Inibitori specifici ed aspecifici della coagulazione

INIBITORI IDIOPATICI

Antonio Coppola

Centro di Riferimento Regionale per le Emocoagulopatie

AOU Federico II, Napoli

un venerdì pomeriggio al Centro Emostasi…

‘ Rianimazione, vorremmo veniste per un uomo di 68 anni che abbiamo dovuto intubare in Maxillo…
… in poche ore si è fatto un ematoma della lingua e del retrofaringe spaventoso… stamattina ha praticato una biopsia di una lesione dietro il pilastro tonsillare, pare sia un linfoma…

… i parenti dicono che ha avuto tanti interventi, ma mai nessun problema… ‘

o ancora bussano in Ambulatorio…

‘ scusa, quando hai un attimo vorrei parlarti di un vecchietto che seguiamo in Cardiologia, ha messo due stents coronarici un anno fa, da qualche tempo fa delle grosse ecchimosi…

… era in doppia antiaggregazione. Abbiamo tolto il clopidogrel…

…e invece di andare meglio, si è presentato stamattina con un ematoma
gli prende tutto l’arto inferiore dx ’

Cosa hanno in comune questi casi ?

- Manifestazioni emorragiche, talora gravi, ad insorgenza recente, improvvisa, spontanee o post-traumatiche
- assenza di storia familiare e personale di emorragia

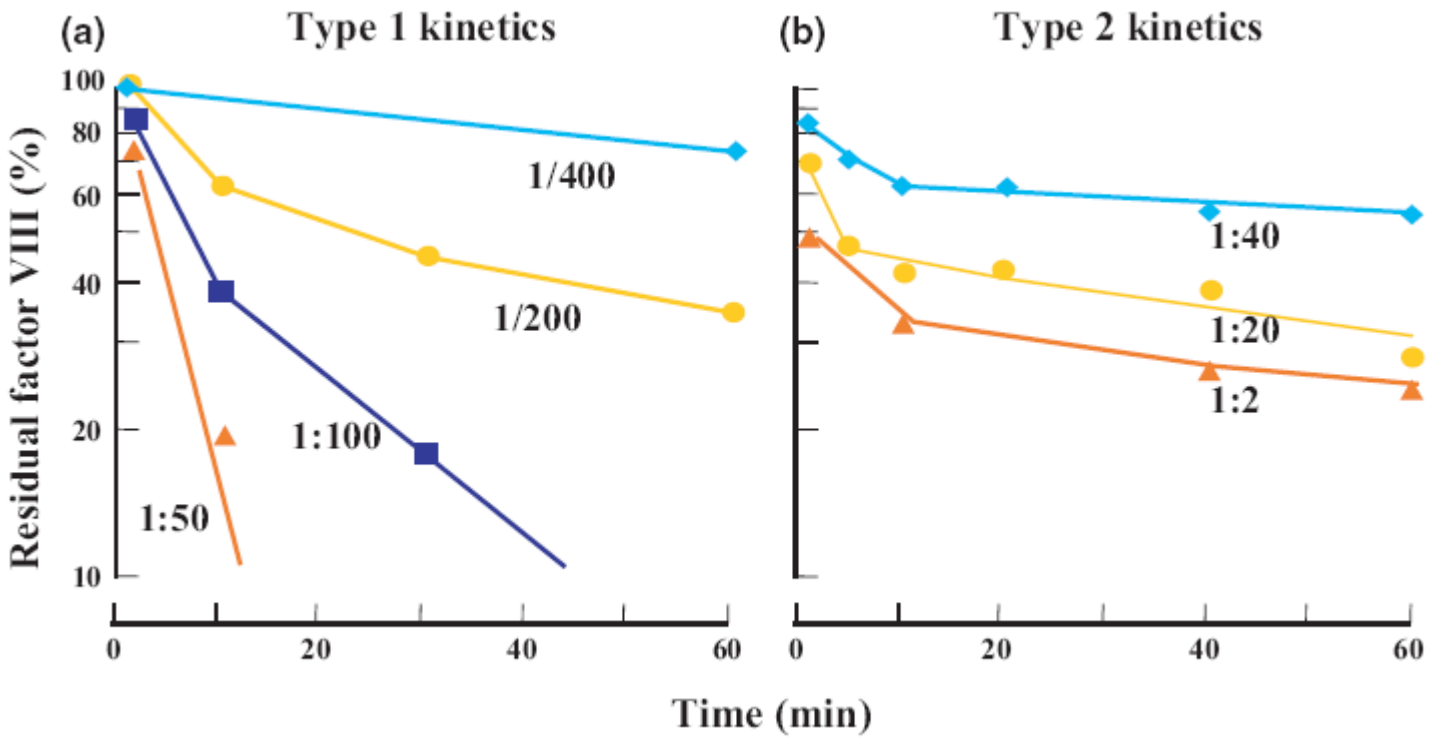
e agli esami di laboratorio

- **Allungamento di APTT**

Emofilia acquisita

Acquired hemophilia

- Rare bleeding disorder (**~ 1.5 in 1x10^6 year**) occurring in subjects with negative personal and family history of bleeding.
- caused
  partiall
  and/or
  coagul



Acquired hemophilia

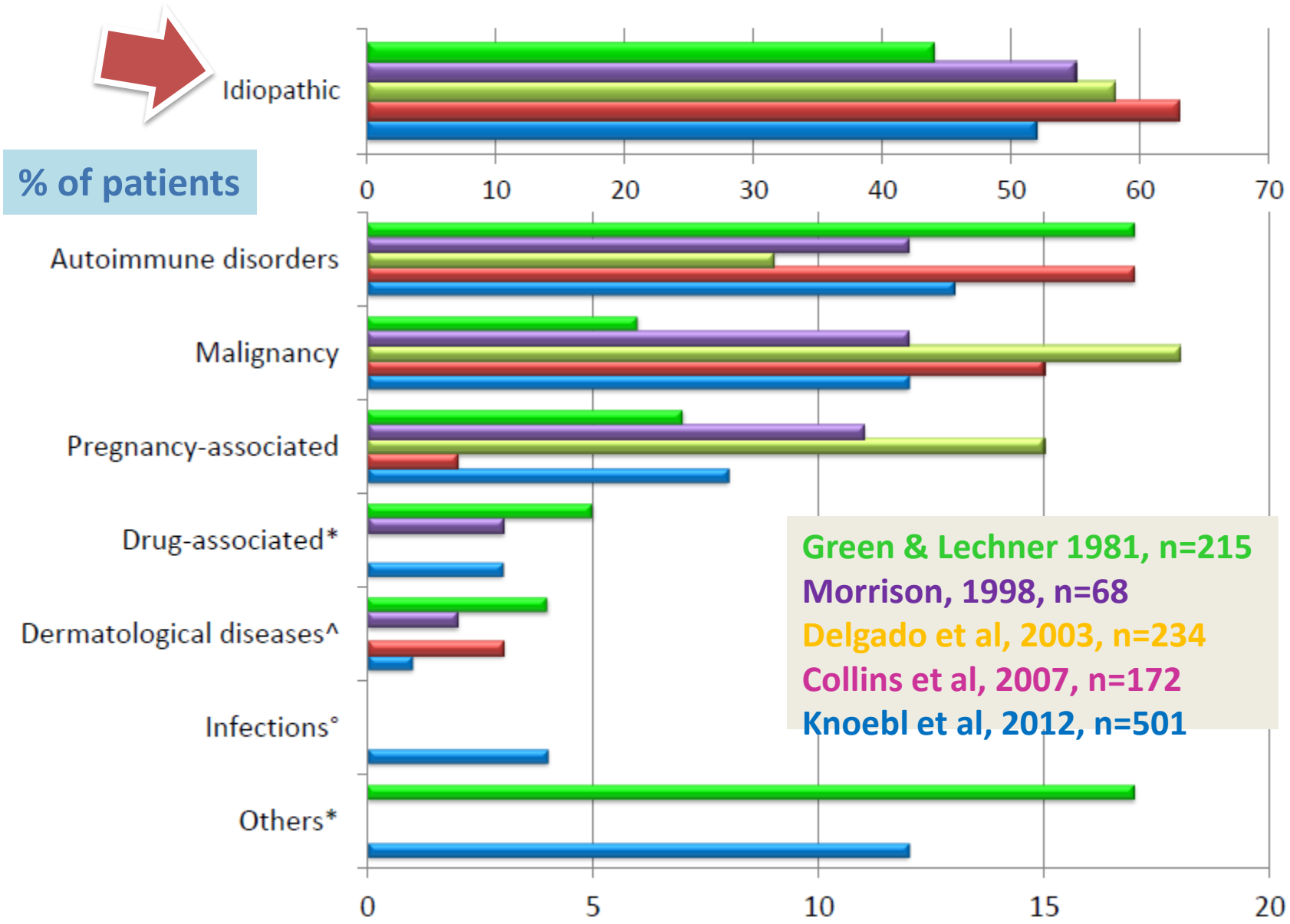
- Rare bleeding disorder (**~ 1.5 in 1x10^6 year**) occurring in subjects with negative personal and family history of bleeding.
- caused by **circulating auto-antibodies**, that partially or completely neutralize function and/or accelerate clearance of a specific coagulation factor (inhibitors).
- Factor VIII (FVIII) inhibitors are the most commonly reported autoantibodies, therefore AH is in the majority of cases an acquired Factor VIII deficiency (**acquired hemophilia A, AHA**).

Acquired coagulation inhibitors

Autoantibody Against	Characteristic	Associated Conditions
FI	IgG, IgA, IgM	Idiopathic, pregnancy, autoimmune disorders, interferon therapy
FII	IgG	Idiopathic, bovine thrombin, autoimmune disorders (SLE, RA)
FV	IgG	Bovine thrombin, surgery, antibiotic therapy (β-lactam group), malignancies
FVII	IgG	Idiopathic, malignancies, autoimmune disorders
FIX	IgG_4	Idiopathic, autoimmune disorders, postpartum
FX	IgG	Idiopathic, malignancies, autoimmune disorders, antibiotic
FXI	IgG	Malignancies, autoimmune disorders (SLE)
FXIII	IgG directed against A or B FXIII subunits	MGUS, autoimmune disorders (RA, SLE), drugs (isoniazid, penicillin, phenytoin, and amiodarone)

Franchini et al, Semin Thromb Hemost 2012

Prevalence of idiopathic and secondary AHA

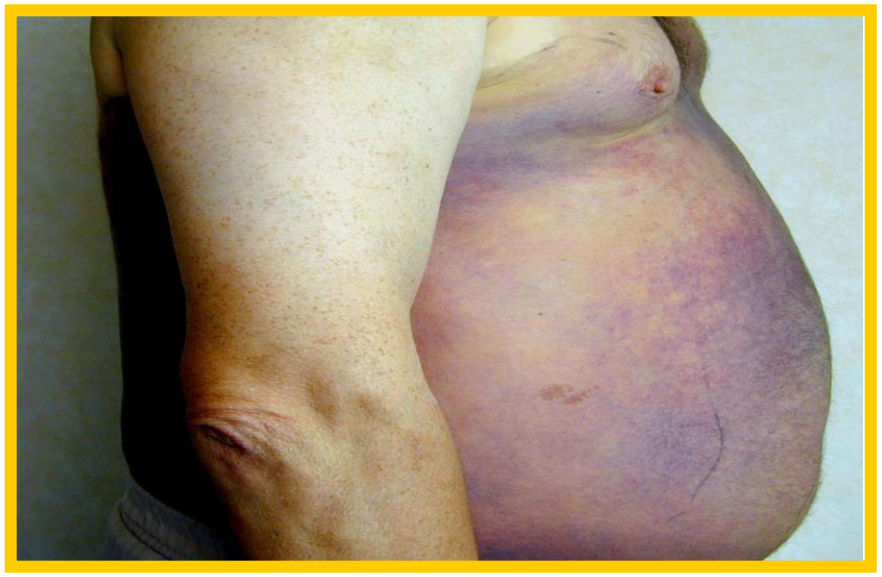


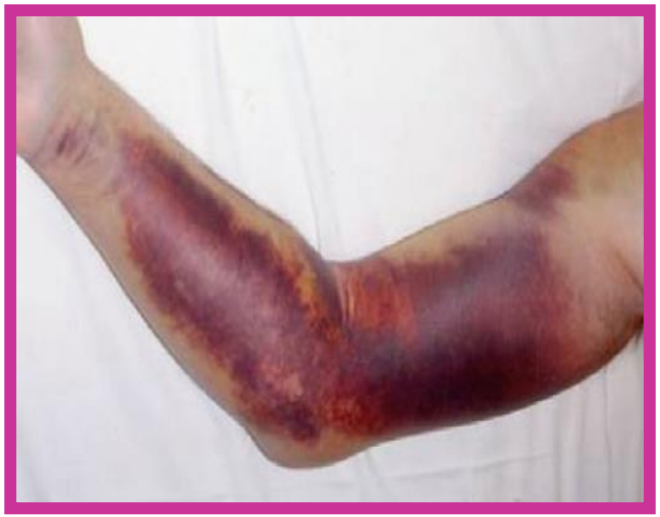
Coppola et al, Semin Thromb Hemost 2012

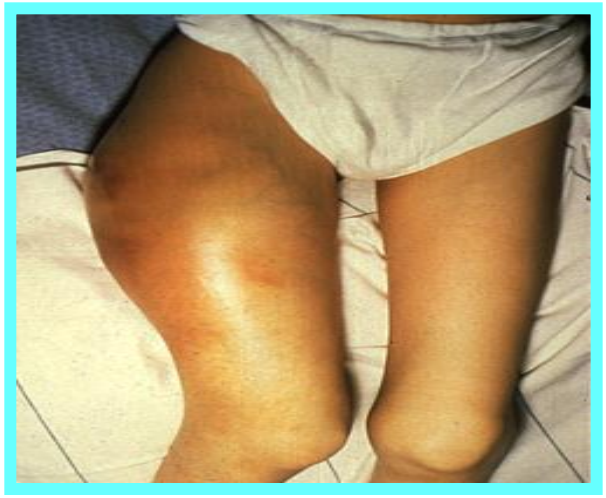
The Registries in the 2000s

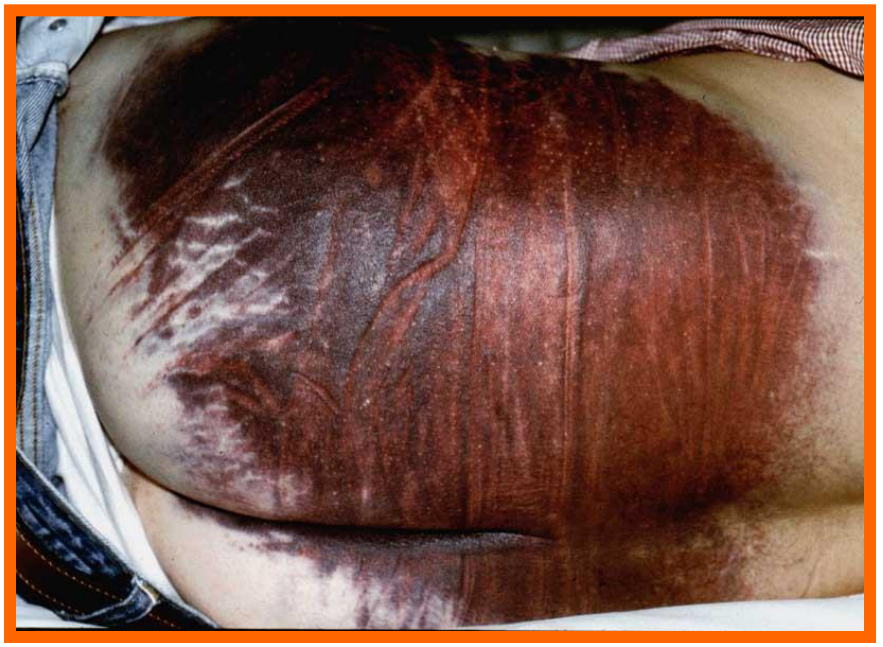
- **RIEA**: Italian Registry, prospective, 2001-2002
- **UKHCDO** Survey: prospective, 2001-2003
- **SACHA**: **S**urveillance des **A**uto-anti**C**orps anti-facteur **H**uit **A**cquise, France, prospective, 2001-2005
- **EACH**: European Registry, retrospective, 2003-2005
- **EACH2**: European Registry, Prospective, web-based collection, 2003-2008

A clinical challenge









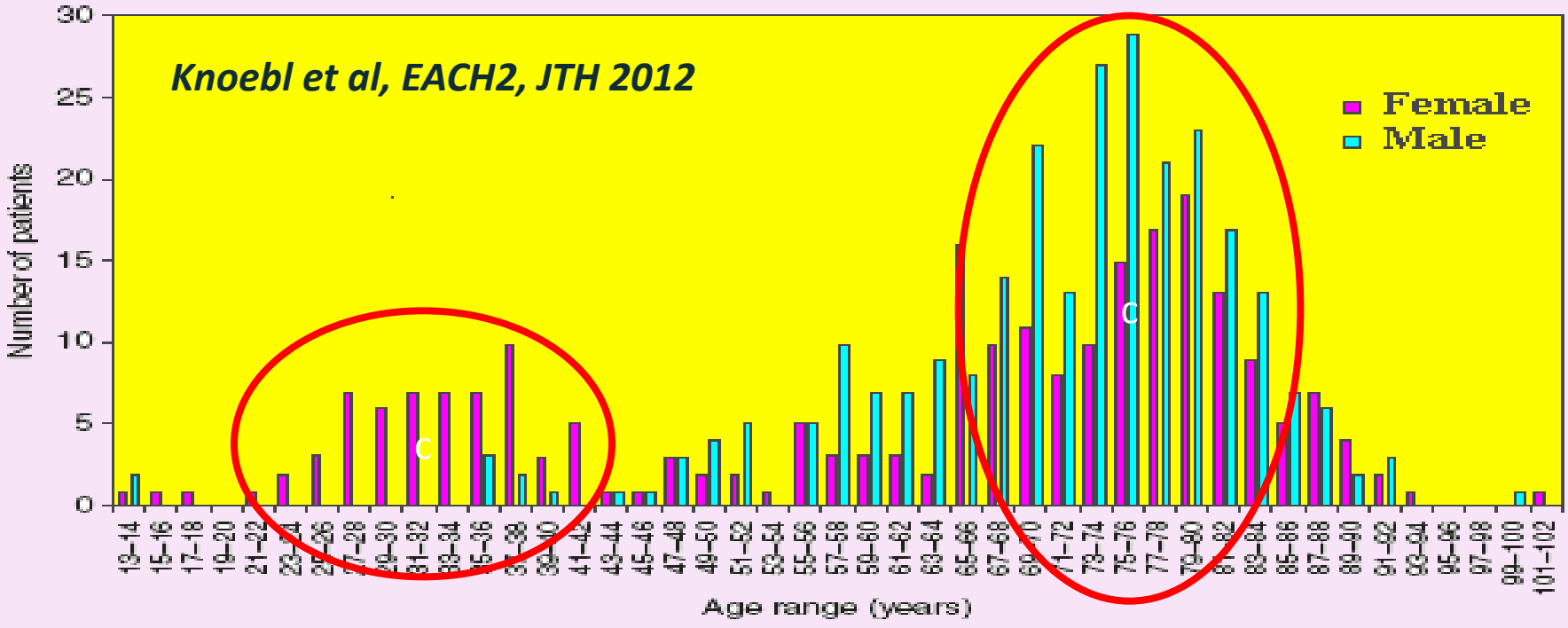
Bleeding and mortality rates in AHA*

Author, Year (Patients)	Bleeding			Mortality	
	Major or Severe	Requiring Hemostatic Treatment	No Bleeding	Bleeding-Related	Overall
Green and Lechner, 1981 ($n = 215$)[3]	87%				22%
Morrison et al, 1993 ($n = 65$)[21]				6.2%	15.4%
Bossi et al, 1998 ($n = 34$)[22]	75%				
Yee et al, 2000 ($n = 24$)[23]				11%	
Delgado et al, 2003 ($n = 234$)[2]					20%
Collins et al, 2004 ($n = 18$)[12]		66%	0%	5.6%	33.3%
Baudo et al, 2004 ($n = 28$)[5]		92.8%			26.7%[b]
Collins et al, 2007 ($n = 172$)[4]		76%[c]	1.3%[c]	9.1%[c]	41.8%[d]
Tay et al, 2009 ($n = 24$)[24]		54.1%		4.2%	25%
Knoebl et al, 2012 ($n = 501$)[8]	70.3%	70.5%	6.6%	4.5%[e]	26.3%[e]

***literature review of studies reporting at least 15 patients, unselected according to AHA-associated conditions, Coppola et al, Semin Thromb Hemost 2012**

Epidemiology of AHA

Age and gender

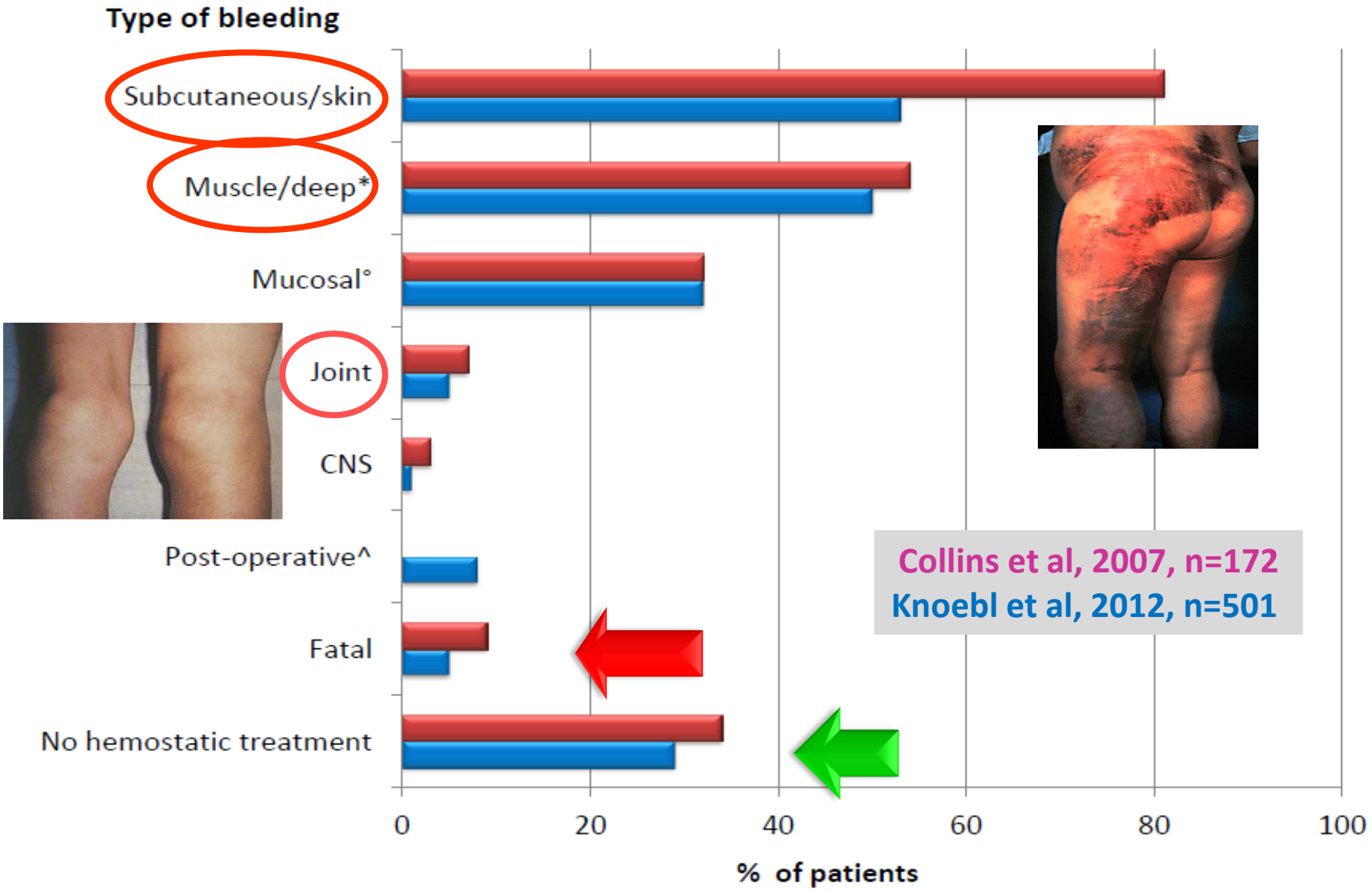


Registri	Età anni	Sesso M/F %	Pz ≥ 60 anni %
Knoebl 2012	75 (6-102)	58 / 42	79.5
Collins 2007	78 (2-98)	57 / 43	88.2

Incidence (in $1x10^6$ yr)

< 65 yrs	0.28
65-85 yrs	5.97
> 85 yrs	16.6

Types of bleeding



Collins et al, 2007, n=172
Knoebl et al, 2012, n=501

Coppola et al, Semin Thromb Hemost 2012

Bleeding and laboratory data at AHA diagnosis

	All	Severe	Non-se
Total no. of bleeding episodes [*n* (%)]	474	333 (70.3)	
Cause [*n* (%)]			
Spontaneous	367 (77.4)		
Trauma	40 (8.[illegible])		
Surgery			
Peripartum			2 (1.5)
Other			4 (3.0)
Site/type [*n* (%)]			
Skin		152 (46.2)	97 (71.9)
[illegible]	(30.2)	214 (65.0)	21 (15.6)
[illegible]	150 (31.6)	113 (34.4)	35 (25.9)
[illegible]	23 (4.9)	17 (5.2)	6 (4.4)
[illegible]	5 (1.1)	5 (1.5)	0 (0)
Bleed[illegible]			
Median age [years]	74.0 (61.1–80.3)	74.4 (64.1–80)	71.7 (51.8–80.9)
Gender male:female [*n* (ratio)]	242:222 (1.1)	175:154 (1.14)	67:68 (1.0)
Median FVIII activity [U dL^{-1}]	2 (1–5)	2 (1–5)	2 (0–5)
Median inhibitor titer [BU mL^{-1}]	19 (5.5–64.0)	13 (4.9–40.8)	10 (1.9–32.5)
Hb [g dL^{-1}]	8.9 (7.3–11.1)	8.5 (7.0–10.0)	11.1 (9.2–12.8)

FVIII levels and inhibitor titers at diagnosis do not predict severity of bleeding

Knoebl P, Marco P, Baudo F, Collins P, Huth-Kühne A, Nemes L, Pellegrini F, Tengborn L, Lévesque H, on behalf of the EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2) *J Thromb Haemost* 2012; **10**: 622–31.

Manifestazioni emorragiche,
storia personale e familiare negativa
per emorragia,
Allungamento APTT con PT normale

Escludere presenza
di eparina
(anamnesi, tempo di
trombina e di reptilasi)

Tests di miscela
(APTT su miscele a diverso rapporto di plasma
del paziente e controllo. **Incubazione ≥2 h, 37 C**)

APTT corretto

Deficit specifico di uno o più
fattori della "via intrinseca"

APTT allungato

Escludere
Lupus Anticoagulant*

Dosaggi FVIII, FIX, FXI, FXII

Riduzione
di **più** fattori

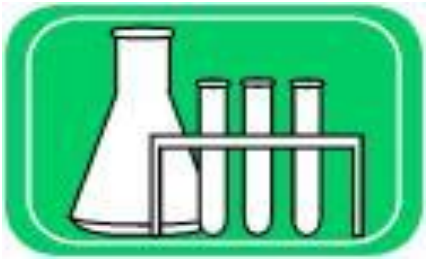
Riduzione del **FVIII:C**

Tests su
plasma diluito

Titolazione dell'inibitore
(metodo Bethesda mod. Nijmegen)

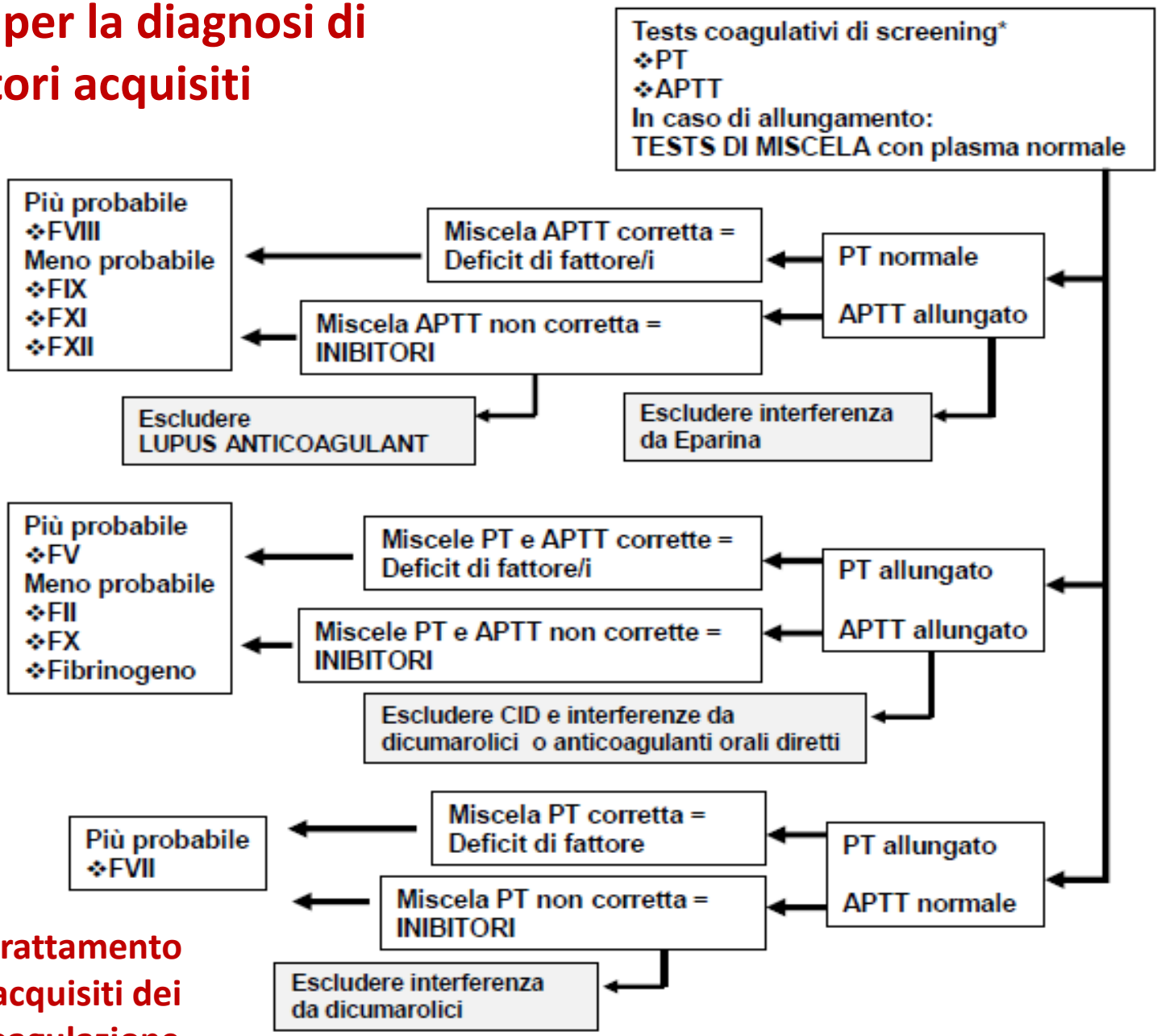
**DIAGNOSI DI
EMOFILIA A ACQUISITA**

Algoritmo per la diagnosi di emofilia A acquisita



Diagnosi e trattamento degli inibitori acquisiti dei fattori della coagulazione. Raccomandazioni AICE 2014

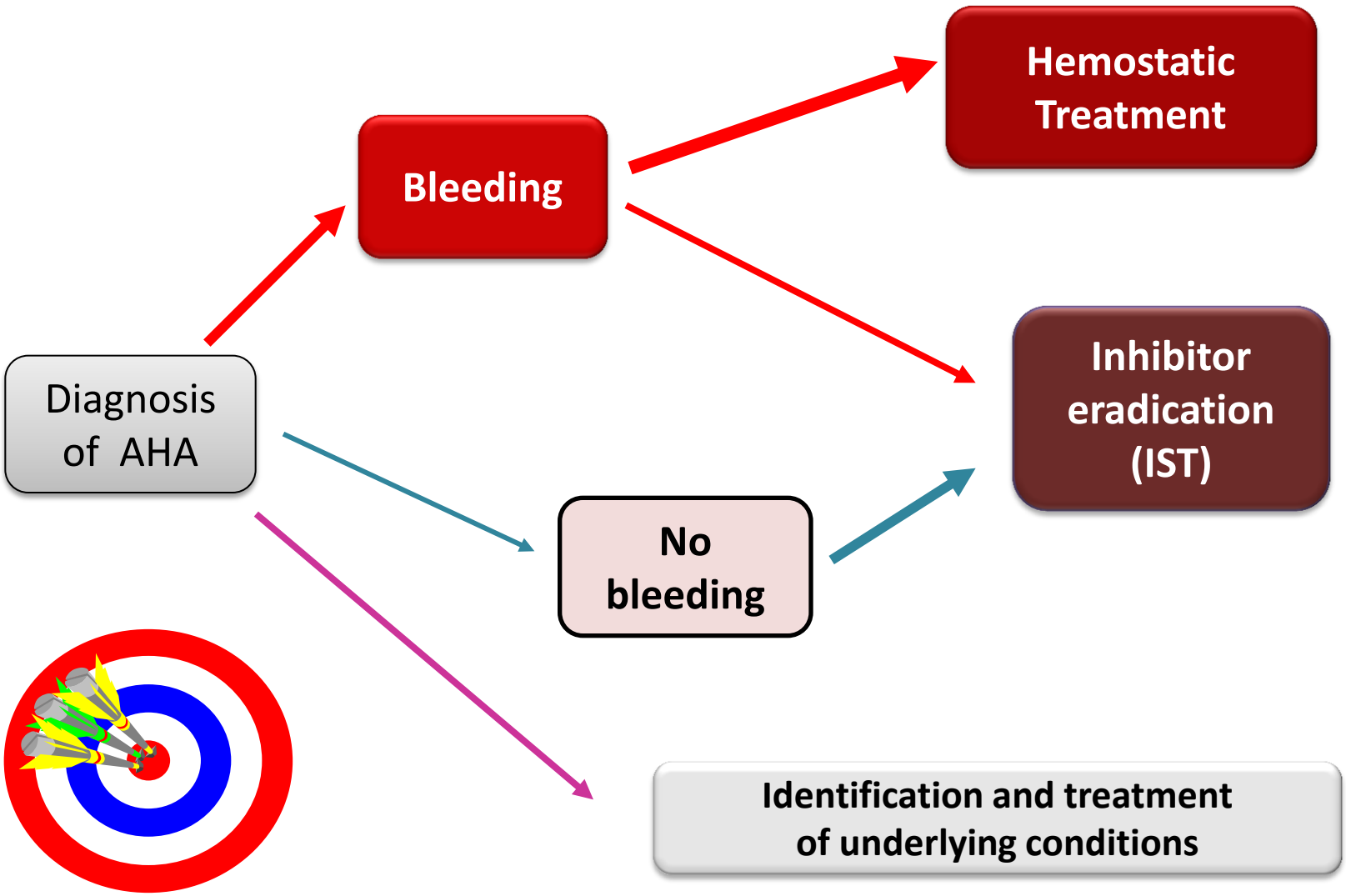
Algoritmo per la diagnosi di inibitori acquisiti



*nella norma in caso di inibitore anti-FXIII

Diagnosi e trattamento degli inibitori acquisiti dei fattori della coagulazione. Raccomandazioni AICE 2014

Management


Hemostatic Treatment
Bleeding
Inhibitor eradication (IST)
Diagnosis of AHA
No bleeding
Identification and treatment of underlying conditions

International recommendations on the diagnosis and treatment of patients with acquired hemophilia A

Angela Huth-Kühne,[1] Francesco Baudo,[2] Peter Collins,[3] Jørgen Ingerslev,[4] Craig M. Kessler,[5] Hervé Lévesque,[6] Maria Eva Mingot Castellano,[7] Midori Shima,[8] and Jean St-Louis[9]

ABSTRACT

Acquired hemophilia A (AHA) is a rare bleeding disorder characterized by autoantibodies directed against circulating coagulation factor (F) VIII. Typically, patients with no prior history of a bleeding disorder present with spontaneous bleeding and an isolated prolonged aPTT. AHA may, however, present without any bleeding symptoms, therefore an isolated prolonged aPTT should always be investigated further irrespective of the clinical findings. Control of acute bleeding is the first priority, and we recommend first-line therapy with bypassing agents such as recombinant activated FVII or activated prothrombin complex concentrate. Once the diagnosis has been achieved, immediate autoantibody eradication to reduce subsequent bleeding risk should be performed. We recommend initial treatment with corticosteroids or combination therapy with corticosteroids and cyclophosphamide and suggest second-line therapy with rituximab if first-line therapy fails or is contraindicated. In contrast to congenital hemophilia, no comparative studies exist to support treatment recommendations for patients with AHA, therefore treatment guidance must rely on the expertise and clinical experience of specialists in the field. The aim of this document is to provide a set of international practice guidelines based on our collective clinical experience in treating patients with AHA and contribute to improved care for this patient group.

Haematologica 2009; 94:566-575

Raccomandazioni per il trattamento delle emorragie

Sintesi della raccomandazione	Grado
'Wait and watch' nei pazienti senza manifestazioni emorragiche di rileivo	2C
Rimozione ove possibile della verosimile condizione scatenante approccio prioritario	2C
Acido tranexamico per emorragie mucose non gravi	2B
Agenti bypassanti trattamento di prima linea in pazienti con emofilia A acquisita ed emorragie clinicamente significative	1B
FVIII e DDAVP da riservare in paziento con FVIII misurabile e bassi titoli anticorpali. Monitoraggio assiduo livelli FVIII raggiunti e risposta anamnestica	2C
Switch precoce ad agente bypassante alternativo in caso di insuccesso	2C
Plasmaferesi e immunoadsorbimento da considerare in pazienti con emorragie gravi, non responsive ai bypassanti o per procedure invasive urgenti	2B

Diagnosi e trattamento degli inibitori acquisiti dei fattori della coagulazione. Raccomandazioni AICE 2014

[Intervention Review]

Interventions for treating acute bleeding episodes in people with acquired hemophilia A

Yan Zeng[1a], Ruiqing Zhou[2], Xin Duan[3], Dan Long[4], Songtao Yang[5]

Authors' conclusions

No randomised clinical trials of hemostatic therapies for acquired hemophilia A were found. Thus, we are not able to draw any conclusions or make any recommendations on the optimal hemostatic therapies for acquired hemophilia A based on the highest quality of evidence. GIven that carrying out randomized controlled trials in this field is a complex task, the authors suggest that, while planning randomised controlled trials in which patients can be enrolled, clinicians treating the disease continue to base their choices on alternative, lower quality sources of evidence, which hopefully, in the future, will also be appraised and incorporated in a Cochrane Review.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.
Publication status and date: New, published in Issue 8, 2014.
Review content assessed as up-to-date: 14 August 2014.

THE COCHRANE COLLABORATION®

Bypassing agents or replacement treatment ?

Table 2. Hemostatic treatment used for patients with acquired hemophilia A

Hemostatic treatment modality	Total no. of patients treated (%)	No. of patients treated with only this agent (%)
None	51 (34.2)	–
FEIBA	49 (32.9)	25 (16.8)
rFVIIa	47 (31.5)	21 (14.1)
Human FVIII	38 (25.5)	15 (10.1)
Desmopressin	7 (4.7)	2 (1.3)
Porcine FVIII	3 (1.3)	0 (0)

Many patients treated with more than 1 hemostatic agent. Data on response to treatment not collected.

Collins et al, UKHCDO, Blood 2007

	First-line bleeding control	
Hemostatic agent	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

p= 0.003

Baudo et al, EACH2 Registry, Blood 2012

Bypassing agents in AHA*

Author, Year	Design	Agent	Patients, *n* (Bleeds)	Efficacy, %		Other Findings
				First-Line Therapy	Salvage Treatment	
Hay et al, 1997[69]	Retrospective	rFVIIa	38 (74)	100[b]	75[b]	Median 28 doses (range 1–541), initial dose 90 μg/kg (45–181), every 2–6 h over a median 3.9 d (0–43).
Baudo et al, 2004[5]	Retrospective	rFVIIa	15 (20)	87[b,c]		Median 10 doses (range 1–60), initial dose 90 μg/kg (46–118), every 2–6 h over a median 2.75 d (0–8); 7 patients were treated by continuous infusion.
Sallah, 2004[72]	Retrospective	APCC	34 (55)	85[b,d]		75 IU/kg in 29 patients and 100 IU/kg in 5 patients. Median number of infusions 6 and 10 and time to complete response 36 and 48 h in severe and moderate bleeds, respectively.
Goudemand, 2004[73]	Retrospective	APCC	17 (55)	89[e]		Median dose 68 IU/kg (range 35–80) every 8–24 h over median 3.5 d (1–17).
Sumner et al, 2007[70]	Registries and literature review[f]	rFVIIa	139 (182[g])	83[e]	66[e]	Partially effective in 14% of cases. Ranges of administered dose 60–160 μg/kg, number of bolus 1–33, duration 1–7 d; 10 patients with 12 thrombotic events.
Knoebl et al, 2010[71]	Prospective, EACH2 Registry	rFVIIa APCC	NR (170) NR (64)	91[e] 94[e]		No significant difference in efficacy or severe adverse events between the two bypassing agents (1.4% myocardial infarction, 0.2% stroke, 1.0% venous thromboembolic events).
Ma et al, 2011[6]	Retrospective, HTRS Registry	rFVIIa	87 (193)	95[e]		Partially effective in 12% of bleeds. Median 3 doses (range 1–240), initial dose 90 μg/kg (22–270), over a median 1 d (1–60); One thromboembolic event.
Borg et al, 2011[7] 2013	Prospective, FEIBAHC study	APCC	23 (NR) 33	95[e]	91	Only 1 patient switched because of lack of efficacy. 75 IU/kg doses, 1–3 times daily. Treatment ≤ 7 d in 70% of patients. Two deep vein thromboses (in the same patient) and one DIC.
Borg, 2013	Prospective SACHA	rFVIIa APCC	27 6	81 100		

*studies reporting at least 15 treated patients; ***Coppola et al, Semin Thromb Hemost 2012***

rFVIIa: concerns

- Costs
- Thromboembolic risk

IN FOCUS

J Thromb Haemost 2004; 2: 1700–08.

Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity

L. M. ALEDORT
Mount Sinai School of Medicine, New York, New York, USA

MedWatch pharmacovigilance program and published case reports, 1999-2002

aPCC: 8.24 x 10^5 infusions (CI 4.71-13.4)

rFVIIa: 24.6 x 10^5 infusions (CI 19.1-31.2)

Adverse events - EACH 2 Registry

No. of patients [*n* (%)]	501 (100%)
Adverse events [*n* (%)]	
Total	171 (34.1%)
Stroke	1 (0.2%)
Myocardial infarction	7 (1.4%)
Venous thromboembolism	5 (1.0%)
	64 (12.8%)
	33 (6.6%)
	6 (1.2%)
	35 (7.0%)
	12 (2.4%)

13 (2.6%)

2 / 144 (1.4 %) **untreated patients**
5 / 174 (2.9 %) treated with rFVIIa
3 / 63 (4.8 %) treated with aPCC

3 unknown

Knoebl P, Marco P, Baudo F, Collins P, Huth-Kühne A, Nemes L, Pellegrini F, Tengborn L, Lévesque H, on behalf of the EACH2 Registry Contributors.
Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)
J Thromb Haemost 2012; **10**: 622–31.

aPCC: concerns

- Not lincensed in some Countries
- Anamnestic response
  - 6/63 (9.5%) in the EACH2 Registry (Baudo et al, Blood 2012)
- Association with antifibrinolytics (AF) ?
  - 6 patients (1 AHA), 3 bleeds and 8 surgeries (oral or i.v. AF); 10/11 (91%) rated excellent or good outcome, no thromboembolic adverse event

ORIGINAL ARTICLE *Inhibitors*

Combined treatment with APCC (FEIBA®) and tranexamic acid in patients with haemophilia A with inhibitors and in patients with acquired haemophilia A – a two-centre experience

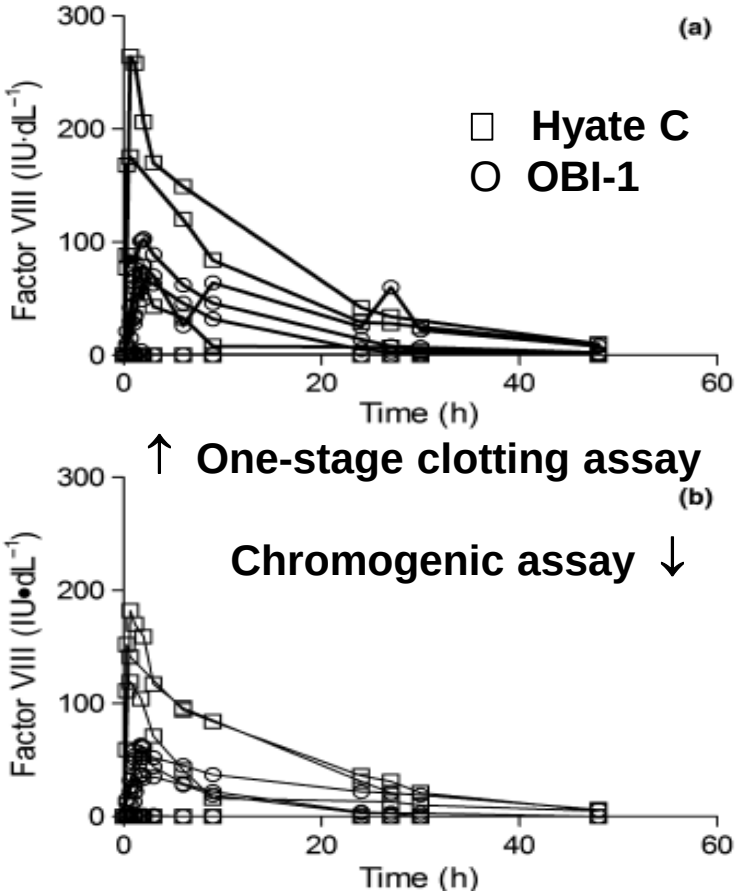
Haemophilia (2012), **18**, 544–549

M. HOLMSTRÖM,* H. T. T. TRAN† and P. A. HOLME‡

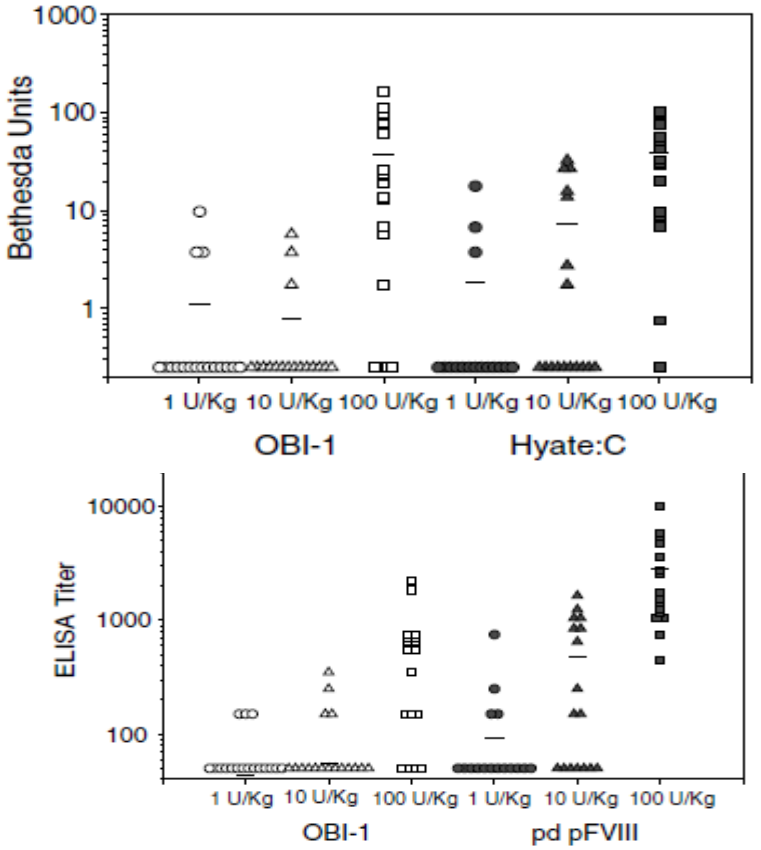
Back to the future: Recombinant Porcine FVIII

OBI-1

B-domain deleted
Synthesized in baby hamster kidney cells
Serum-free medium (no other porcine or animal proteins)

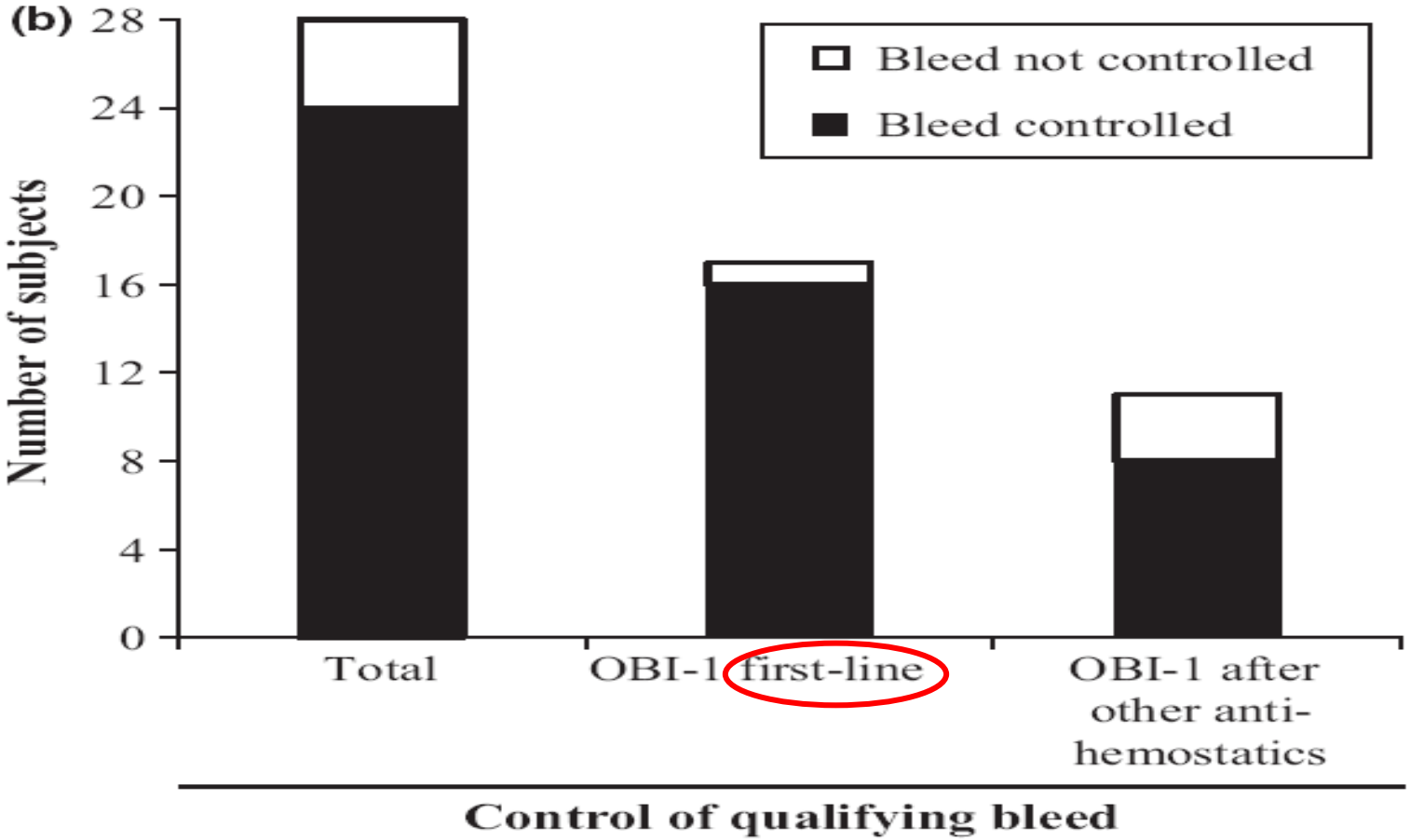


Kempton et al, Haemophilia 2012



Parker et al, J Thromb Hemost 2004

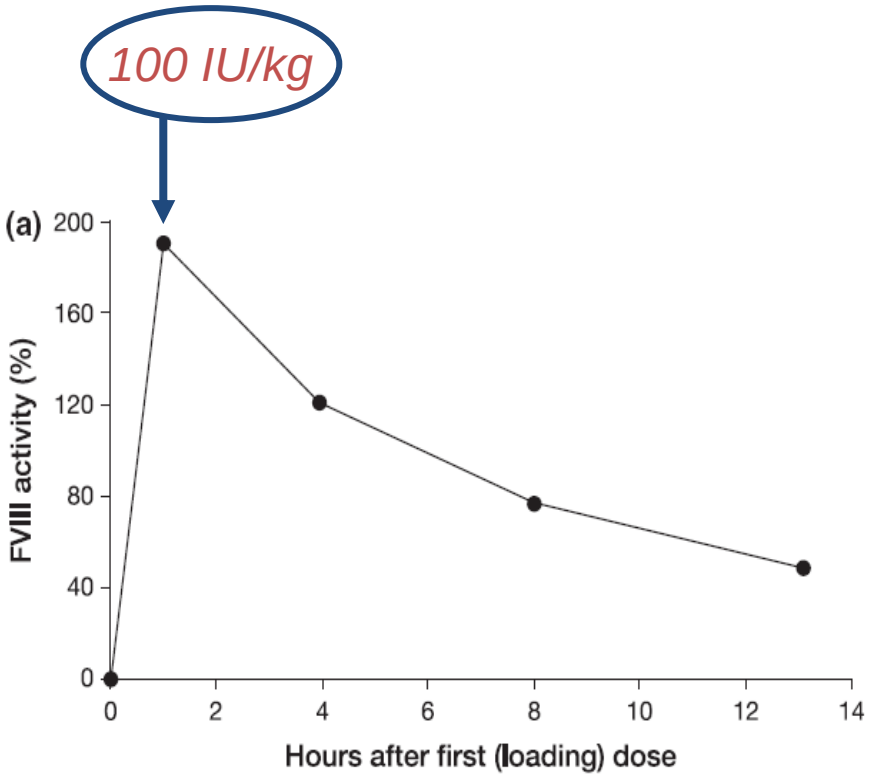
OBI-1 Phase 2/3 trial
Initial fixed dose: *200 IU/kg*

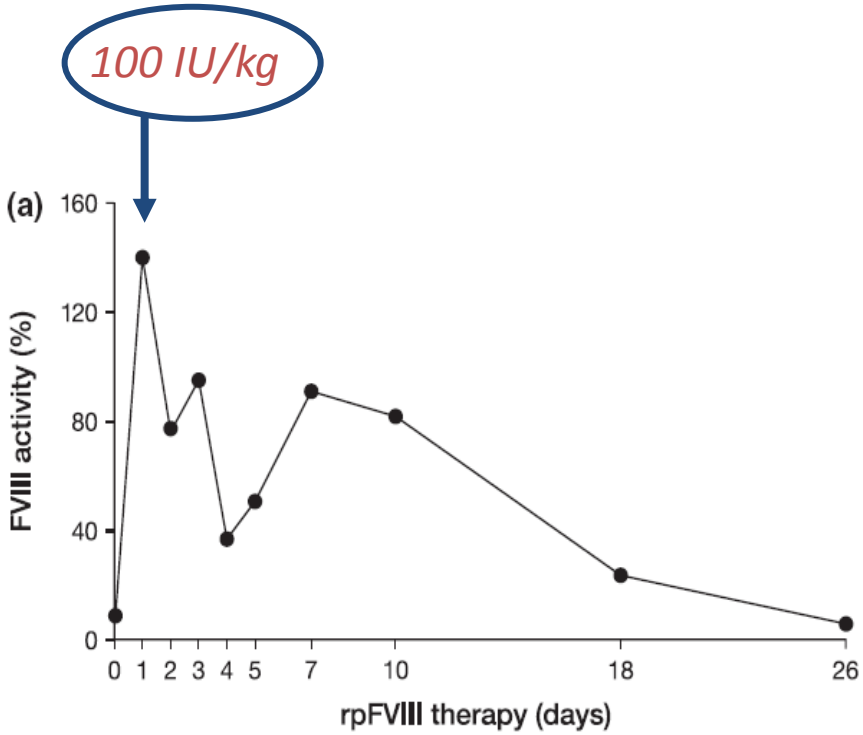


29 patients, median age 70 years

Kruse-Jarres R et al. Haemophilia 2015; 21: 162-70

Clinical experience ongoing





Case series, 7 patients, median age: 78 years

Tarantino D et al. Haemophilia 2016

Supplemental Table 1: Efficacy assessment criteria

Assessment criteria			Efficacy[a] assessment	Response
Control of bleeding	Clinical assessment	FVIII activity levels		
Bleeding stopped	Clinical control	≥50%	Effective	Positive
Bleeding reduced	Clinical stabilization, or Improvement, or Alternative reason for bleeding	≥ 20%	Partially effective	Positive
Bleeding slightly reduced or unchanged	Not clinically stable	<50%	Poorly effective	Negative
Bleeding worsening	Clinically deteriorating	<20%	Not effective	Negative

[a] If a clinical assessment was positive but FVIII activity levels were below targeted levels, the response was determined by the clinical assessment.

Kruse-Jarres et al, rpFVIII, Haemophilia 2015

Eradication: steroid-based or rituximab-based immunosuppression ?

Table 3. Response to first-line immunosuppression

Regimen	n	CR, n (%)	Days from start of immunosuppression, median (IQR)			Relapse, n (%)	Stable CR, n (%)
			Inhibitor negative	FVIII > 70 IU/dL	IS stopped		
Steroids alone	142	83 (58)	66%	32 (15-51)	108 (55-208)	15 (18)	68 (48)
Steroids + cyclophosphamide	83	66 (80)		40 (18-81)	74 (52-151)	8 (12	58 (70)
Steroids + rituximab	28	18 (64)	46 (28-109)	35 (26-189)	62 (31-113)	0 (0)	18 (64)
Cytotoxic + rituximab	3	2 (67)	ND	ND	ND	0 (0)	2 (67)
Steroids + cytotoxic + rituximab	8	6 (75)	50 (20-122)	67 (45-113)	67 (29-129)	1 (17)	5 (63)
Rituximab alone	12	5 (42)	53, 145, 209, 334*	145, 209, 252, 334*	21, 21, 21, 21, 22*	0 (0)	5 (42)
Rituximab + any other agent	39	26 (67)	49 (28-93)	42 (28-138)	67 (31-109)	1 (3)	25 (64)
All rituximab-based regimens	51	31 (61)	65 (29-144)	64 (28-206)	43 (22-96)	1 (3)	30 (59)

56%

The outcome of first-line immunosuppressive therapy (IS) is shown. Complete remission (CR) was defined as inhibitor-negative, FVIII > 70 IU/dL, and immunosuppressive therapy stopped. Stable CR was defined as achieving CR with no relapse during follow-up. Because the groups are not matched, it is not appropriate to make statistical comparisons between the treatment arms.

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Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)

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Raccomandazioni per la terapia eradicante: AHA

Sintesi della raccomandazione	Grado
La terapia immunosoppressiva deve essere iniziata non appena possibile, idealmente appena formulata la diagnosi di emofilia A acquisita	1B
Prednisone (1-2 mg/Kg os) in monoterapia o in combinazione con ciclofosfamide (1-2 mg/Kg os) trattamento di prima linea	1B
Rituximab in monoterapia o in combinazione con altri agenti terapia di seconda linea in caso di mancata risposta a ter. di I linea entro 8-12 settimane	2B
Rituximab può essere indicato come agente di prima linea in pazienti con controindicazioni all'uso di farmaci immunosoppressori	2B
Associazione di più farmaci immunosoppressori (inclusa ciclosporina) e regimi di immunotolleranza ulteriori alternative in caso di mancata risposta	2C
HDIg non indicate come trattamento eradicante	1B
Risposta completa: persistente riscontro di inibitore negativo e FVIII >70%	2B
Tromboprofilassi nei pazienti con fattori di rischio tromboembolico, specie in caso di livelli di FVIII elevato in corso/al termine di terapia eradicante	2C

Diagnosi e trattamento degli inibitori acquisiti dei fattori della coagulazione. Raccomandazioni AICE 2014

Mortality - EACH2 Registry

Deaths* Cause of death	100 n (%)	20%
Fatal bleeding	16 (16)	3.2% of patients
Hemostatic therapy	0 (0)	
IST complications	**16 (16)**	3.2% of patients 3.3% of those receiving IST
Underlying disease	**45 (45)**	9% of patients 18.8% of patients with underlying disease
Other/unknown	39 (39)	

*n=501, median (range) follow-up: 318 (111-759) days

ORIGINAL ARTICLE

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Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2)

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Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study

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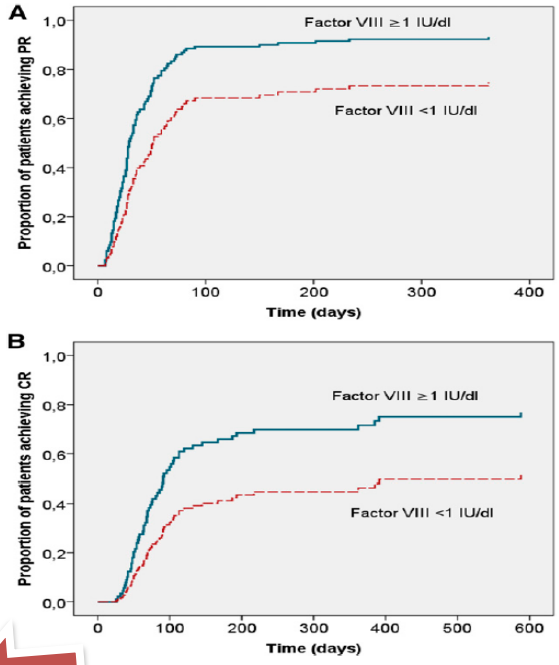
Table 4. Predictors of remission and survival: multivariate analysis

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).
*$P < .05$.
**$P < .01$.



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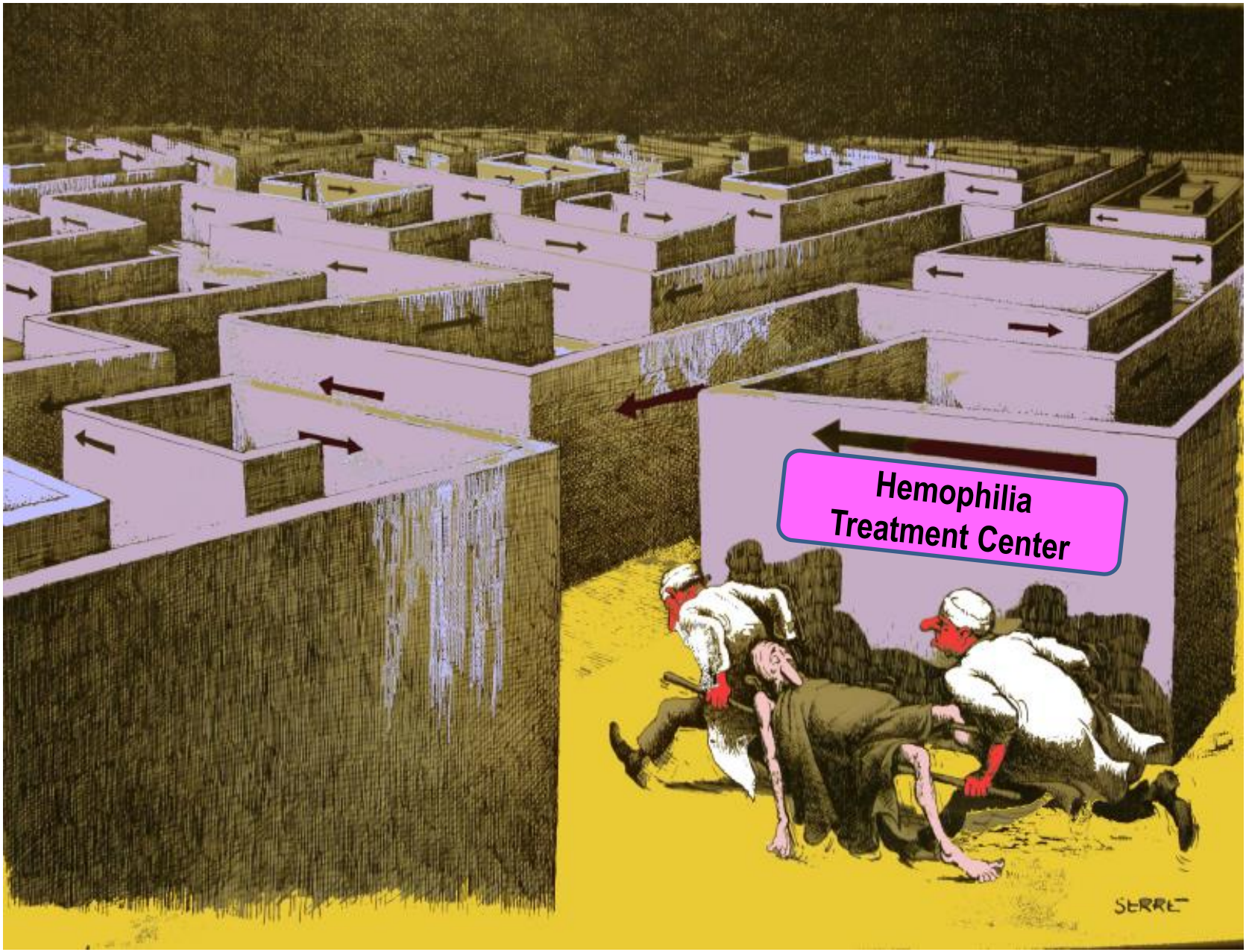
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