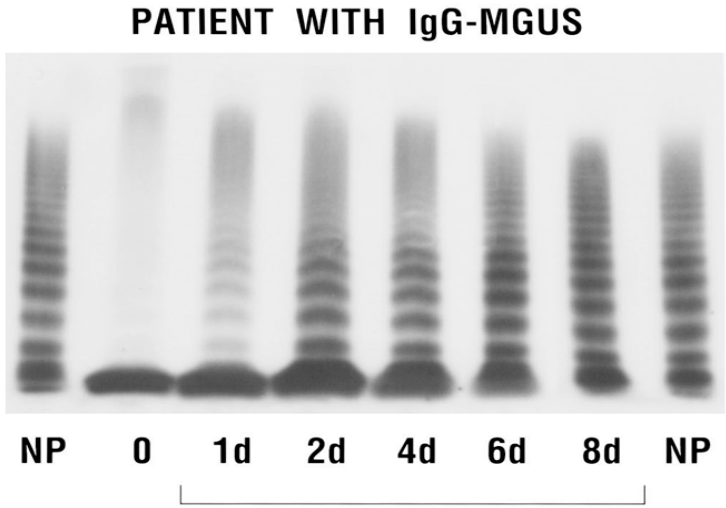


IgM, immunoglobulin M.

Federici AB et al. Blood. 1998;92:2707-11.

High-dose IVIG in AVWS associated with IgG-MGUS

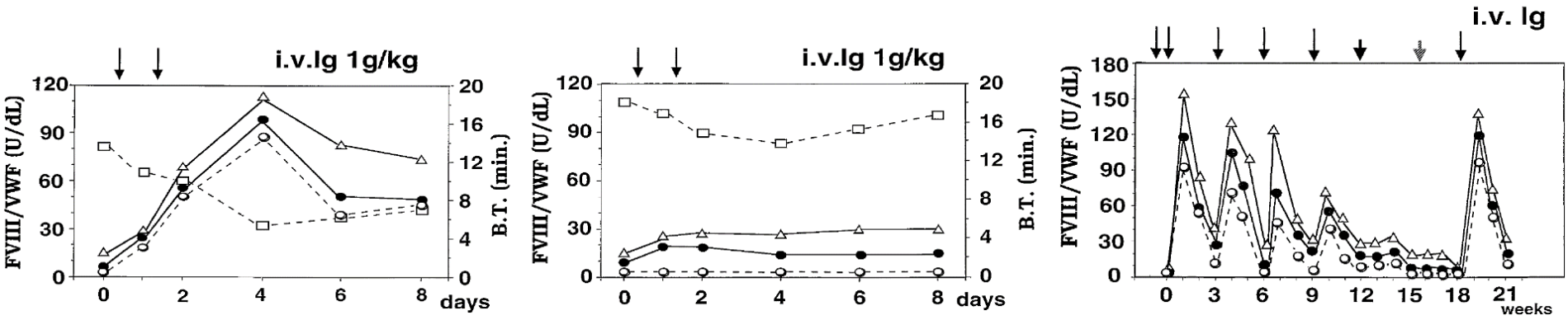




IVIG, intravenous immunoglobulin.

Federici AB et al. Blood. 1998;92:2707-11.

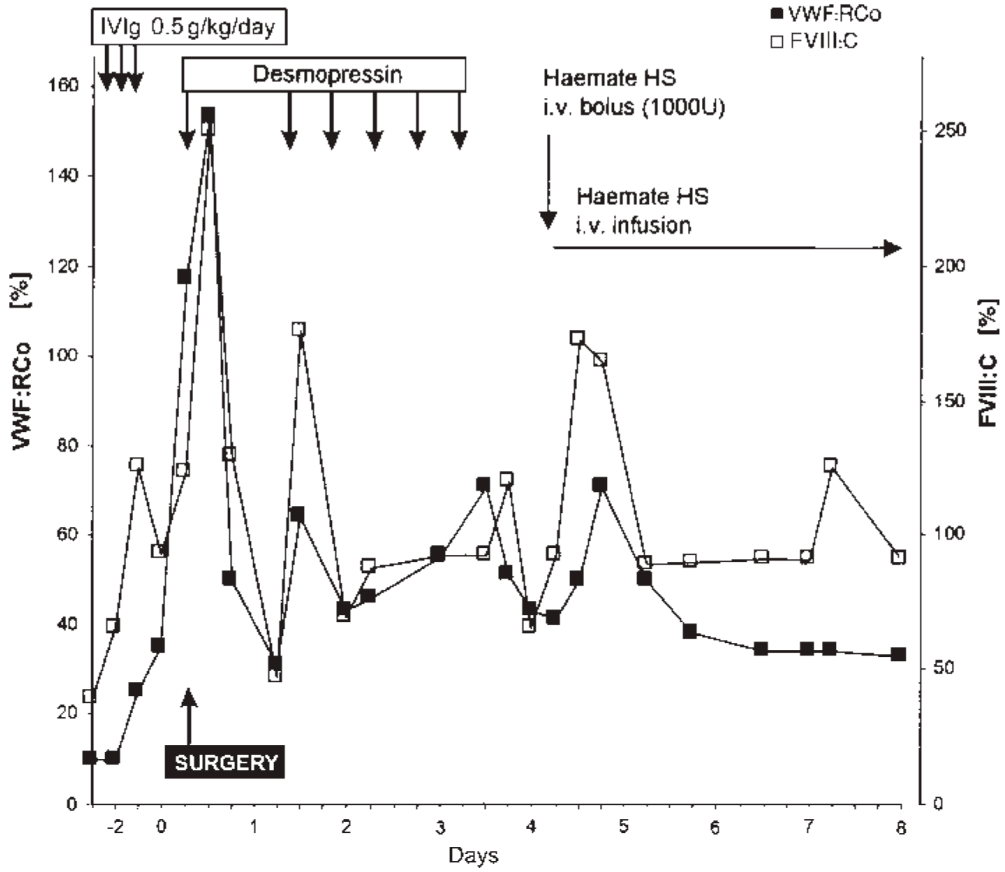
High-dose IVIG not always effective in AVWS



Federici AB et al. Blood. 1998;92:2707-11.

High-dose IVIG + DDAVP or concentrates in AVWS with urgent bleeds/surgery

RCo, ristocetin cofactor.



Michiels JJ et al. Semin Thromb Hemost. 2006;32:636-45.

Recombinant activated FVII in patients with AVWS associated with MGUS

- Successful **treatment with rFVIIa** in a patient with acquired VWS associated with MGUS and severe bleeding resistant to standard therapy
  - **90 µg/kg** *(bolus)* **+ 17.5 µg/kg/h for 6 days of rFVIIa**

Friederich PW et al. Am J Hematol. 2001;66:292-4.

Management of AVWS in 2020

Discussion

- Despite many reports and recommendations, the **diagnosis of AVWS remains difficult in most cases**, and therapeutic approaches are not standardized;
- **Clinical prospective studies** are required in large numbers of patients with centralized diagnosis of AVWS to **assess specific therapies according** to the actual mechanisms causing AVWS.

Interactive **R**egistry on **A**cquired von **Wil**lebrand syndrome: **Ma**nagement **P**rospective **S**tudy **[IntRAWilMaPS] (2021-2024)**

www.intreavws.com