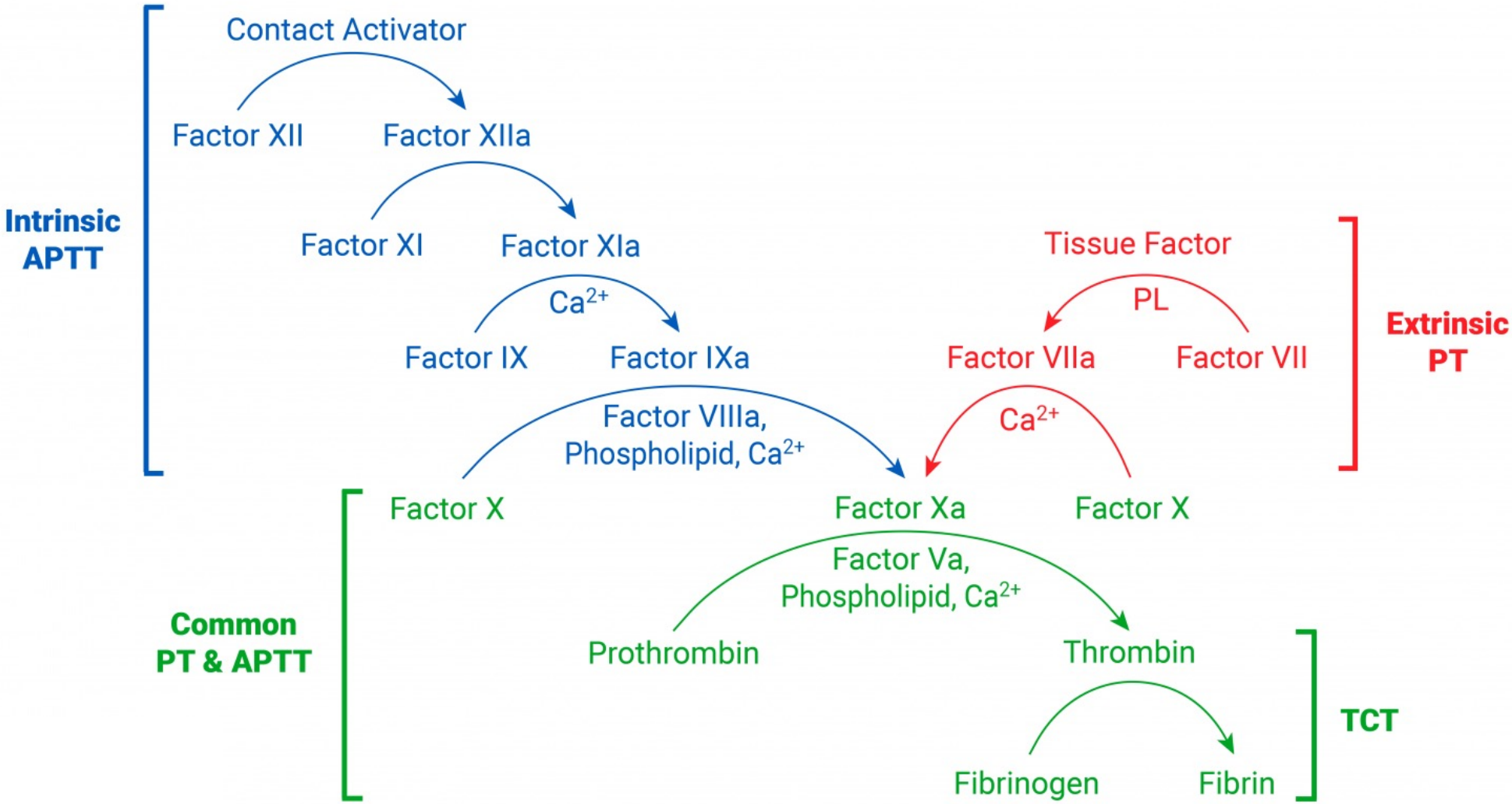
Bellodi Andrea

Clinica di Medicina Interna a indirizzo oncologico
Ospedale Policlinico San Martino Genova

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

Emofilia acquisita


Intrinsic
APTT
Contact Activator
Factor XII
Factor XIIa
Factor XI
Factor XIa
Ca2+
Factor IX
Factor IXa
Factor VIIIa,
Phospholipid, Ca2+
Tissue Factor
PL
Factor VIIa
Factor VII
Extrinsic
PT
Ca2+
Factor X
Factor Xa
Factor X
Common
PT & APTT
Factor Va,
Phospholipid, Ca2+
Prothrombin
Thrombin
Fibrinogen
Fibrin
TCT

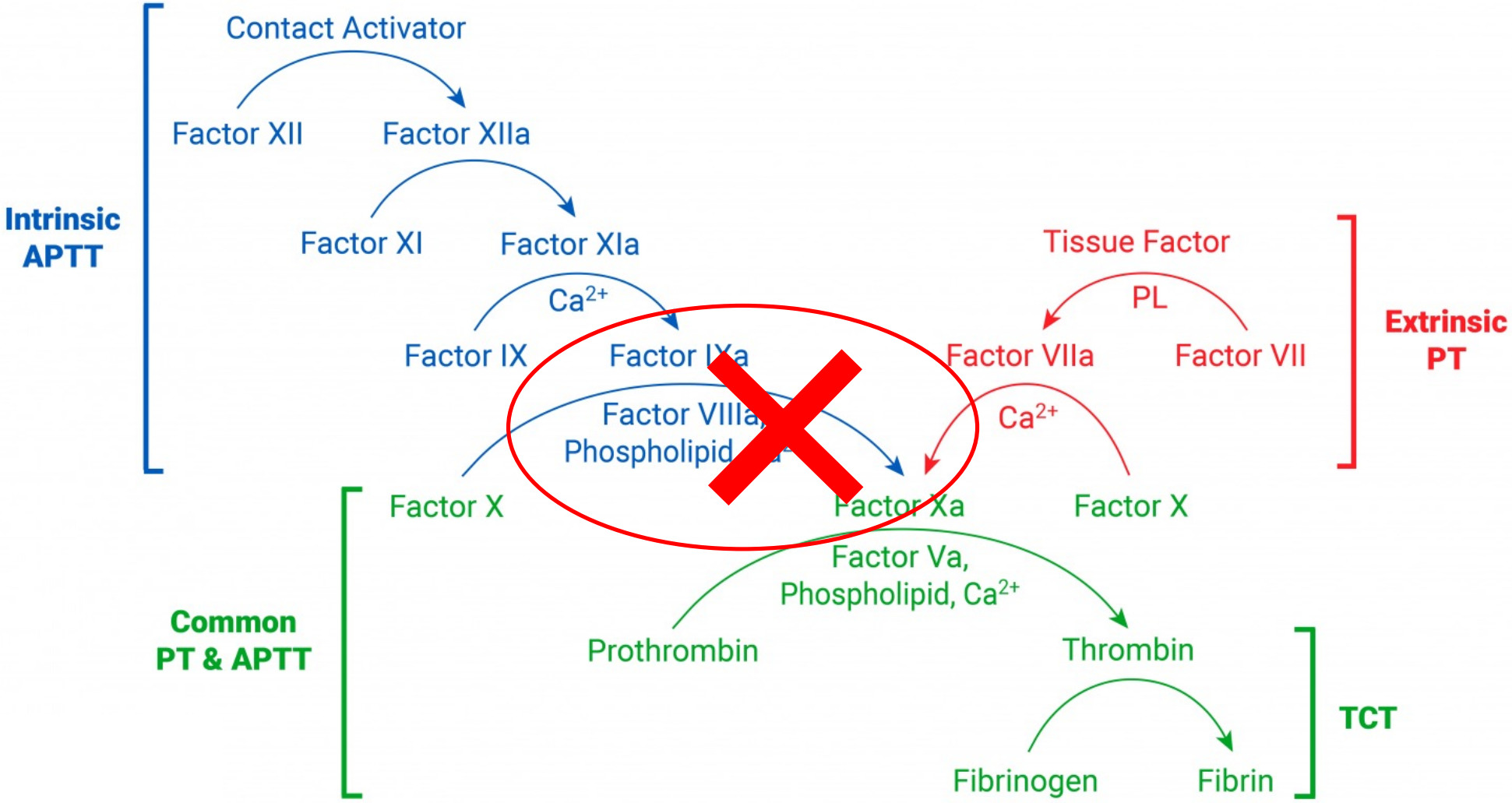
Natura del problema

Emofilia acquisita A

Disordine coagulativo acquisito causato da anticorpi anti fattore VIII (inibitori)

Inibitori potenzialmente di tutti i fattori

Anticorpi IgG →interferenza FVIII – FX e FIXa oppure FVIII – fosfolipidi e FVW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Factor Va,
Phospholipid, Ca2+
Prothrombin
Thrombin
Fibrinogen
Fibrin
TCT

Table 1. Recent studies and registries in acquired hemophilia A.

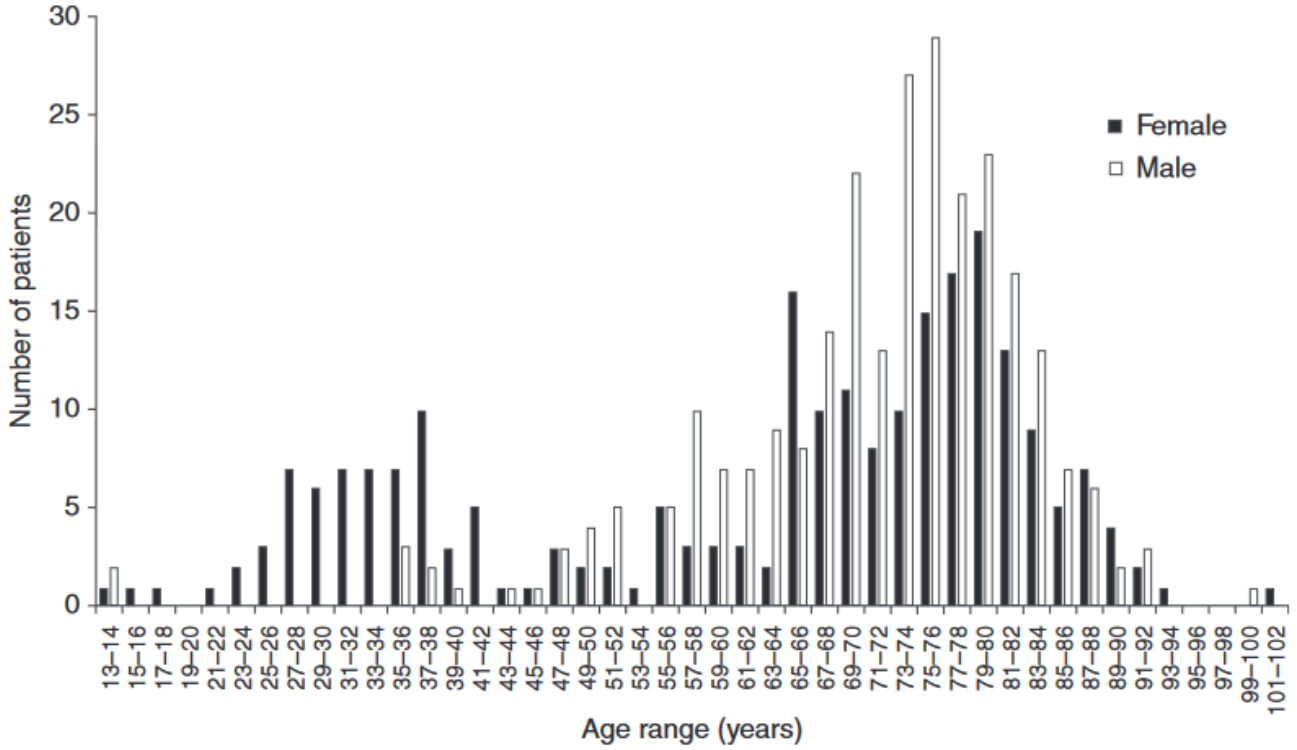
Study name	Study type	Design	Collection period	Total n. of patients	Treatment/outcome data available information				Survival information (pts)	Reference
					Hemostatic therapy (n. of pts)*	Bleeding resolved (n. of pts or episodes)	IST (n. of pts)**	Remission (n. of pts)		
UK surveillance study	Registry	Prospective, consecutive	2001–2003	172	97	-	151	105	113	(2)
EACH2	Registry	Retrospective (3 years); prospective (3 years)	2003–2009	501	307	288 patients (1st episodes)	331	331	331	(3, 5, 7, 8)
SACHA	Registry	Prospective	2001–2006	82	38	38 patients	77	77	82	(9)
GTH-AH 01/2010	Registry	Prospective	2010–2013	102	70	162 episodes	101	101	102	(10-12, 37)
HTRS	Registry	Prospective	2004–2011	166	68 (rFVIIa only)	139 episodes	-	-		(14)
OBI-1	Clinical trial	Prospective, single-arm	-	29	28 (rpFVIII only)	28 patients	-	-	29	(15)

*Number of patients reported to have received recombinant activated factor VII (rFVIIa), activated prothrombin concentrate complex (APCC), factor VIII (FVIII) and/or recombinant porcine factor VIII (rpFVIII). Differences in the numbers reported vs. the total number of patients may be due to no treatment or lack of reporting. **Number of patients reported to have received immunosuppressive therapy. N: number; IST: immunosuppressive therapy; UK: United Kingdom; EACH2: European ACquired Haemophilia; SACHA: *Surveillance des Auto-antiCorps au cours de l'Hémophilie Acquise*; GTH: *Gesellschaft für Thrombose- und Hämostaseforschung*; HTRS: Hemostasis and Thrombosis Research Society; OBI-1: susoctocog alfa.

Tiede A et al Haematologica 2020

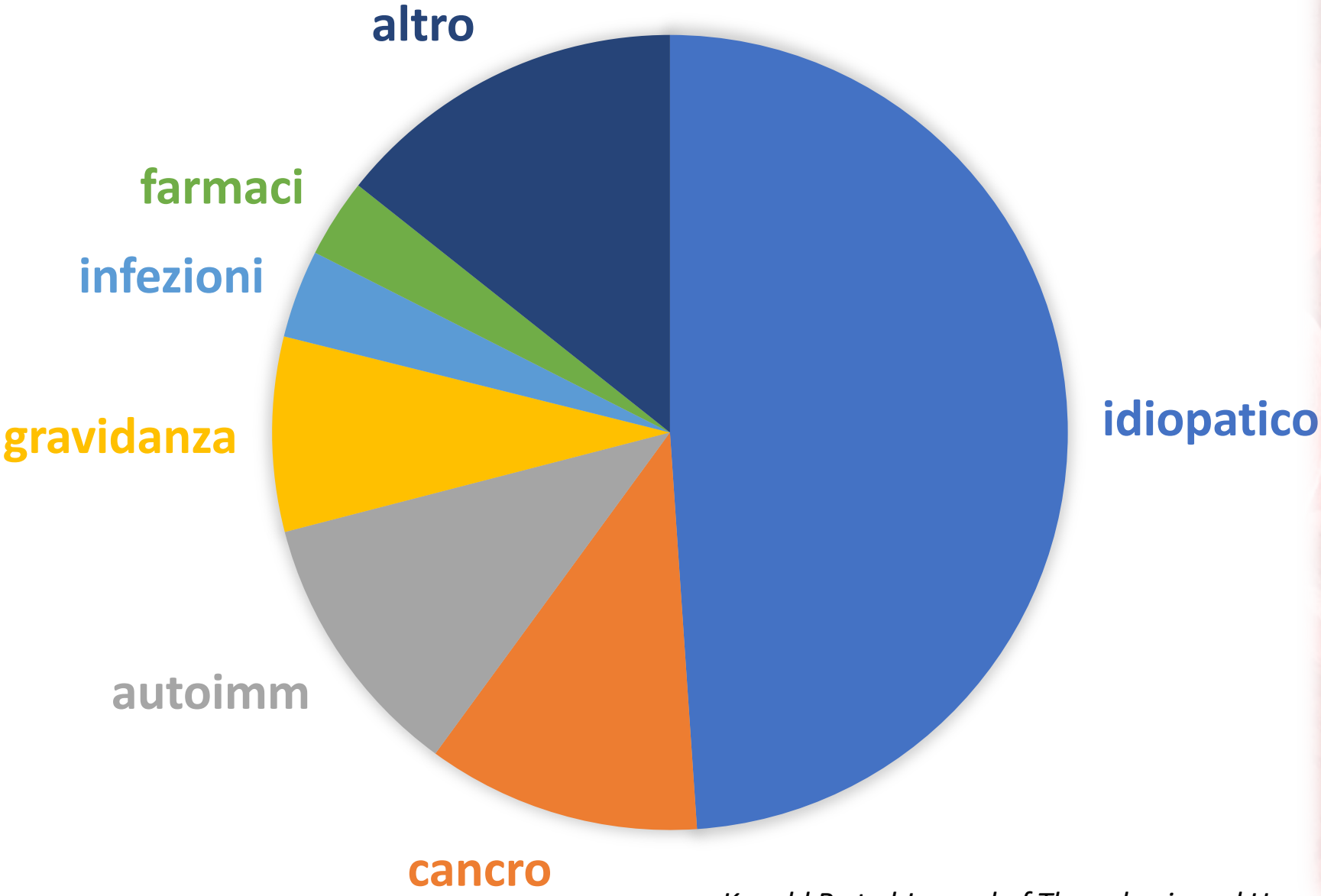
Epidemiologia

Malattia rara: 1-2 /1.000.000
Fattori genetici, ambientali → autoimmunità
Non noti fattori predittivi di rischio
Mortalità 15 – 50%



Knoebl P et al Journal of Thrombosis and Haemostasis 2012

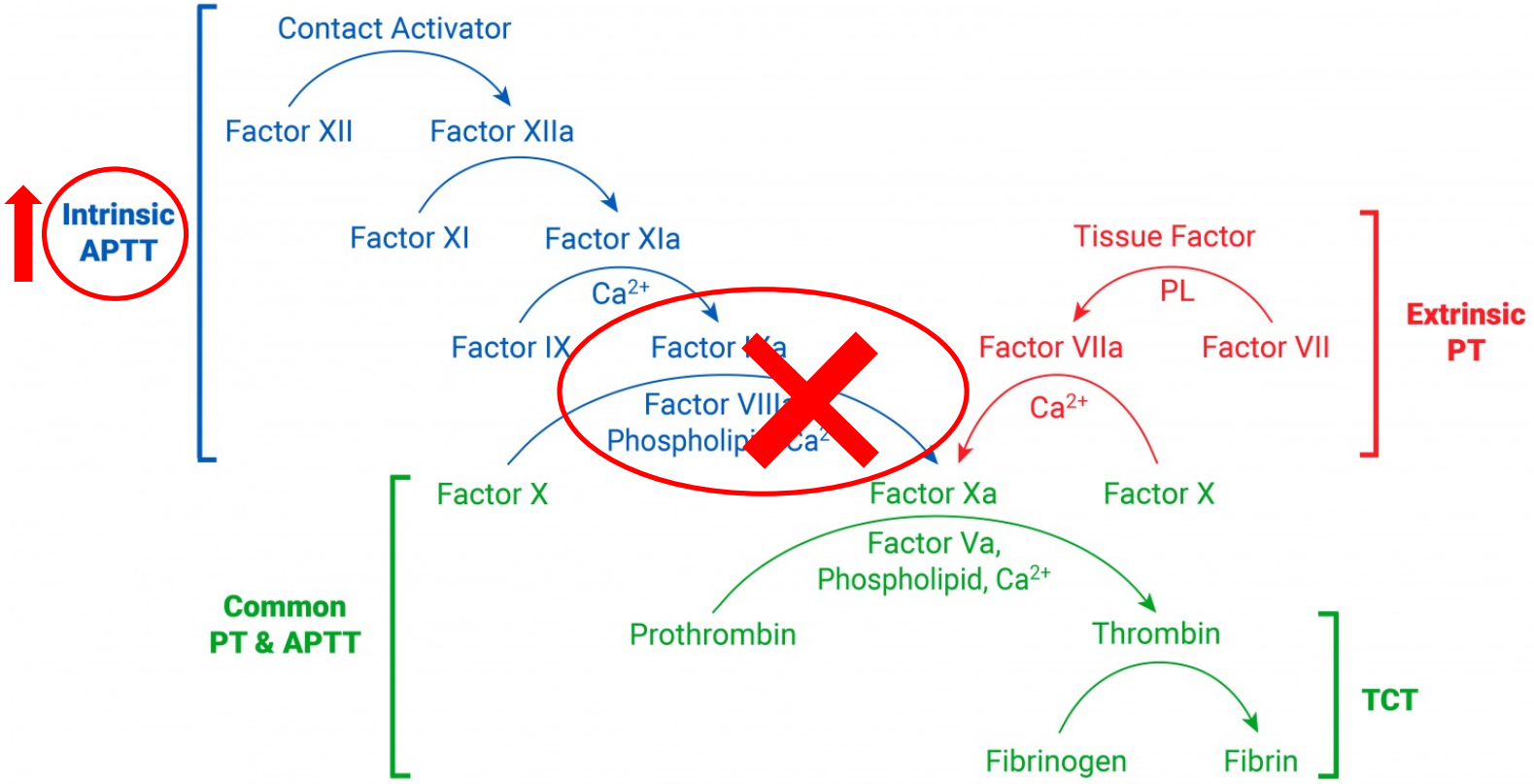
DISORDINE SOTTOSTANTE



Knoebl P et al Journal of Thrombosis and Haemostasis 2012

Approccio

Valutazione clinica



Sospetto clinico: emorragia + aPTT allungato

Approccio

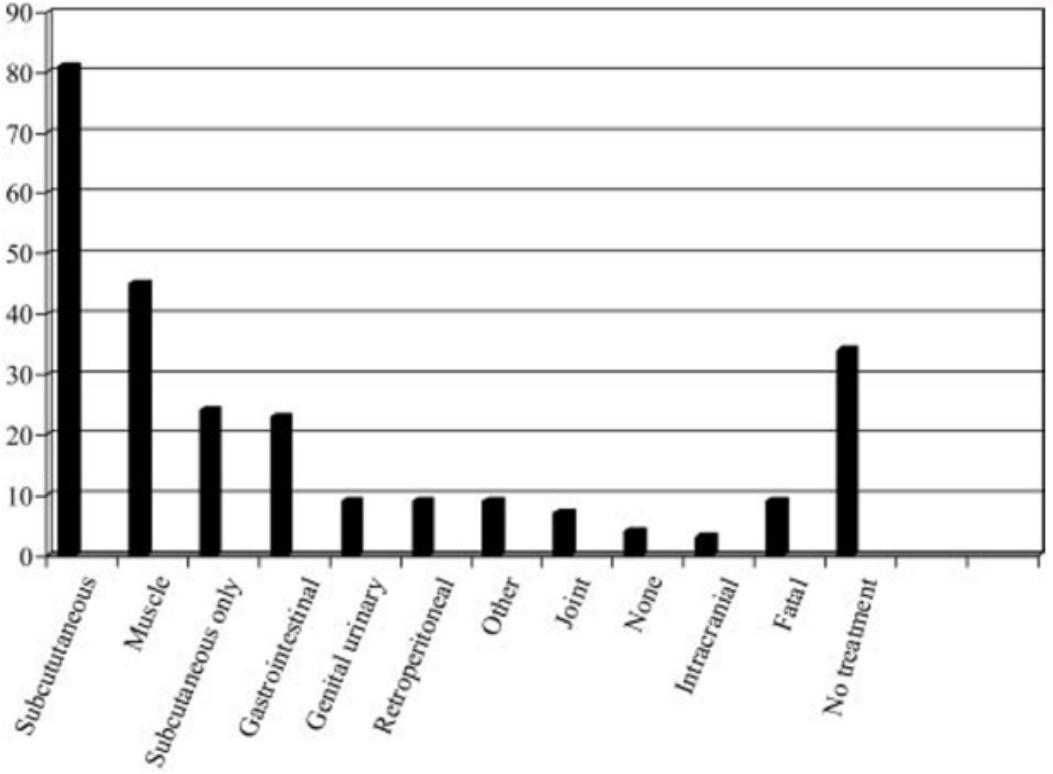
Valutazione clinica

Emofilia A congenita	**Emofilia A acquisita**
Emartrosi	Emorragie
Emorragie	• **tessuti molli**
• Mucosali	• **muscolari**
• Muscolari	• Mucosali
• Viscerali	• Gastrointestinali
• Post chirurigico	• Intracraniche
M > F	**M=F**
Esordio pediatrico	**Esordio adulto**

Menaka P Hematol Oncol Clin N Am 2021

Knoebl P et al Journal of Thrombosis and Haemostasis 2012

	Entire collective
Bleeding as trigger for diagnosis [*n* (%)]	467 (89.0)*
Time from bleeding event to definite diagnosis	
Median [days (IQR)]	3 (0–12)
More than 6 months [*n* (%)]	6 (1.3)
1–6 months [*n* (%)]	46 (9.8)
1 week–1 month [*n* (%)]	105 (22.4)
1 week [*n* (%)]	122 (26.1)
0 (−1 to 1 day) [*n* (%)]	174 (37.2)
Bleeding after diagnosis [*n* (%)]	
1 week–1 month	6 (1.3)
1 month–1year	4 (0.9)
> 1 year	5 (1.1)
No bleeding [*n* (%)]	33 (6.6)



Collins PW et al Blood 2007

Knoebl P et al Journal of Thrombosis and Haemostasis 2012

	All	Severe	Non-severe	*P**
Total no. of bleeding episodes [*n* (%)]	474	333 (70.3)	137 (28.9)	NA
Cause [*n* (%)]				
Spontaneous	367 (77.4)	250 (76.0)	113 (83.7)	NS
Trauma	40 (8.4)	33 (10.0)	7 (5.2)	NS
Surgery	39 (8.2)	30 (9.1)	9 (6.7)	NS
Peripartum	17 (3.6)	14 (4.3)	2 (1.5)	NS
Other	13 (2.7)	8 (2.4)	4 (3.0)	NS
Site/type [*n* (%)]				
Skin	252 (53.2)	152 (46.2)	97 (71.9)	< 0.0001
Deep (musculoskeletal, retroperitoneal)	238 (50.2)	214 (65.0)	21 (15.6)	< 0.0001
Mucosa	150 (31.6)	113 (34.4)	35 (25.9)	NS
Hemarthrosis	23 (4.9)	17 (5.2)	6 (4.4)	NS
Central nervous system	5 (1.1)	5 (1.5)	0 (0)	NS
Bleeding episodes by clinical and laboratory assessments [median (IQR)]				
Median age [years]	74.0 (61.1–80.3)	74.4 (64.1–80)	71.7 (51.8–80.9)	NS
Gender male:female [*n* (ratio)]	242:222 (1.1)	175:154 (1.14)	67:68 (1.0)	NS
Median FVIII activity [U dL^{-1}]	2 (1–5)	2 (1–5)	2 (0–5)	NS
Median inhibitor titer [BU mL^{-1}]	19 (5.5–64.0)	13 (4.9–40.8)	10 (1.9–32.5)	0.02
Hb [g dL^{-1}]	8.9 (7.3–11.1)	8.5 (7.0–10.0)	11.1 (9.2–12.8)	< 0.0001
Body weight [kg]	69 (60–78)	70 (60–78)	67.5 (60–77)	NS
Time to diagnosis [days]	3 (0–12)	3 (0–11)	2 (0–25)	NS
Bleeding episodes by underlying condition [*n* (%)]				
None identified	238 (51.3)	170 (51.7)	68 (50.4)	NS
Autoimmune	61 (13.1)	40 (12.2)	21 (15.6)	NS
Malignancy	57 (12.3)	44 (13.4)	13 (9.6)	NS
Postpartum	41 (8.8)	25 (7.6)	16 (11.9)	NS
Drug exposure	17 (3.7)	11 (3.3)	6 (4.4)	NS
Infections	19 (4.1)	11 (3.3)	8 (5.9)	NS

Approccio

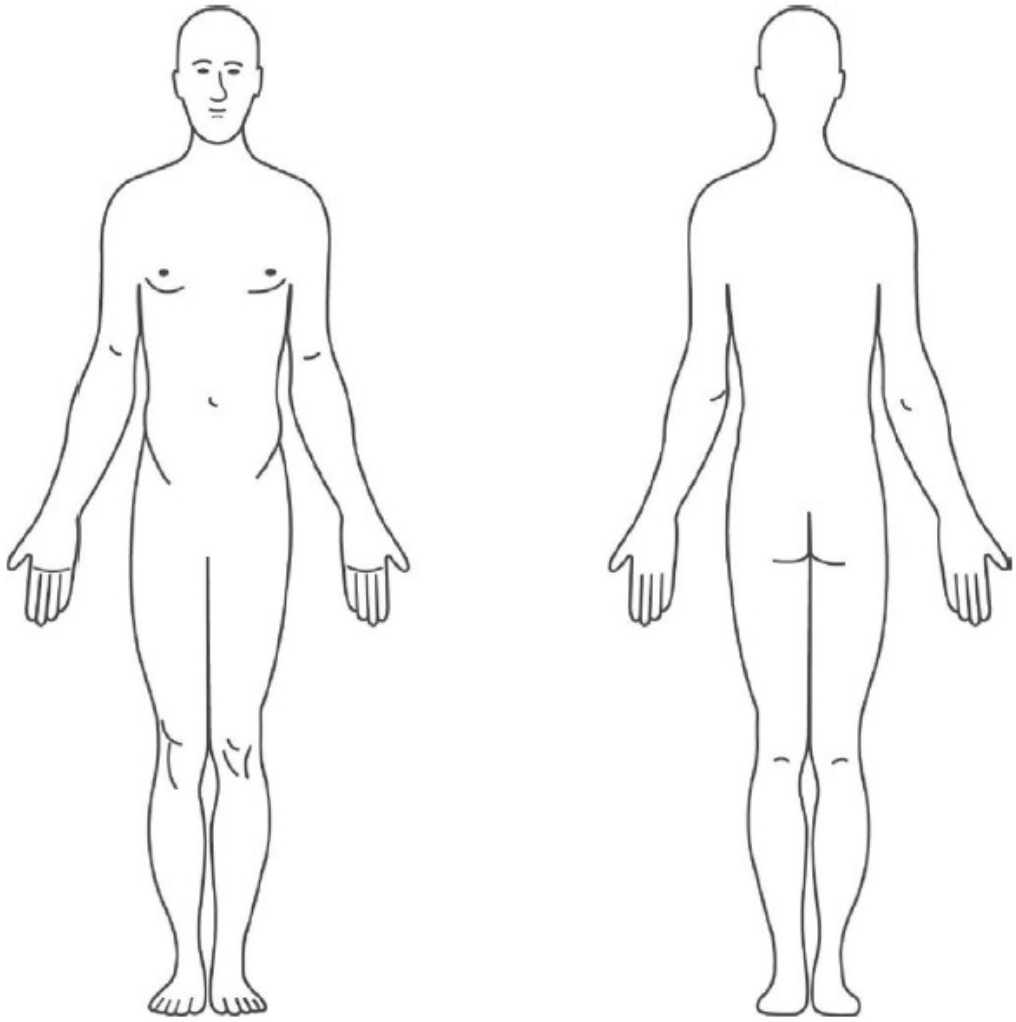
<u>Valutazione clinica</u>

- 80% dei pazienti emorragia significativa che richiede trasfusione
- Prestare attenzione agli arti (**DD con TVP**)
- Rapida progressione a **sindrome compartimentale**
- Monitoraggio serrato, compreso stato neurologico (**emorragia intracranica**)
- Limitare interventi invasivi

Menaka P Hematol Oncol Clin N Am 2021

Use of the body map involves the following steps:

1. Draw any bleeding on body map on admission
2. Draw around bleeds on patient skin to aid monitoring
3. Check patient every shift for new or extended bleeding
4. Report any new or extended bleeding to hemophilia team.



Diagnosi differenziale della AHA

- ❑ Disordini coagulativi ereditari (deficit/insufficienza fattori coagulazione)
- ❑ Emofilia A (carenza di FVIII) – X linked
- ❑ Emofilia B (carenza di FIX) – X linked
- ❑ Emofilia C (carenza di FXI) – autosomica recessiva
- ❑ von Willebrand disease (VWD)
- ❑ Lupus anticoagulant e eparine

Constantinescu C et al Blood rev 2022

Approccio

laboratorio

Diagnosi differenziale:

- Deficienza fattori congenita
- Inibitori non specifici
- Anticoagulanti
- **Altre coagulopatie**

Sospetto clinico: emorragia + aPTT allungato

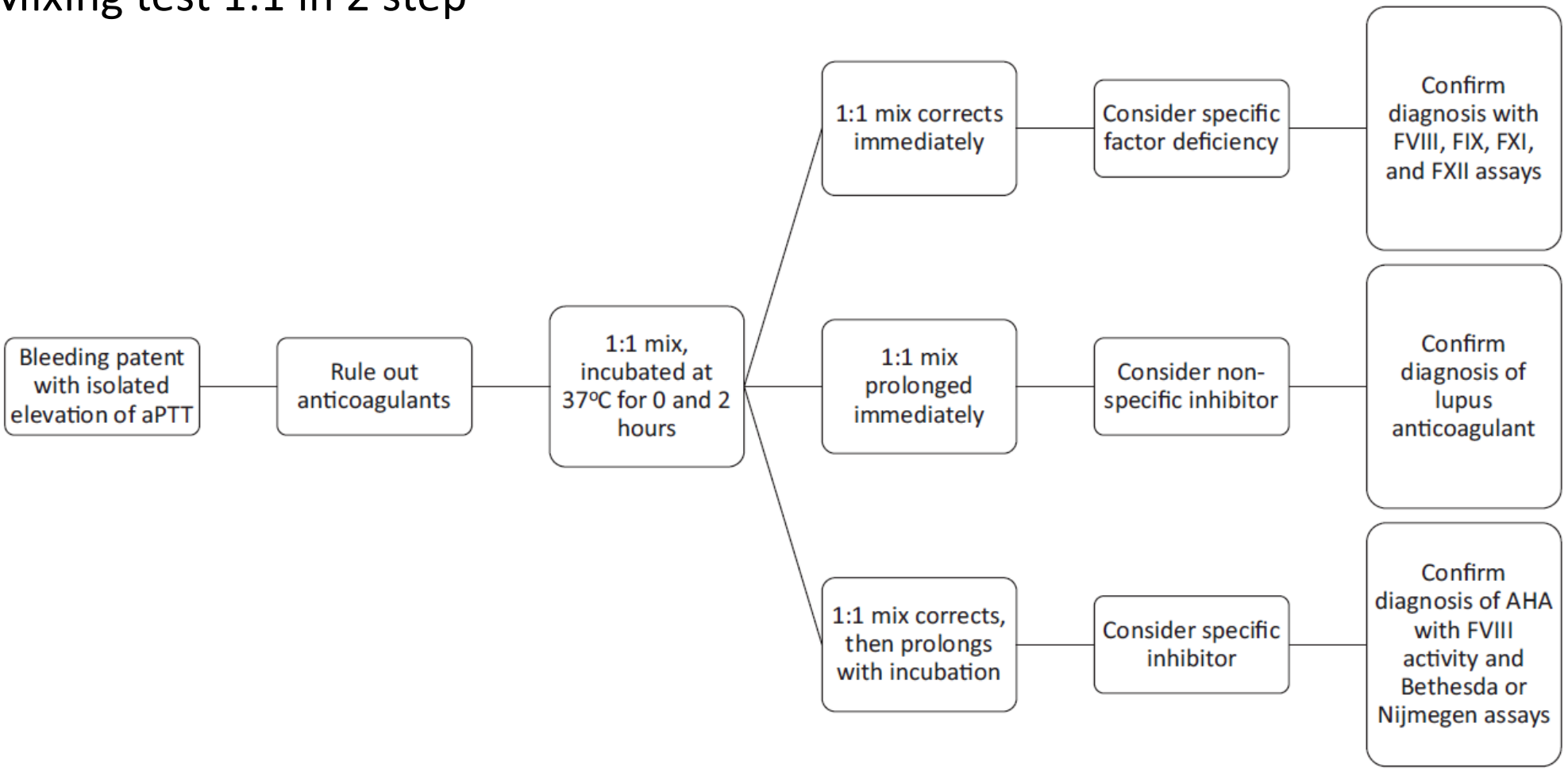
Tempo di protrombina
Tempo di trombina
INR
Fibrinogeno
Conta piastrininca

} **NORMALI**

Approccio

Laboratorio

Mixing test 1:1 in 2 step



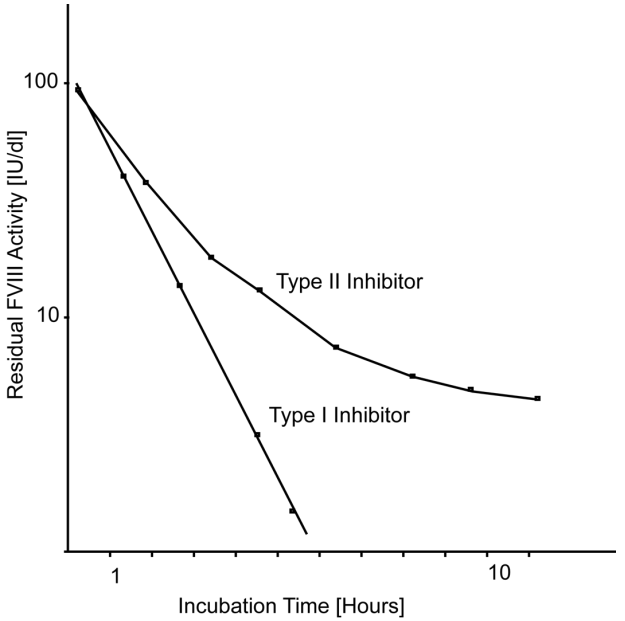
Approccio

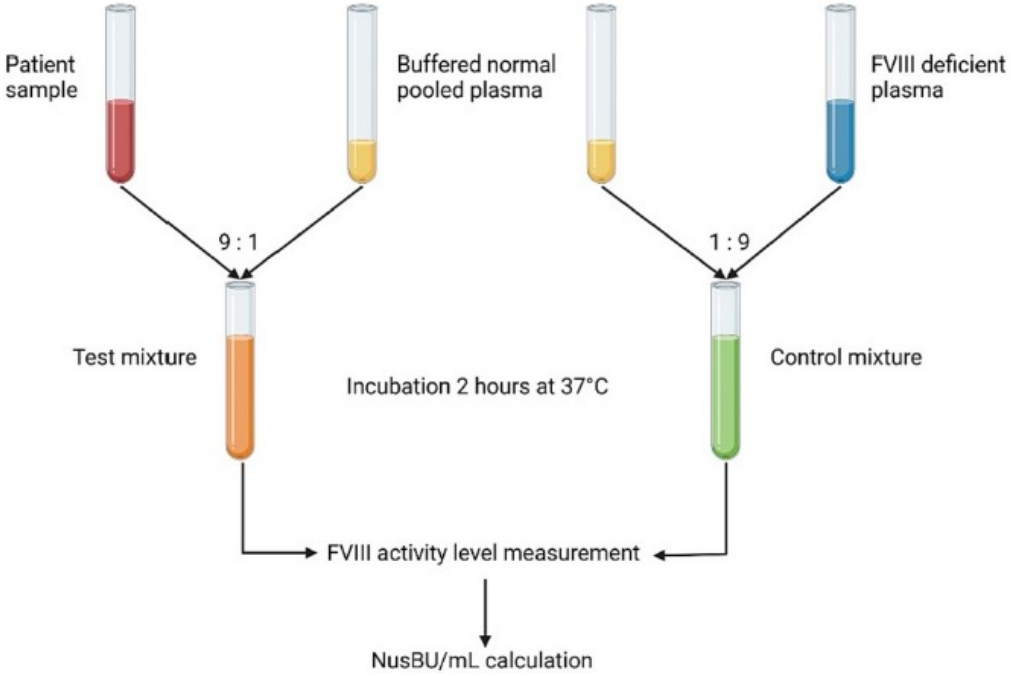
Laboratorio

Test diagnostici:

- Attività FVIII
- Test di Bethesda

(Bethesda - Nijmegen)





Bethesda Units:

Basso titolo < 5 BU

Alto titolo > 5 BU

Valke Lars LFG et al Thrombosis Research 231 (2023)

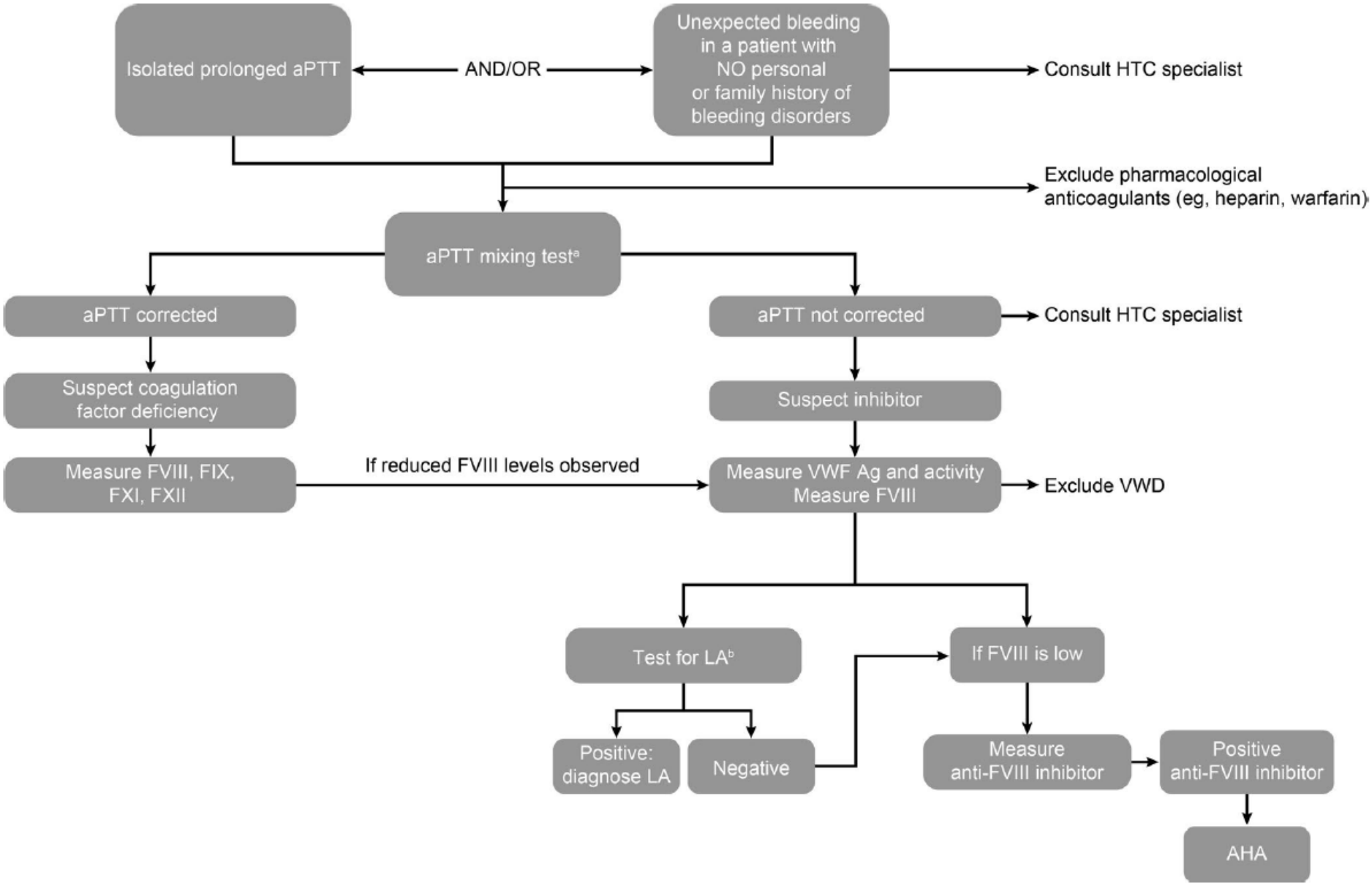


FIGURE 2 Key steps in diagnosing AHA. AHA, acquired hemophilia A; aPTT, activated partial thromboplastin time; FVIII, factor VIII; FIX, factor IX; FXI, factor XI; FXII, factor XII; HTC, hemophilia treatment center; LA, lupus anticoagulant; VWD, von Willebrand disease; VWF, von Willebrand factor

Strategie terapeutiche

1. Prevenire e trattare il sanguinamento

- Aumentare livelli di FVIII
- Bypassare FVIII per attivare la coagulazione

2. Eradicare l'inibitore

3. Trattare la patologia sottostante (se identificata)

Trattare il sanguinamento

- 70% pazienti necessita trattamento emostatico
- EACH2 registry: unico parametro significativo per il successo del trattamento è il **tempo**
- L'attività del FVIII e il titolo dell'inibitore non devono influenzare la decisione di iniziare il trattamento
- Qualsiasi trattamento emostatico è associato al rischio di eventi trombotici
- **Il trattamento emostatico deve essere prontamente iniziato in pazienti con sanguinamento clinicamente significativo**

Baudo F et al Blood 2012

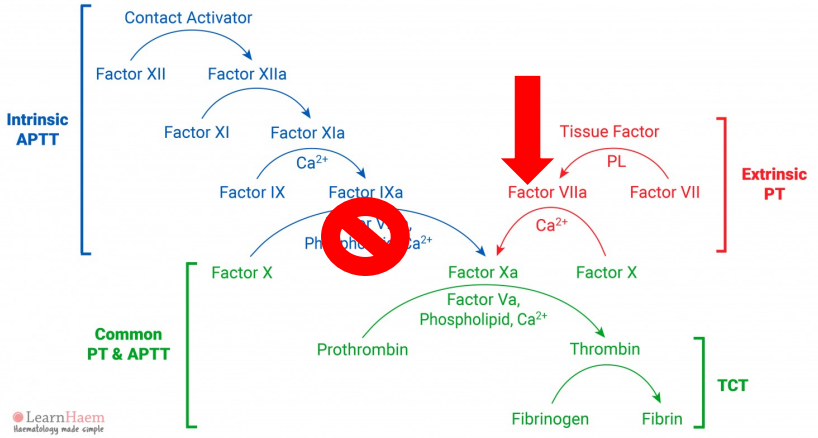
Knoebl P et al Journal of Thrombosis and Haemostasis 2012

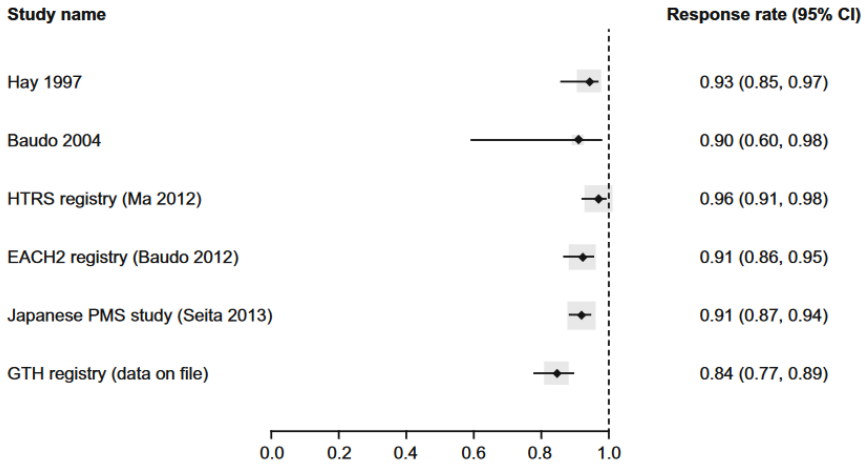
1. Prevenire e trattare il sanguinamento

Bypassare FVIII per attivare la coagulazione

Fattore VII attivato ricombinante umano (rFVIIa, eptacog alfa)

- Dati da review 12 studi, 671 pazienti e 1063 eventi emorragici
- Usato in prima linea in emorragie severe (39-90% dei casi)
- Efficacia >90% su controllo emostasi e livelli aPTT
- 8 su 12 studi riportano eventi trombotici 0-5% dei pazienti





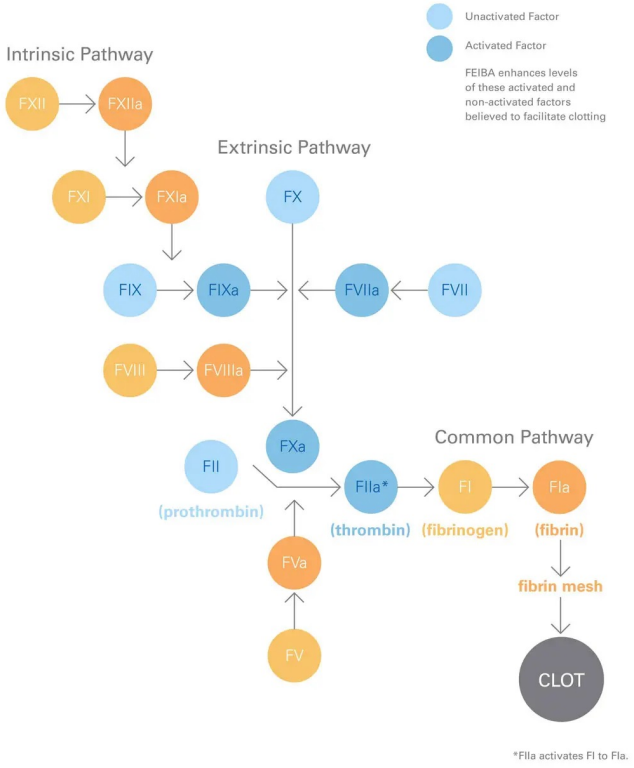
Tiede A et al Ann Hematol 2018

1. Prevenire e trattare il sanguinamento

Bypassare FVIII per attivare la coagulazione

APCC (activated prothrombin complex concentrate)

- Indicato in trattamento e prevenzione emorragia in pz con emofilia congenita
- Largo utilizzo in AHA
- Non dati da review sistematiche
- EACH2: Nessuna differenza in efficacia rispetto a rFVIIa
- >90% controllo emorragia se utilizzo in prima linea

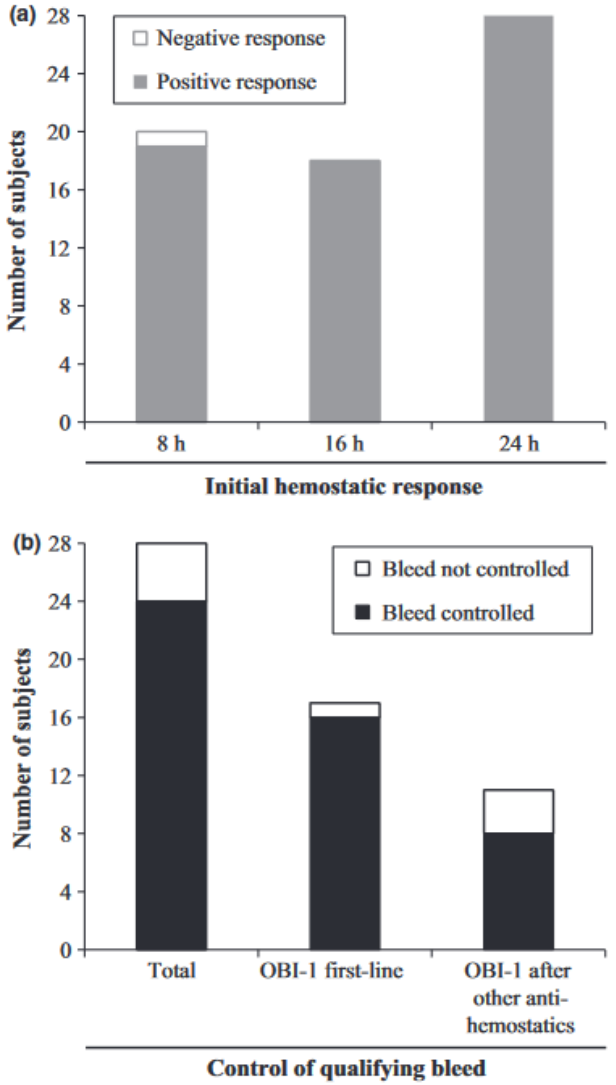


Baudo F et al Blood 2012
Dimichele D et al Haemophilia 2006

1. Prevenire e trattare il sanguinamento

Aumentare livelli di FVIII/replacement

- Terapia sostitutiva con **FVIII ricombinante porcino (rpFVIII)**
- Dosaggio inibitori rpFVIII sul pz
- Indicato se bassa attività autoanticorpi vs FVIII porcino
- Studio prospettico su 28 pz: emorragia controllata 86%
- Monitoraggio FVIII



Kruse-jarres et al Haemophilia 2015

1. Prevenire e trattare il sanguinamento

Aumentare livelli di FVIII

- Desmopressina (rilascio FVIII da cellule endoteliali)
- Fattore VIII ricombinante umano

Dati da registro EACH2:

- comparato con bypassing agents significativa minore efficacia emostatica (68% vs 93%)
- rischio di sovraccarico di fluidi, iponatriemia e scompenso cardiaco
- evitare in anziani
- Utilizzo solo se non disponibili agenti bypass

Tiede A et al Haematologica 2020

Hemostatic treatment

• We recommend that hemostatic treatment be initiated in patients with AHA and clinically relevant bleeding irrespective of inhibitor titer and residual FVIII activity.	1B
• We recommend the use of rFVIIa, APCC or rpFVIII instead of human FVIII concentrates or desmopressin for the treatment of clinically relevant bleeding in patients with AHA.	1B
• We recommend that alternative treatment strategies from among the first-line agents be used if appropriate initial treatment fails.	1C
• For initial treatment with rFVIIa, we recommend bolus injection of 90 μg/kg every 2–3 h until hemostasis is achieved.	1B
• For initial treatment with APCC, we recommend bolus injections of between 50–100 U/kg every 8–12 h, up to a maximum of 200 U/kg/day.	1B
• For initial treatment with rpFVIII, we recommend the approved dose of 200 U/kg, followed by further doses to maintain trough levels >50%.	1B
• We recommend close monitoring of FVIII activity during therapy with rpFVIII.	1B
• We suggest the use of recombinant or plasma-derived human FVIII concentrates only if bypassing agents or rpFVIII are unavailable or ineffective and the inhibitor titer is low. We recommend against the use of desmopressin.	1B
• We recommend the prophylactic use of bypassing agents or rpFVIII to cover minor or major invasive procedures.	1B

Tiede A et al Haematologica 2020

1. Prevenire e trattare il sanguinamento

Anti-fibrinolitici (acido tranexamico)

- Rischio trombotico con APCC e rFVII
- Utilizzo topico
- Eventi fatali riportati in associazione ad agenti bypassanti (rFVIIa)

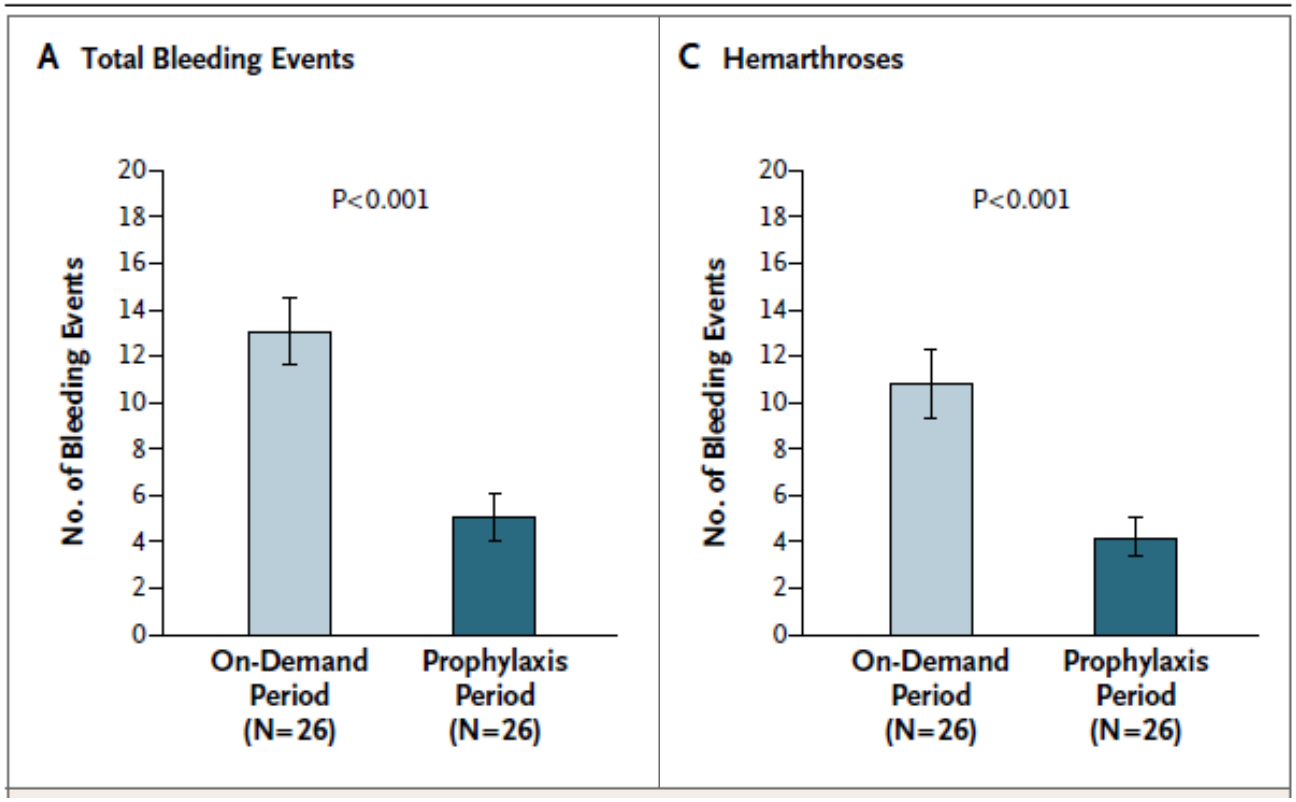
Tiede A et al Blood. 2015

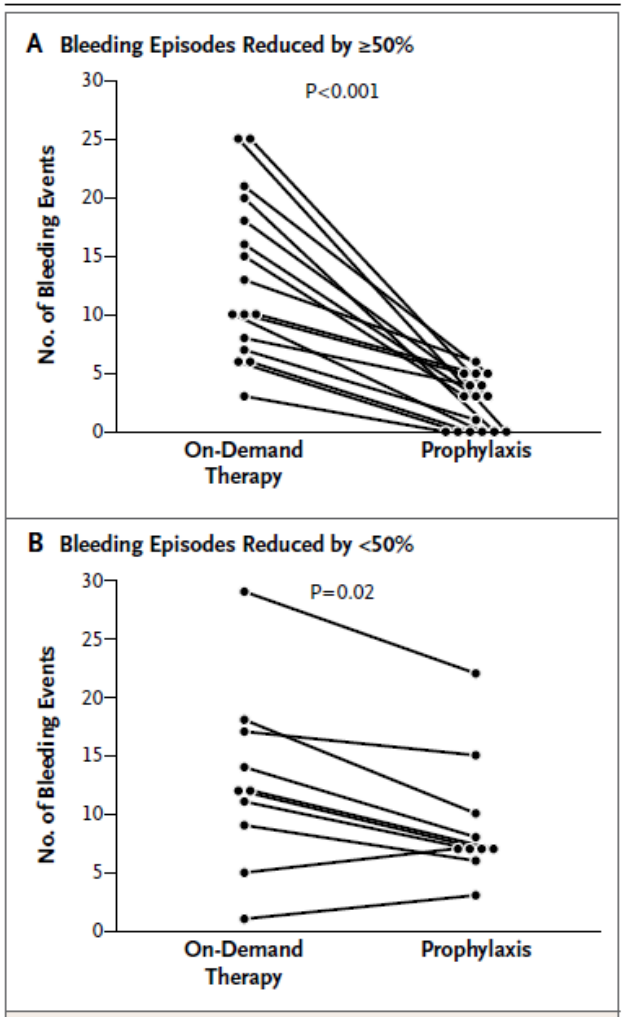
Hemostatic agent	First-line bleeding control	
	n	%
Unmatched samples		
Bypassing agent	219	91.8
FVIIa	159	91.2
aPCC	60	93.3
Replacement therapy	69	69.6
FVIII	55	70.1
DDAVP	14	64.3
PS-matched samples		
Bypassing agent	60	93.3
Replacement therapy	60	68.3
rFVIIa	57	93.0
aPCC	57	93.0

Baudo F et al Blood 2012

1. Prevenire e trattare il sanguinamento

Profilassi con APCC





Leissinger C et al NEJM 2011

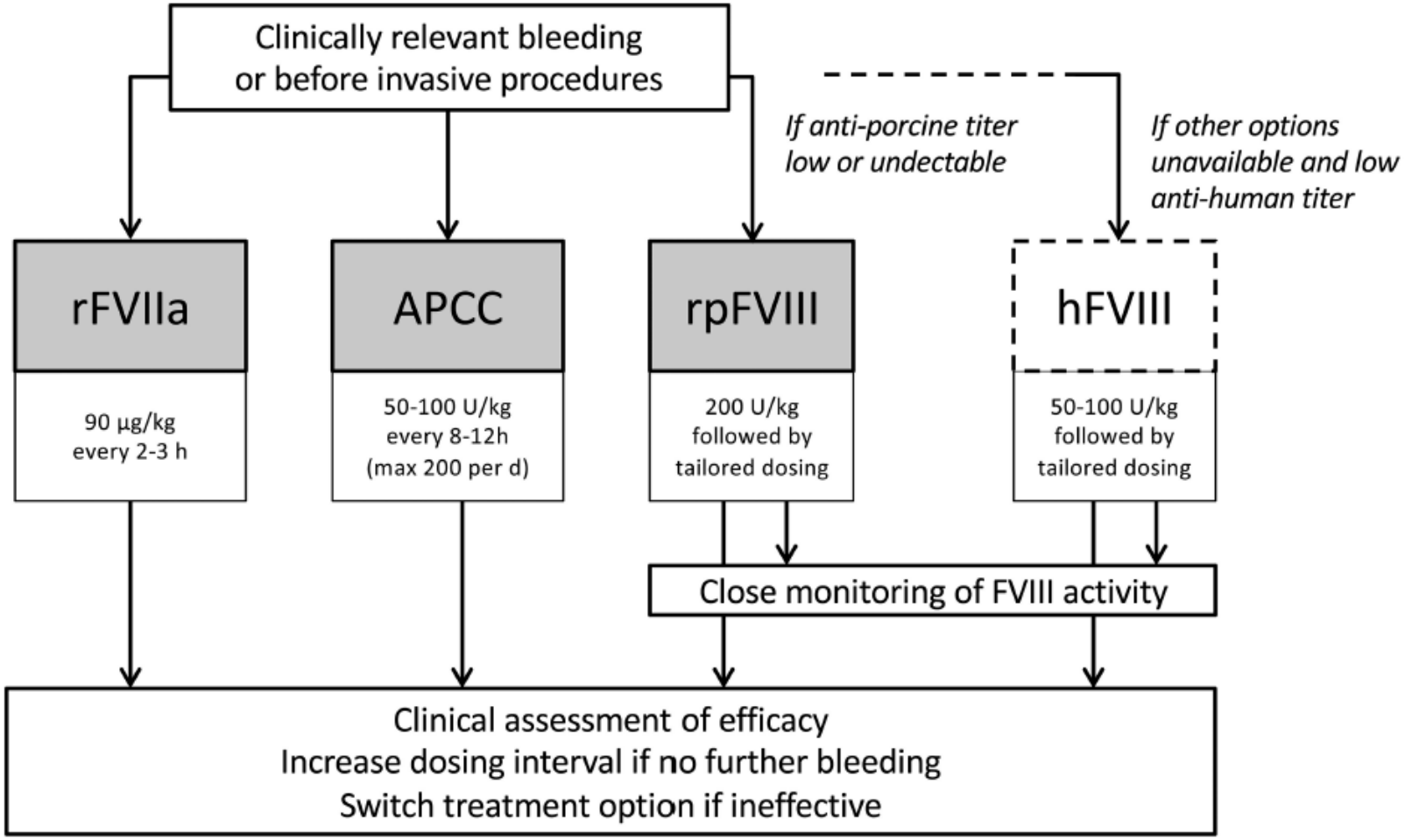
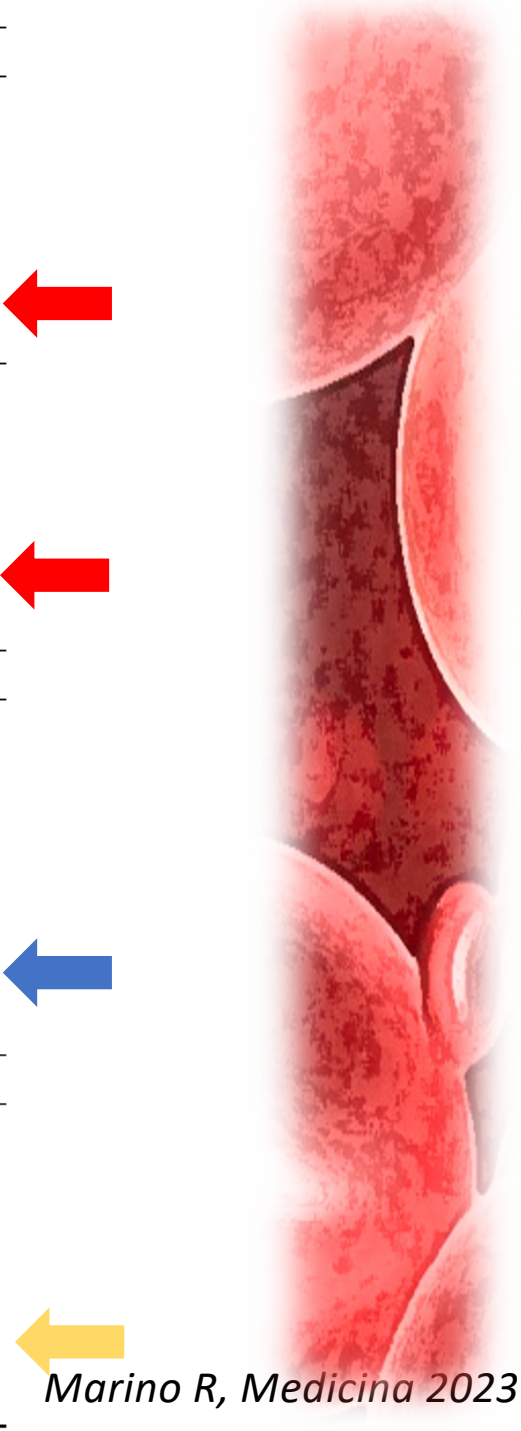


Figure 2. Choice and monitoring of hemostatic therapy in acquired hemophilia A. rFVIIa, recombinant activated factor VII (eptacog alfa); APCC, activated prothrombin complex concentrate; rpFVIII: recombinant porcine factor VIII (susoctocog alfa), hFVIII, human (plasma-derived or recombinant) factor VIII; h: hour; d: day.

Tiede A et al Haematologica 2020

First-Line Therapy	Recommended Dosage	PROS and CONS
Bypassing agents		
Activated Prothrombin Complex Concentrate	50–100 IU/kg every 8–12 h until hemostasis is obtained, then at longer intervals as required Maximum dose: 200 IU/kg daily	PROS Proven efficacy for clinical bleeding Easily available Usable also with the absence of a specialized laboratory. CONS No specific laboratory assay to monitor efficacy and the appropriateness of dosages. Possible thrombotic risk
Activated recombinant Factor VII	90–120 µg/kg every 2–3 h until hemostasis is obtained, then at longer intervals as required	PROS Proven efficacy for clinical bleeding Easily available Usable also with the absence of a specialized laboratory. CONS No specific laboratory assay to monitor efficacy and appropriateness of dosages. Possible thrombotic risk
Replacement therapy		
Recombinant porcine Factor VIII	200 IU/Kg as starting dose, subsequent doses according to the clinical response, Factor VIII levels and the type or severity of bleeding; generally, infusions every 4–12 h	PROS Can be monitored with a simple assay. It determines a measurable increase in Factor VIII levels. Documented clinical efficacy (studies still limited) No thromboembolic complications described. CONS Less effective in cases of presence and/or development of anti-porcine Factor VIII antibodies Availability of a laboratory around the clock to monitor Factor VIII levels
Second-line therapy		
Plasma-derived or recombinant factor VIII	Variable depending on severity of bleeding, inhibitor titter, infusion modalities (bolus or continuous infusion)	PROS It determines a measurable increase in factor VIII levels. Proven efficacy in patients with low inhibitor titer (<5 UB) Easily available Can be monitored with a simple assay. CONS Possible anamnestic response High dose required. Strict laboratory monitoring (daily)



Marino R, Medicina 2023

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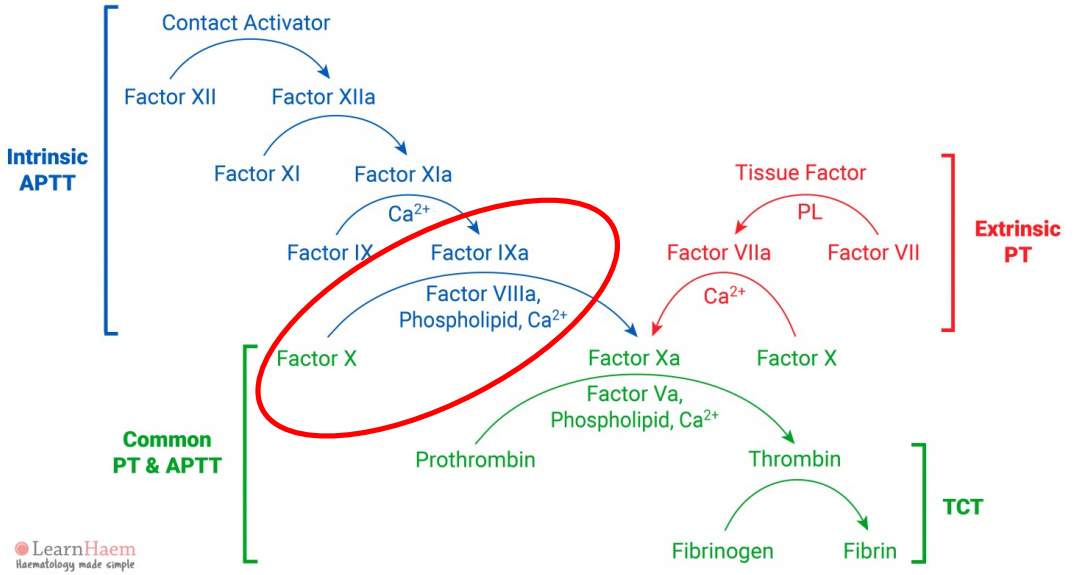
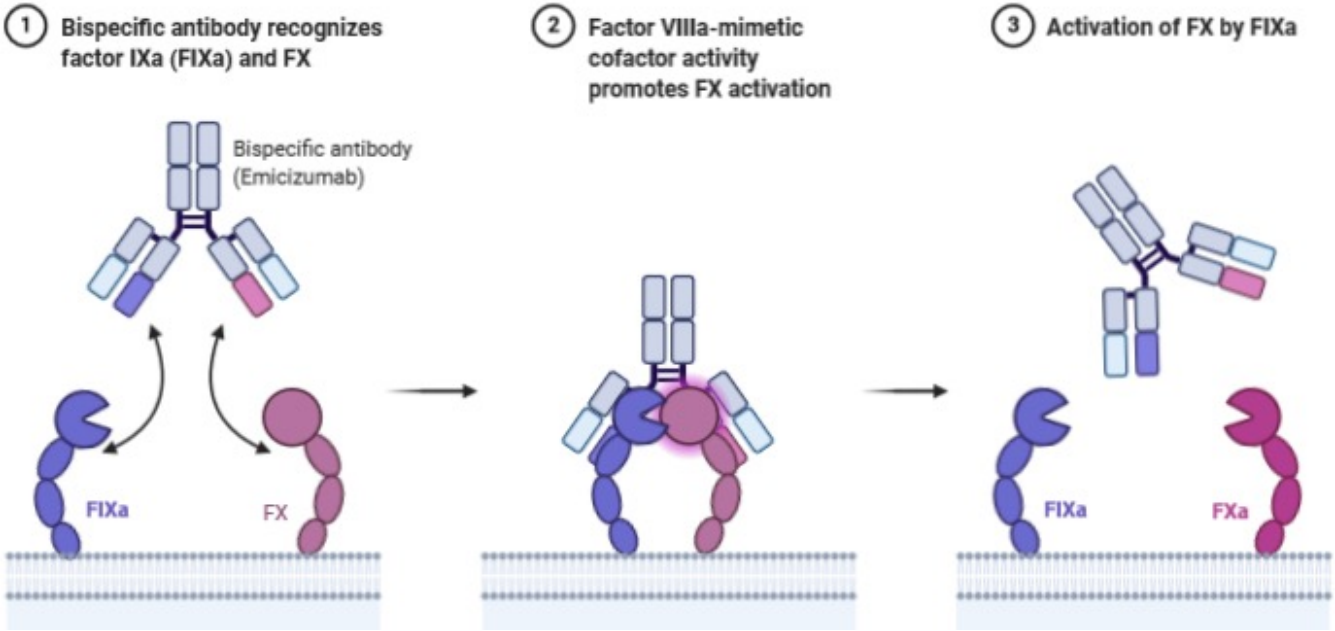
Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D., Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D., Guy Young, M.D., Elena Santagostino, M.D., Ph.D., Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D., Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanius, M.Sc., Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.





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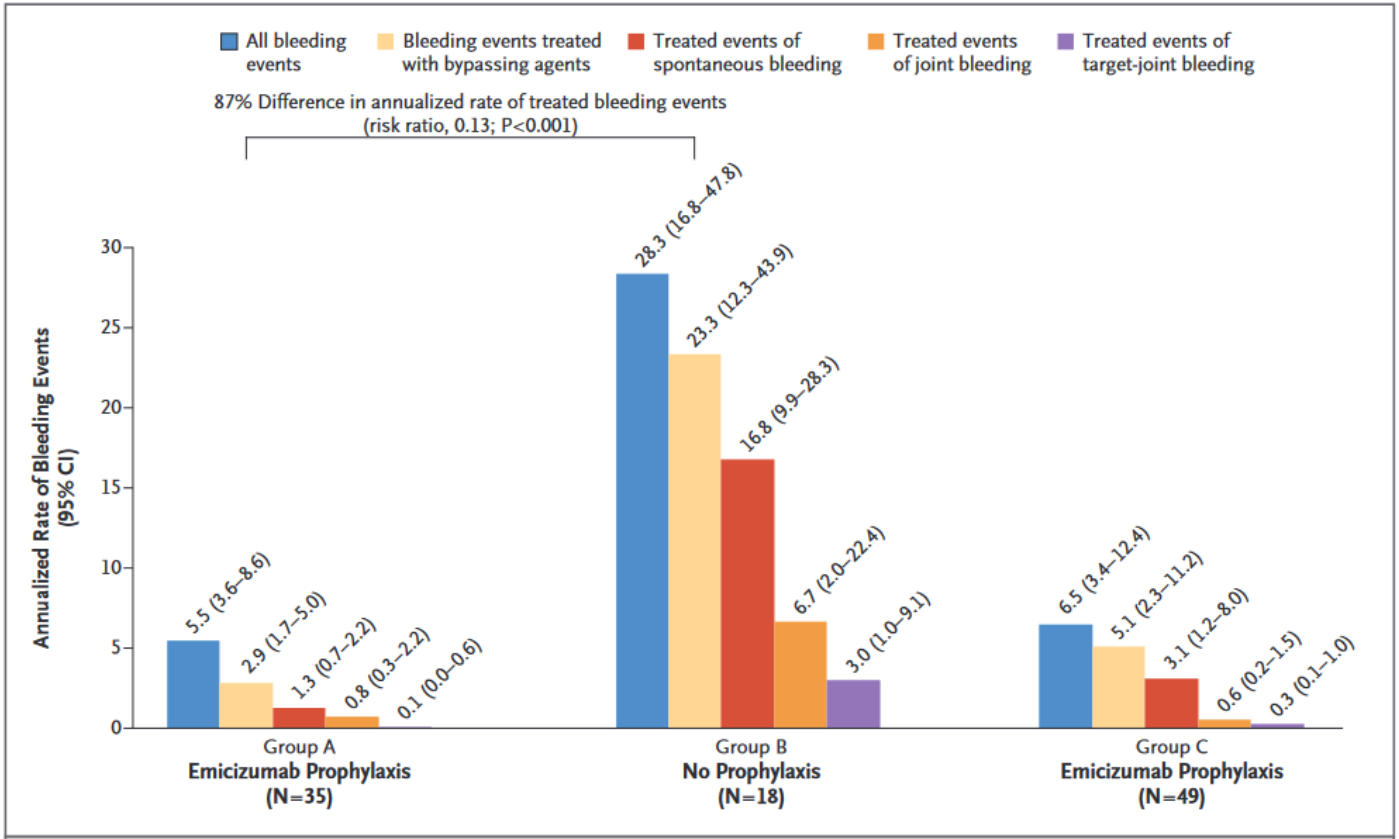
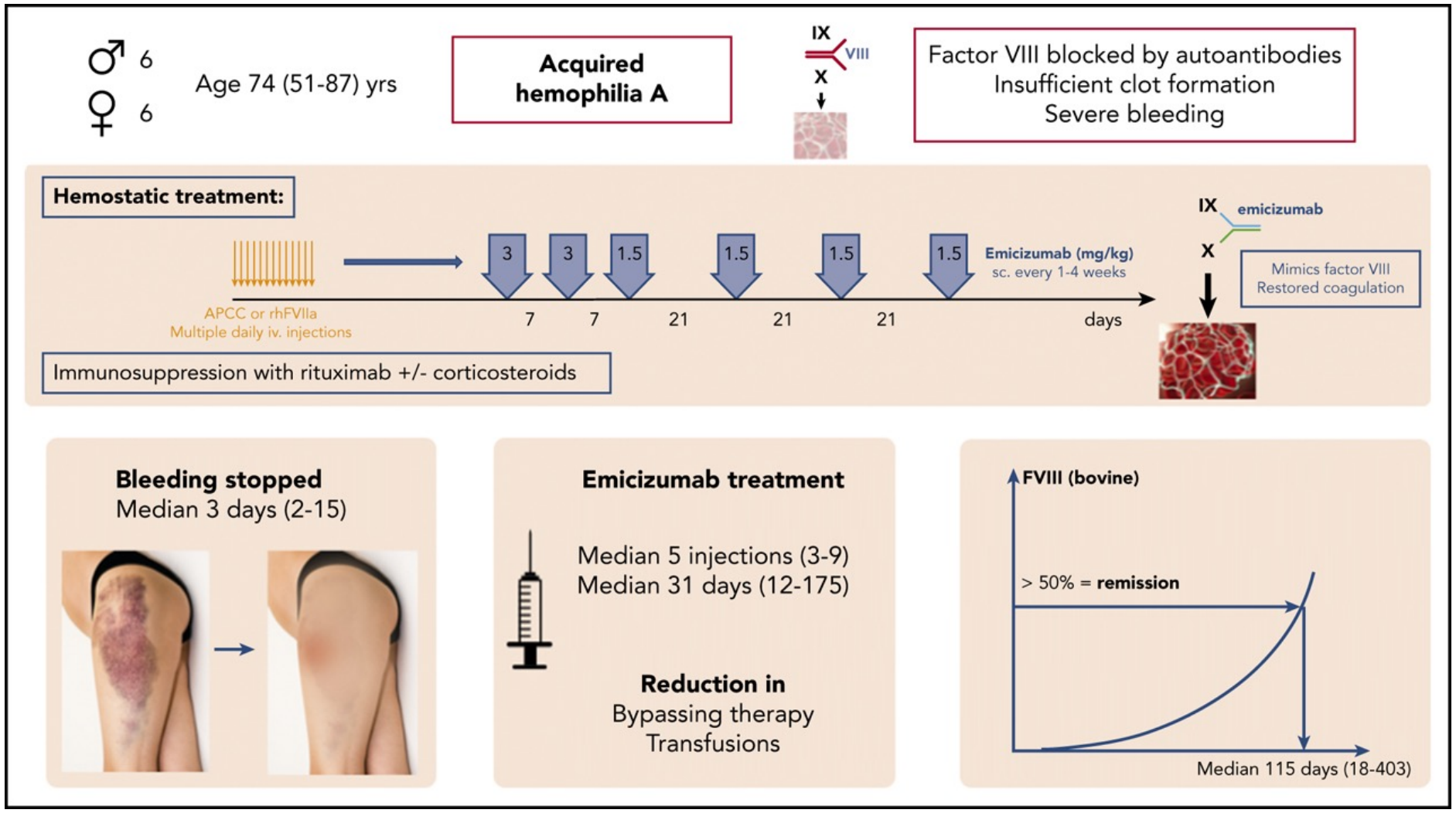


Figure 1. Annualized Bleeding Rate in Trial Groups A, B, and C.

The annualized bleeding rate was calculated with the use of a negative binomial-regression model. Participants in groups A and B had previously received episodic treatment with bypassing agents; participants in group C had previously received prophylaxis with bypassing agents. Group D was not included in the current analysis owing to the short follow-up at the time of data cutoff.



Knoebl P et al Emicizumab for the treatment of acquired hemophilia A NEJM 2017

Participant No.	Bypassing-Agent Prophylaxis: Duration of efficacy period (days)	Bypassing-Agent Prophylaxis: No. of events	Emicizumab Prophylaxis: Duration of efficacy period (days)	Emicizumab Prophylaxis: No. of events	Prophylactic treatment with bypassing agents	Emicizumab prophylaxis, 1.5 mg/kg weekly
1	313	39	85	9	45.5	38.7
2	239	6	48	3	9.2	22.8
3	127	11	175	8	31.6	16.7
4	133	1	286	4	2.8	5.1
5	113	2	224	3	6.5	4.9
6	210	6	245	2	10.4	3.0
7	131	7	246	1	19.5	1.5
8	106	0	317	0	0	0
9	77	0	296	0	0	0
10	57	0	295	0	0	0
11	84	4	282	0	17.4	0
12	189	7	259	0	13.5	0
13	272	31	240	0	41.6	0
14	187	7	226	0	13.7	0
15	253	5	224	0	7.2	0
16	240	3	198	0	4.6	0
17	243	21	181	0	31.6	0
18	240	5	140	0	7.6	0
19	322	7	118	0	7.9	0
20	219	3	98	0	5.0	0
21	345	16	93	0	16.9	0
22	231	28	90	0	44.3	0
23	313	12	58	0	14.0	0
24	240	19	44	0	28.9	0

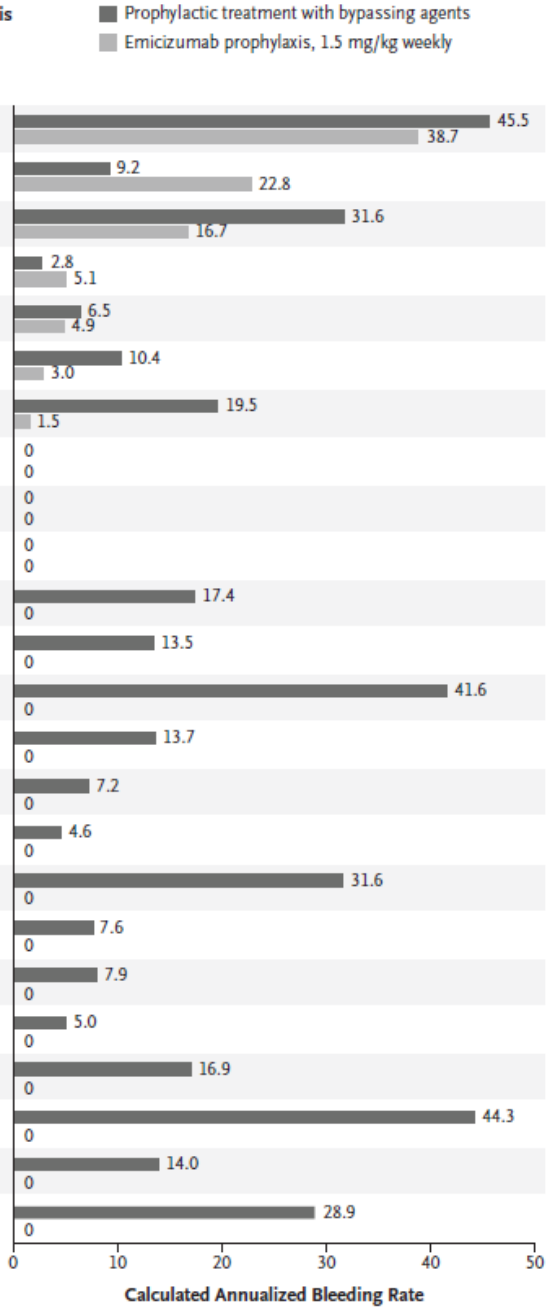
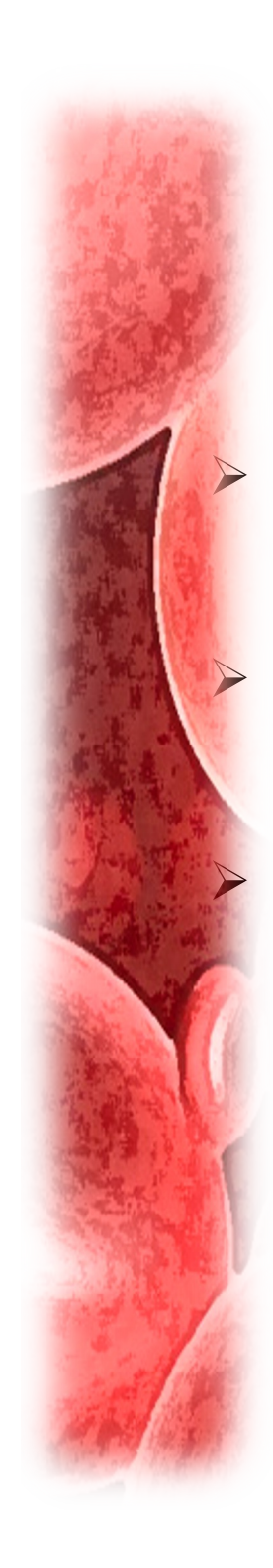


Figure 2. **Intraindividual Comparison of Treated Bleeding Events in Participants Receiving Emicizumab Prophylaxis (Group C) versus Previous Prophylactic Treatment with Bypassing Agents before Trial Entry.**

Oldenburg J et al A NEJM 2017



Emicizumab

- Il trattamento (inclusa la profilassi di routine) con agenti bypassanti deve essere interrotto il giorno prima di iniziare la terapia con emicizumab
- La profilassi con il fattore VIII (FVIII) può essere proseguita per i primi 7 giorni di trattamento con emicizumab
- La dose raccomandata è di 3 mg/kg una volta a settimana per le prime 4 settimane (dose di carico); a partire dalla settimana 5: dose di mantenimento pari a 1,5 mg/kg una volta a settimana (3 mg/kg ogni due settimane o 6 mg/kg ogni quattro settimane)

Hemlibra ® scheda tecnica

Strategie terapeutiche

2. Eradicare l'inibitore

- L'inibitore scompare spontaneamente in un terzo dei pz
- Necessaria terapia immunosoppressiva nella maggior parte
- No trial randomizzati di superiorità immunosoppressori

- **Prima scelta: corticosteroidi 1 mg/kg giorno**

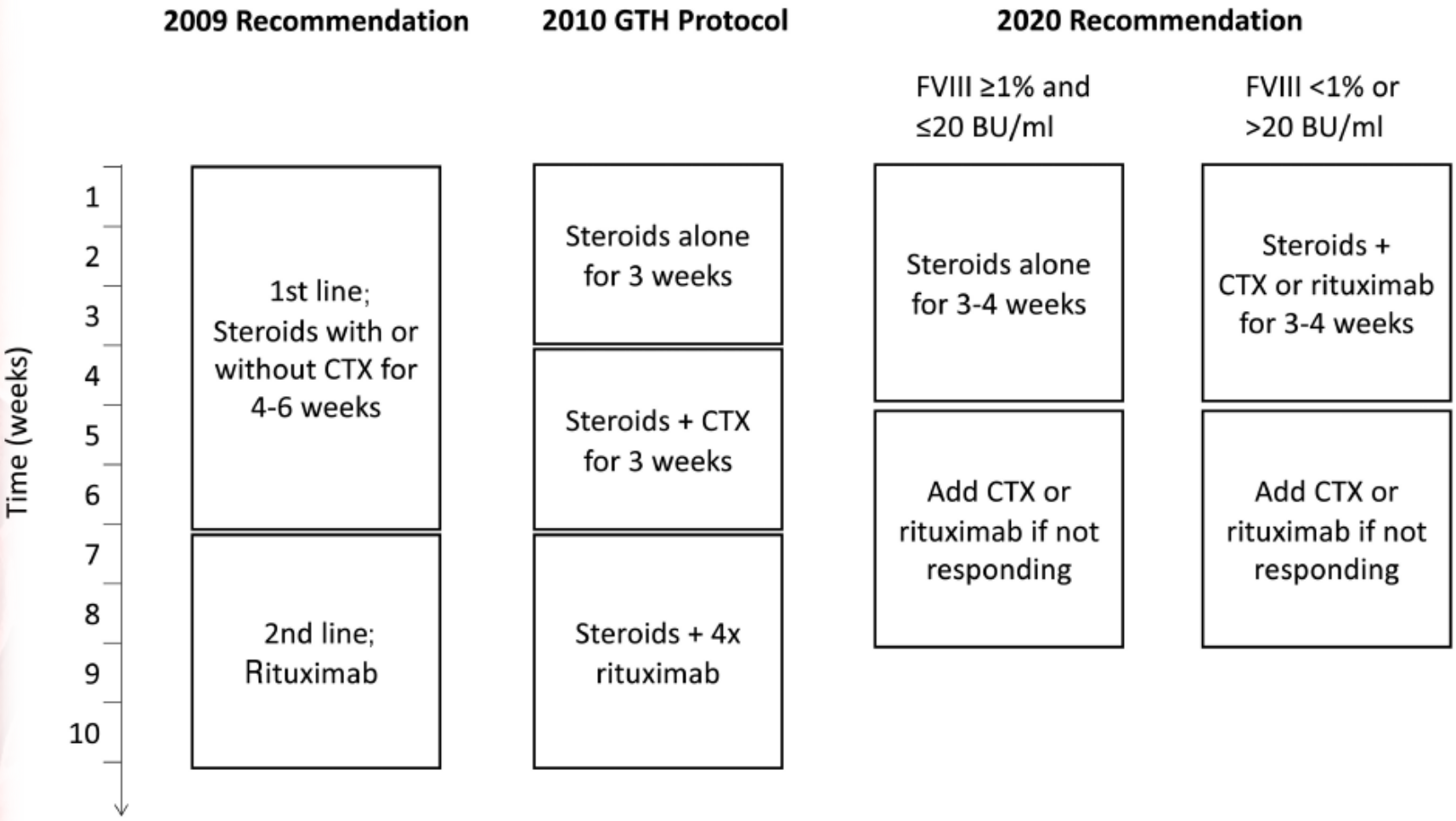
- Seconda scelta: rituxumab 375 mg/m2 q7 x 4
- Seconda scelta: ciclofosfamide 2 mg/kg giorno

- Regimi alternativi: plasmaferesi, azatioprina, vincristina, micofenolato, IgVena
- Protocolli combinati

Tiede A et al Haematologica 2020

Strategie terapeutiche

Eradicare l'inibitore



Tiede A et al Haematologica 2020

Gravidanza

- ✓ EACH2: 42 donne con AHA associate a gravidanza
- ✓ Risposta a terapia analoga a restante coorte
- ✓ Steroide 70% vs steroide + immunosoppressore 30%: non differenze significative
- ✓ Mortalità inferiore (effetto età)
- ✓ Attenzione a farmaci embriotossici

Knoebl P et al Journal of Thrombosis and Haemostasis 2012

Take home messages

- Sospettare in ogni paziente con emorragia e prolungamento isolato aPTT
- Tessuti molli, mucose, muscoli regioni maggiormente coinvolte
- Spesso emorragie di entità severa, mortalità non trascurabile
- 50% delle AHA sono sottese da patologia sottostante
- Test diagnostici: mixing test, attività FVIII e test FVIII inibitore (Bethesda)
- Strategie parallele: trattare sanguinamento ed eradicazione inibitore

Clinica di Medicina Interna a indirizzo oncologico

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