GLI INIBITORI DELL'EMOSTASI NELLE MGUS

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Disclosures:
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Employment	*NONE*
Research support	*NONE*
Scientific advisory board	*BAXTER, CSL-BEHRING, GRIFOLS, KEDRION-LFB, OCTAPHARMA, WERFEN-IL*
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Patents	*NONE*
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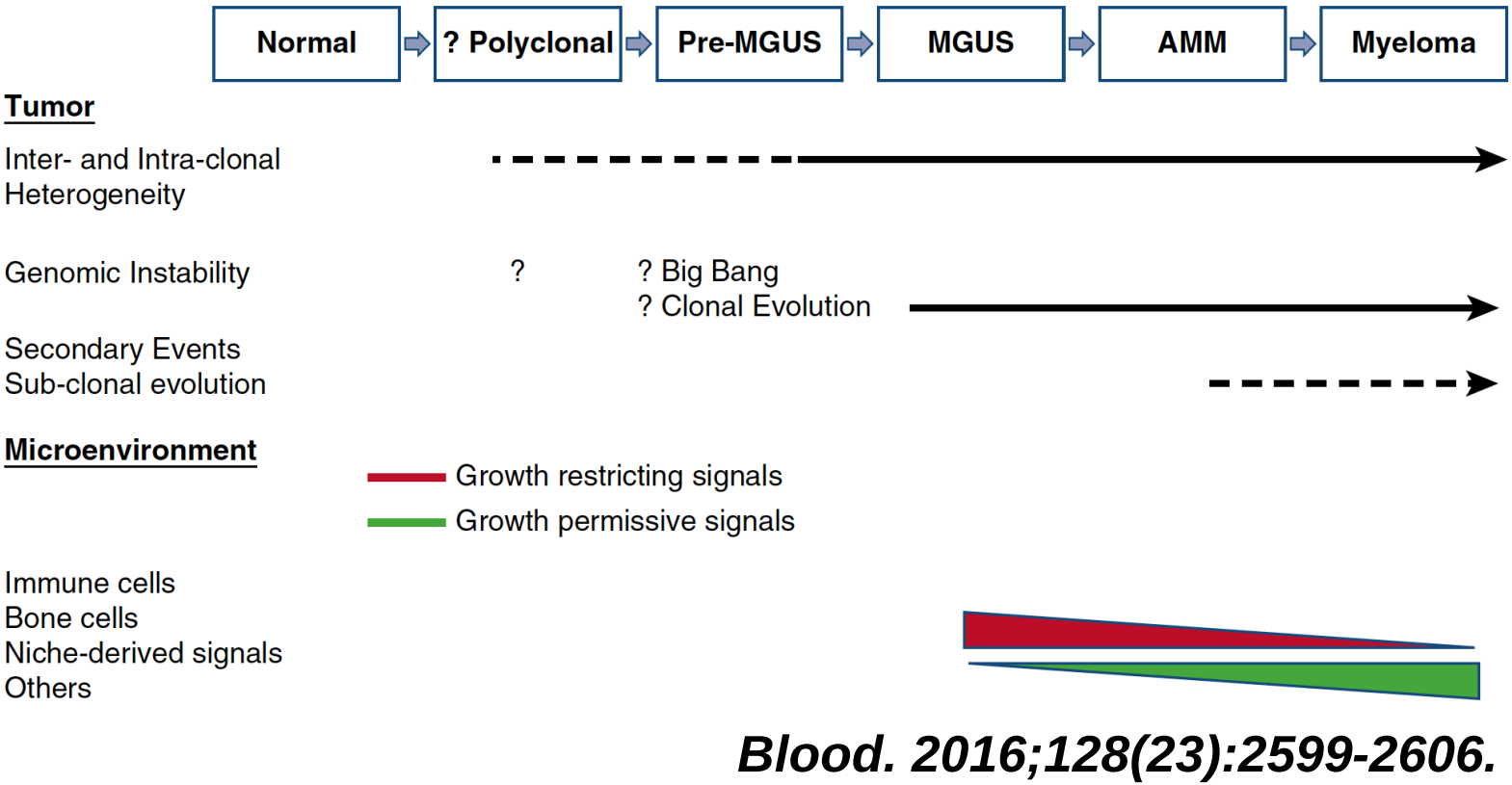
Travel support	*NONE*
Other	*NONE*

Monoclonal Gammopathy of Undetermined Significance
MGUS: General Definitions (1)

- **MGUS is a frequent finding** in the older adult population, affecting **3% of whites age 50 or older** and with prevalence **increasing with age**.
- **Prevalence varies** among different races, being **2-fold higher in black population** and less frequent in Asian compared with whites.
- **MGUS is a premalignant plasma cell discrasia**, carrying a lifelong risk of transformation to hematologic malignancy, mainly MM, **at a fixed but unremitting rate** of approximately **1% per year**.

MGUS to myeloma: a mysterious gammopathy of underexplored significance

Madhav V. Dhodapkar



Blood. 2016;128(23):2599-2606.

Monoclonal Gammopathy of Undetermined Significance
MGUS: General Definitions (2)

- **Because MM remains an incurable disease with significant associated morbidity from skeletal and renal events, close monitoring of MGUS patients has been recommended to diagnose malignant transformation before the onset of serious complications.**
- **Current guidelines recommend that newly diagnosed MGUS patients should undergo a general physical examination and routine laboratory screen (complete blood count, creatinine, calcium) with a repeated serum protein electrophoresis in 6 months, and, if stable, yearly thereafter (optimal MGUS follow-up)**

MGUS and Acquired Haemostatic Inhibitors (AHI) General Definitions and Frequency (3)

- **There are no data about the prevalence of AHI in MGUS because no prospective observational studies are available in a large number of individuals with MGUS**
- **The most frequent haemostatic lab abnormality shown in MGUS is the prolonged PTT due to reduced levels of FVIII (acquired HA) associated with VWF defects (AVWS)**
- **Among the 456 cases of MGUS followed up for the last 6 years at the Division of Hematology and Transfusion Medicine of L. Sacco University Hospital 12/456 (2.5%) developed a prolonged PTT (defects of FVIII and VWF) with bleeding symptoms**

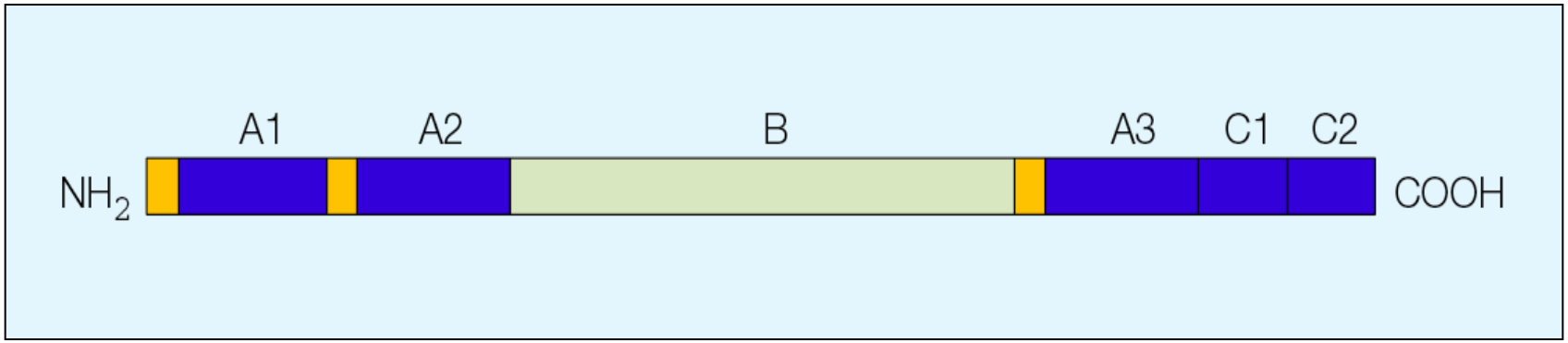
Acquired Haemostatic Inhibitors (AHI)
General Classification (4)

The acquired defects of the complex FVIII/VWF are known as Acquired Hemophilia A (AHA) and Acquired von Willebrand Syndrome (AVWS).

Besides AVWS and AHA other very rare AHI have been reported against Factor V, VII, IX, X, XI, XII and XIII.

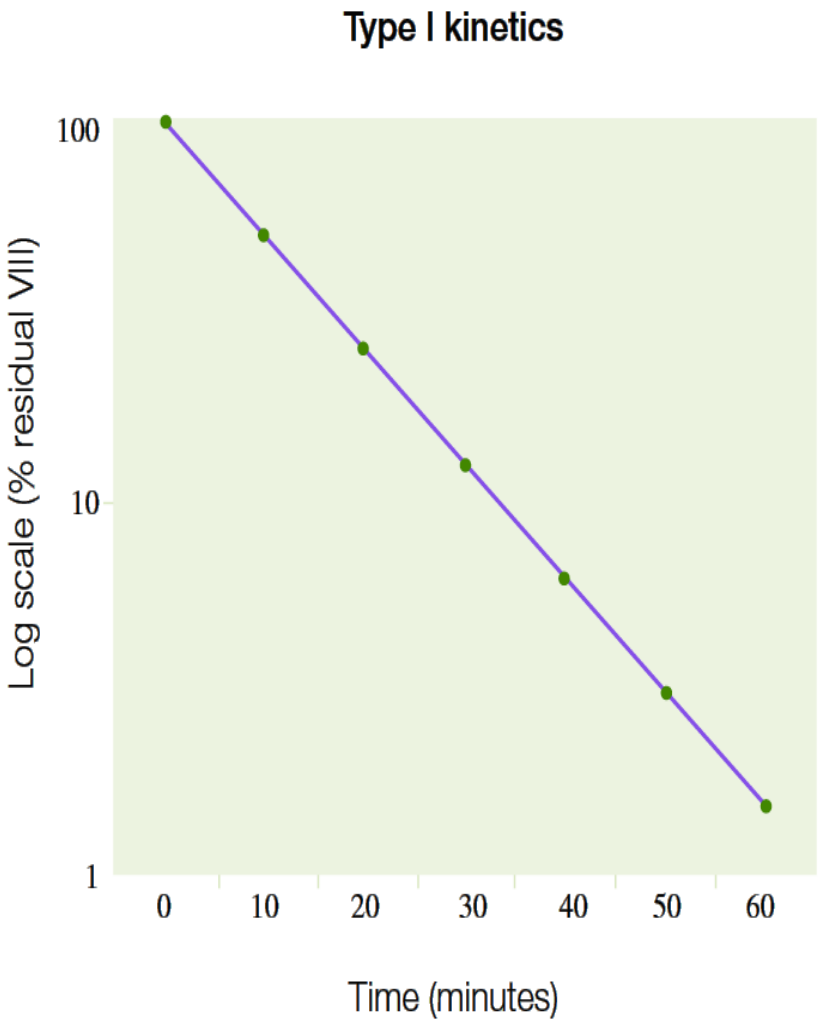
The management of patients with AVWS, AHA and other AHI is difficult and costly: the attention of an experienced hematologist consultant is always required.

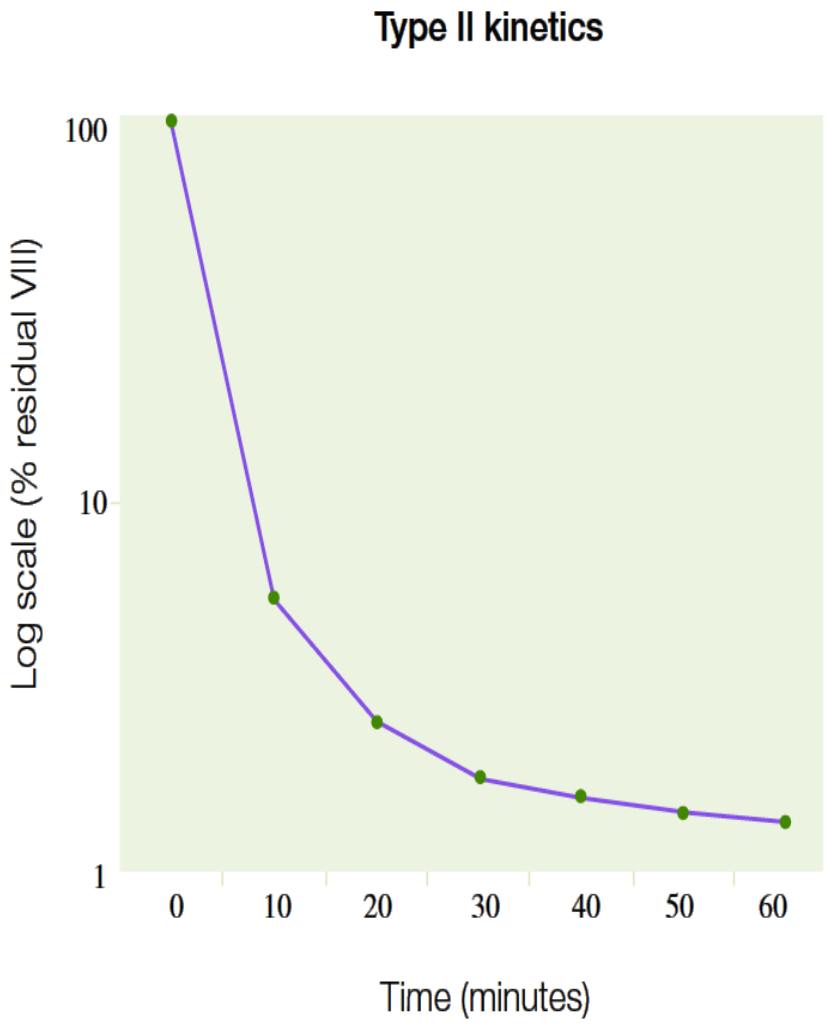
Domains of FVIII: anti-FVIII auto-antibodies



A2-A3 domains - binding sites for activated Factor IX
C2 domain - binding to VWF
- binding to the phospholipid membrane

Kinetics of anti-FVIII inhibitors





Acquired VW Syndrome
Definitions

Acquired Von Willebrand Syndrome (AVWS) is a rare acquired bleeding disorder similar to inherited VWD in term of lab findings:

- **prolonged BT, defects of VWF activities.**

But differently from inherited VWD occurs:

- **later in life in subjects without personal and familial history of bleeding.**

AVWS Reported in the Literature
(1968-2016)

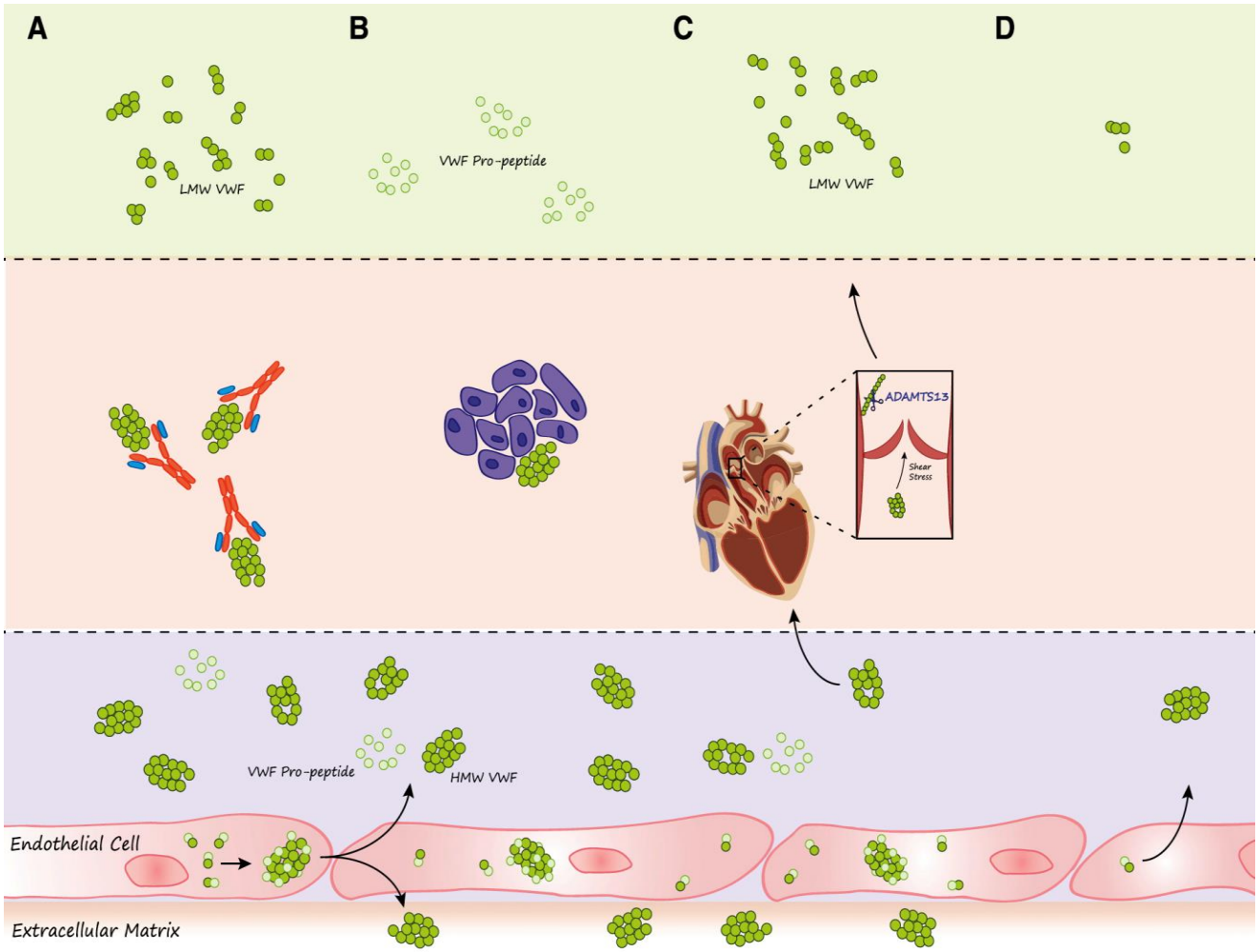
1060 Pub Med citations up to Dec 2016.

622 scientific reports including:

- **7 national or expert recommendations**
- **1 prospective + 4 retrospective studies**
- **2 "How I treat" in Blood**

Cochrane library: no reports

Main Mechanisms Causing AVWS:
not only Auto-Antibodies to VWF



Callaghan MU et al, Blood 2013

Acquired VW Syndrome
Prevalence of AVWS

- **No large prospective studies available**
- **Only one single institution study: *25/260 patients* with hematological disorders showed a form of AVWS**

Mohri et al, Blood 1998

Retrospective Studies on AVWS
(1968-2000)

Scientific and Standardization Committee Communication

Acquired von Willebrand Syndrome: Data from an International Registry

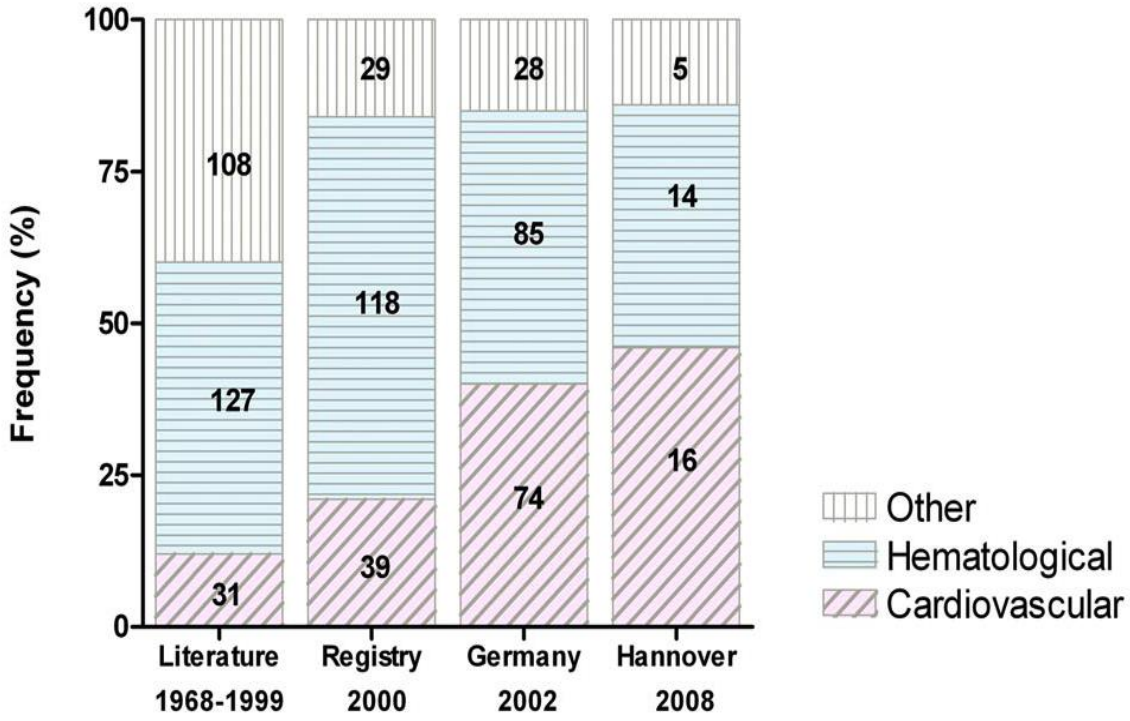
On behalf of the Subcommittee on von Willebrand Factor

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 AVWS in the literature (1968-1999)**
- **186 cases reported by the ISTH-SSC Registry**

Thromb Haemost 2000

The Current Changing Spectrum of AVWS-Associated Disorders



Tiede A et al, Blood 2011

Differential Diagnosis Between AVWS and VWD

Aspect	In favor of AVWS	In favor of VWD	Limitations
Personal history	Late onset of bleeding	Early onset of bleeding	Variable penetrance of VWD
	Uneventul surgery before onset of bleeding	No uneventful surgery or no previous high risk situations	
Family history	Negative	Positive	Variable penetrance of VWD
AVWS-associated disorder	Present	Absent	Coincidental presence of highly prevalent disorders, *e.g.* MGUS in the elderly
Laboratory evaluation	Presence of inhibitor or VWF-binding antibodies	VWF gene mutation	Low frequency of detectable inhibitors in AVWS
			Alloantibodies in rare cases of VWD type 3
Treatment response	Remission after treatment of underlying disorder	Normal recovery and half-life of VWF-containing concentrate	Cannot be assessed before treatment
	Response to IVIG (in IgG MGUS associated AVWS	Sustained response to desmopressin	
	Short-lived response to VWF containing concentrates or desmopressin		

Auto-Antibodies in AVWS
Neutralizing *vs* Non-Neutralizing Abs

Neutralizing auto-antibodies interact with the functional portions of VWF: they are associated with loss of specific VWF activities

Non Neutralizing auto-antibodies can remove VWF from circulation without interaction with functional portions of VWF

Methods Used to Identify Anti-VWF Auto-Antibodies

- **Mix experiments with VWF/FVIII activities tested after 1-4 hour incubation at 37° C.**

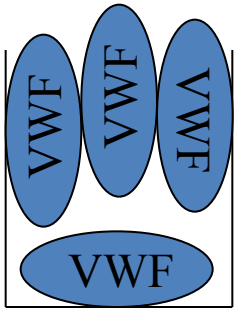
  Mannucci PM et al, Blood 1984

- **Some solid phase tests proposed by different authors**

- **More recently, an assay to test anti-VWF antibodies by using a sandwich ELISA (Ex-VWF-Plasma-HRP goat anti-human IgG-IgM) has been published.**

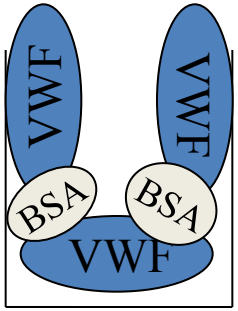
  Siaka C et al, Haemophilia. 2003

Method (1)
ELISA Test for Auto-Antibodies Against VWF



Coating: of γ-irradiated polystyrene plates (Nunc Maxisorp) with 100 µl of purified VWF solution (Wilfactin, LFB) at final concentration of 0.35 UI VWF:RCo/mL.

Incubation: One night at 2-8 ºC



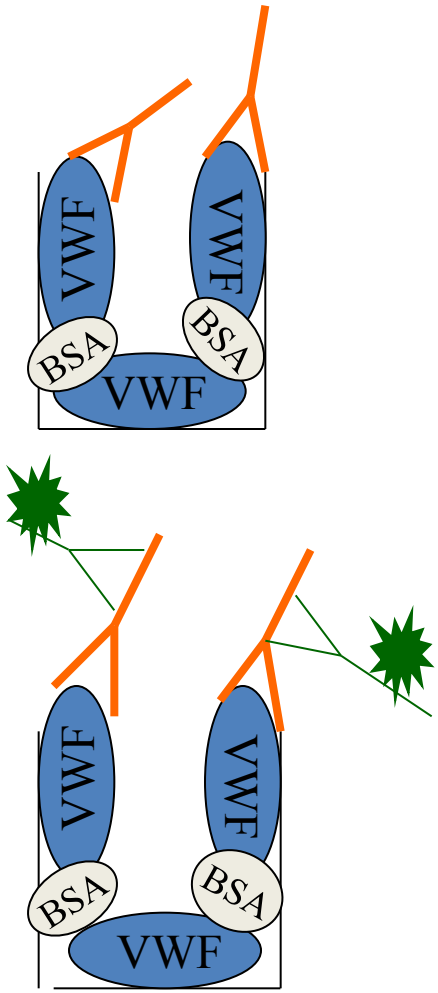
Washing: Unbound VWF removed by 5 washes with PBS pH 7.4

Saturation: of the wells with PBS-1% BSA 2 hours at 20-22 ºC

Aspiration: Then, PBS aspiration

Siaka C et al, Haemophilia 2003

Method (2)
ELISA Test for Auto-Antibodies Against VWF



Addition of plasma samples: **at 1:10 or 1:50. In PBS-0.05% Tween20, in VWF-coated and control-uncoated wells**

Incubation: **2 hours at 20-22 ° C. Washes (5)**

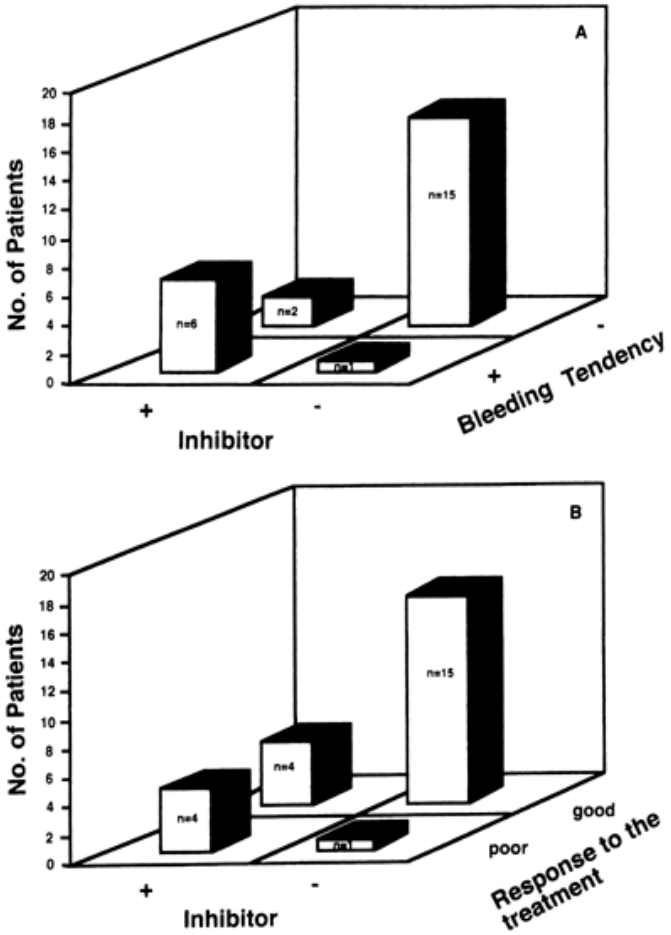
Addition of the immuno-conjugated:
Either HRP-goat antihuman IgG Or HRP- goat antihuman IgM

Incubation: **2 hours at 20-22 °C. Washes (5)**
Addition of the substrate (OPD):
Coloration development (5 min)

Measurement of the absorbance: **at 490 nm**

Result expression: **OD coated-OD uncoated**

Clinical Significance of the Presence of Auto-Antibodies Against VWF



Mohri H et al, Blood 1998

VWF Propeptide
is this a Useful Parameter in AVWS?

Acquired von Willebrand syndrome: von Willebrand factor propeptide to von Willebrand factor antigen ratio predicts remission status

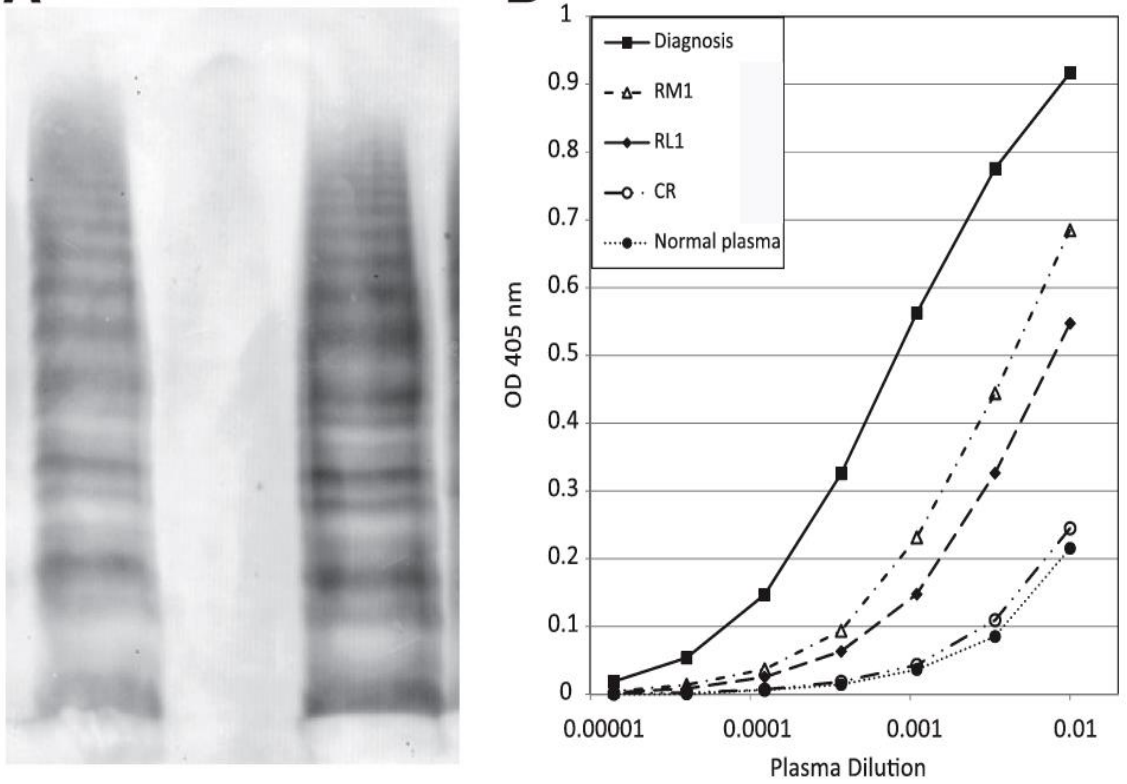
Adrienne Lee,[1] Gary Sinclair,[2,3] Karen Valentine,[1] Paula James,[4] and Man-Chiu Poon[1,3]

VWF and FVIII levels and VWFpp results

	VWF:Ag (IU/dL)	VWF:Act (IU/dL)	FVIII:C (IU/dL)	GTi VWF:Ag (IU/dL)	GTi VWFpp (IU/dL)	GTi VWFpp:Ag†	CRP (mg/L)
Diagnosis	4	7	2	<1	202	>202	31
RM1	147	135	92	116	227	1.96	6.9
RL1	<10	<10	3	<1	105	>105	27
Pre-DDAVP*	<10	<10	5	<1	129	>129	—
1 hour post-DDAVP*	<10	<10	7	<1	172	>172	—
CR	97	129	128	90	118	1.3	3.0
NPP	—	—	—	119	100	0.8	—

Blood 2014

VWF Propeptide + Anti-VWF Auto-ABS to Evaluate Remission or Relapse of AVWS



Lee A et al, Blood 2014

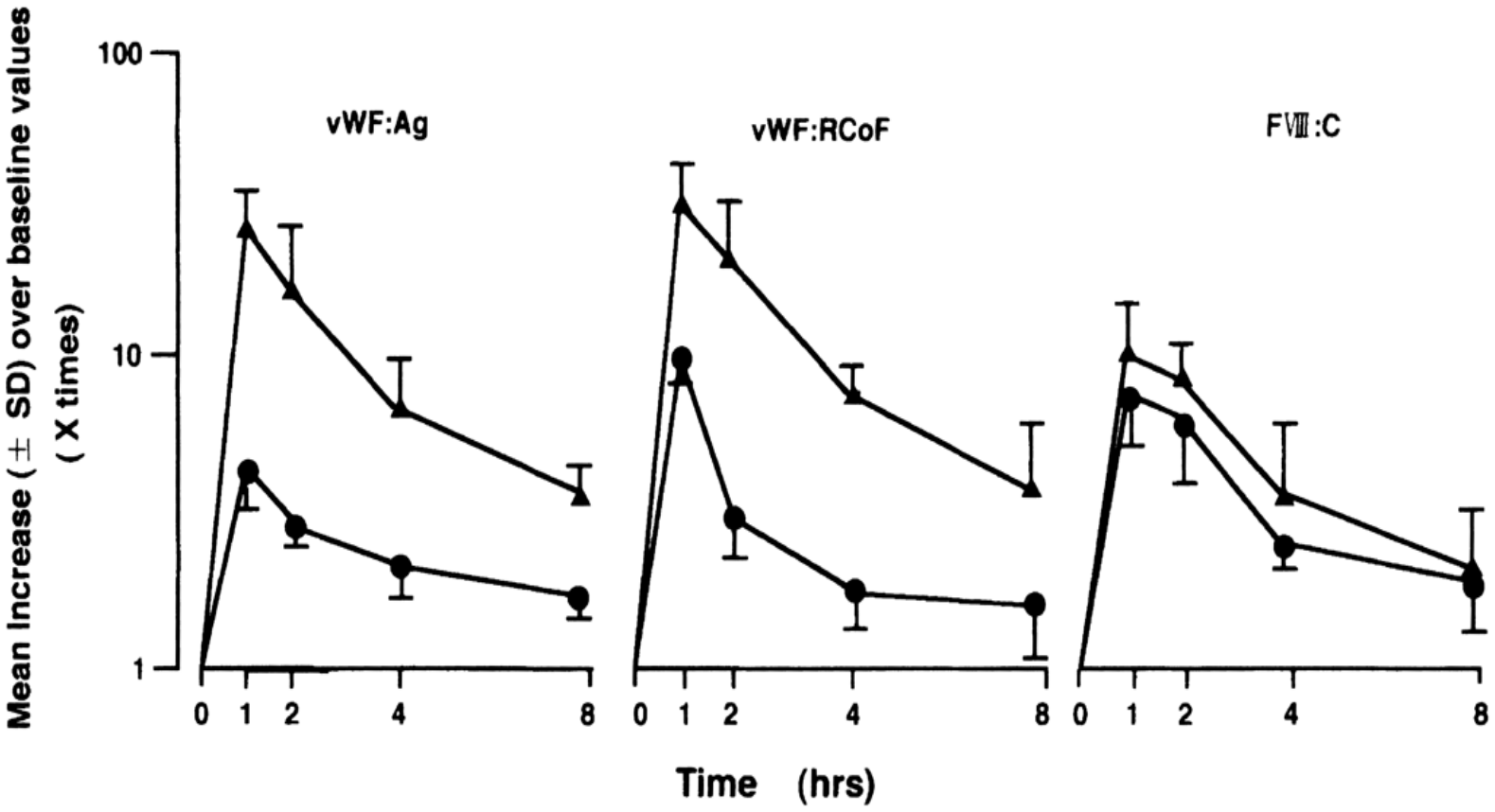
Acquired VW Syndrome
Aims of Treatment

- ***Treat the Underlying Disorder:***
  CHT, RT or Surgery
- ***Management of Acute Bleeding***

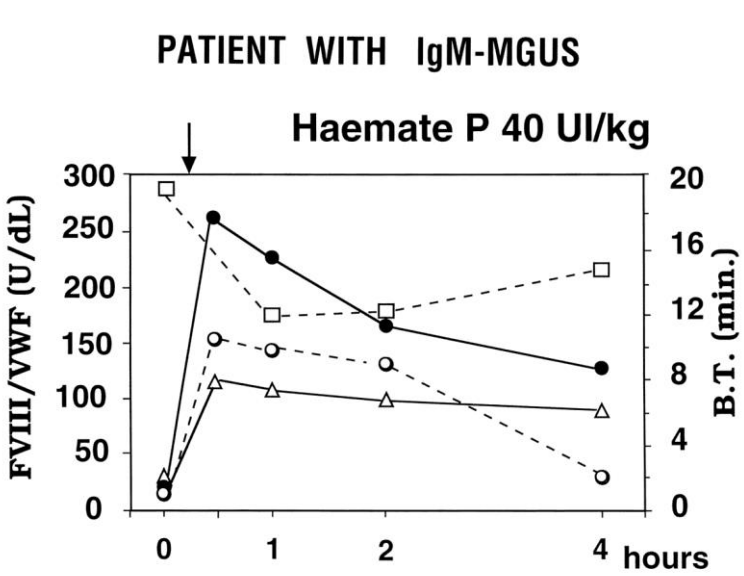
Therapeutic Options in AVWS According to Underlying Disorder

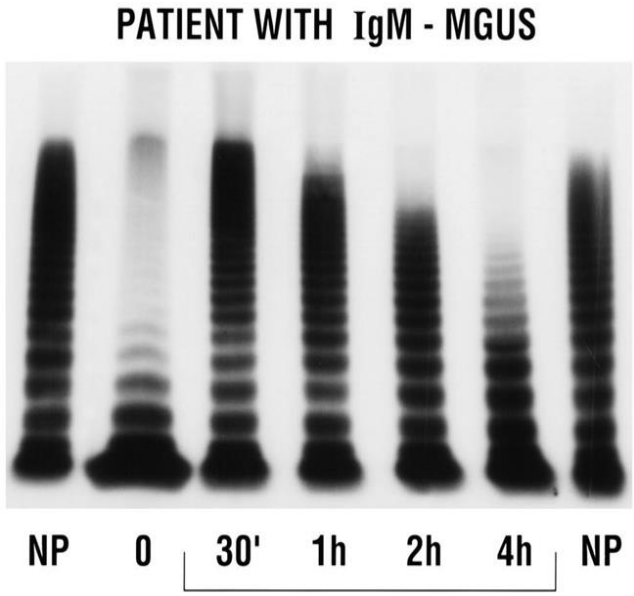
Underlying disorder	Causal treatment	Additional treatment options
Autoimmune disorders		**IVIG (only IgG-MGUS or anti-VWF IgG), plasmapheresis or immunoadsorption, antifibrinolytics, VWF-containing concentrate, rFVIIa**
Systemic lupus erythematosus	Steroids, cyclophosphamide	
Lymphoproliferative disorders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

Biological Response to DDAVP in Inherited VWD *versus* AVWS



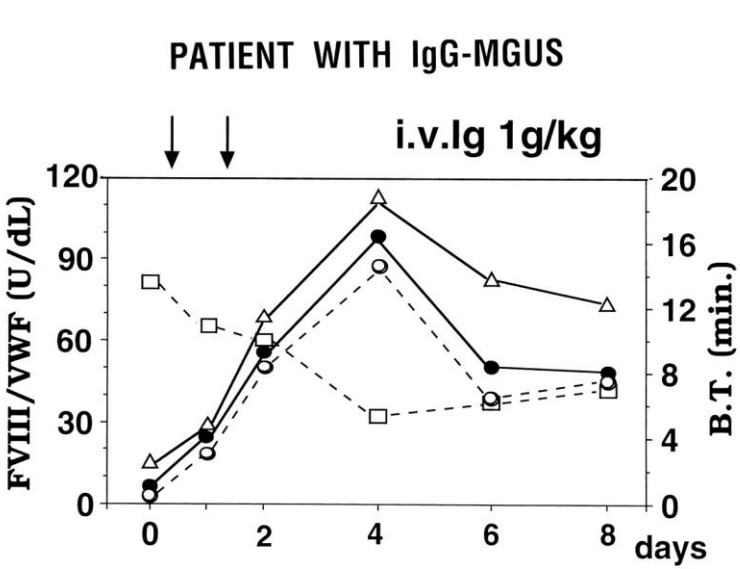
VWF/FVIII Concentrates in AVWS Associated with IGM-MGUS

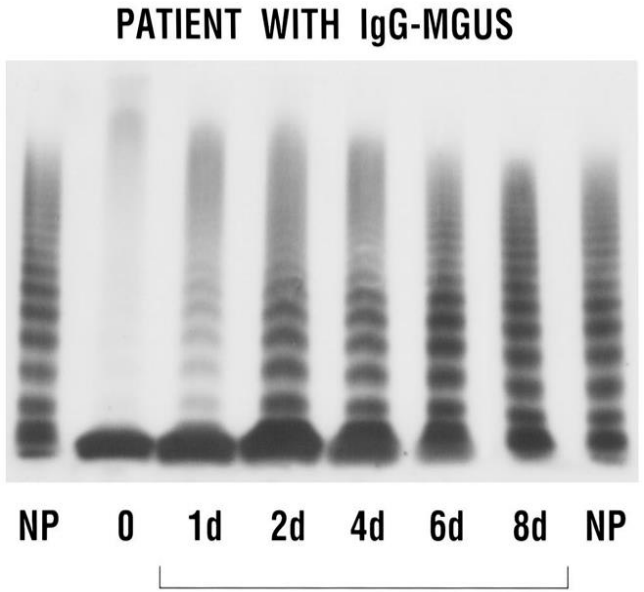




Federici AB et al, Blood 1998

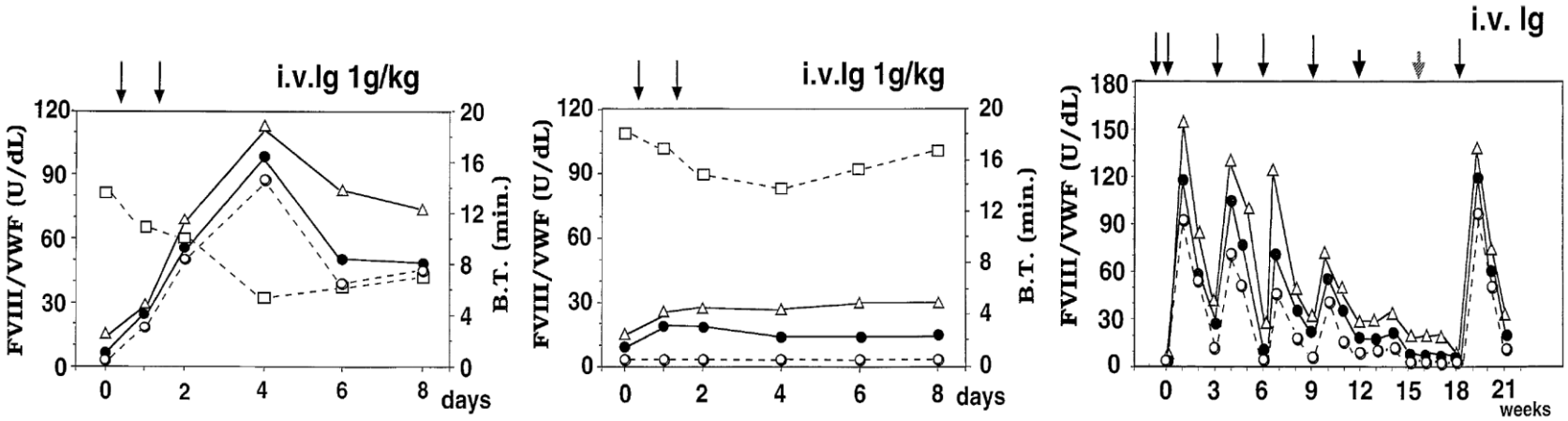
High Dose IV Immunoglobulin in AVWS Associated with IGG-MGUS





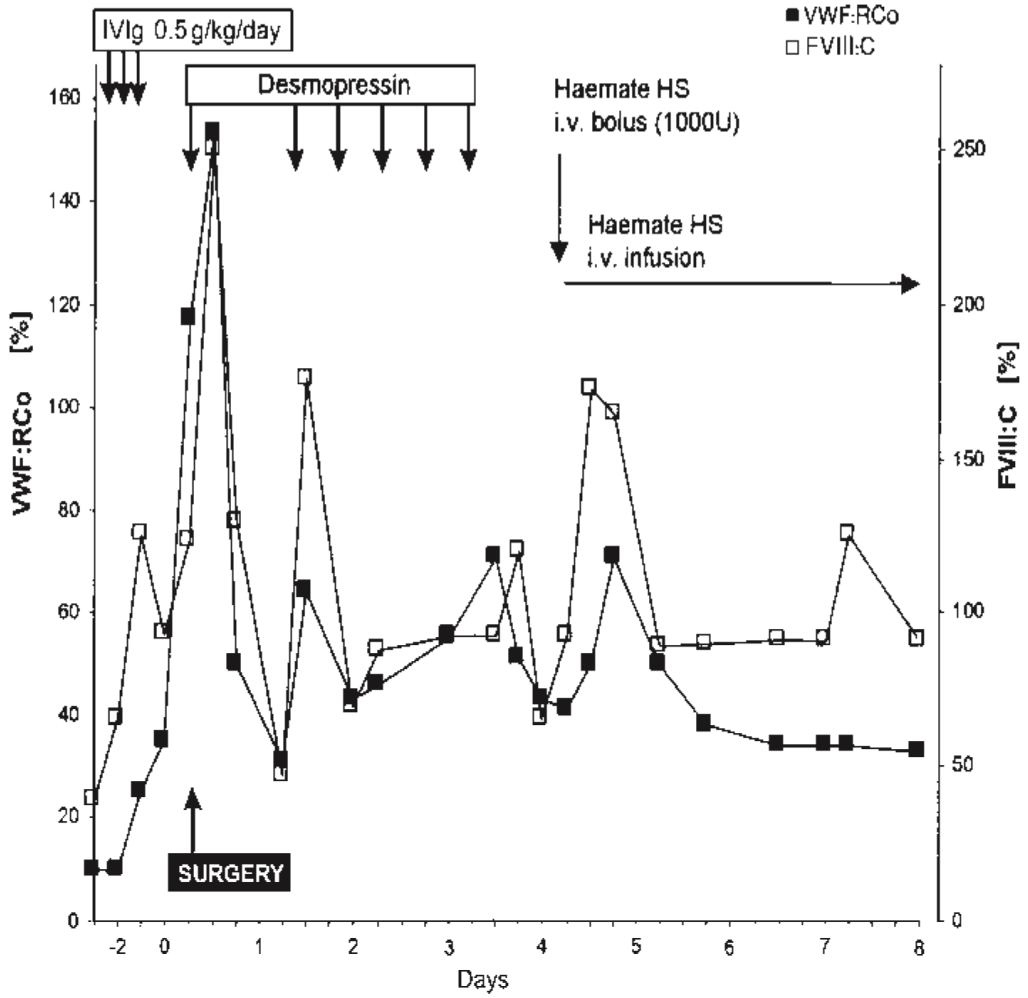
Federici AB et al, Blood 1998

High Dose IV Immunoglobulin: not Always Effective in AVWS



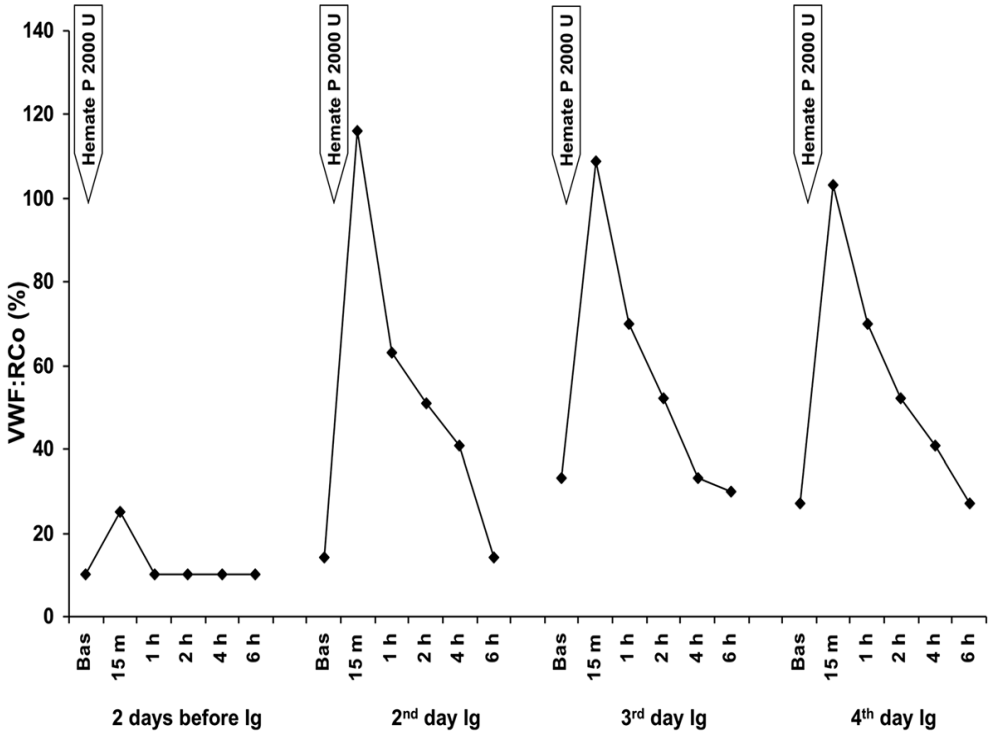
Federici AB et al, Blood 1998

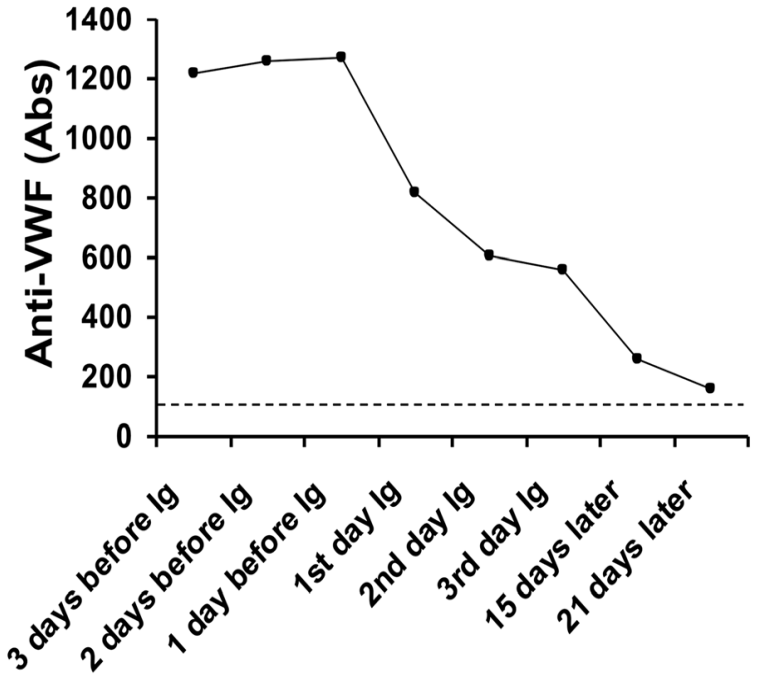
High Dose IV IG + DDAVP or Concentrates in AVWS with Urgent Bleeds/Surgery



Michiels JJ et al, Semin Thromb Hemost 2006

High Dose IV IG + VWF Concentrates in Acute Patients with AVWS





Cugno M et al, Exp Hematol Oncol 2014

Recombinant FVIIa in AVWS
Unresponsive to Standard Drugs

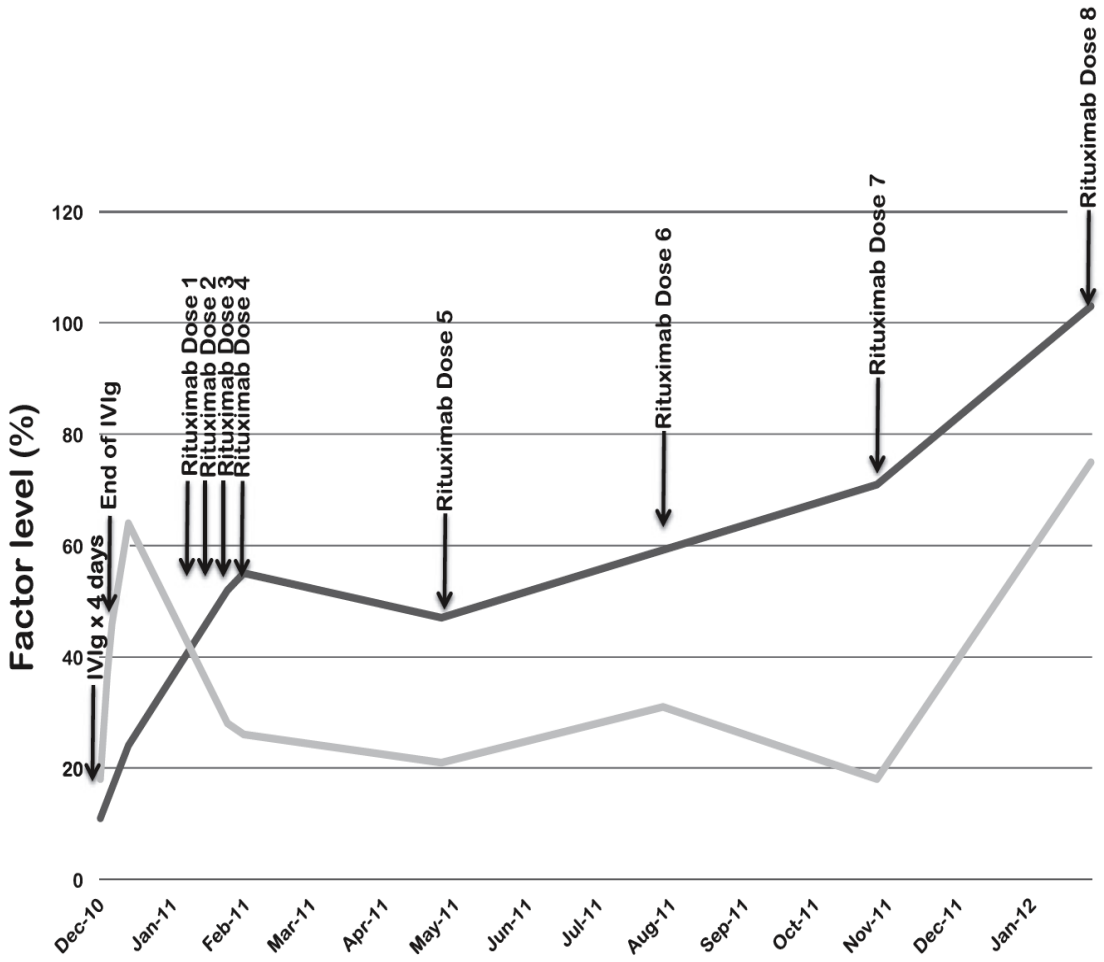
Successful *treatment with rFVIIa* in a patient with AVWS associated with MGUS and severe bleeding resistant to standard therapy:

90 ug/kg (bolus) + 17.5 ug/Kg/h for 6 days of rFVIIa

Friederich PW et al, Am J Hematol 2001

High Dose IV IG + RETUXIMAB

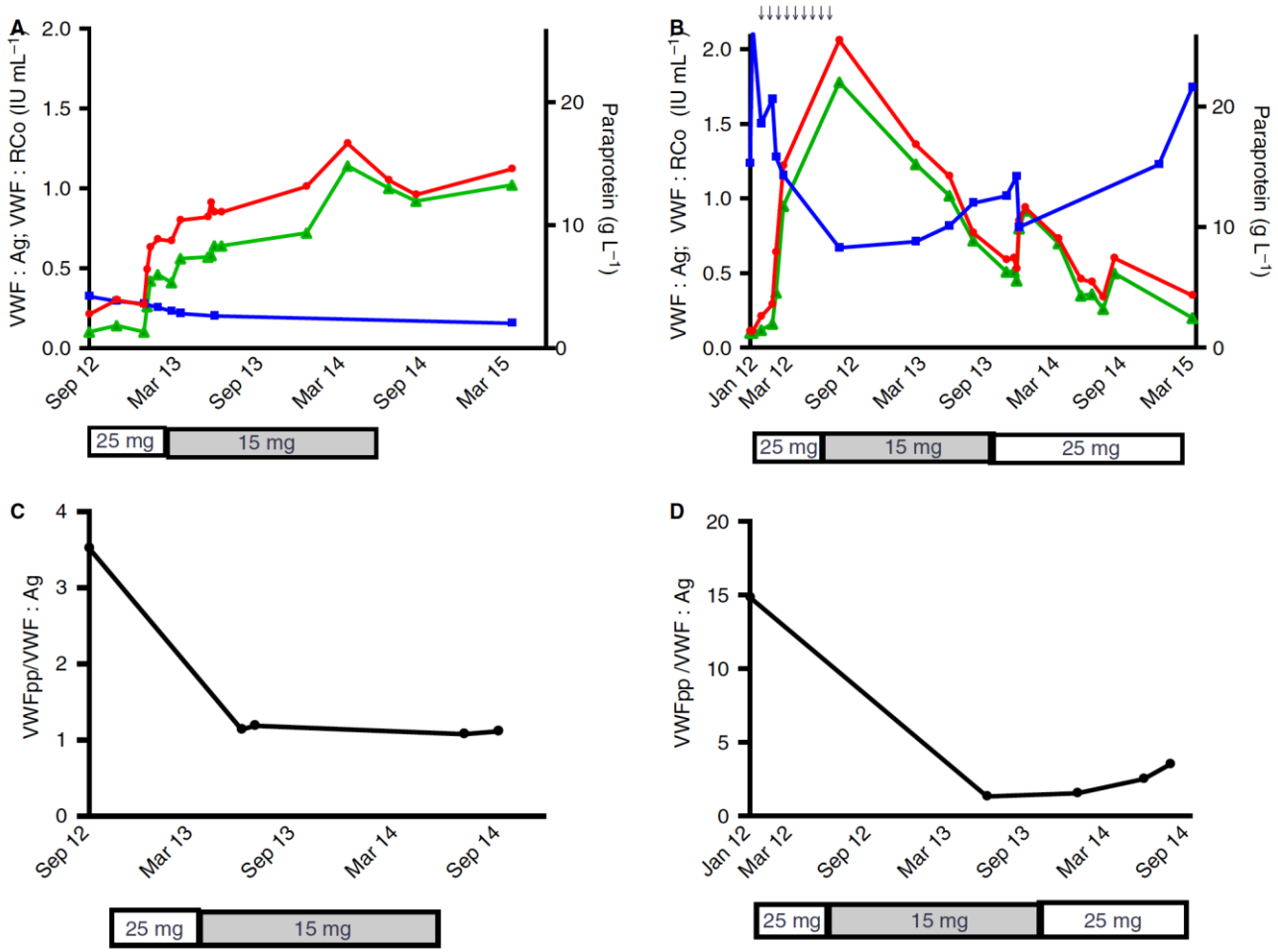
Case Report



Kanakry JA & Gladstone DE, Transfusion 2013

Lenalidomide as a novel treatment for refractory acquired von Willebrand syndrome associated with monoclonal gammopathy

M. LAVIN,*† T. M. BROPHY,† O. RAWLEY,† J. M. O'SULLIVAN,† P. J. HAYDEN,‡ P. V. BROWNE,‡ K. RYAN,* N. O'CONNELL* and J. S. O'DONNELL*†



J Thromb Haemost. 2016;14:1200-5.

Management of AVWS in 2017
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 number of patients with centralized diagnosis of AVWS to assess specific therapies according to the actual mechanisms causing AVWS

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INTERNATIONAL CONFERENCE

ROME, ITALY | 15/17 SEPTEMBER **2017**

SCIENTIFIC COMMITTEE

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