Medizinische Hochschule Hannover

Acquired Hemostasis Disorders

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Disclosures

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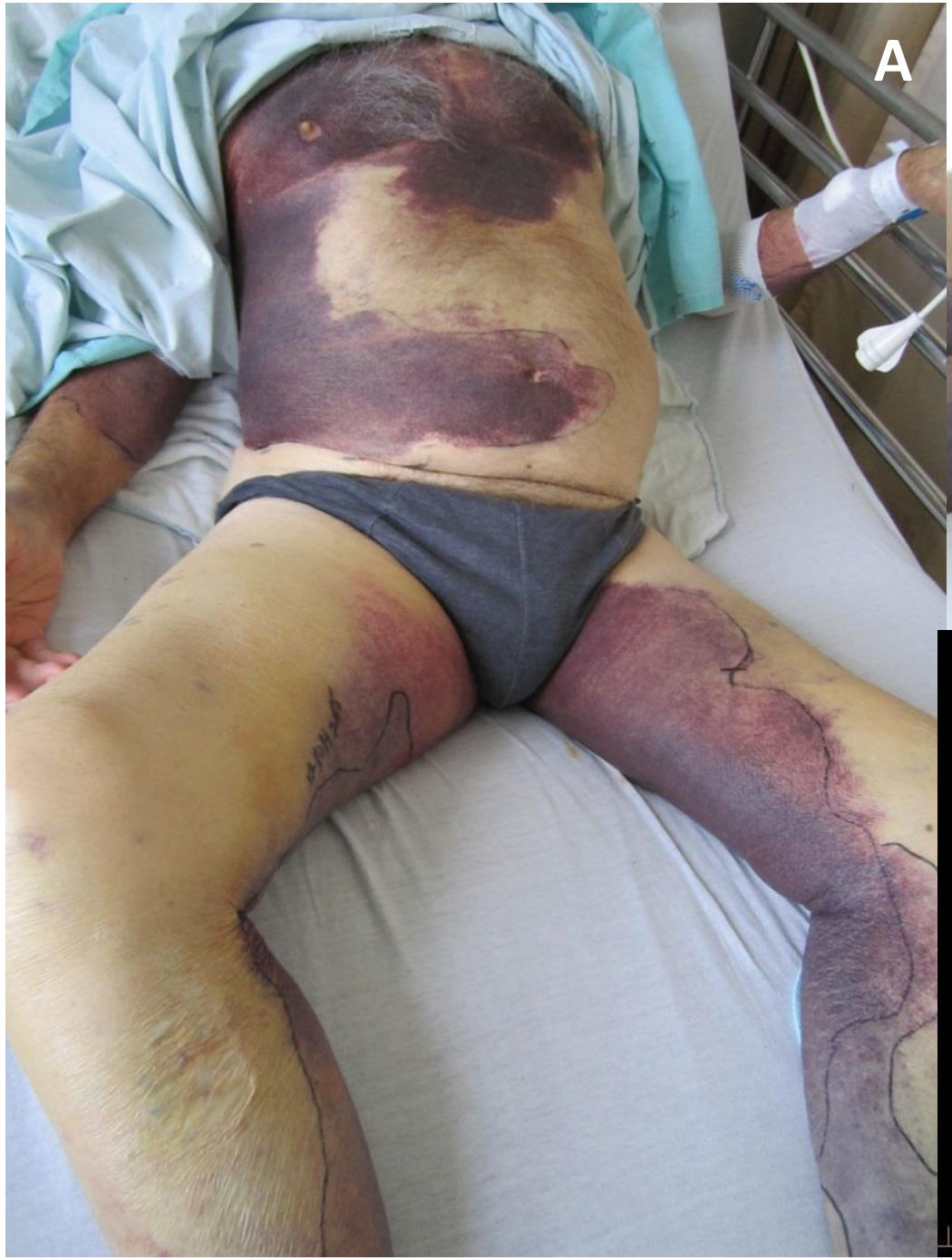
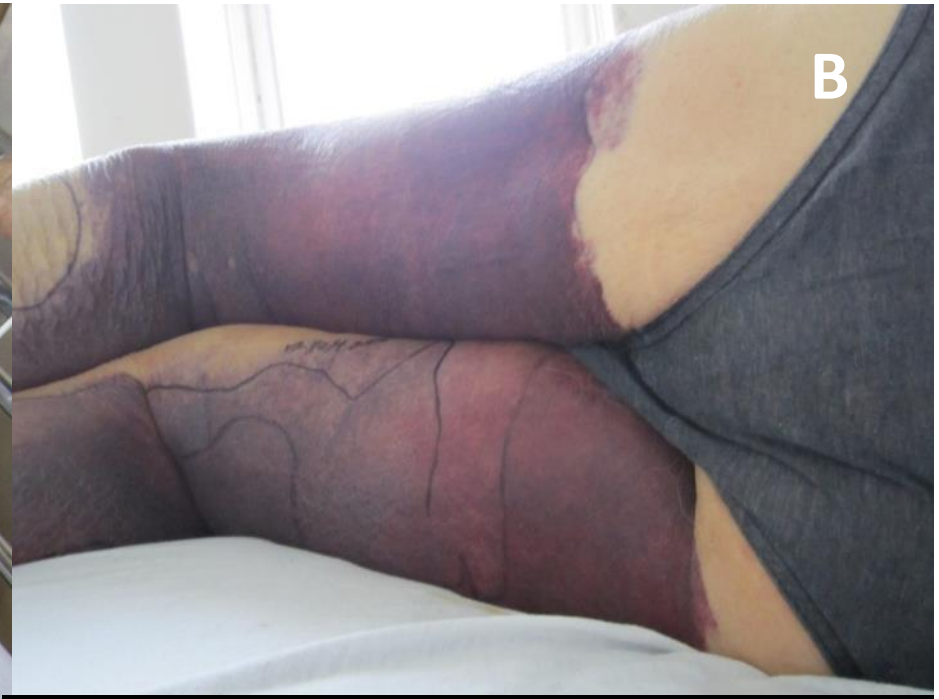
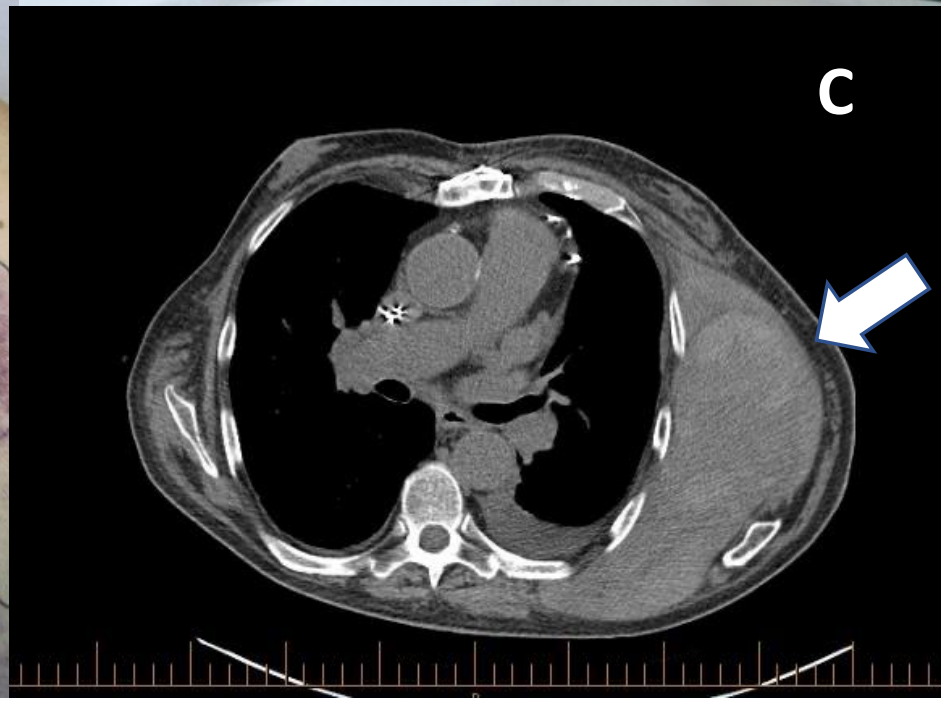
Bayer, Biotest, Novo Nordisk, Octapharma, Pfizer, Roche, Takeda, SOBI

Lectures and consultancy

Bayer, Biotest, Chugai, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Takeda, SOBI







St. Louis , JM:
Blood 2020
136 (3): 262-264

CBC

Severe thrombocytopenia?

Basic Coag Lab (PT, APTT, Fib)

Isolated APTT prolongation?

- Factor VIII
- Factor IX
- Factor XI

Isolated PT prolongation?

- Factor VII

Combined prolongation?

- Factors of “common” pathway
- Vitamin K deficiency / antagonist
- Disseminated intravascular coagulation

Acquired deficiencies in Factor VIII

- Acquired haemophilia A (AHA)

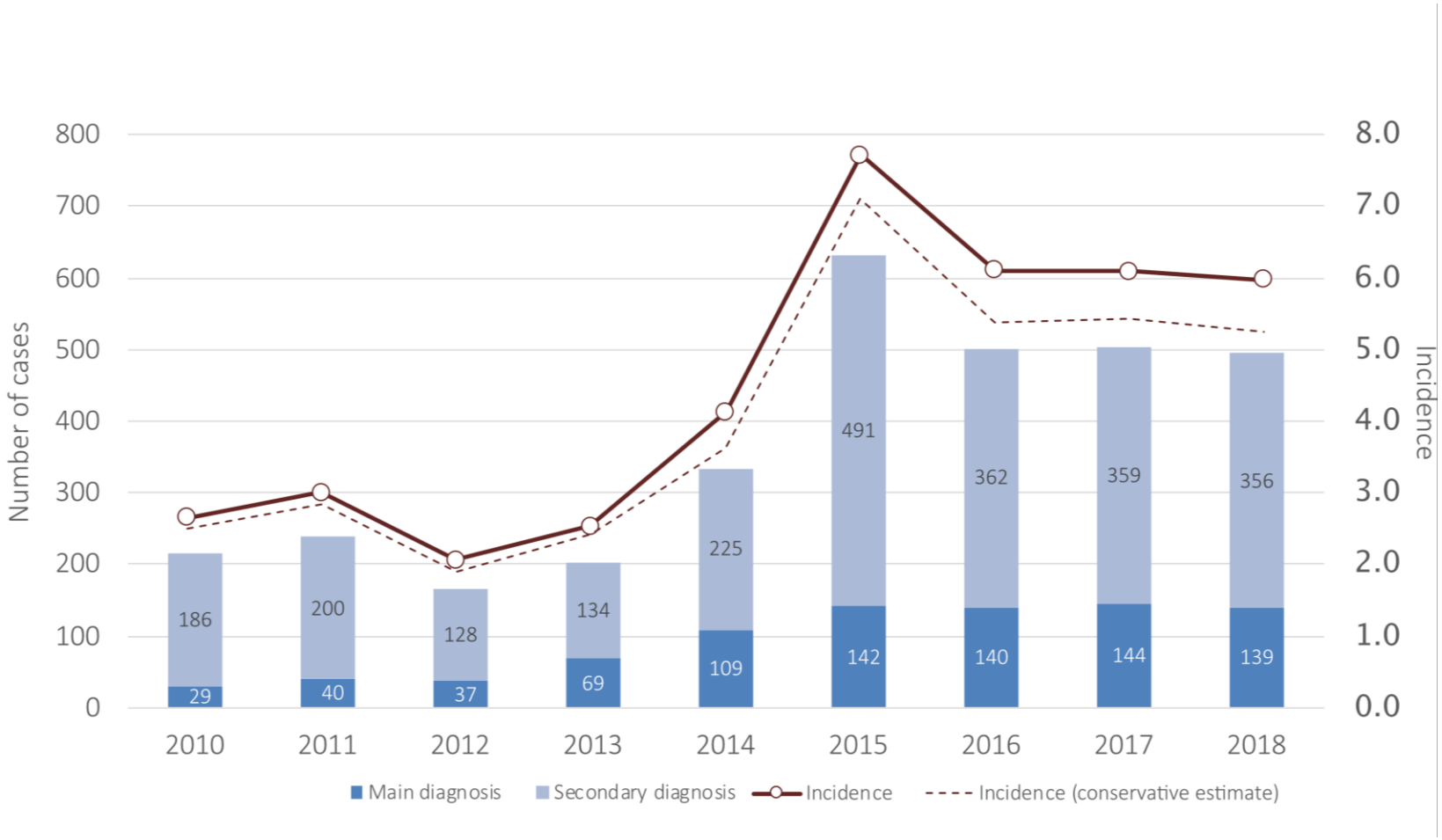
- Acquired von Willebrand syndrome
- Lupus anticoagulant

Inzidenz der erworbenen Hämophilie

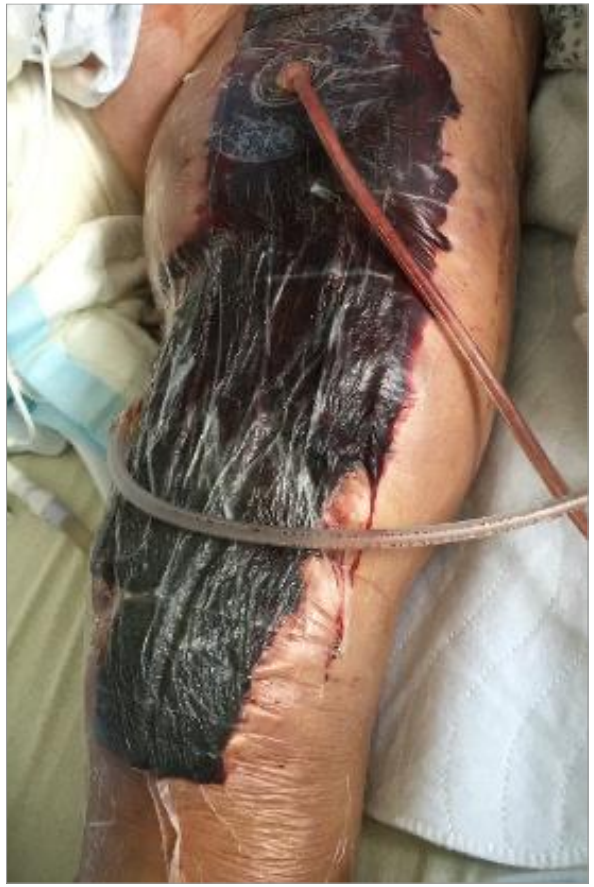
Fälle pro 1 Mio. Einwohner pro Jahr

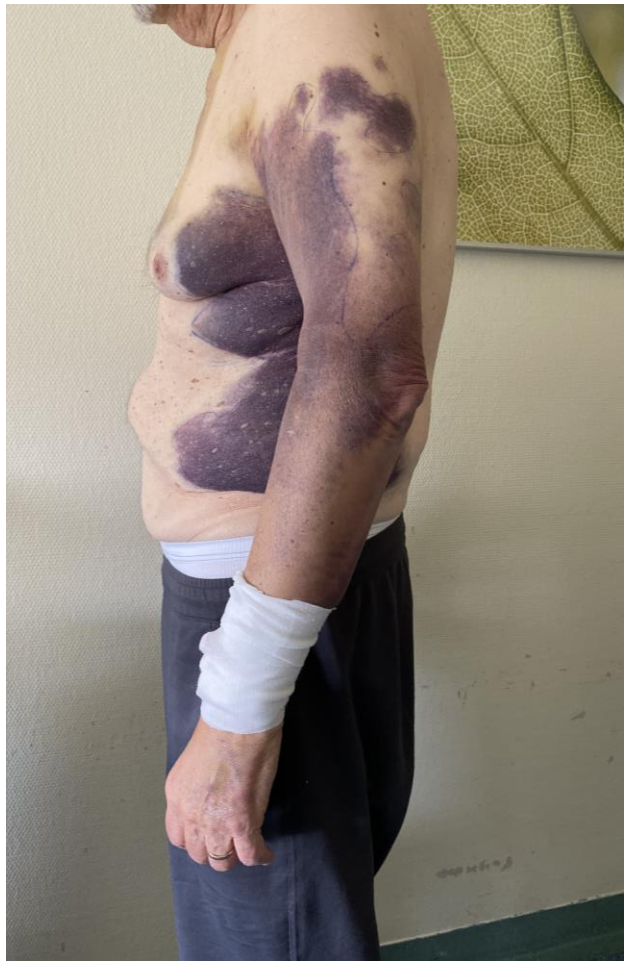
Deutschland

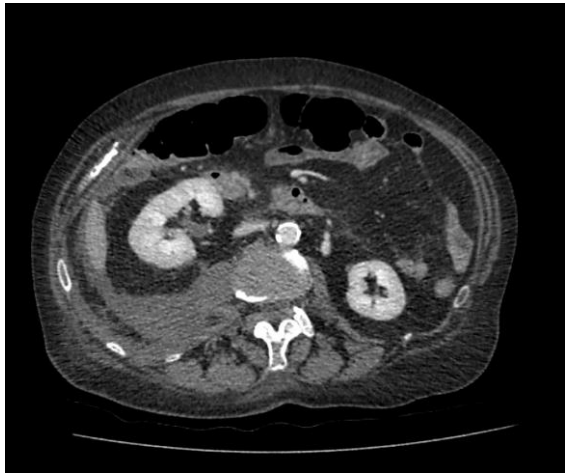
Fälle pro 1 Mio. Einwohner pro Jahr

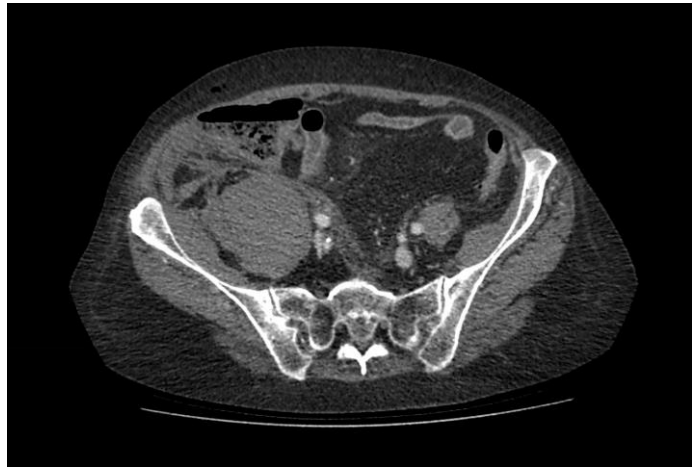


Tiede & Wahler *Haemophilia* 2021; 27 (4): e466-e468

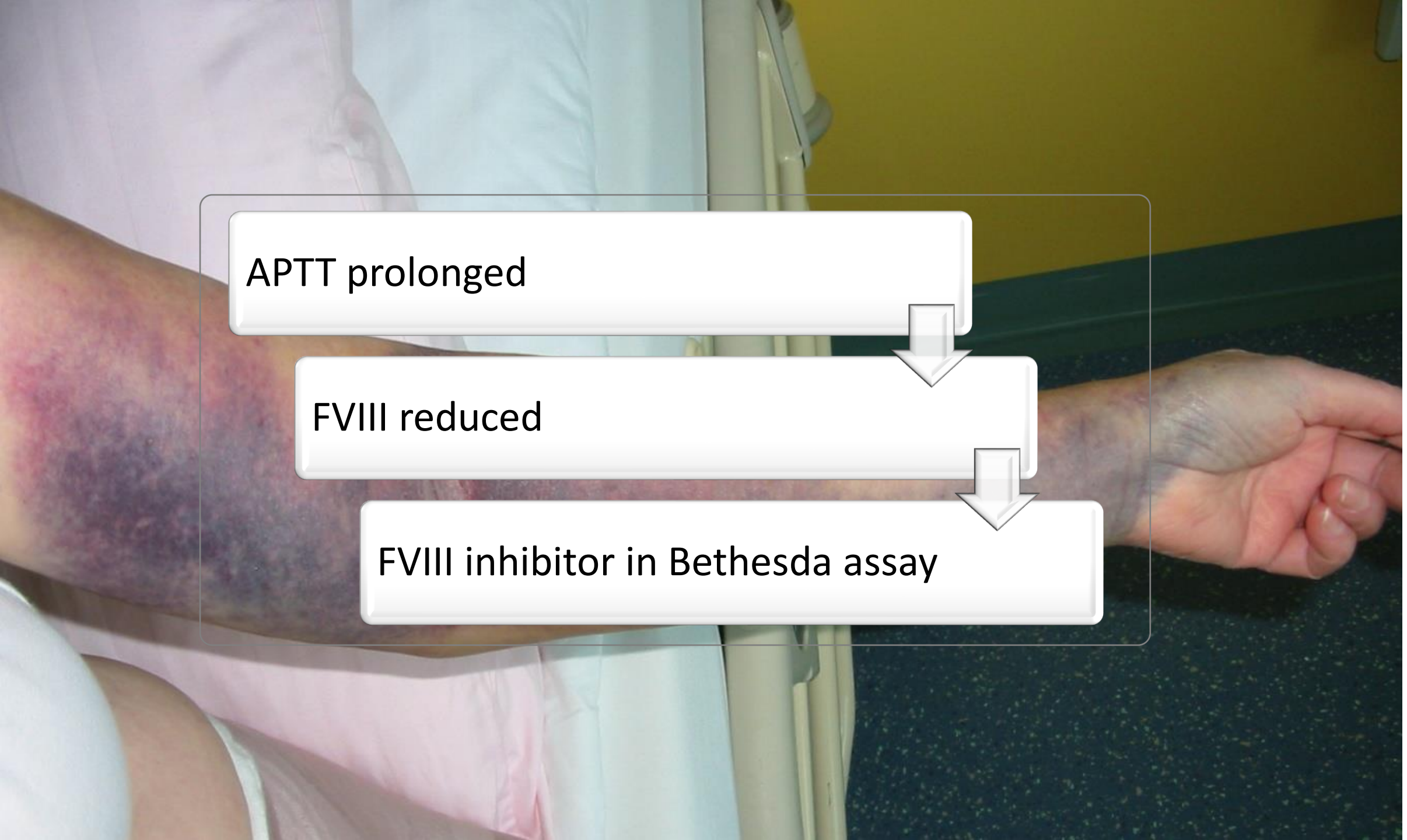








Tiede et al. *J Thromb Haemost* 2021;19:637–644


APTT prolonged
FVIII reduced
FVIII inhibitor in Bethesda assay

GTH Study Data

Thematik	Referenz
Outcomes and prognostic factors	Blood 2015; 125: 1091-1097
Anti-FVIII immunoglobulin and subclasses	Blood 2016; 127: 2289-97
Diagnostic use of ELISA	J Thromb Haemost 2016; 14: 940-947
Antibodies against rpFVIII (susoctocog alfa)	J Thromb Haemost 2020; 18: 36-43
Risk of bleeding and hemostatic therapy	Blood 2020; 136: 279-287

GUIDELINE ARTICLE

International recommendations on the diagnosis and treatment of acquired hemophilia A

Andreas Tiede,[1] Peter Collins,[2] Paul Knoebl,[3] Jerome Teitel,[4] Craig Kessler,[5] Midori Shima,[6] Giovanni Di Minno,[7] Roseline d'Oiron,[8] Peter Salaj,[9] Victor Jiménez-Yuste,[10] Angela Huth-Kühne[11] and Paul Giangrande[12]

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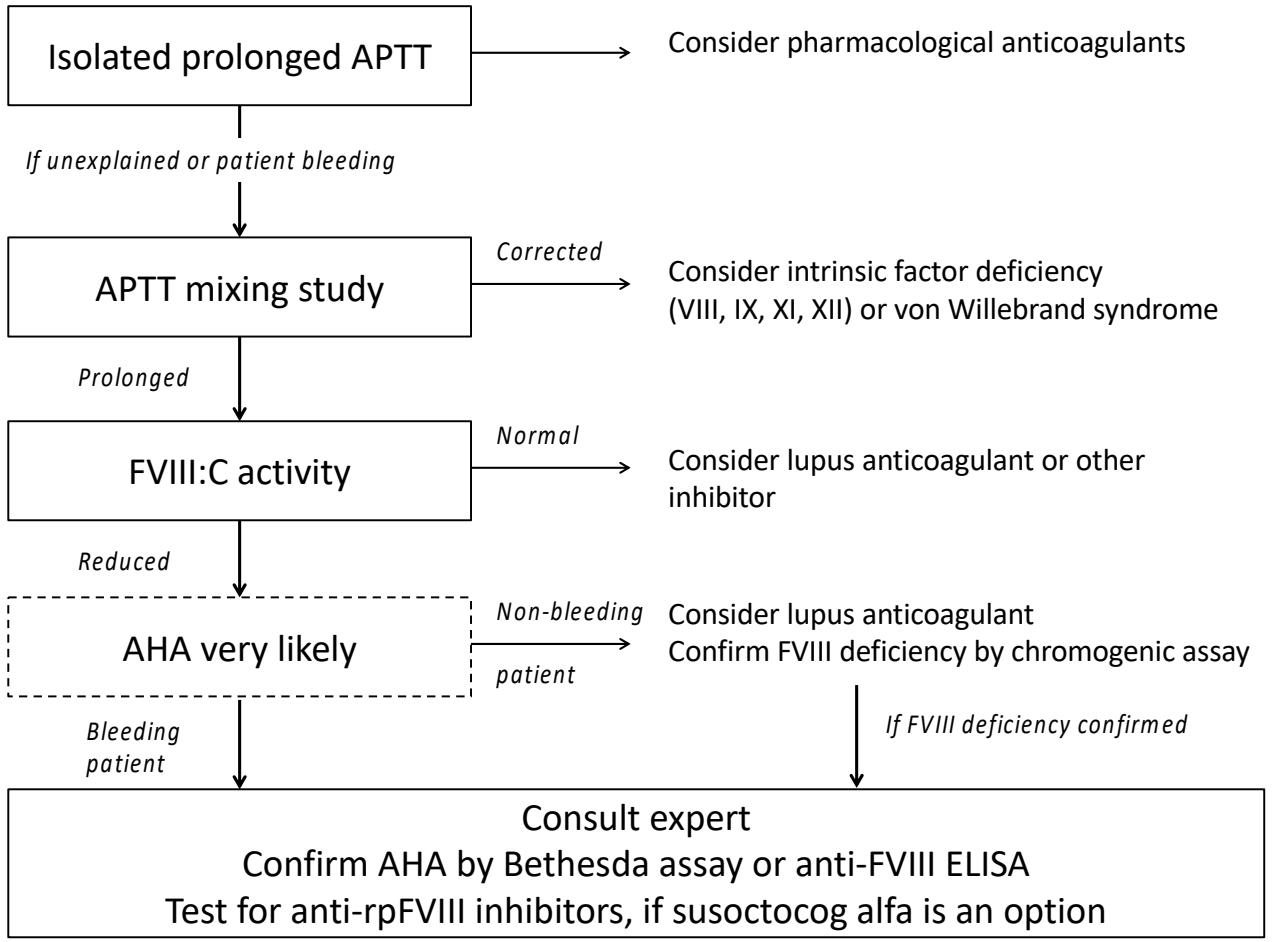
Ferrata Storti Foundation

Haematologica 2020
Volume 105(7):1791-1801

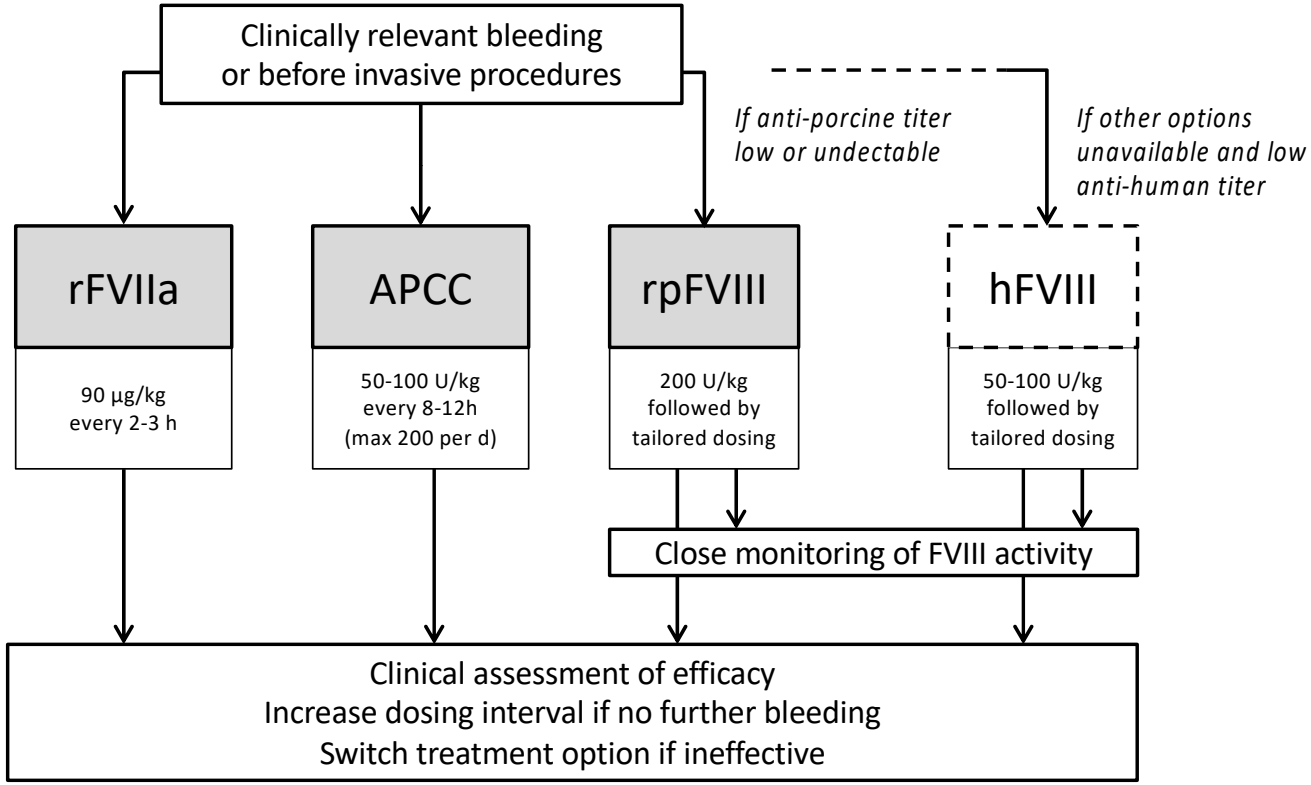
Diagnosis



Tiede et al. Haematologica 2020; 105: 1791-1801

Bleed Management

Treatment of bleeds



Tiede et al. Haematologica 2020; 105: 1791-1801

First and second line

Agent	Recommended starting dose and interval	Laboratory monitoring	Hemostatic effectiveness	Thromboembolic risk
Bypassing agents				
Recombinant factor VIIa (eptacog alfa activated, NovoSeven)	90 μg/kg q 2–3 h	None	Systematic review: 84–96%[12] Registries: EACH2 91%[7]	Systematic review: 0–5%[12] Registries: EACH2 2.9%[7]
Activated prothrombin complex concentrate (FEIBA)	50–100 U/kg q 8–12 h[a]	None	Systematic review: not available Registries: EACH2 93%,[7] US 76–100%[30]	Systematic review: not available Registries: EACH2 4.8%[7]
Recombinant porcine FVIII				
Susoctocog alfa (Obizur)	200 U/kg q 4–12 h	FVIII one-stage clot assay • 30 min and 3 h after first dose • Before and 30 min after subsequent doses	Systematic review: not available Clinical trial: 100% effective or partially effective at 24 h; 86% control of qualifying bleed[14]	Systematic review: not available Clinical trial: 0%[14]

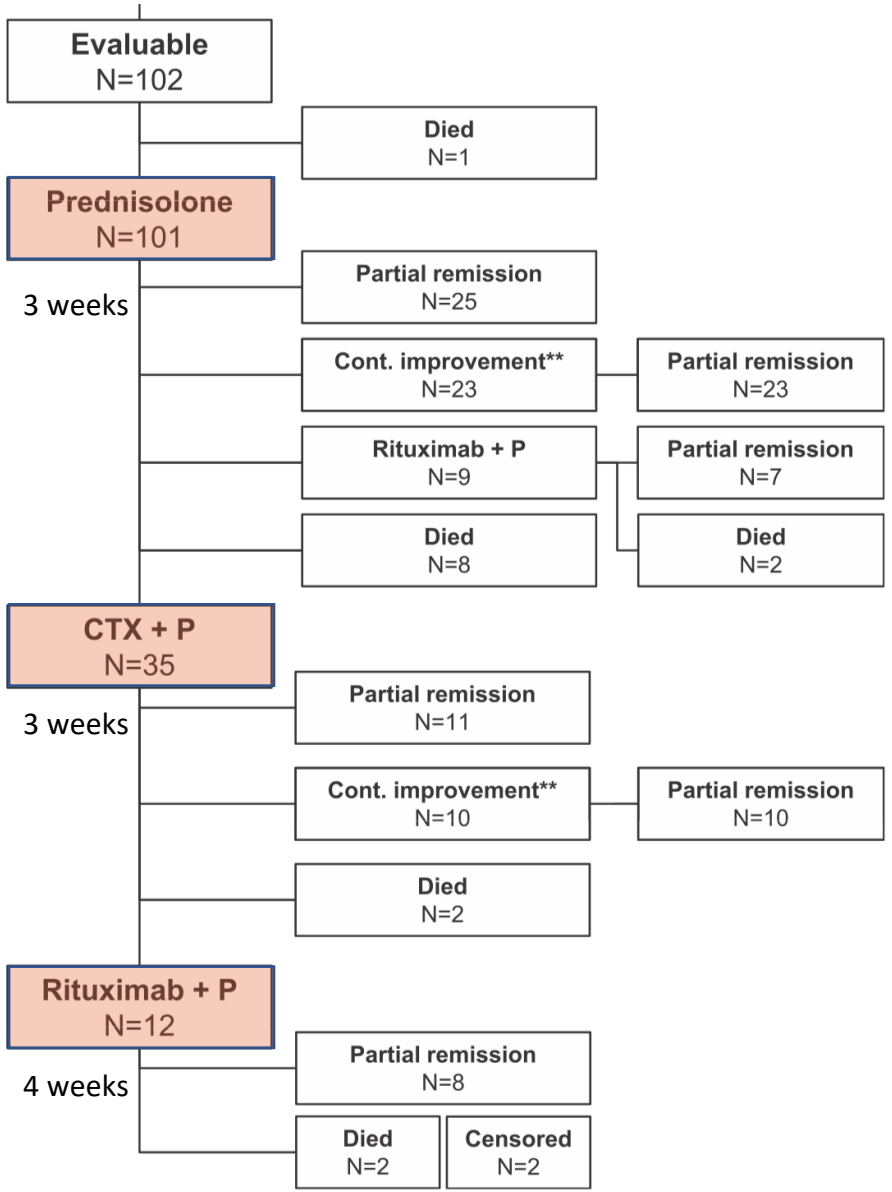
Abbreviations: AHA, acquired hemophilia A; EACH2, The European Acquired Hemophilia Registry.
[a]Maximum daily dose of 200 U/kg body weight must not be exceeded.

Immunosuppressive therapy

- *Huth-Kühne et al. Haematologica 2009; 94: 566-575*
- *Tiede et al. Haematologica 2020; 105: 1791-1801*

2009 Recommendations	2020 Recommendations	GRADE
We recommend that all patients diagnosed with AHA receive immunosuppressive therapy immediately following diagnosis.	We recommend IST in all patients with AHA. However, particular caution should be exercised in frail patients.	1B

GTH 2010 Protocol



Prognostic factors

Table 4. Predictors of remission and survival: multivariate analysis[1]

Baseline variable	PR	CR	OS
FVIII activity <1 IU/dL	0.52 (0.33-0.81)**	0.49 (0.29-0.85)*	2.40 (1.10-5.22)*
Inhibitor concentration >20 BU/mL	0.77 (0.49-1.21)	0.75 (0.43-1.29)	1.20 (0.54-2.67)
Female gender	1.22 (0.77-1.91)	1.30 (0.76-2.24)	0.58 (0.26-1.31)
Age >74 y	0.94 (0.58-1.50)	0.76 (0.43-1.32)	1.76 (0.82-3.78)
Underlying disorder			
Autoimmunity	1.32 (0.77-2.28)	0.88 (0.45-1.72)	1.02 (0.36-2.84)
Malignancy	0.58 (0.28-1.21)	0.62 (0.27-1.44)	2.91 (1.12-7.52)*
Pregnancy	0.61 (0.23-1.65)	0.74 (0.27-2.04)	—
WHO-PS >2	0.76 (0.48-1.21)	0.39 (0.21-0.72)**	3.38 (1.55-7.37)**

Data are presented as adjusted HR (CI).
*$P < .05$.
**$P < .01$.

Adverse prognostic factors towards remission and survival:

Low factor VIII[1]
High inhibitor titer[2]

Malignancy[1]
Poor WHO-OS[1]
Age[2]

Anti-FVIII IgA[3]

1. Tiede et al. Blood 2015; 125: 1091-1097
2. Mingott-Castellano et al. Blood Adv 2021; 5: 3821-3829
3. Tiede et al. Blood 2016; 127: 2289-2297

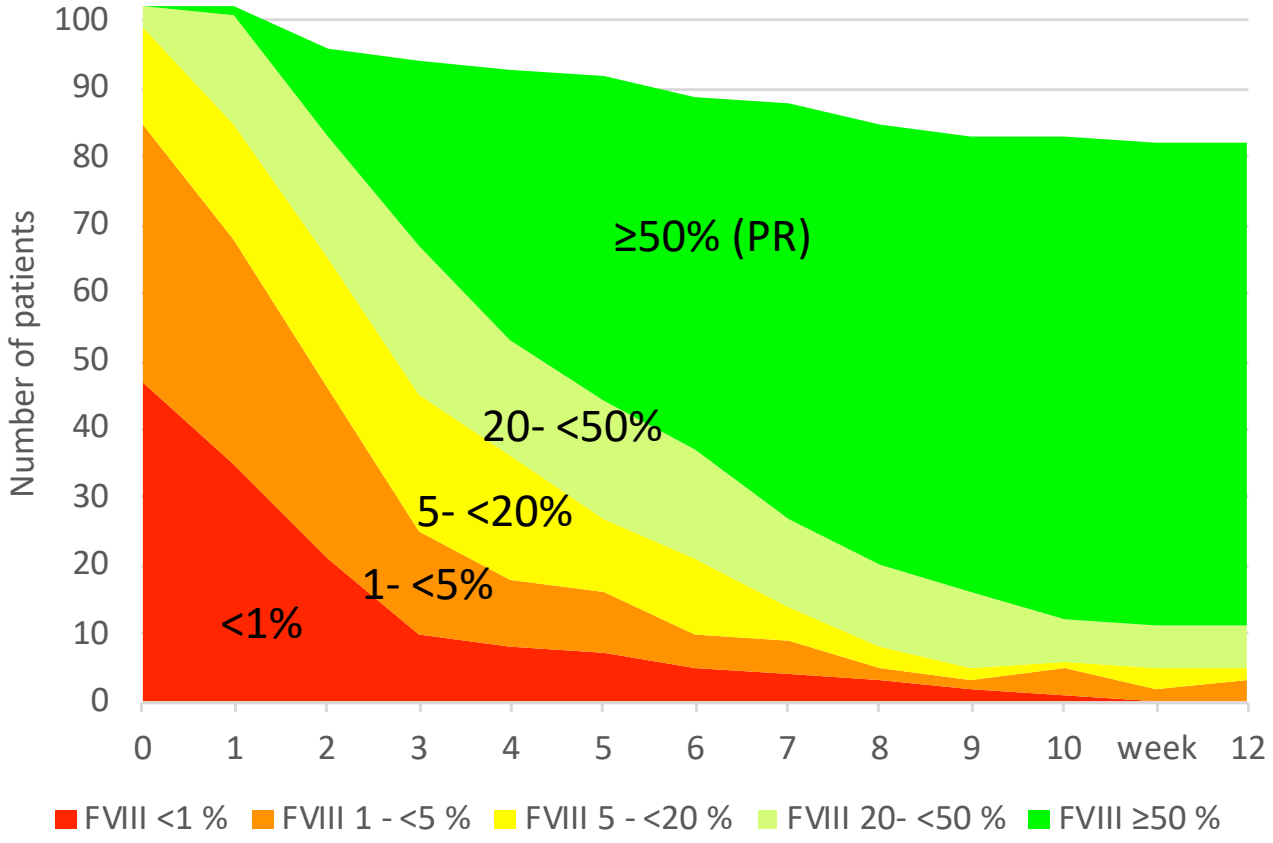
Risk-stratific immunosuppression

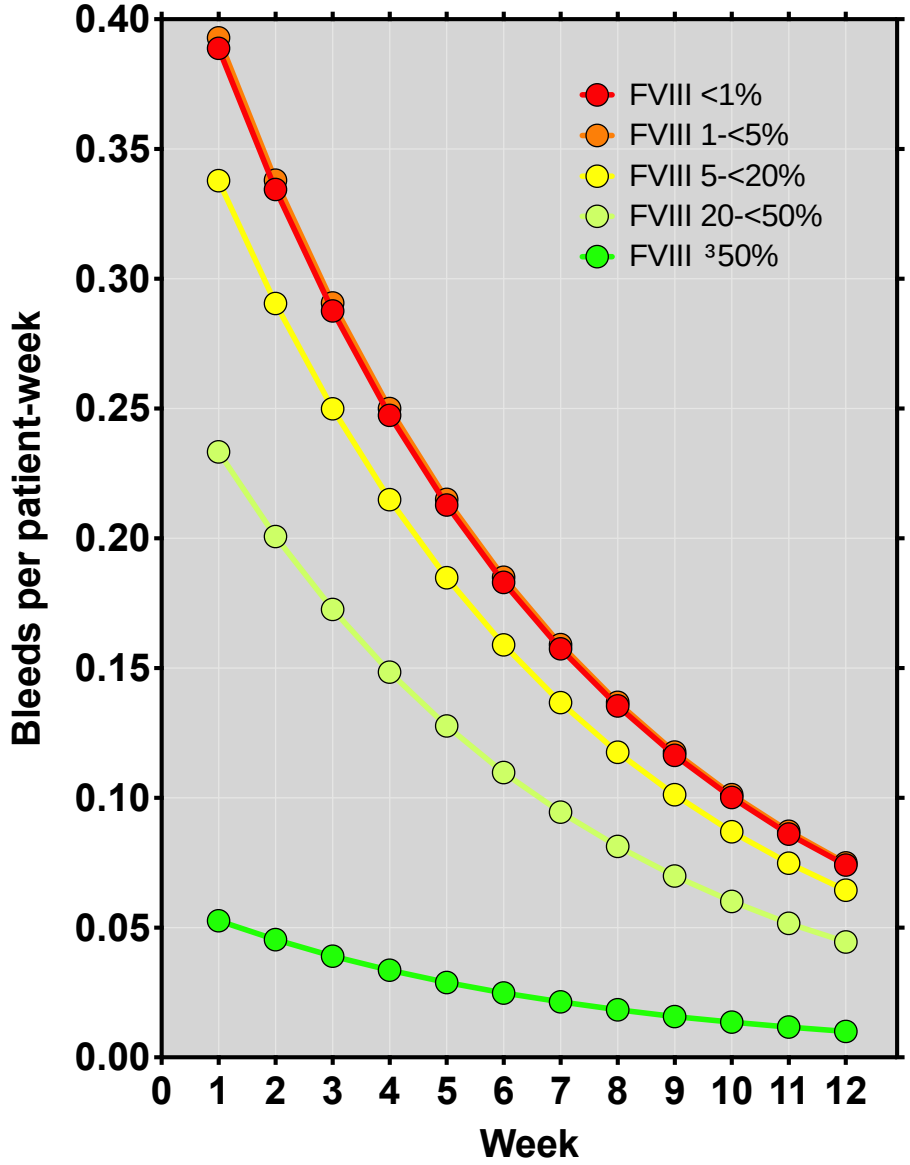
2020 Recommendation

FVIII ≥1% and ≤20 BU/ml	FVIII <1% or >20 BU/ml
Steroids alone for 3-4 weeks	Steroids + CTX or rituximab for 3-4 weeks
Add CTX or rituximab if not responding	Add CTX or rituximab if not responding

Tiede et al. Haematologica 2020; 105: 1791-1801

Prophylaxis of bleeds?





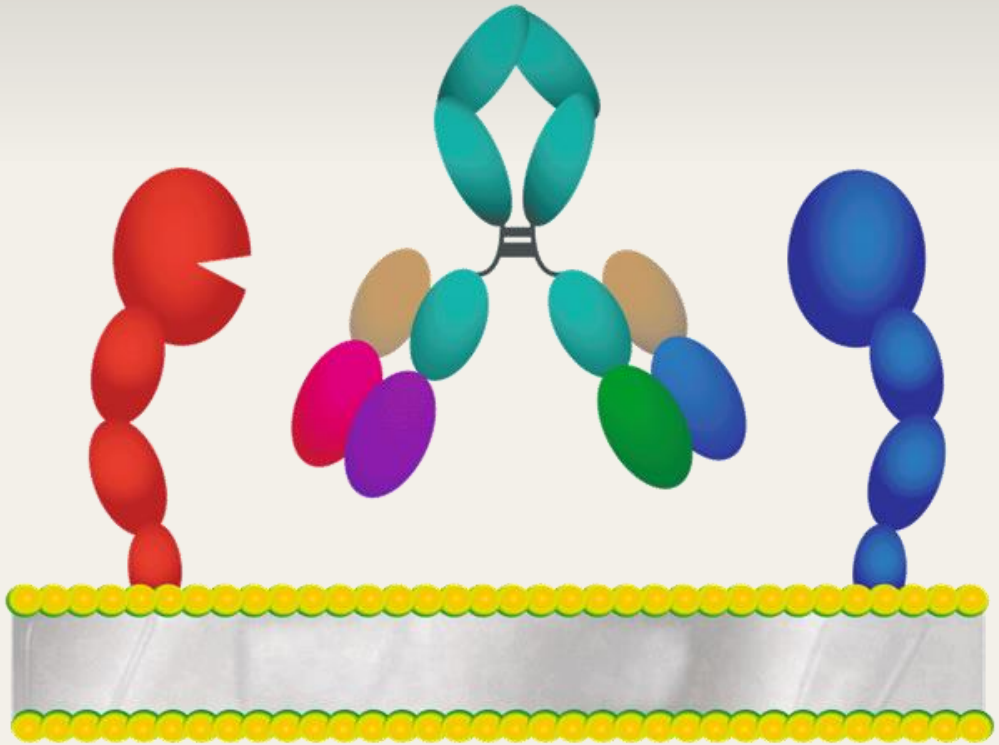
Holstein et al. BLOOD 2020; 136: 279-287

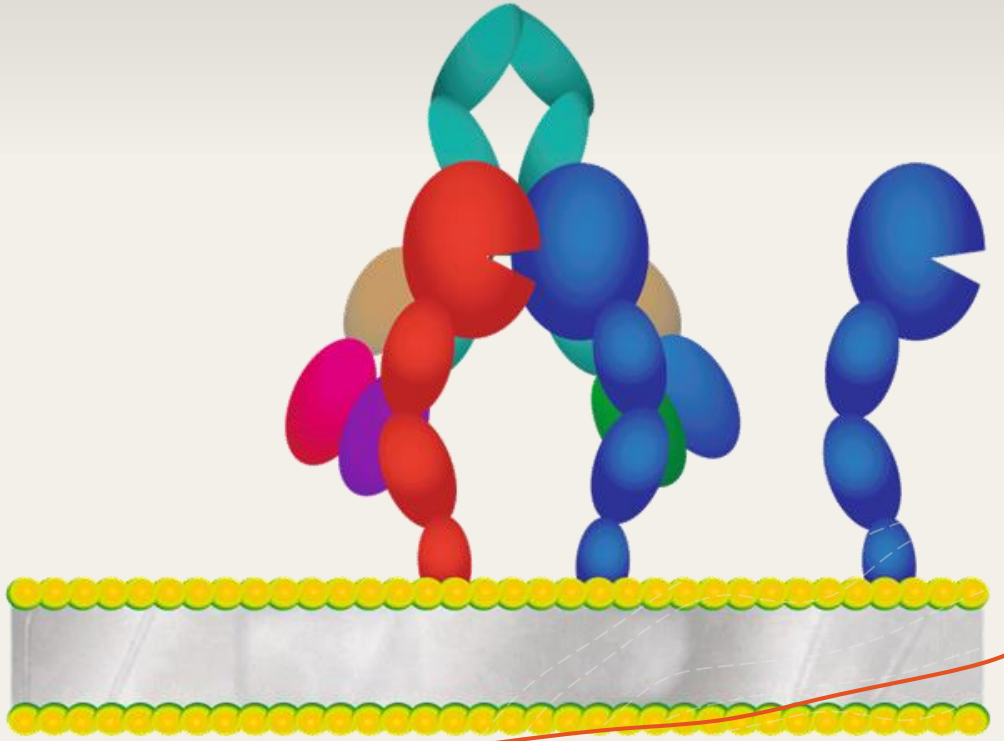
Survival and Causes of Death

	UK Study[1]	EACH2[2]	SACHA[3]	GTH[4]
N	134	331	82	102
Mean age	78	74	77	74
1year survival	55% (Steroid) 72% (Steroid+CTX)	72%	62%	68%
Fatal bleeding	9.1%	4.5%	3.5%	2.9%
Fatal IST complications	11%	4.2%	12%	16%
Fatal CV complications	n.r.	n.r.	7.3%	6%

1. Collins PW, et al. Blood 2007;109:1870-7
2. Knöbl et al. J Thromb Haemost 2012; 10: 622–31
3. Borg et al. Haemophilia 2013;19:564-70
4. Tiede et al. Blood 2015; 125(7):1091-7

Will emicizumab help to reduce the need for IST?





Kitazawa T et al. *Nature Medicine* 2012;18(10):1570

Published experience with emicizumab

First author, publication date	Patients Age, gender	Reason for emicizumab	Dosing of emicizumab	Efficacy	Safety
Möhnle 14/06/19	N=1 83 y, m	Severe bleeding	1x 3 mg/kg, 2x 1.5 mg/kg	Bleeding stopped, no bleeding	Died 36 d after last dose (unknown cause)
Dane 12/07/19	N=1 72 y, m	Prophylaxis for planned PCI	4x 3 mg/kg weekly, 5 months 1.5 mg/kg weekly	No bleeding	No AE
Al-Banaa 19/07/19	N=1 87 y, f	Prophylaxis	4x 3 mg/kg weekly, 2 months 1.5 mg/kg weekly	No bleeding	No AE
Hess 08/05/20	N=1 91 y, m	Recurrent bleeding	4x 3 mg/kg weekly, 6 months 1.5 mg/kg weekly	No bleeding	No AE
Knöbl 09/08/20	N=12 51-87 y (range), 6 f, 6 m	Various	1.7-3.5 mg/kg for 3-9 doses (range)	Initial bleeding stopped after median 3 d (range 2-15)	Minor stroke in 1 patient on concomitant rFVIIa, 1 patient died of peritonitis

Tiede et al. J Thromb Haemost 2021;19:637–644.

AHA-Emi Study

- Accelerated loading
- 12 weeks of emicizumab
- 24 weeks of follow-up
- No immunosuppressive treatment

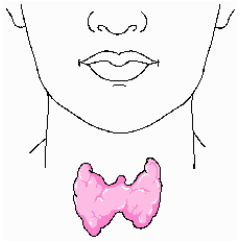
- Sponsor: GWT (Uni Dresden), Financier: Hoffmann La Roche

Acquired deficiencies in Factor VIII

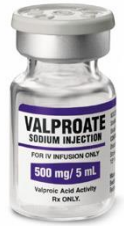
- Acquired haemophilia A (AHA)

- Acquired von Willebrand syndrome
- Lupus anticoagulant

// Pathogenesis

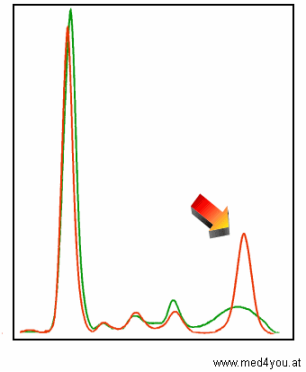


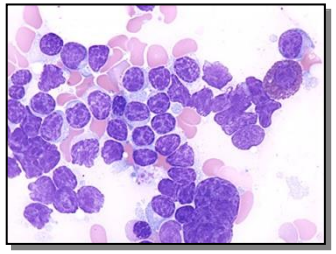
Hypothyroidism



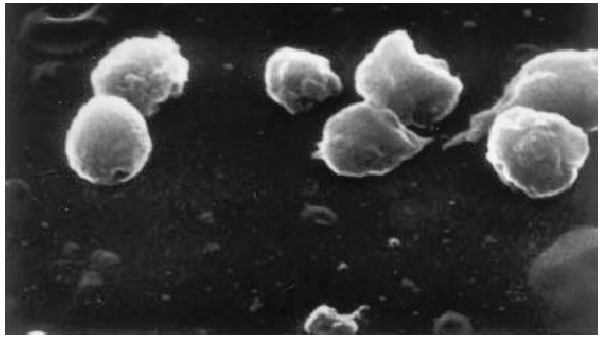
Drugs
(e.g. valproic acid)

Reduced synthesis



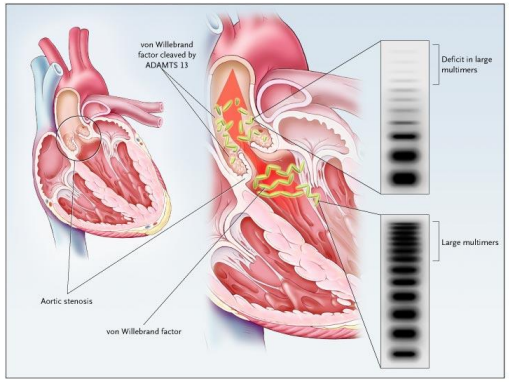


Paraproteins, inhibitors



Adsorption

Sadler JE, NEJM 2003; 349:323



Shear stress, proteolysis

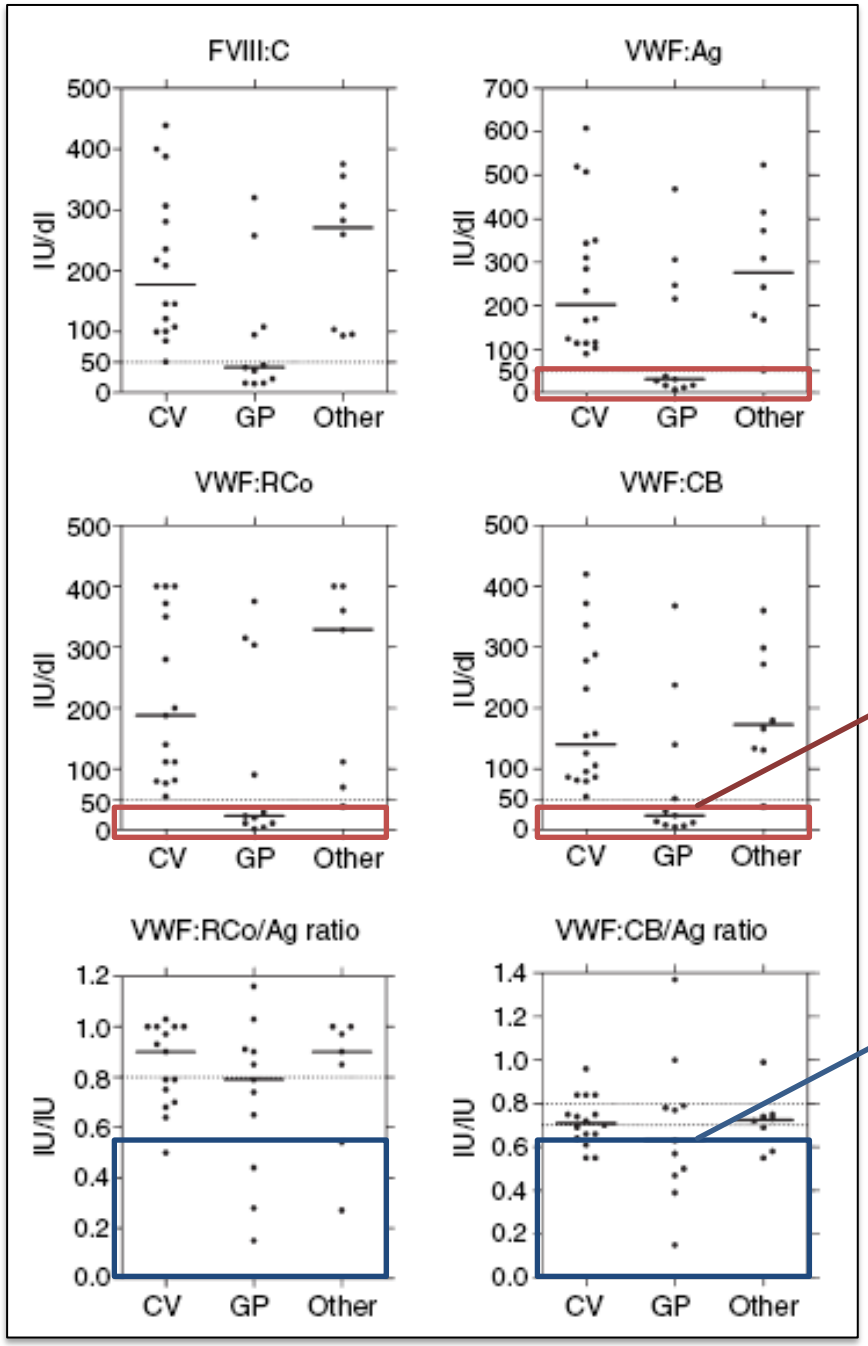
// Diagnosis

Routine tests:

- VWF:Ag
- VWF:RCo or VWF:Ac
- VWF:CB
- Multimer analysis

Special tests:

- Inhibitor tests (mixing tests)
- VWF-binding antibodies (ELISA)
- VWF propeptide
- Active-conformation VWF



35 pts. with AVWS
(all had VWF multimer defects and bleeding)

CV = cardiovascular disorders
GP = gammopathy / lymphoproliferative disorders

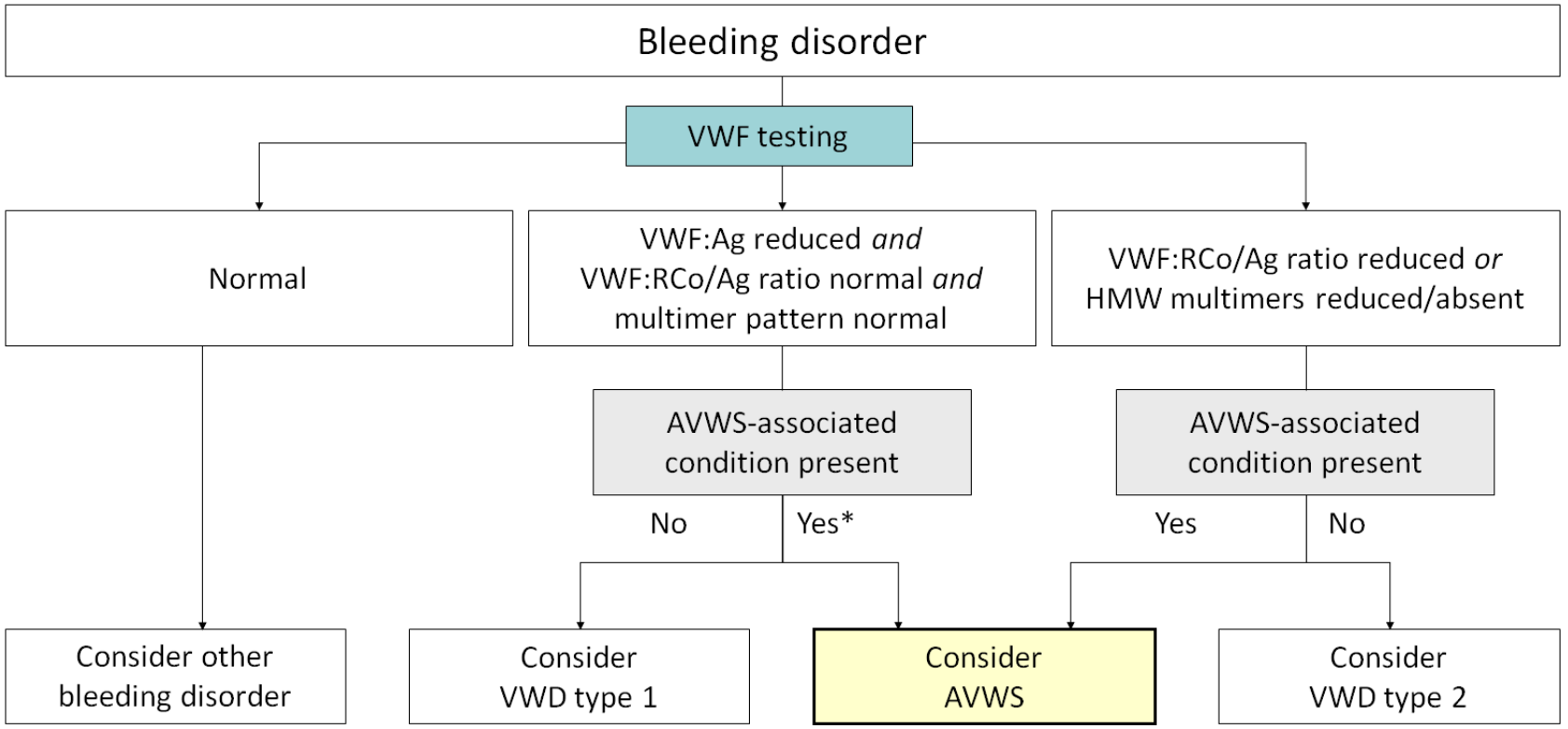
Only some patients have reduced antigen or function tests

Some patients have reduced function/antigen ratios

Tiede, et al. J Thromb Haemost 2008; 6: 569-76

// Diagnosis

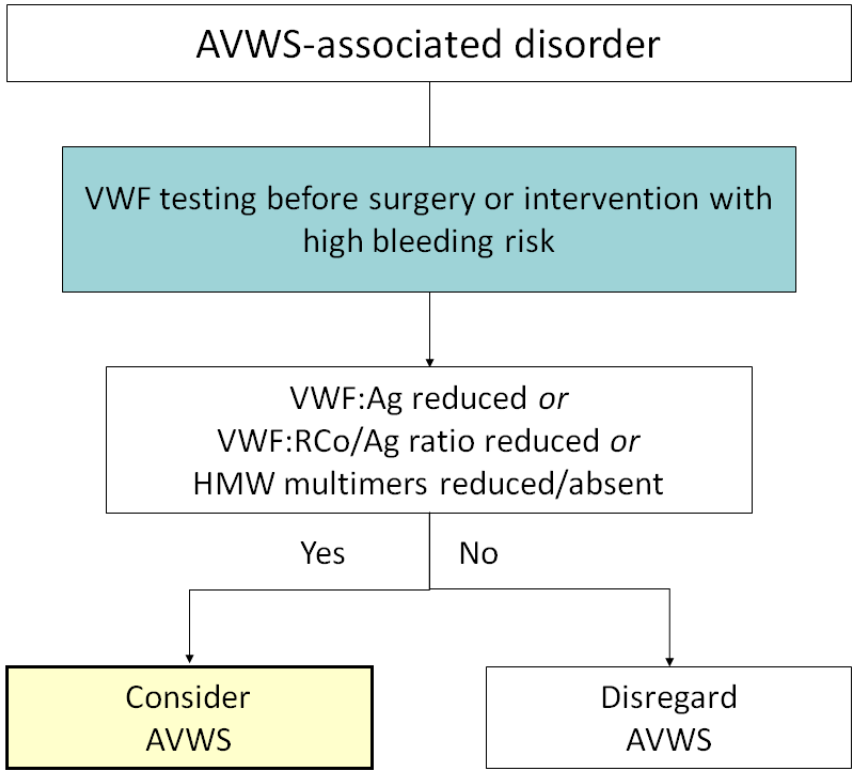
Suggested diagnostic algorithm



Tiede, Rand, Budde, Ganser, Federici. Blood 2011; 117: 6777-85

// Diagnosis

Suggested diagnostic algorithm



Tiede, Rand, Budde, Ganser, Federici. Blood 2011; 117: 6777-85

// Treatment

Correct diagnosis is always required…

- VWD or AVWS?
- AVWS due to cardiovascular defect, gammopathy or other?

… because:

- Treatment of the underlying disorder is always a first consideration
- Replacement therapy or desmopressin does not always work in AVWS

// Treatment

Underlying disorder	Causal treatment	Additional treatment options
Autoimmune disorders		IVIG (works best with IgG-MGUS), plasmapheresis, 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 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		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	

Mod. from Tiede, Rand, Budde, Ganser, Federici. Blood 2011; 117: 6777-85

// Treatment

VWF-containing concentrates

- Appear effective in most cases
- Half-life can be short (monitor if parameter available)
- Humate P (30-100 FVIII IU/kg) was effective in 80 % of cases[1]

Desmopressin

- Lower reported efficacy rates (10-75%)[2]
- Consider potential side effects in patients at risk

Intravenous immunoglobulin (IVIG):

- Very effective in AVWS due to IgG antibody or IgG paraprotein[3]
- 0.5-1.0 g/kg for 2 days
- VWF:Ag increases after 3 to 4 days, lasting appr. 3 weeks

Other options

- Tranexamic acid
- Recombinant factor VIIa (off-label, very few case reports)

1 Tiede, et al. J Thromb Haemost 2008; 6: 569-76. **2** Federici et al. Thromb Haemost. 2000; 84:345-49. **3** Federici et al. Blood. 1998;92: 1707-11.

Summary

- AHA and AVWS are rare disorders of hemostasis
- Awareness and rapid diagnosis are key to safe lifes
- Intensity of immunosuppression is under consideration
- Emicizumab is a promising agent under investigation