UNIVERSITA' DI PADOVA
Dipartimento di Medicina (DIMED)
UOSD – Malattie Trombotiche ed Emorragiche

MALATTIE EMORRAGICHE ACQUISITE E GESTIONE DEL SANGUINAMENTO ACUTO

Luca Spiezia
UOSD Malattie Trombotiche ed Emorragiche

Parte 1

COAGULOPATIE ACQUISITE

TROMBOTICHE

- SDR. DA ANTICORPI ANTIFOSFOLIPIDI
- GRAVIDANZA & TERAPIA ORMONALE
- NEOPLASIE (SOLIDE ED EMATOLOGICHE)
- EMOGLOBINURIA PAROSSISTICA NOTTURNA (EPN)
- MALATTIA DI BEHCET
- SDR. NEFROSICA

EMORRAGICHE

- AUTOIMMUNI
- DIFETTO DI VIT. K
- TERAPIA ANTICOAGULANTE
- COAGULOPATIA DILUIZIONALE

COMPLESSE

- TRAUMA
- TROMBOCITOPENIA INDOTTA DA EPARINA (HIT)
- COAGULAZIONE INTRAVASCOLARE DISSEMINATA
- CIRROSI EPATICA

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LE COAGULOPATIE EMORRAGICHE ACQUISITE AUTOIMMUNI

- Autoanticorpi specifici che neutralizzano l'attività specifica di un fattore (es. emofilia acquisita)

- Autoanticorpi specifici o aspecifici che formano un complesso immune col fattore aumentando la sua clearance dal circolo (es. VWD acquisita)

Emofilia Acquisita

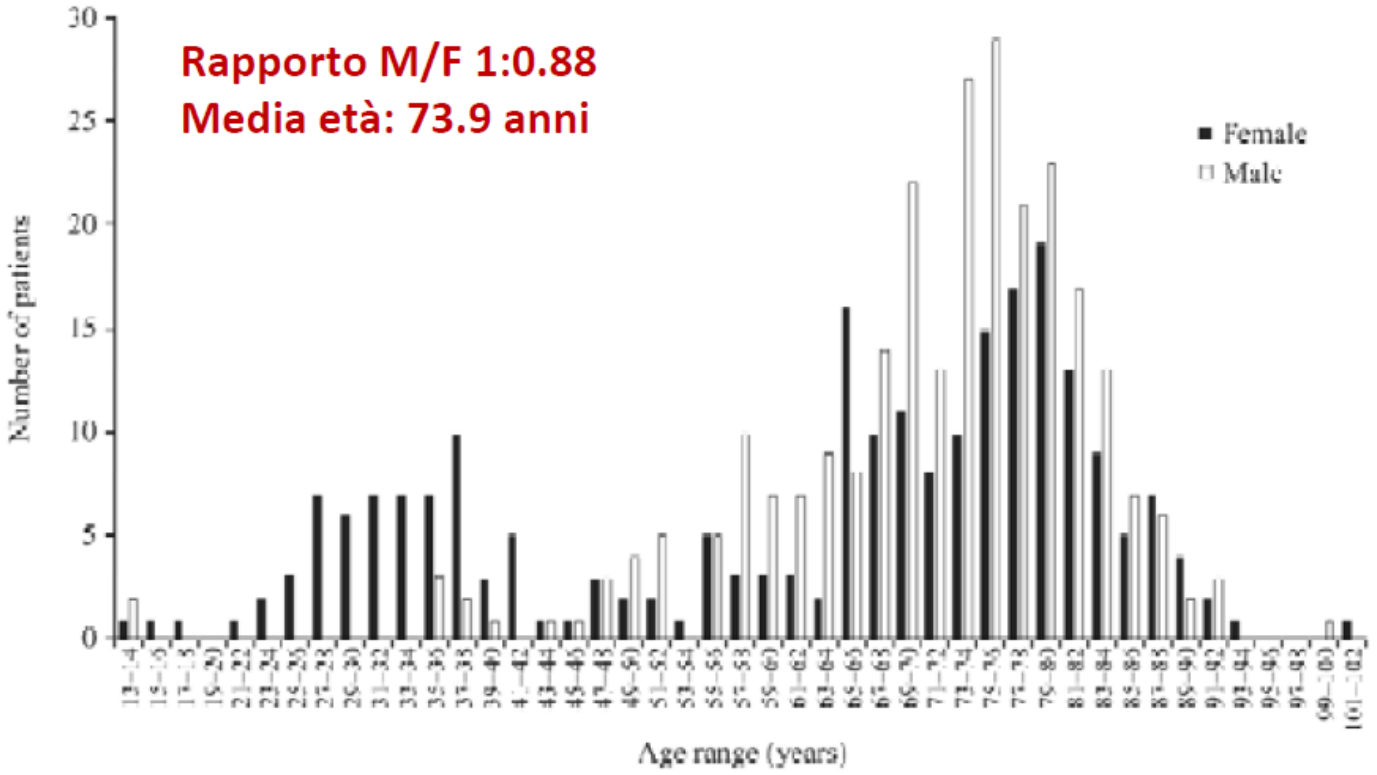
- Diatesi emorragica dovuta alla comparsa di autoanticorpi diretti contro un fattore della coagulazione (>95% dei casi: anticorpi anti –FVIII)

- Incidenza da 1 a 4 casi/milione anno

- Mortalità per emorragia ~10-15%

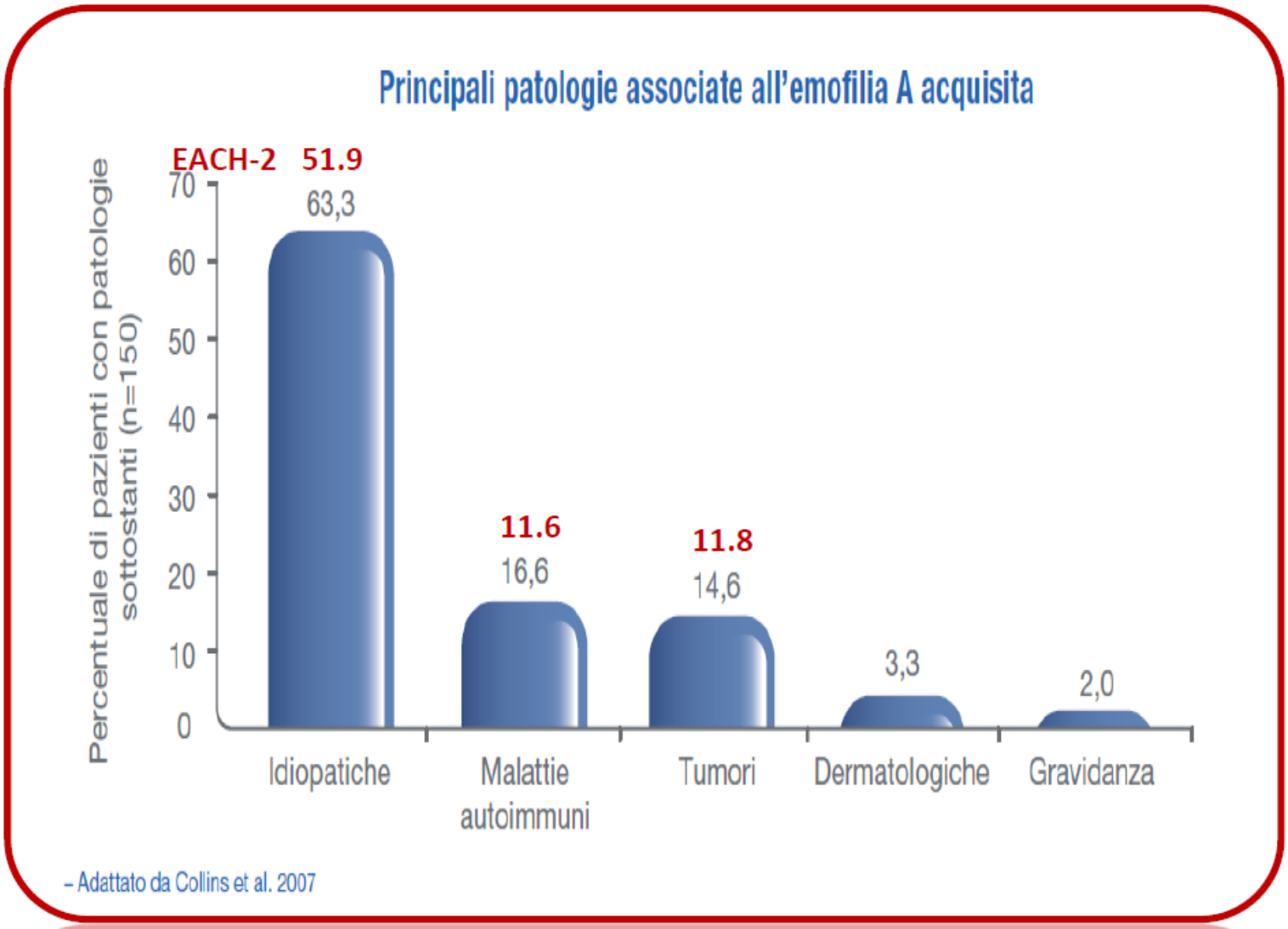
EACH-2: distribuzione per sesso e età

Figure 1. Histogram of age at diagnosis according to gender.



- Più frequente nell'anziano (14,7/milione/anno età >85 anni)
- Tra 20 e 40 anni picco di incidenza nelle donne nel peri- e post-partum

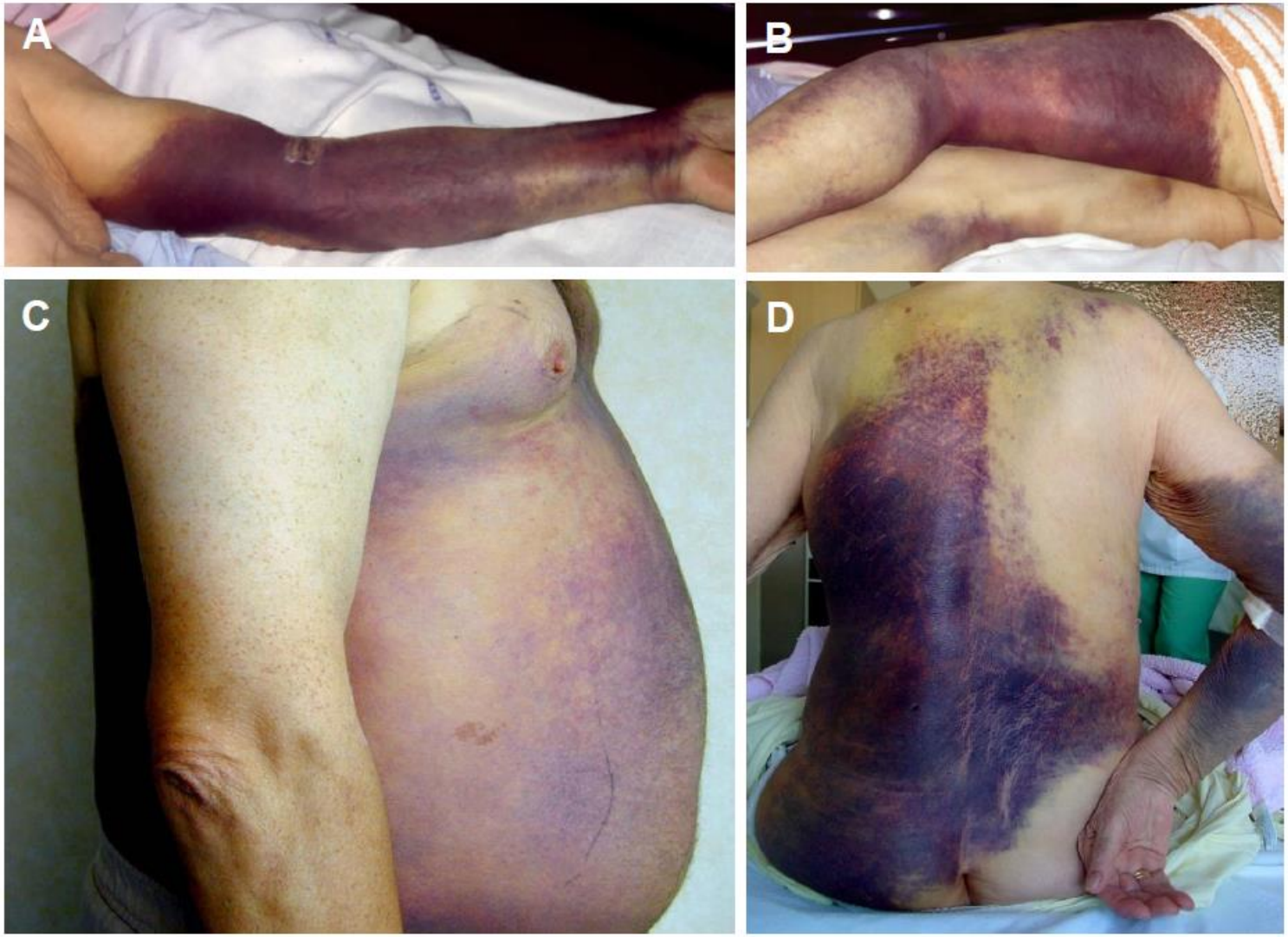
Emofilia A Acquisita



Rischio emorragico nell'emofilia acquisita

- **Diagnosi in seguito a emorragia 467/501 (93.2 %)**
  (Knoebl et al EACH-2, 2012)
- Vaste ecchimosi, spontanee (>80 % casi)
- Ematomi muscolari (ileo-psoas)
- Emorragie retroperitoneali
- Melena, epistassi, gengivorragia, ematuria, menorragia
- Spesso associati ad anemia acuta
- ***Emartri rari***

Manifestazioni cliniche all'esordio



Emofilia Acquisita: EMERGENZA CLINICA

Elevata mortalità da emorragia

- Variabile da 7.9% a 22%
- Più frequente entro le prime settimane dall'esordio
  - 9.1% (in meno di 9 giorni[1])
  - 16.9%[2]
- Correlata a:
  - procedure invasive per controllare l'emorragia
  - ritardo nella diagnosi
  - inadeguata terapia sostitutiva

1. Collins P. Blood, 2007;109:1870. 2. Baudo F. Blood Disorders in the Elderly In: Balducci L, et al. Cambridge University Press; 2007:389

DIAGNOSI DI LABORATORIO

Sospetto

- paziente senza anamnesi personale o familiare di patologie emorragiche
- **prolungamento isolato del aPTT** e PT normale

Diagnosi

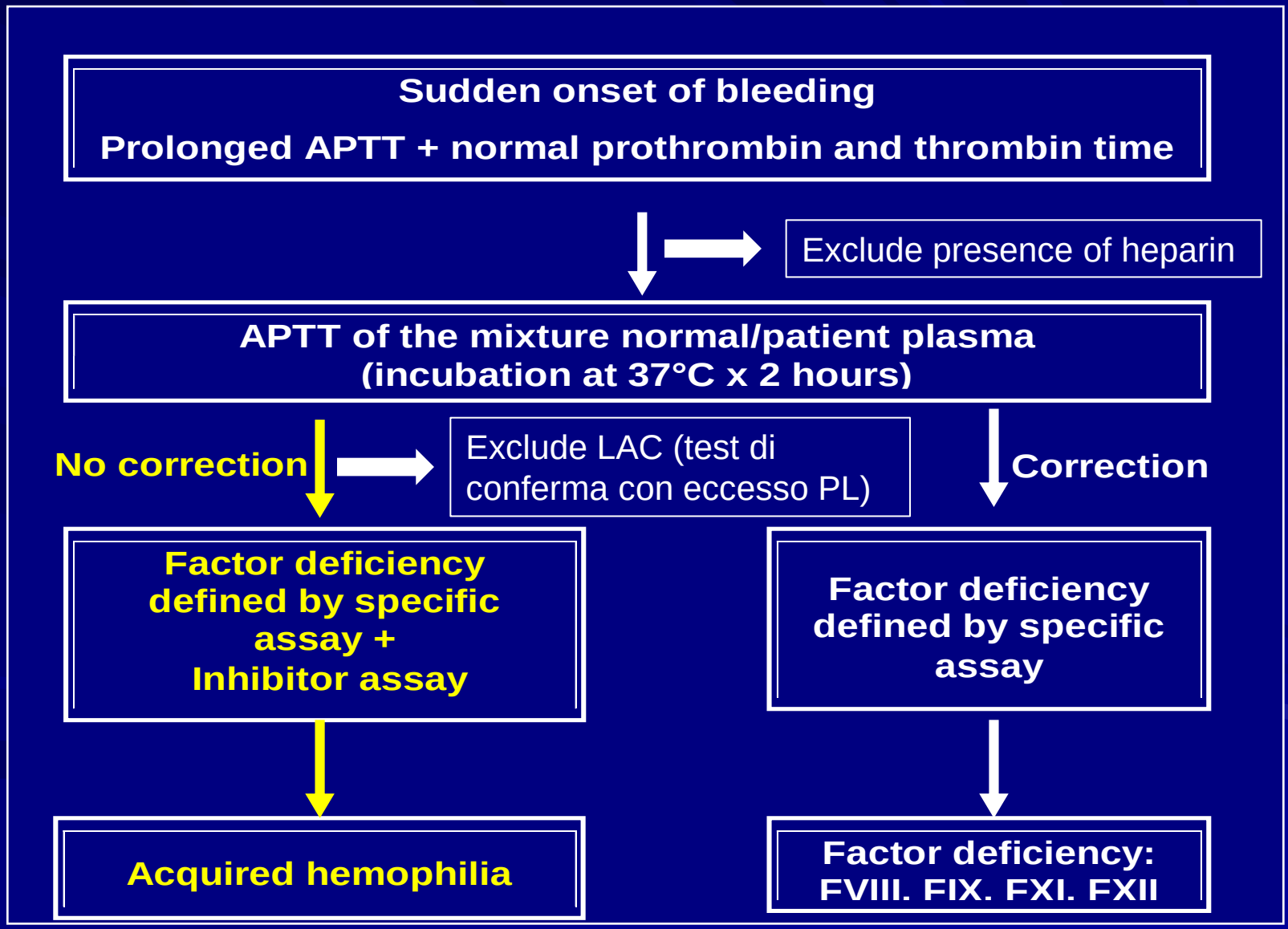
- aPTT non corretto dal "*mixing test*"

(incubazione del plasma del paziente con un volume equivalente di plasma normale a 37° per due ore)

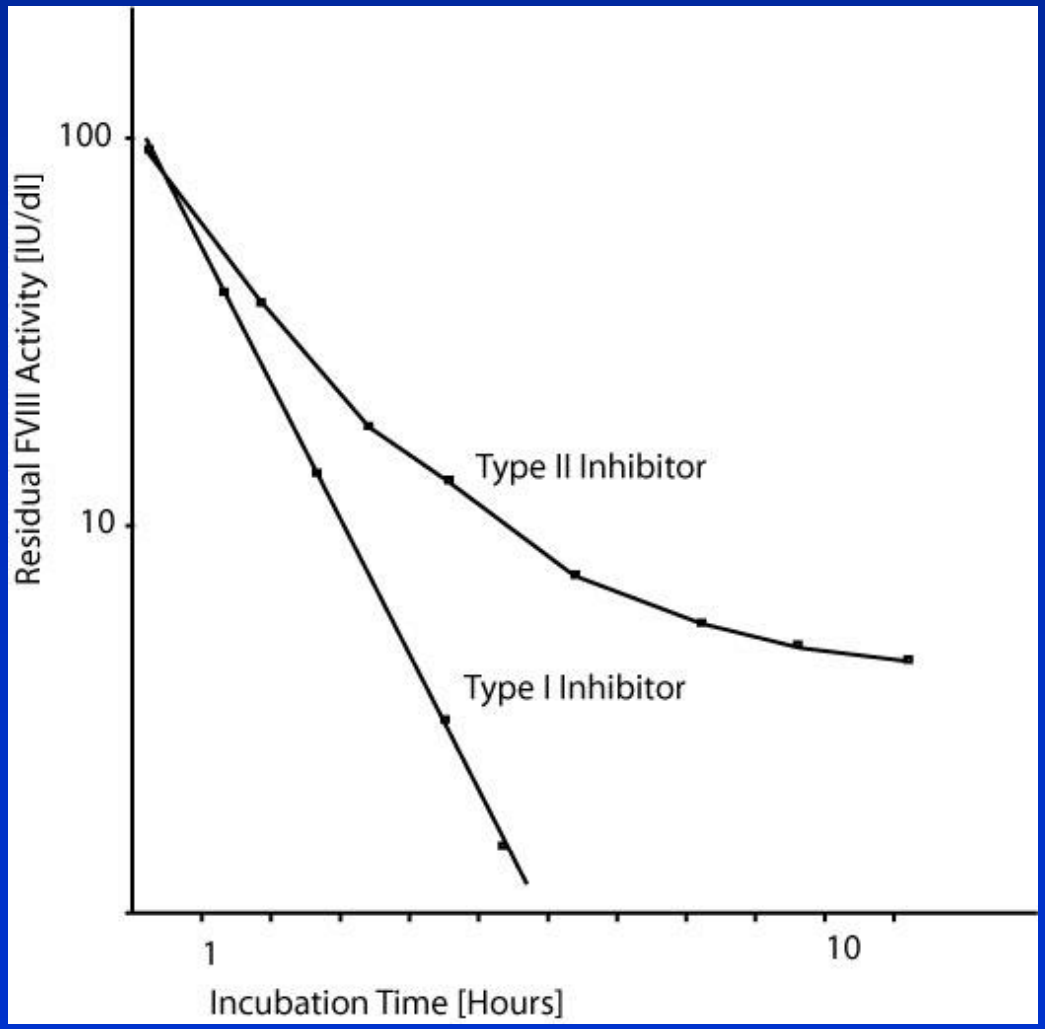
Test di 2 livello

- attività ridotta del FVIII
- presenza inibitori contro il FVIII

Algoritmo dei test di laboratorio



Second-order kinetics of the anti-FVIII autoantibodies

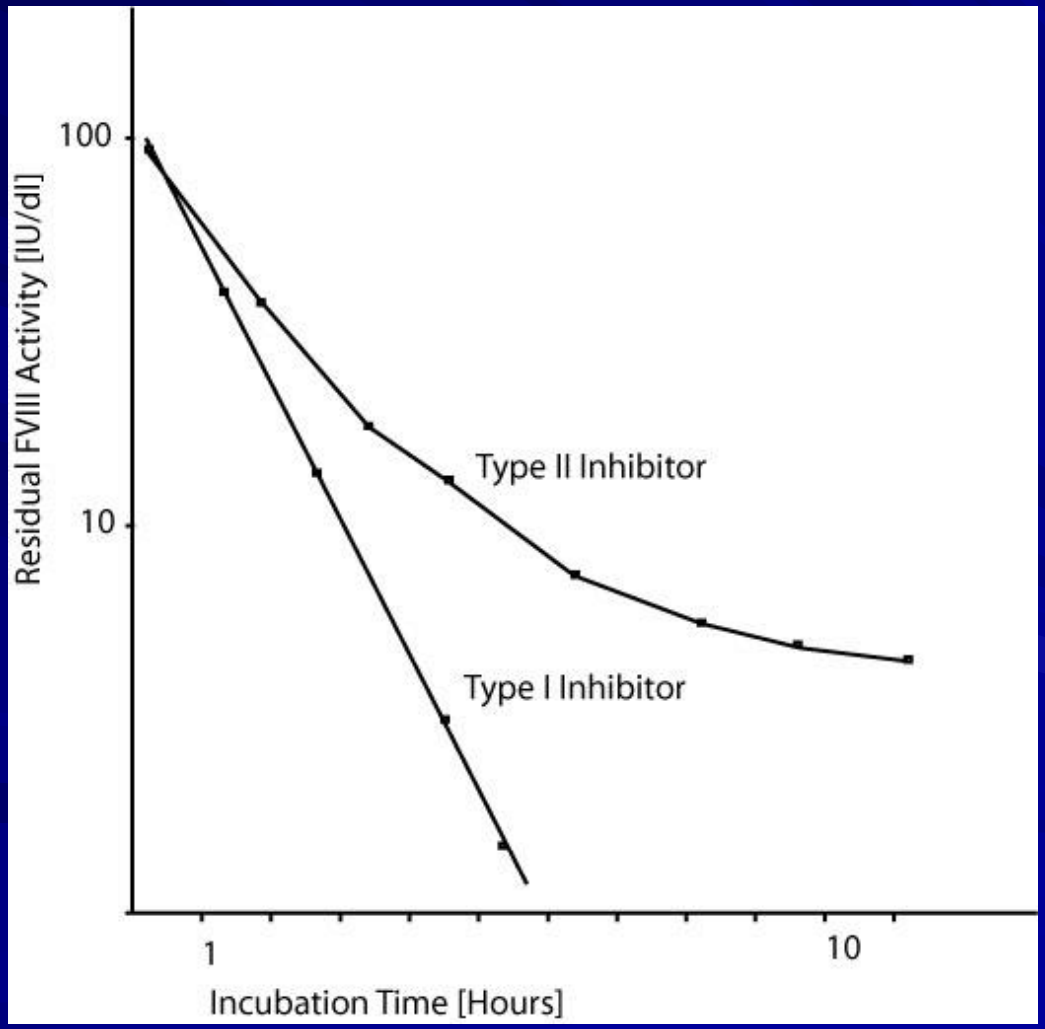


Trattamento

PRINCIPI GENERALI

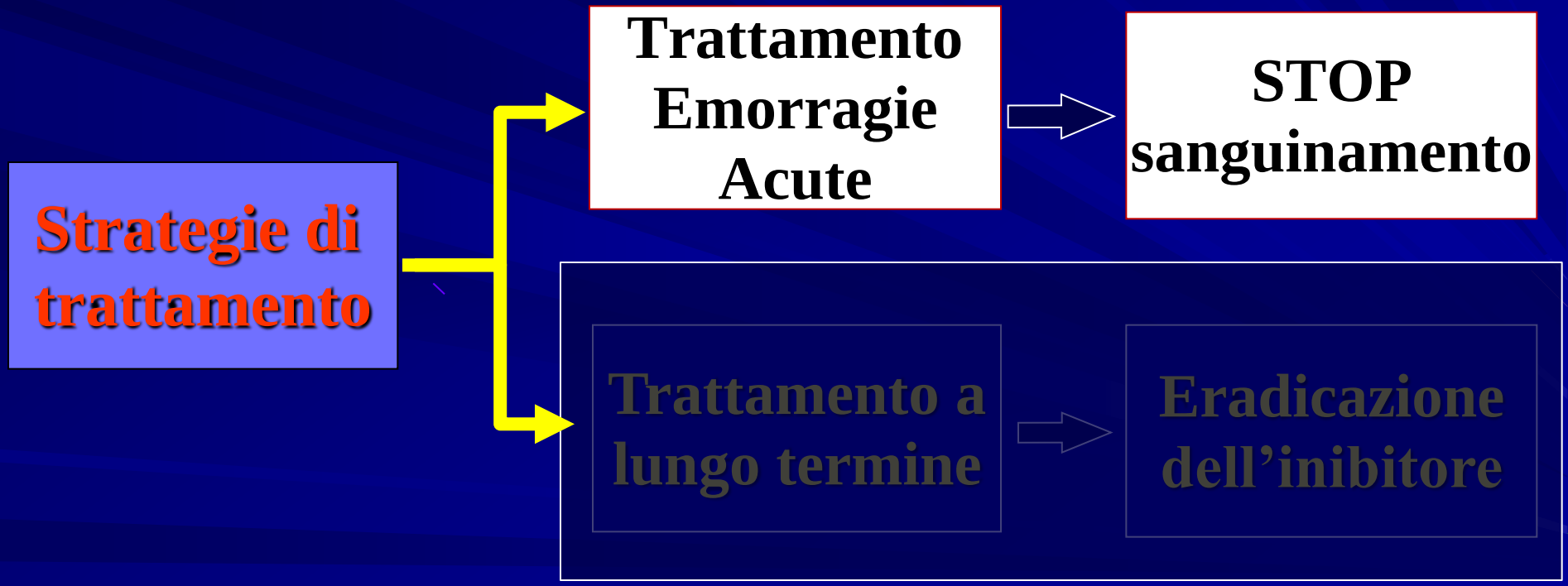
- IL CONTROLLO DEL SANGUINAMENTO RAPPRESENTA LA PRIORITA' IMMEDIATA
- FONDAMENTALE LA RICERCA DI PATOLOGIE ASSOCIATE, IN MOLTI CASI IL LORO TRATTAMENTO PUO' DETERMINARE ANCHE LA SCOMPARSA DEGLI INIBITORI
- INVIO DI QUESTI CASI IN CENTRI SPECIALIZZATI NEL TRATTAMENTO
- IL 30% CIRCA DEI PAZIENTI NON RICHIEDE TRATTAMENTO EMOSTATICO
- **Il titolo dell'inibitore non è direttamente correlato alla gravità delle manifestazioni emorragiche ma è fondamentale per decidere l'approccio terapeutico**

Second-order kinetiks of the anti-FVIII autoantibodies



Trattamento

Doppio obiettivo



Trattamento

Trattamento Emorragie Acute

- Complesso protrombinico attivato, aPCC (60-100 U/kg e.v. ogni 8-12 ore fino alla risposta clinica, massimo 200 U/Kg/die)
- rFVII (90-120 mg/Kg ogni 2-3 ore)
- Concentrati di Fatt VIII
- Desmopresina (DDAVP)
- Immunoadsorbimento e plasmaferesi
- Acido Tranexamico

1. Collins, P. et al Br. J Haematol 2013;162:758-73. 2. Hurth-Huhne A. ed al Haematologica 2009;94:566-575. 3. Coppola Semin Thromb Hemost 2012; 38: 433-466.

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]

Haematologica 2009

Table 2. Anti-hemorrhagic treatment strategies in acquired hemophilia A.

First-line treatment
rFVIIa
aPCC
Alternative treatment – if bypassing therapy unavailable
Human FVIII
DDAVP
Alternative treatment – currently unavailable
Porcine FVIII
Alternative treatment – if first-line treatment fails
Immunoadsorption and/or plasmapheresis

Under **special circumstances**, including the management of a refractory bleeding episode or necessary surgical intervention, **acute reduction or removal** of the inhibitor to facilitate hemostasis **using plasmapheresis or immunoadsorption** may be applied

Controllo dell'emorragia

Inibitori a basso titolo (<5 UI)

Normalizzazione/correzione del livelli plasmatici di FVIII

a) concentrati di FVIII

b) DDAVP

Inibitori ad alto titolo (>5 UI)

Agenti by-passanti:

a) rFVIIa

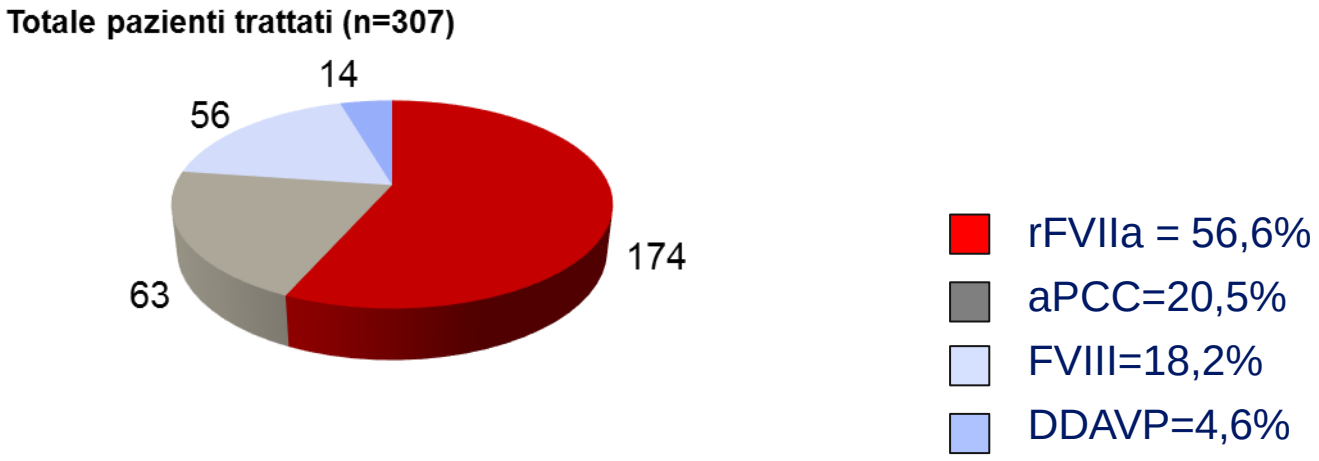
b) aPCC

Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry

Francesco Baudo,[1] Peter Collins,[2] Angela Huth-Kühne,[3] Hervé Lévesque,[4] Pascual Marco,[5] László Nemes,[6] Fabio Pellegrini,[7] Lilian Tengborn,[8] and Paul Knoebl,[9] on behalf of the EACH2 registry contributors

- **Registro multicentrico istituito nel 2003 per valutare la reale gestione clinica dell'emofilia acquisita con particolare riferimento al trattamento dei primi episodi emorragici in tutti i pazienti di nuova diagnosi, giunti all'osservazione nel periodo di studio tra Gennaio 2003 e Dicembre 2008.**

- **I dati raccolti su 501 pazienti, di cui 307 sottoposti a trattamento, hanno evidenziato l'uso in prima linea dei seguenti agenti**



Blood 2012

Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry

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Bleeding control was significantly higher in patients treated with bypassing agents versus FVIII/DDAVP

93.3% vs 68.3%, p .003

Bleeding control was similar between rFVIIa and aPCC

91.8% vs 93.3%, p 1

<u>Thrombotic events</u> were reported in 3.6% of treated patients with a similar incidence between rFVIIa (2.9%) and aPCC (4.8%).

Blood 2012

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Therapy	n	Baseline FVIII level, IU/dL	Baseline inhibitor titer, BU/mL	Initial dose, µg/kg or U/kg	Initial dosing interval, hours	Total doses per patient, n	Total dose per patient
rFVIIa	174	2.0	15.5	90 µg/kg	3	12	84 mg
		(0.0-32.0)	(1.0-2765)	(84.71-102.86)	(2-6)	(3-35)	(24-216 mg)
aPCC	63	1.0	18.0	66.67 U/kg	12	8	30 000 U
		(0.0-40.0)	(0.1-1700)	(52.63-82.19)	(12-12)	(3-15)	(12 000-56 000 U)
FVIII	56	3.0	7.5	52.91 U/kg	12	5	20 000 U
		(0.0-34.0)	(0.8-180)	(40.00-81.97)	(8-12)	(2-10)	(9000-49 500 U)
DDAVP	14	3.5	8.0	0.3 µg/kg	12	2.5	40 µg
		(0.0-17.0)	(0.3-200)	(0.3-0.3)	(8-24)	(1-3)	(21-64 µg)

1.5 gg

4 gg

Blood 2012

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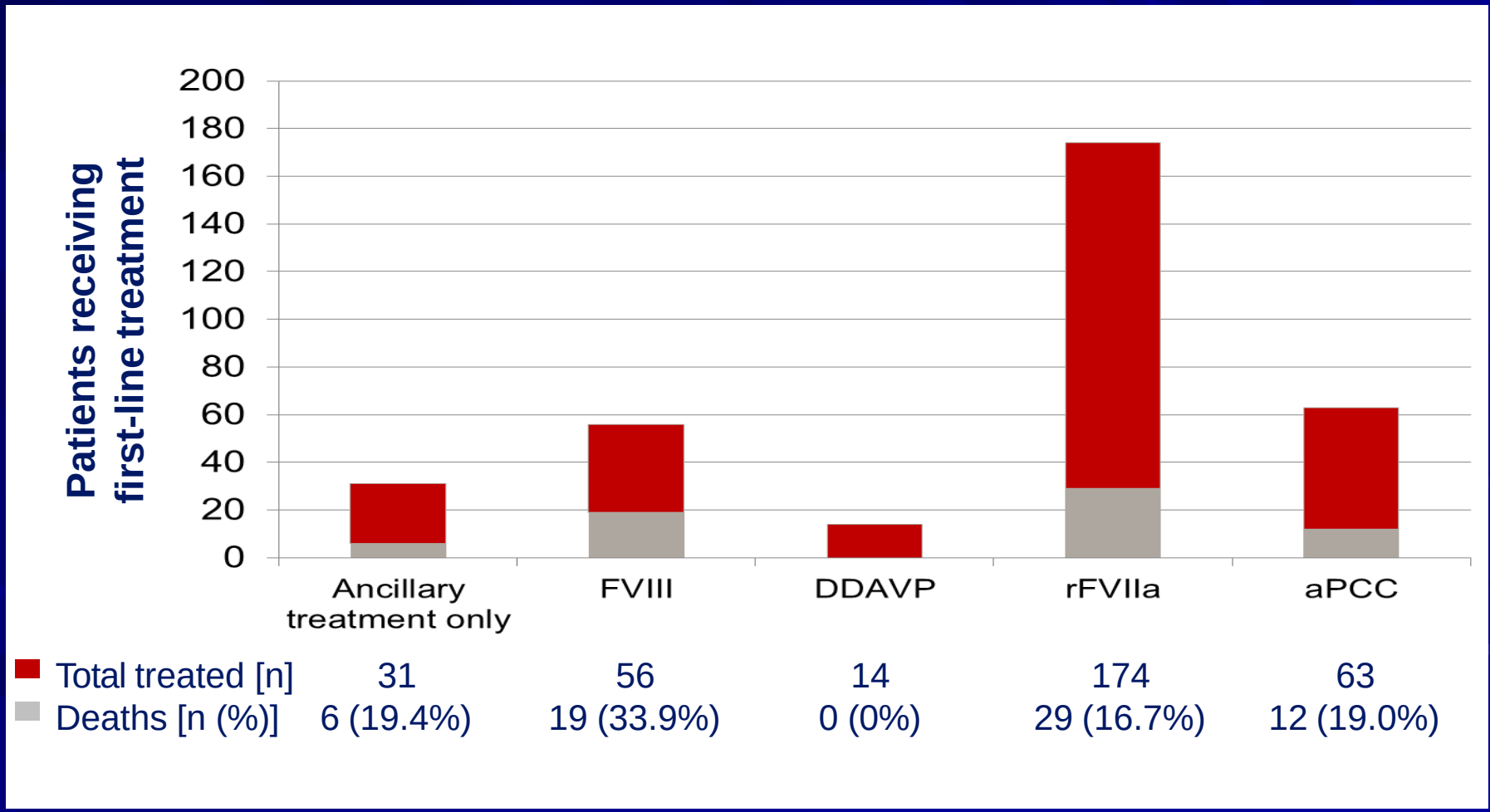


Blood 2012

Terapie emostatiche alternative

Indicate SOLO se:

- non disponibili gli agenti by-passanti
- titolo inibitore molto basso
- sanguinamento non grave

Concentrati di FVIII:

Dose di carico per neutralizzare l'inibitore
+
Dose 20-50 UI/Kg ogni 6-8 ore

Non garantito il controllo emostatico

DDAVP (analogo sintetico vasopressina):

- Incremento transitorio dei livelli di FVIII
- Può indurre tachifilassi

Ritardo nell'uso di agenti più efficaci

1. Huth-Kuhne et al. International recommendations of the diagnosis and treatment of patients with acquired hemophilia A. Haematologica 2009; 94(4): 566-75

Obizur ®

BAX 801 (OBI-1)

NEWS

- **FVIII porcino ricombinante** (rpFVIII), privo del dominio B, prodotto in cellule renali di criceto (BHK) e sottoposto a due inattivazioni virali (solvente/detergente e nanofiltrazione)
- OBI-1 è **puro >99%** il che consente di ridurre il rischio degli eventi avversi (trombocitopenia e reazioni allergiche)
- Il FVIII porcino è:
  - abbastanza diverso da presentare bassa cross-reattività con gli anticorpi anti FVIII umano
  - sufficientemente simile al FVIII umano da indurre emostasi
- La possibilità di **dosare i livelli di FVIII** fornisce una misura surrogata obiettiva di efficacia e sicurezza emostatica

Baxalta

Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A

Haemophilia (2015), **21**, 162–170

R. KRUSE-JARRES,* J. ST-LOUIS,† A. GREIST,‡ A. SHAPIRO,‡ H. SMITH,§ P. CHOWDARY,¶ A. DREBES,¶ E. GOMPERTS,** C. BOURGEOIS,†† M. MO,‡‡ A. NOVACK,‡‡ H. FARIN‡‡ and B. EWENSTEIN‡‡

Type of Bleeding	Factor VIII Level Required (U/dL or % of normal)	Initial Dose (U/kg)	Subsequent Dose	Frequency and Duration of Subsequent Dosing
Minor and Moderate Superficial muscle/no neurovascular compromise, and joint	50-100	200	Titrate subsequent doses to maintain recommended factor VIII trough levels and individual clinical response	Dose every 4 to12 hours; frequency may be adjusted based on clinical response and measured factor VIII levels
Major Moderate to severe intramuscular bleeding, retroperitoneal, gastrointestinal, intracranial	• 100-200 (To treat an acute bleed) • 50-100 (After acute bleed is controlled, if required)			

Median Dosing of OBIZUR

Primary Bleeding Episode	Median Number of Infusions/Days	Median Dose
Initial 24 hours	Infusions: 3	200 U/kg
Beyond 24 hours	Infusions: 10.5 Days: 6	100 U/kg
Bleed Control		Median dose per infusion: 133 U/kg Median total dose: 1523 U/kg
Titrate subsequent doses and frequency to maintain recommended factor VIII trough levels and individual clinical response.		
Assess inhibitory antibody level to porcine FVIII only if plasma FVIII activity levels are not attained, or if bleeding is not controlled with the expected dose of OBIZUR. Porcine factor VIII inhibitor level determination is not necessary prior to initiating treatment with OBIZUR.		

Baxalta

ORIGINAL ARTICLE

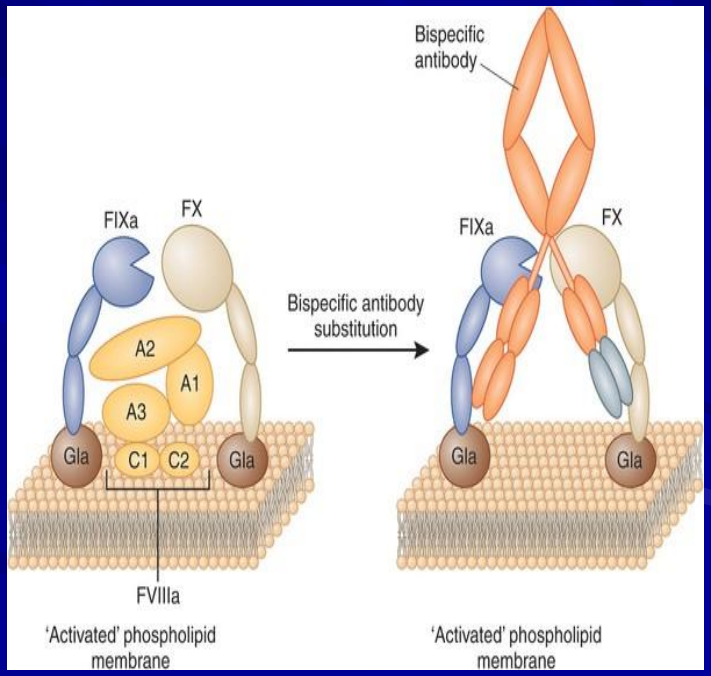
Anti-factor IXa/X bispecific antibody (ACE910): hemostatic potency against ongoing bleeds in a hemophilia A model and the possibility of routine supplementation

A. MUTO,* K. YOSHIHASHI,* M. TAKEDA,* T. KITAZAWA,* T. SOEDA,* T. IGAWA,* Y. SAKAMOTO,* K. HARAYA,* Y. KAWABE,* M. SHIMA,† A. YOSHIOKA‡ and K. HATTORI*

Research Division, Chugai Pharmaceutical Co., Ltd, Gotemba, Shizuoka; †Department of Pediatrics, Nara Medical University; and ‡Nara Medical University, Kashihara, Nara, Japan

EMICIZUMAB (HEMLIBRA)

- ACE910 is a bispecific Ab to FIXa and FX that mimics the cofactor function of FVIII
- In non-human primate model: prolonged half-life and high subcutaneous bioavailability



Lillicrap *et al* Nat Med 2012;18:1460-61

Principali problemi terapeutici

Limiti nel trattamento dell'emorragia

- Risposta valutabile solo in base a parametri clinici, emocromo ed esami strumentali
- Non disponibili parametri di laboratorio predittivi dell'efficacia del trattamento. Infatti, né i livelli plasmatici di FVIII né il titolo dell'inibitore hanno valore prognostico
- Rischio trombotico aumentato dalla somministrazione di agenti by-passanti soprattutto in pazienti anziani e con comorbidità
- Il trattamento con agenti by-passanti è gravato da costi elevati

Trattamento

Doppio obiettivo

Strategie di trattamento

Trattamento Emorragie Acute → **STOP sanguinamento**

Trattamento a lungo termine → **Eradicazione dell'inibitore**

Trattamento

Eradicazione dell'inibitore

Trattamento di prima linea

Prednisone 1 mg/kg/die per 4-6 settimane da solo o in combinazione con Ciclofosfamide 1-2 mg/Kg/die per un massimo di 5 settimane

Trattamento di seconda linea

Rituximab 375 mg/m^2 settimana per 4 settimane; Azatioprina, Ciclosporina, Micofenolato, Vincristina, induzione di immunotolleranza

1. Collins, P. et al Br. J Haematol 2013;162:758-73. 2. Hurth-Huhne A. ed al Haematologica 2009;94:566-575. 3. Coppola Semin Thromb Hemost 2012; 38: 433-466.

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

Peter Collins,[1] Francesco Baudo,[2] Paul Knoebl,[3] Hervé Lévesque,[4] László Nemes,[5] Fabio Pellegrini,[6] Pascual Marco,[7] Lilian Tengborn,[8] and Angela Huth-Kühne,[9] on behalf of the EACH2 registry collaborators

Response to first-line immunosuppression

Regimen	n	CR, n (%)	Relapse, n (%)	Stable CR, n (%)
Steroids alone	142	83 (58)	15 (18)	68 (48)
Steroids + cyclophosphamide	83	66 (80)	8 (12)	58 (70)
Steroids + rituximab	28	18 (64)	0 (0)	18 (64)
Cytotoxic + rituximab	3	2 (67)	0 (0)	2 (67)
Steroids + cytotoxic + rituximab	8	6 (75)	1 (17)	5 (63)
Rituximab alone	12	5 (42)	0 (0)	5 (42)
Rituximab + any other agent	39	26 (67)	1 (3)	25 (64)
All rituximab-based regimens	51	31 (61)	1 (3)	30 (59)

Median time to complete remission:

~5 weeks for steroids ± cyclophosphamide

rituximab-based regimens approximately twice as long

Stable complete remission : inhibitor undetectable, factor VIII >70 IU/d and immunosuppression stopped

Blood 2012

Emofilia Acquisita

Follow up

- ✓ Dopo l'eradicazione dell'inibitore è raccomandato follow up mensile, monitorando aPTT e livelli di fattore VIII, per i primi 6 mesi circa[1].
- ✓ Follow up ogni 2-3 mesi fino a circa 1 anno.
- ✓ Follow up ogni 6 mesi dal secondo anno e successivi.

Le recidive si presentano con una mediana di circa 7-9 mesi dopo la sospensione dell'immunosoppressione. [2,3]

1.Hurth-Huhne A. ed al Haematologica 2009;94:566-575. 2.Colllins PW Blood 2007;109:1870-7. 3.Delgado Br. J. Haematol. 2003;121:21-35.

Emofilia Acquisita

"Take Home messages I"

- ✓ Il **ritardo diagnostico** è purtroppo comune, anche in presenza di APTT prolungato in pazienti con sanguinamento.
- ✓ **Agenti by-passanti (rFVIIa e FEIBA) sono equamente efficaci** nella gestione del sanguinamento.
- ✓ Entrambi sono tuttavia **associati ad eventi trombotici** quando usati nell'emofilia acquisita.

Emofilia Acquisita

"Take Home messages II"

- ✓ La **terapia steroidea associata alla ciclofosfamide** ha mostrato una remissione più alta dell'inibitore rispetto allo steroide da solo (*anche se l'outcome a lungo termine è simile*)
- ✓ **Rituximab** non è associato a una migliore eradicazione dell'inibitore.
- ✓ Le **recidive sono comuni nel primo anno** dopo lo stop dell'immunosoppressione e per questo il paziente deve eseguire **stretto follow up.**

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Vitamin K Dependent Coagulation

- FII, FVII, FIX, FX, protein C & protein S require calcium to bind for activation
- Calcium can only bind after gamma carboxylation of specific glutamic acid (Glu) residues in these proteins
- Vitamin K acts as a cofactor for this carboxylation reaction
- The role of vitamin K in the carboxylation of specific proteins is a cyclic process called "Vitamin K Cycle"
- Limited body stores of fat-soluble vitamin K (1-2 mg total stores in the adults); metabolic requirement ≈ 0.1 mg/day.

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Expected effects of anticoagulant drugs on commonly used coagulation tests

Drug class	Drug	Brand name(s)	PT	aPTT	Anti-factor Xa activity
Vitamin K antagonists	Warfarin	Coumadin	↑	↑/–*	–
	Acenocoumarol	Sintrom	↑	↑/–*	–
Heparins	Unfractionated heparin		–¶	↑	↑
	LMW heparins Enoxaparin Dalteparin Nadroparin	Lovenox Fragmin Fraxiparine	–	↑/–	↑
	Fondaparinux	Arixtra	–	↑/–	↑
Direct thrombin inhibitors	Argatroban	Acova	↑	↑	–
	Dabigatran	Pradaxa	↑/–	↑	–
Direct factor Xa inhibitors	Rivaroxaban	Xarelto	↑/–	↑/–	↑Δ
	Apixaban	Eliquis	↑/–	↑/–	↑Δ
	Edoxaban	Lixiana	↑/–	↑/–	↑Δ

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 76, NO. 5, 2020

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EXPERT CONSENSUS DECISION PATHWAY

2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

A Report of the American College of Cardiology Solution Set Oversight Committee

1. ASSESS AND IDENTIFY SEVERITY OF BLEEDING

2. MANAGE AND CONTROL BLEED

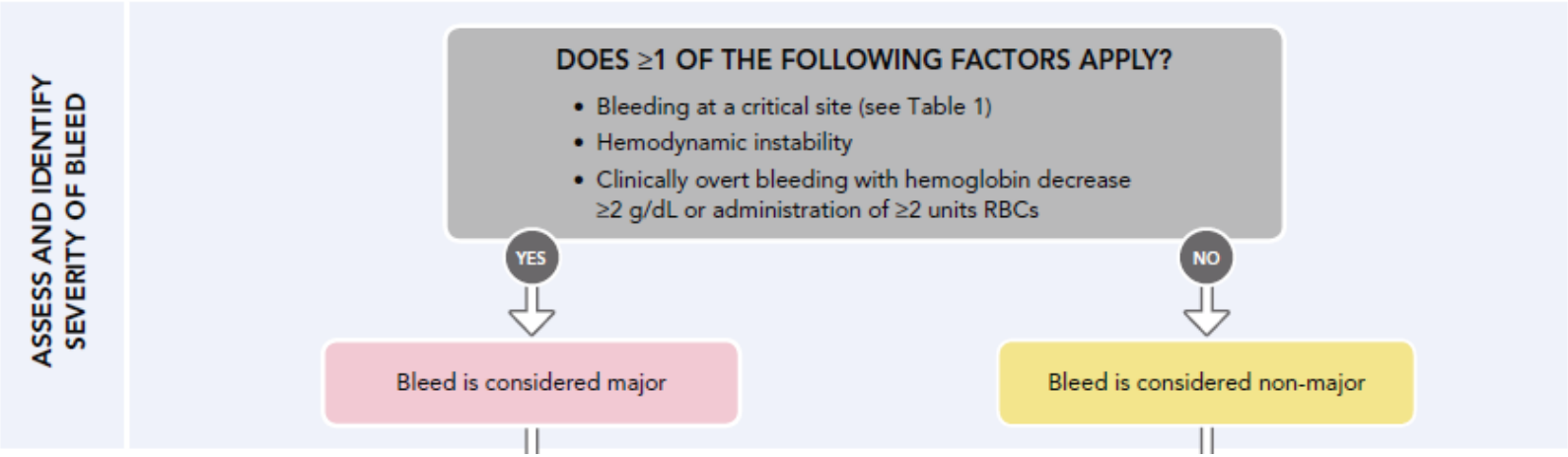
3. WHETHER AND WHEN RESTART TO ANTICOAGULATION

1. ASSESS AND IDENTIFY SEVERITY OF BLEEDING

2. MANAGE AND CONTROL BLEED

3. WHETHER AND WHEN RESTART TO ANTICOAGULATION

SEVERITY OF BLEEDING



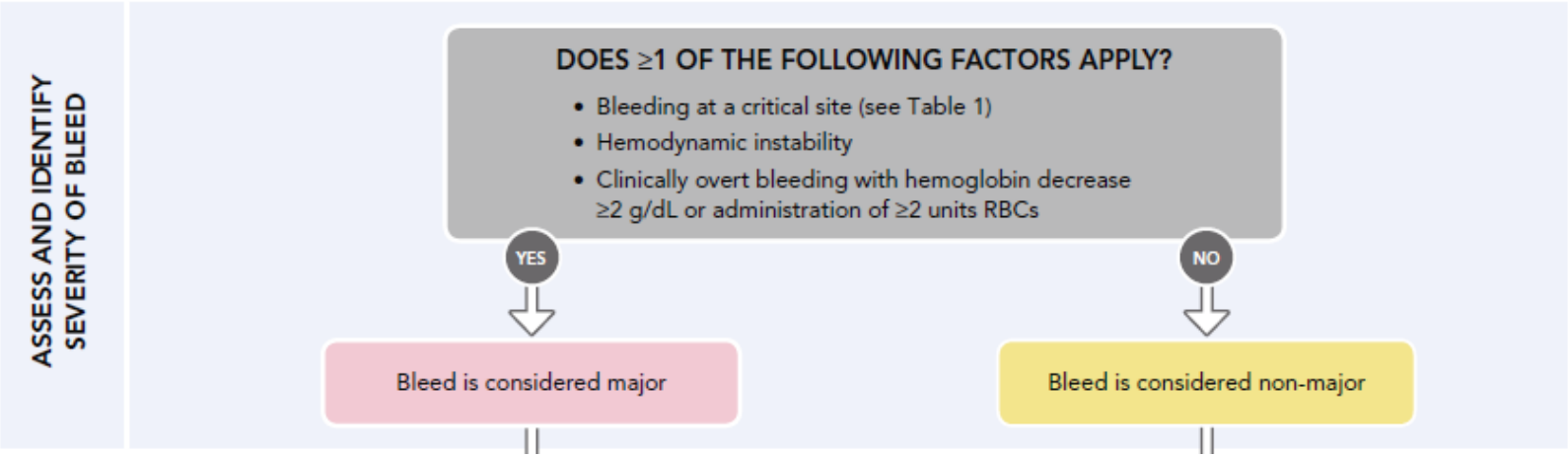
CRITICAL SITE BLEEDS

TABLE 1 Critical Site Bleeds

Type of Bleed	Initial Signs and Symptoms	Potential Consequences of Bleed
ICH: includes intraparenchymal, subdural, epidural, and subarachnoid hemorrhages	• Unusually intense headache, emesis, reduced or loss of consciousness, vision changes, numbness, weakness, aphasia, ataxia, vertigo, seizures	• Stupor or coma • Permanent neurological deficit • Death
Other central nervous system hemorrhage: includes intraocular, intra- or extra-axial spinal hemorrhages	• **Intraocular:** monocular eye pain, vision changes, blindness • **Spinal:** back pain, bilateral extremity weakness or numbness, bowel or bladder dysfunction, respiratory failure	• **Intraocular:** permanent vision loss • **Spinal:** permanent disability, paraplegia, quadriplegia, death
Pericardial tamponade	• Shortness of breath, tachypnea, hypotension, paradoxical pulse, jugular venous distension, tachycardia, muffled heart sounds, rub	• Cardiogenic shock • Death
Airway: includes posterior epistaxis	• **Airway:** hemoptysis, shortness of breath, hypoxia • **Posterior epistaxis:** profuse epistaxis, hemoptysis, hypoxia, shortness of breath	• Hypoxemic respiratory failure • Death
Hemothorax, intra-abdominal bleeding, and retroperitoneal hemorrhage	• **Hemothorax:** tachypnea, tachycardia, hypotension, decreased breath sounds • **Intra-abdominal (non-GI):** abdominal pain, distension, hypotension, tachycardia • **Retroperitoneal hemorrhage:** back/flank/hip pain, tachycardia, hypotension	• **Hemothorax:** respiratory failure • **Retroperitoneal hemorrhage:** femoral neuropathy • **All:** hypovolemic shock, death
Extremity bleeds: includes intramuscular and intra-articular bleeding	• **Intramuscular:** pain, swelling, pallor, paresthesia, weakness, diminished pulse • **Intra-articular:** joint pain, swelling, decreased range of motion	• **Intramuscular:** compartment syndrome, paralysis, limb loss • **Intra-articular:** irreversible joint damage

GI = gastrointestinal; ICH = intracranial hemorrhage.

SEVERITY OF BLEEDING



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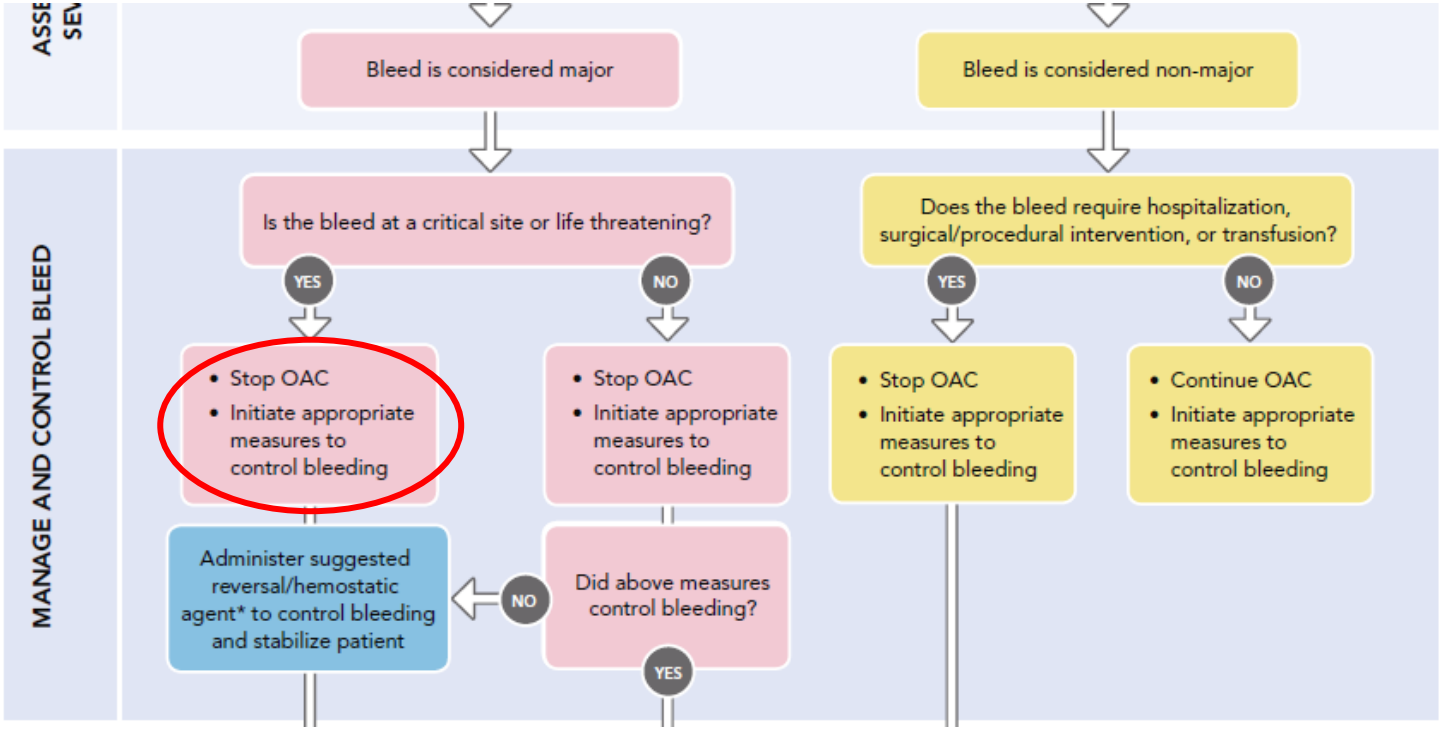
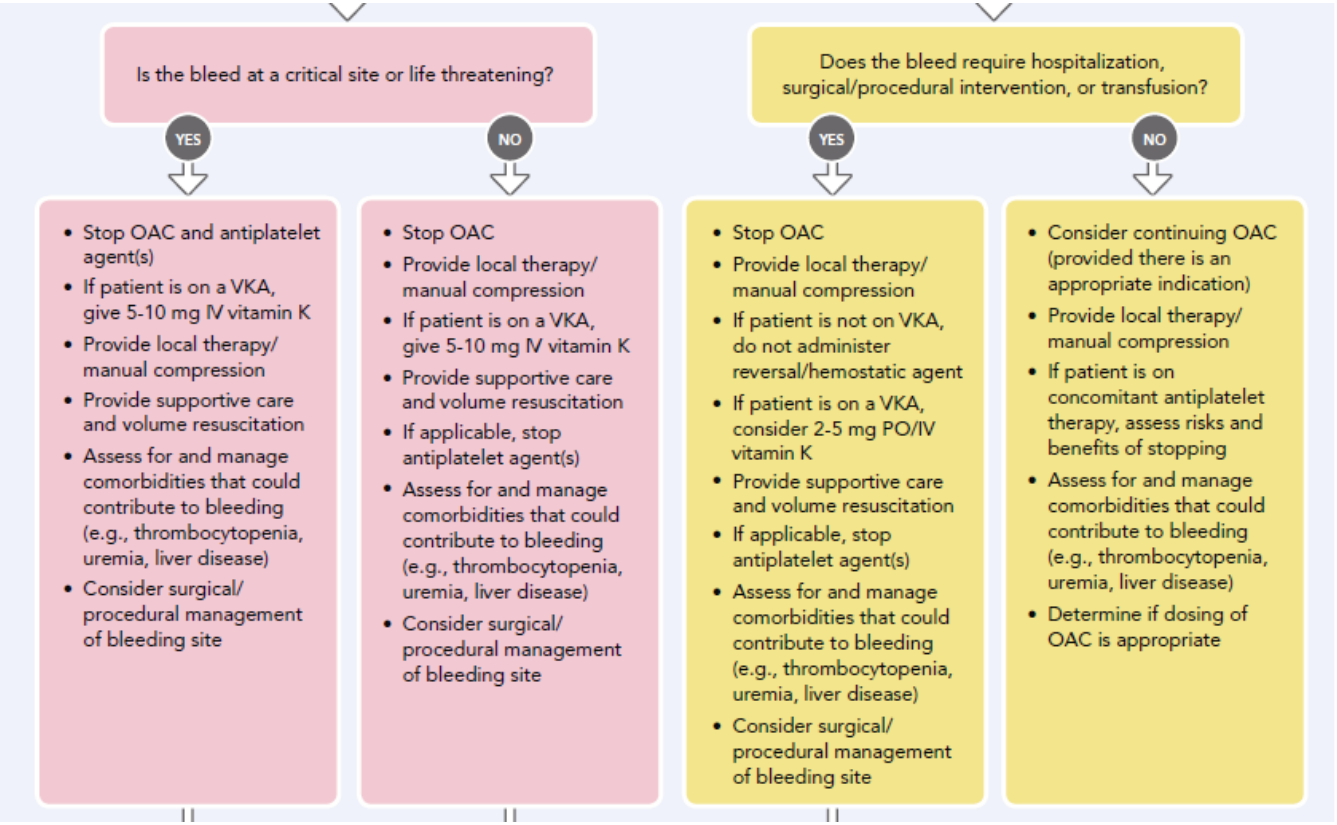
MANAGE AND CONTROL BLEED



MANAGE AND CONTROL BLEED



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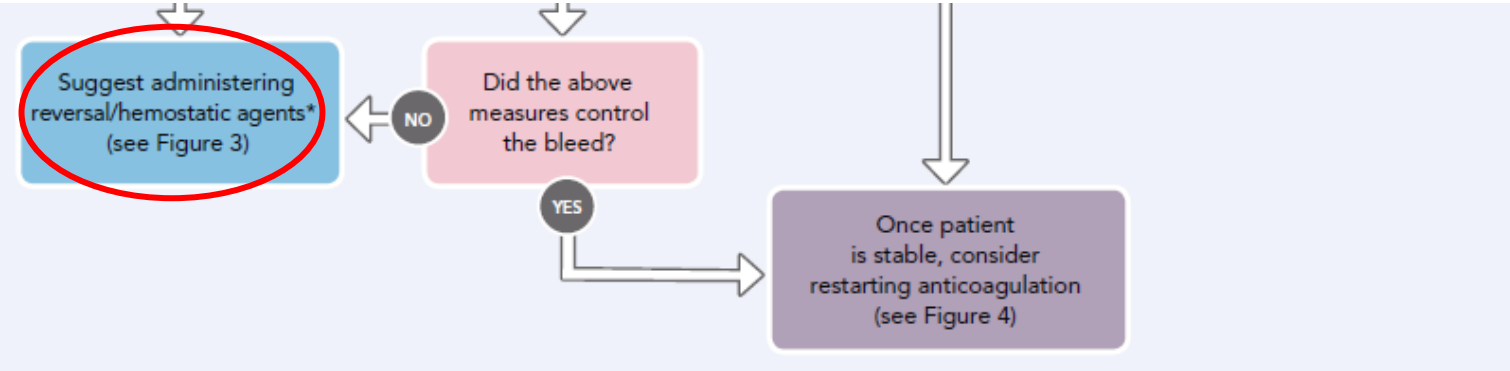

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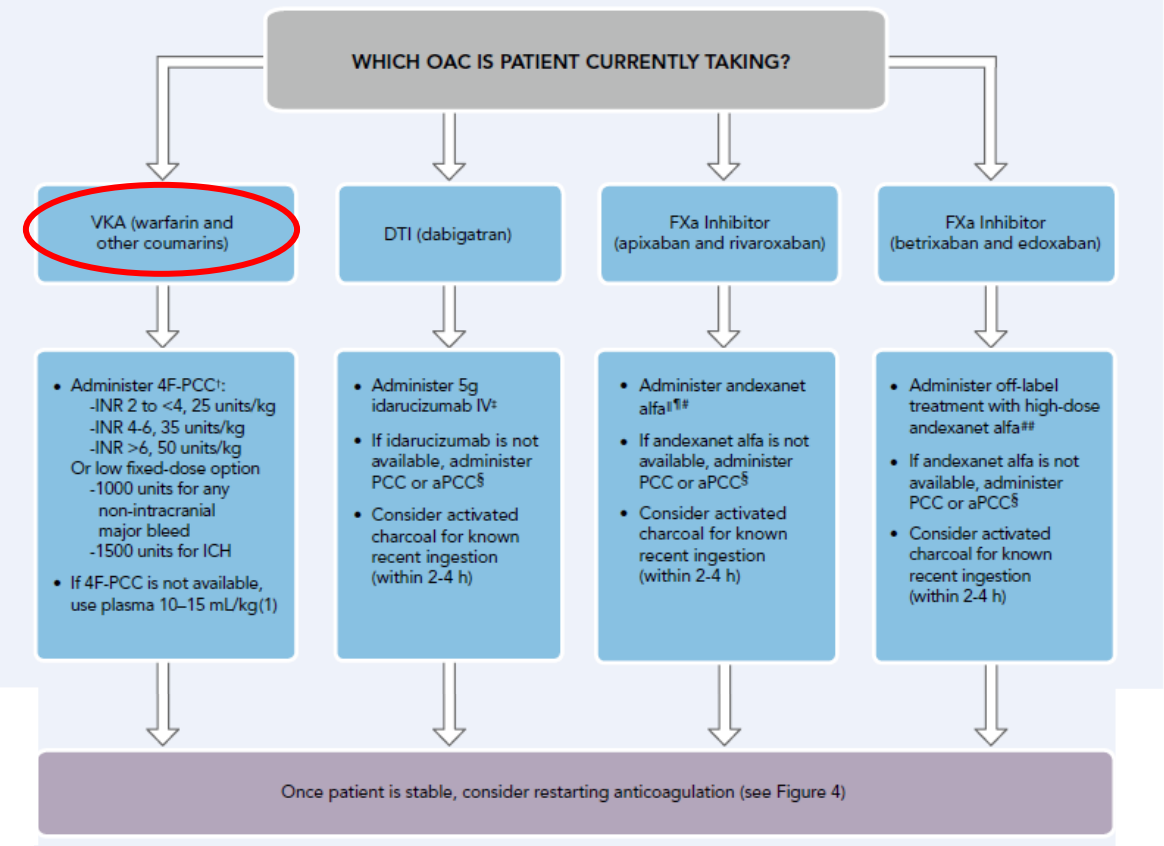


PROTHROMBIN COMPLEX CONCENTRATE(PCC)

3-factor (FII, FIX, FX)

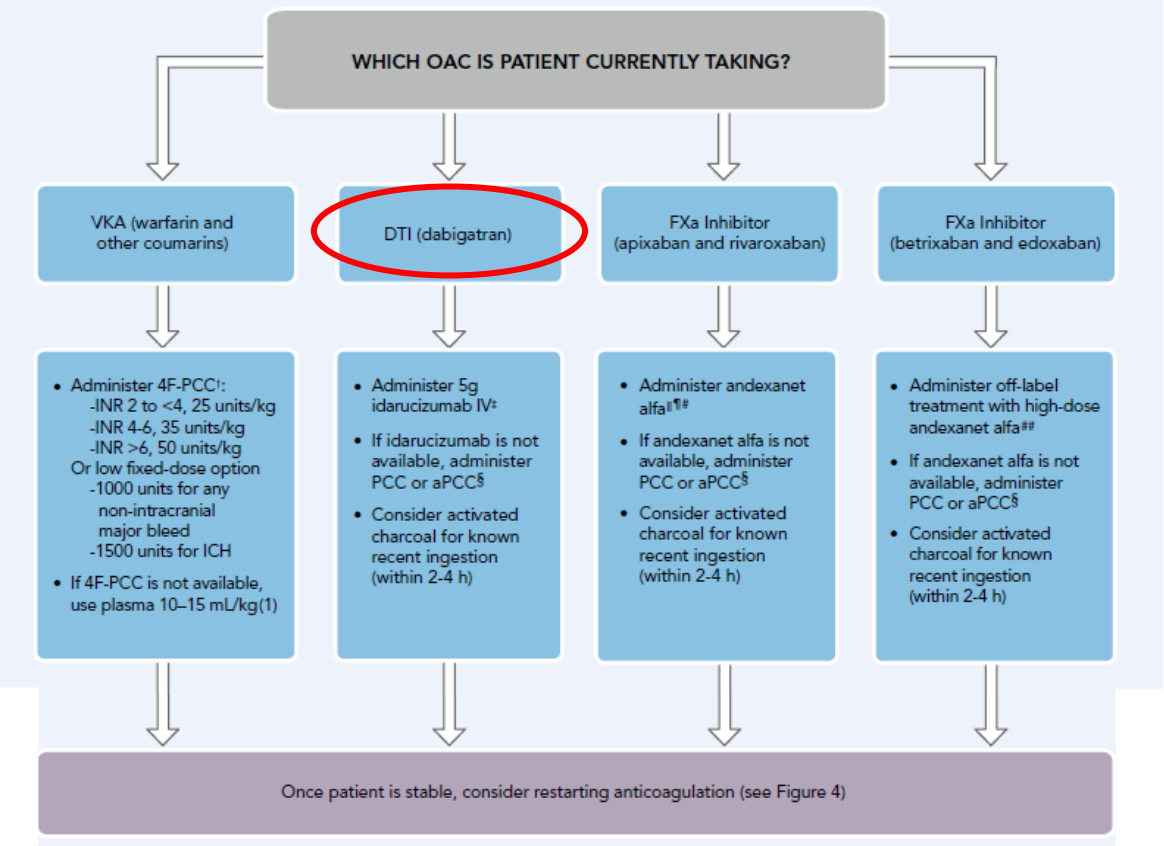
4-factor (FII, FVII, FIX, FX; PC, PS)

activated 4-factor (FII, FVIIa, FIX, FX; PC, PS)

- Quanto: 50 U/Kg
- Come: ev
- In quanto: 10' → 1h

→ potenzialmente pro-trombotico

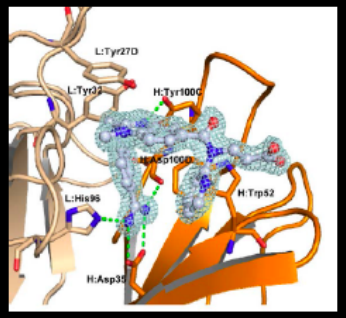
MANAGE AND CONTROL BLEED



IDARUCIZUMAB (PRAXBIND®)

Idarucizumab
(*Praxbind* ®)

Anticorpo monoclonale con affinità per Dabigatran 350 volte superiore a quella della trombina



Emivita breve 45 min circa

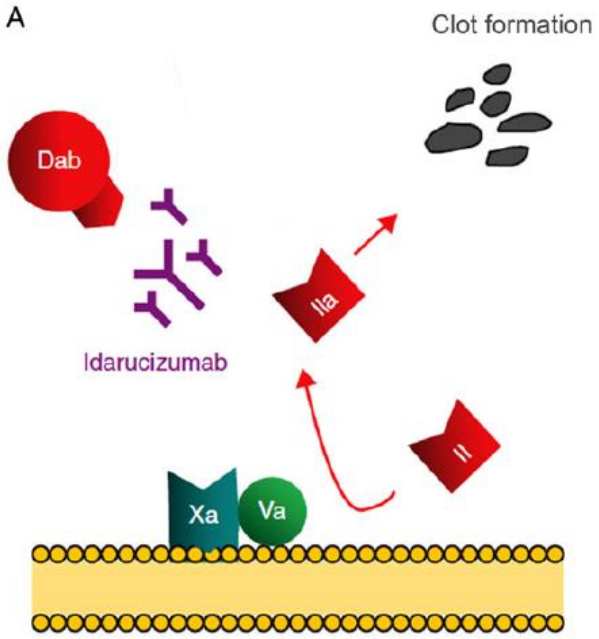
Clearance renale

503 pazienti arruolati: 301 (sanguinamneto non controllabile gruppo A) e 202 da sottoporre a chirurgia (grupoo B).
Reverse ottenuto nel 100 % dei casi.

Eventi trombotici: 4.8%; 14 nel gruppo A e 10 nel gruppo B

Pollack Cv jr et al. N Engl J Med 2017; 377:431-41

IDARUCIZUMAB (PRAXBIND®)



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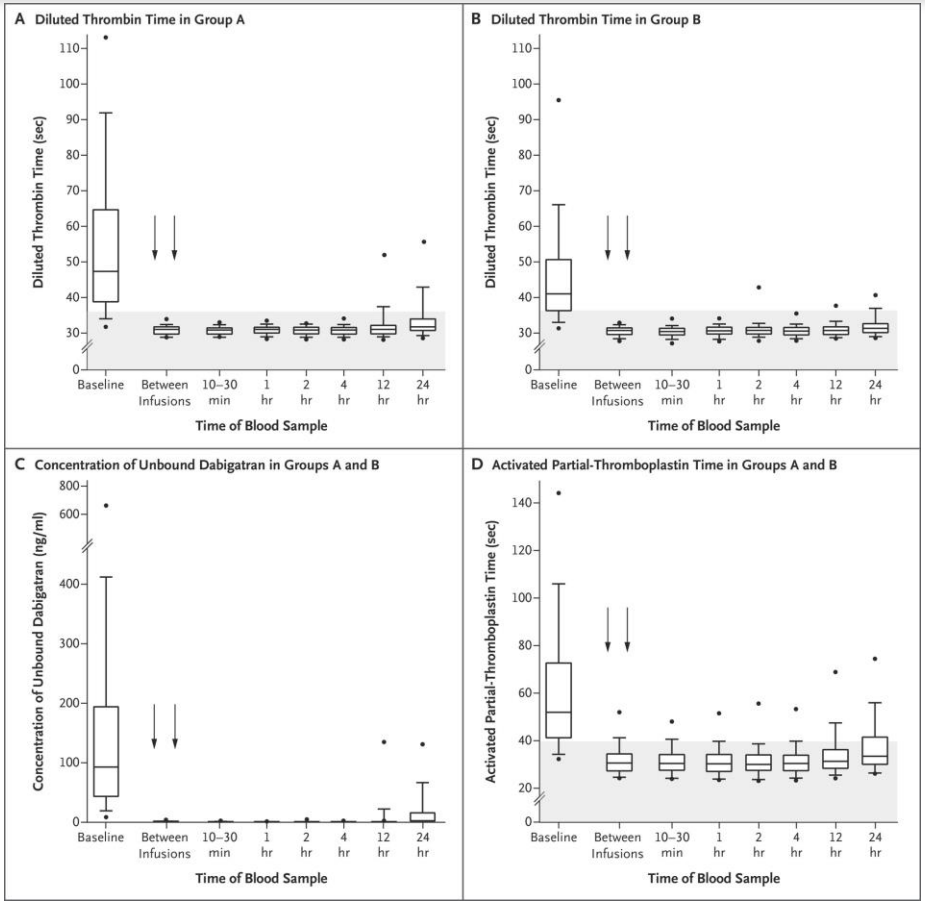


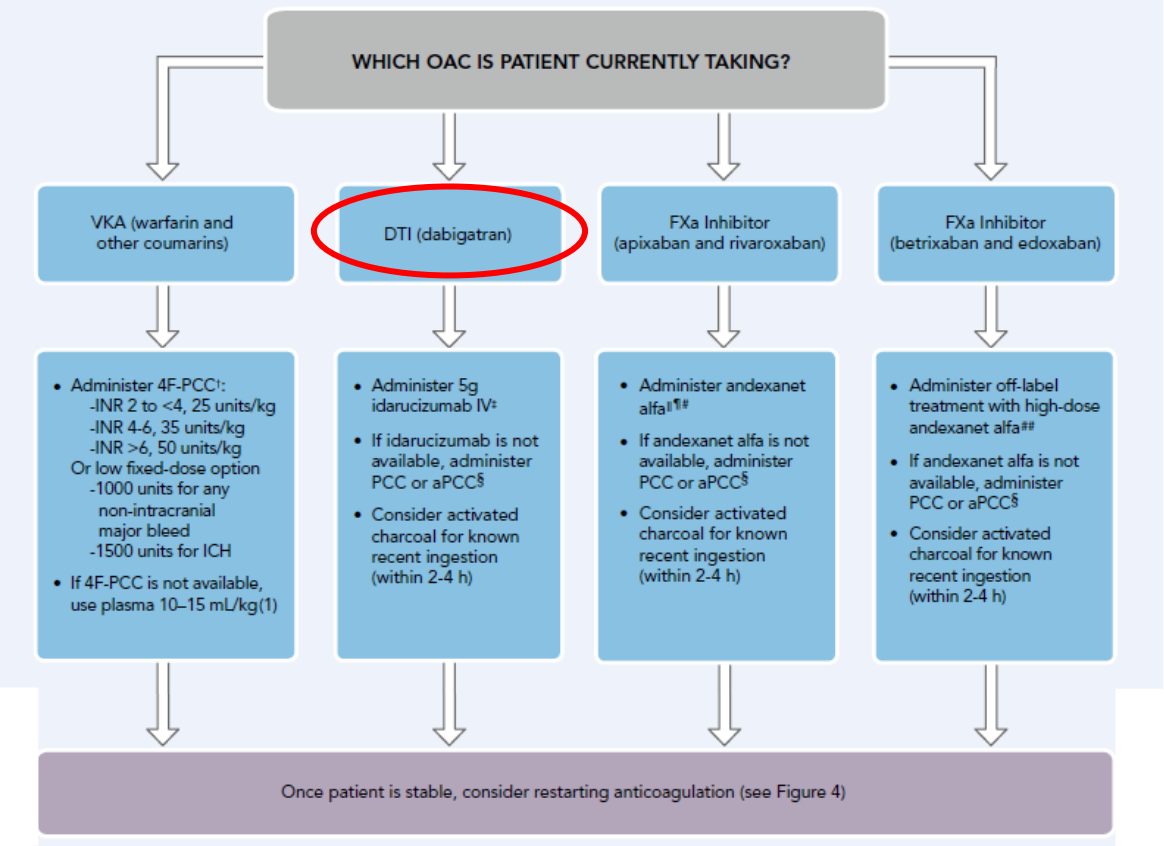
N Engl J Med 2017; 377:431-41

IDARUCIZUMAB (PRAXBIND®)

The recommended dose is 5 g, provided as two separate 50-mL vials, each containing 2.5 g given no more than 15 min apart.

Costo circa 4000 Euro

MANAGE AND CONTROL BLEED



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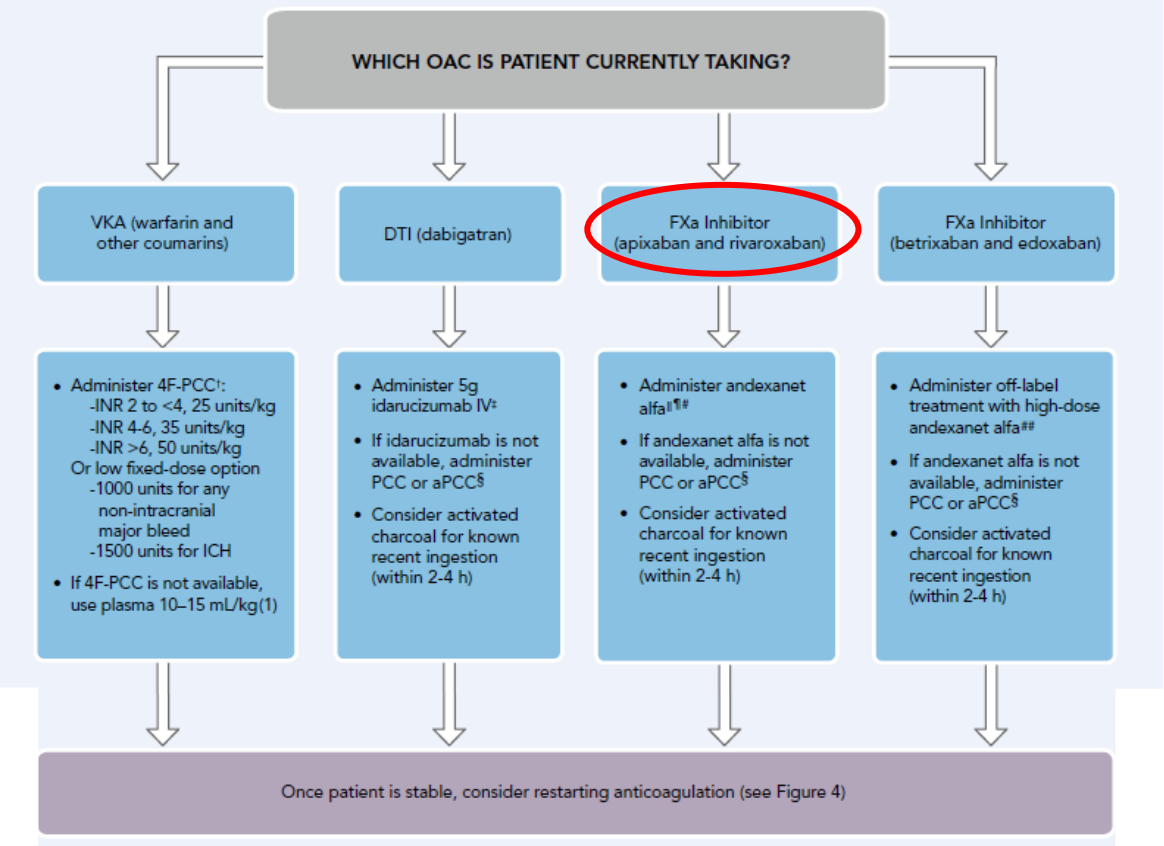
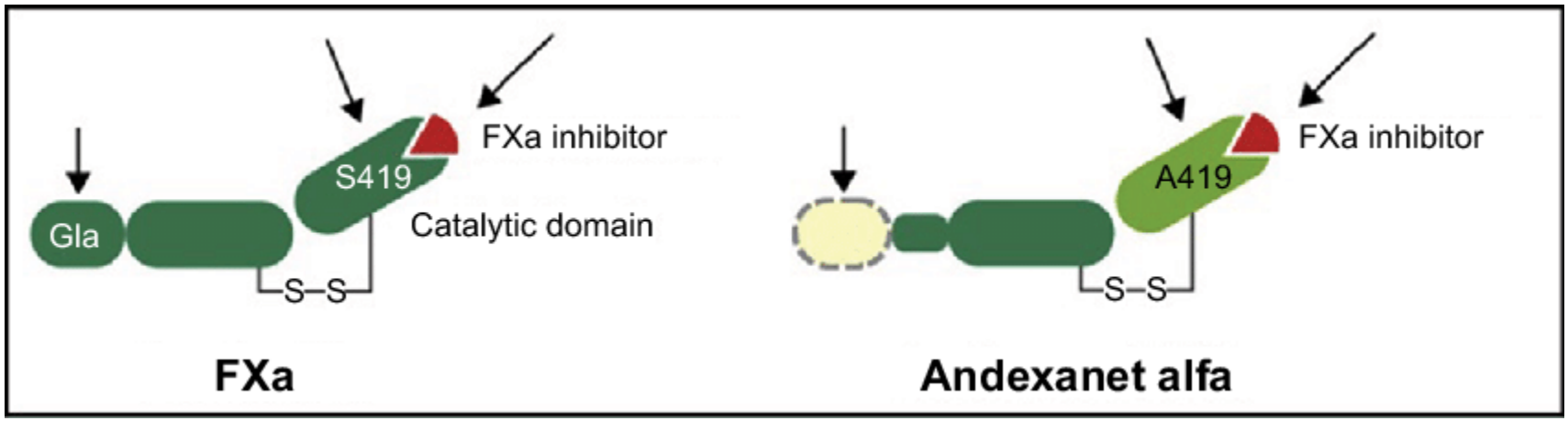


ANDEXANET ALFA



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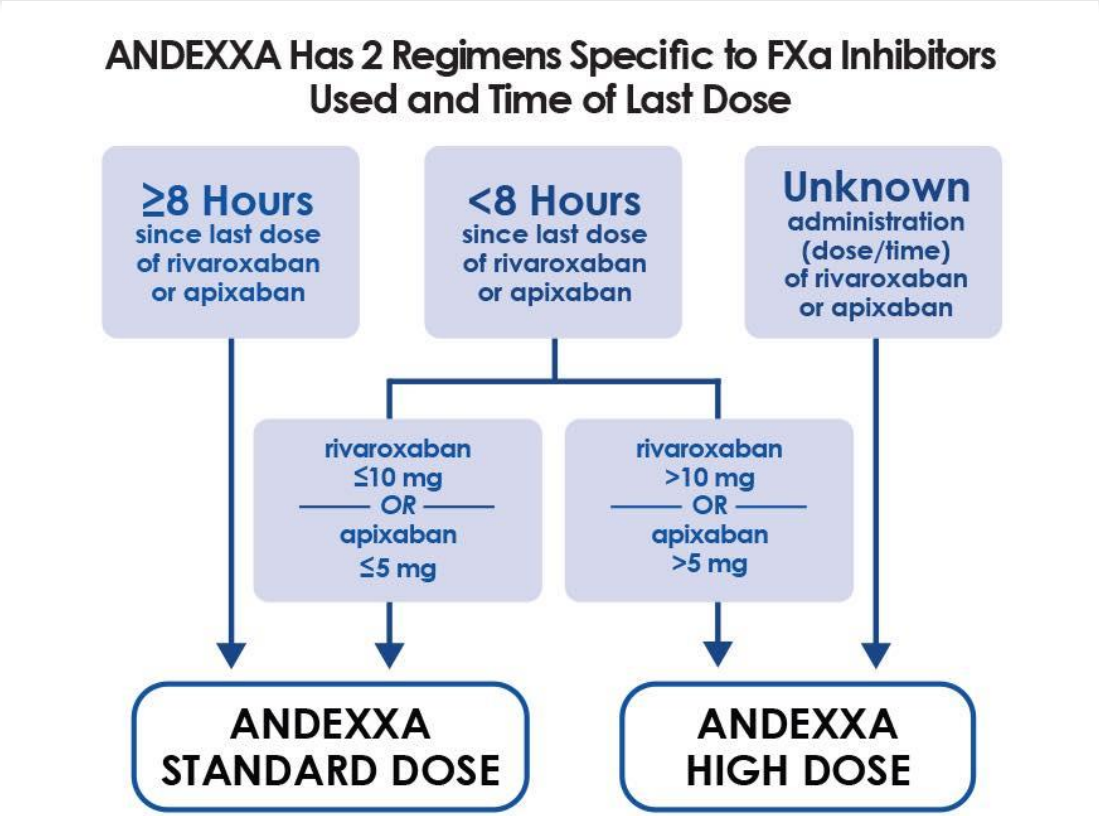

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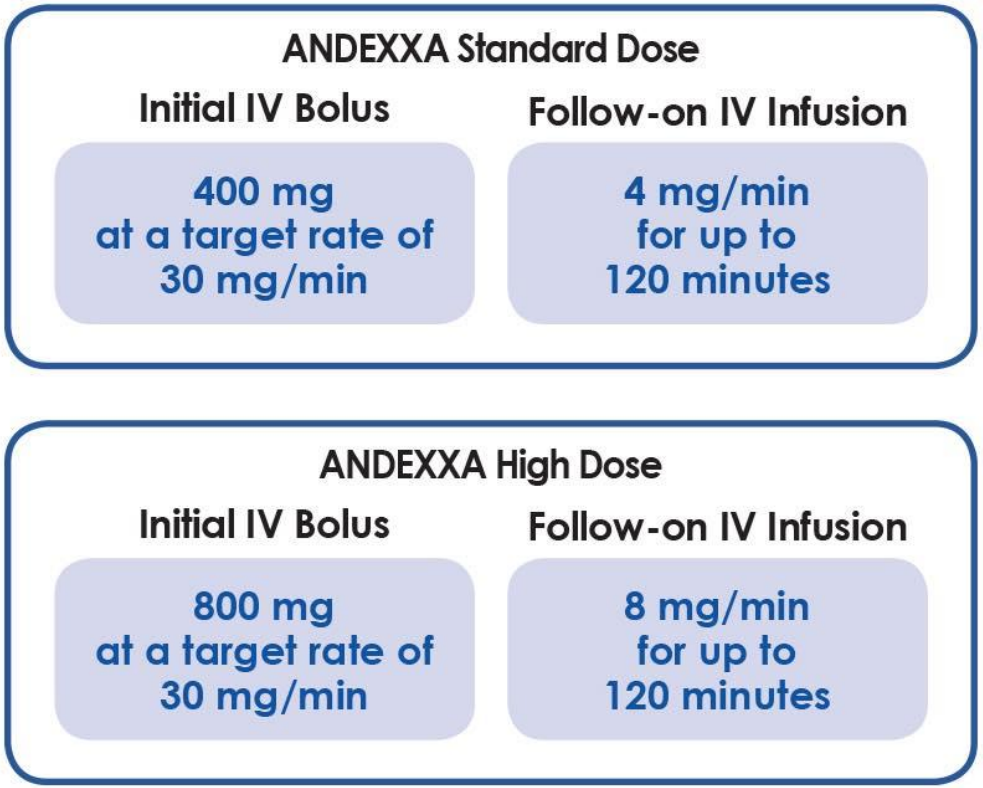

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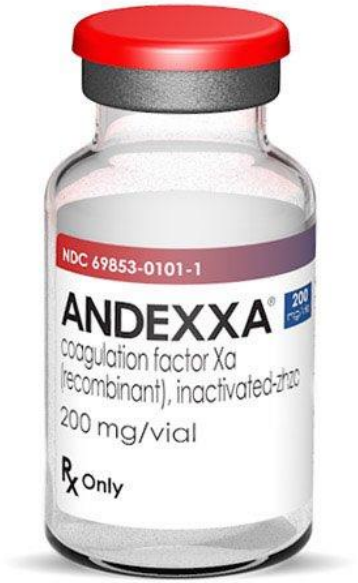


UNA CONFEZIONE DI ANDEXXA CONTIENE 4 FIALE DA 200 MG E COSTA 30.000 EURO

ORIGINAL ARTICLE

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

N ENGL J MED 380;14 NEJM.ORG APRIL 4, 2019

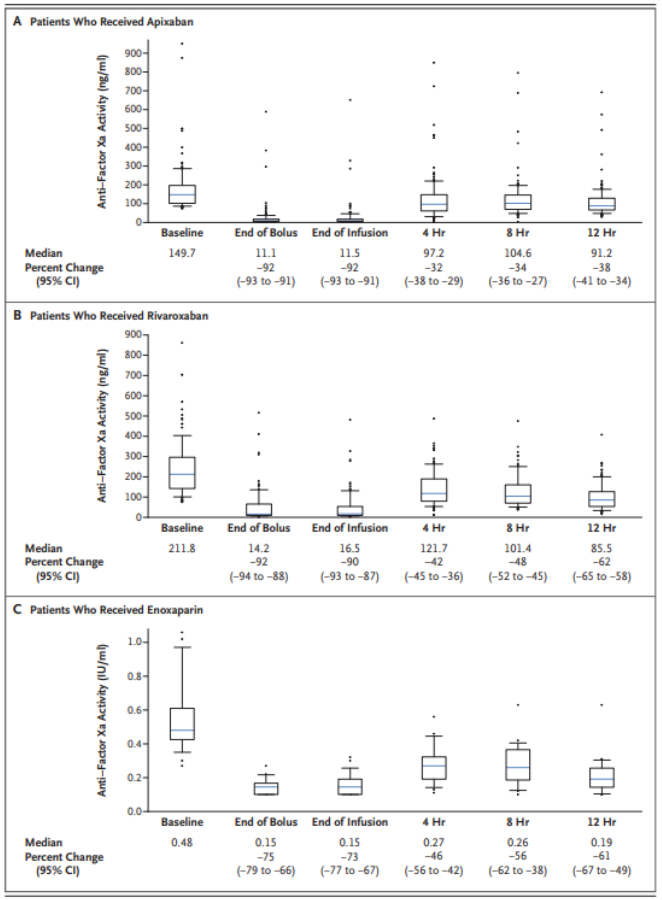
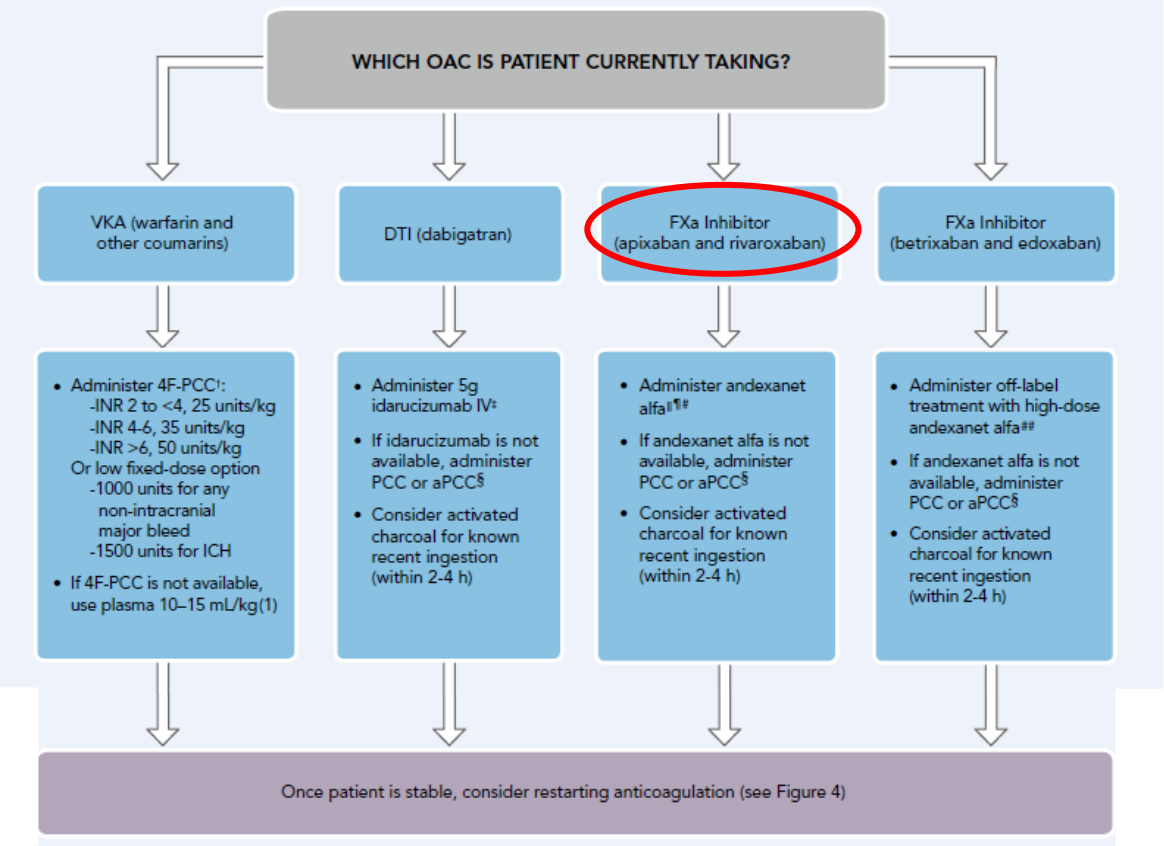


Table 2. Timing of Thrombotic Event and Restarting of Anticoagulation.*

Variable	Safety Population (N=352)			
	Total	<6 Days after Bolus	6–14 Days after Bolus	15–30 Days after Bolus
	number of patients (percent)			
≥ Thrombotic event within 30 days†	34 (10)	11	11	12
Myocardial infarction	7	6	1	0
Ischemic stroke or stroke of uncertain classification	14	5	6	3
Transient ischemic attack	1	0	0	1
Deep-vein thrombosis	13	1	5	7
Pulmonary embolism	5	1	0	4
Death within 30 days‡	49 (14)	8	21	20
Cardiovascular cause	35	7	15	13
Noncardiovascular cause	12	1	5	6
Uncertain cause	2	0	1	1
Restart of any anticoagulation§	220 (62)	145 (41)	46 (13)	29 (8)
Thrombotic event before restart¶	26 (7)			
Thrombotic event after restart	8 (2)			
Restart of oral anticoagulation‖	100 (28)	31 (9)	37 (11)	32 (9)
Thrombotic event before restart¶	34 (10)			
Thrombotic event after restart	0			

* Thrombotic events that occurred on the day of restarting anticoagulation were considered to have occurred before the restart.
† Some patients had more than one thrombotic event.
‡ Two deaths occurred during study follow-up, but after 30 days.
§ Restart of any anticoagulation includes the use of any form of heparin or low-molecular-weight heparin, fondaparinux, or argatroban, or any oral anticoagulant, including vitamin K antagonists and non–vitamin K antagonists (at any dose and for any duration).
¶ Included are thrombotic events that occurred in patients who never restarted anticoagulation.
‖ Restart of oral anticoagulation includes only the use of vitamin K antagonists or non–vitamin K oral anticoagulants (at any dose and for any duration).

MANAGE AND CONTROL BLEED



COAGULOPATIE ACQUISITE

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- SDR. DA ANTICORPI ANTIFOSFOLIPIDI
- GRAVIDANZA & TERAPIA ORMONALE
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- EMOGLOBINURIA PAROSSISTICA NOTTURNA (EPN)
- MALATTIA DI BEHCET
- SDR. NEFROSICA

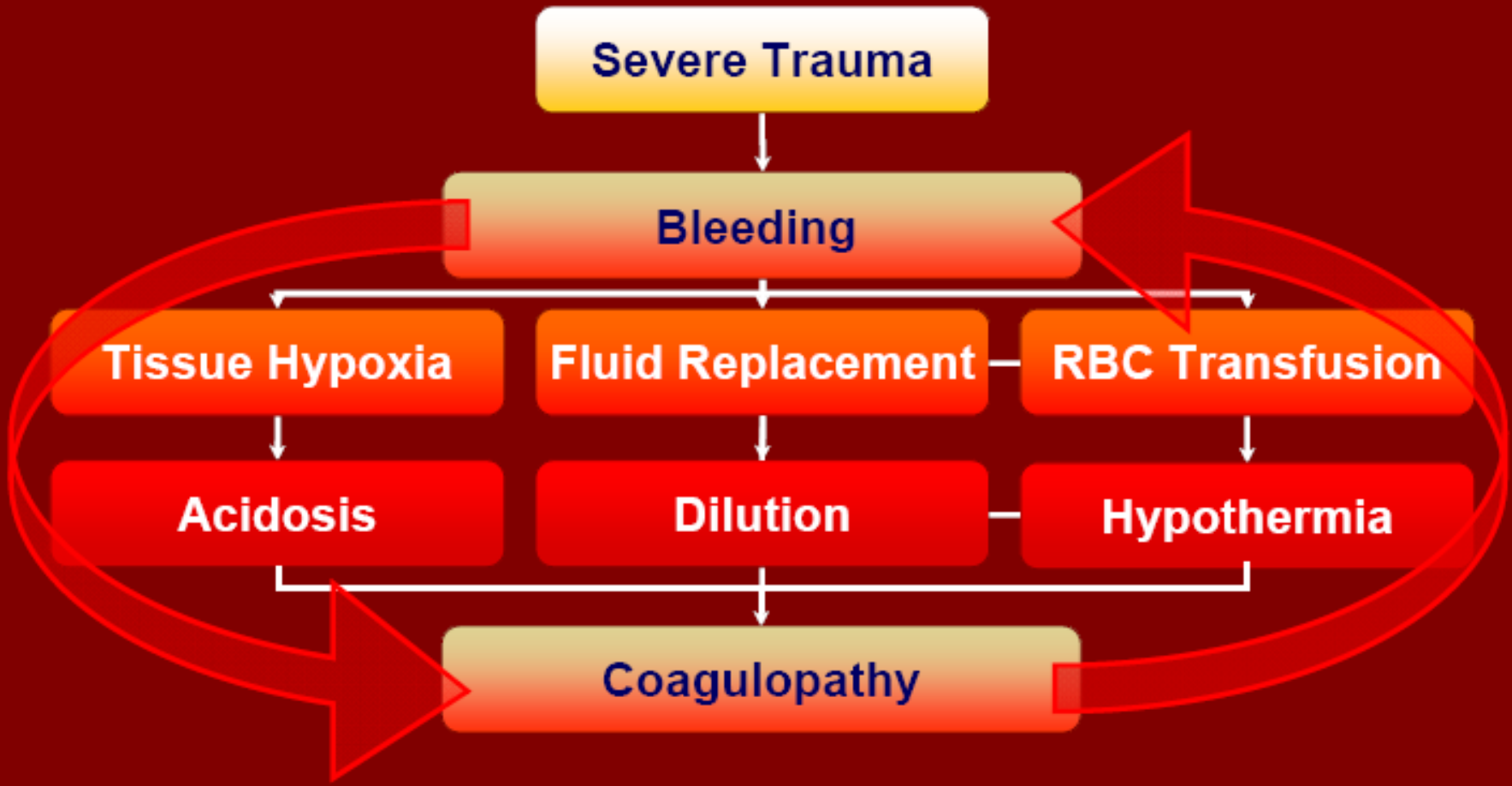
EMORRAGICHE

- AUTOIMMUNI
- DIFETTO DI VIT. K
- TERAPIA ANTICOAGULANTE
- COAGULOPATIA DILUIZIONALE

COMPLESSE

- TRAUMA
- TROMBOCITOPENIA INDOTTA DA EPARINA (HIT)
- COAGULAZIONE INTRAVASCOLARE DISSEMINATA
- CIRROSI EPATICA

The Lethal Triad
Bloody Vicious Cycle



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Intern Emerg Med
DOI 10.1007/s11739-017-1674-0

EM - REVIEW

The current understanding of trauma-induced coagulopathy (TIC): a focused review on pathophysiology

Stefano Giordano[1] · Luca Spiezia[1] · Elena Campello[1] · Paolo Simioni[1]

Received: 10 January 2017 / Accepted: 28 April 2017

TRAUMA INDUCED COAGULOPATHY

Endogenously-induced primary pathologies

FIBRINOLYTIC SHUTDOWN
(diffuse fibrin deposition)

FIBRINOGEN DEPLETION
↓ fibrinogenemia

2

FULMINANT HYPERFIBRINOLYSIS
↑ FDPs, D-Dimer

Pro-coagulant

Anti-coagulant

Thrombin switch

thrombin generation
catecholamines (e.g. epinephrine)
hormones (e.g. vasopressin)
cytokines (e.g. TNF and IL-1)

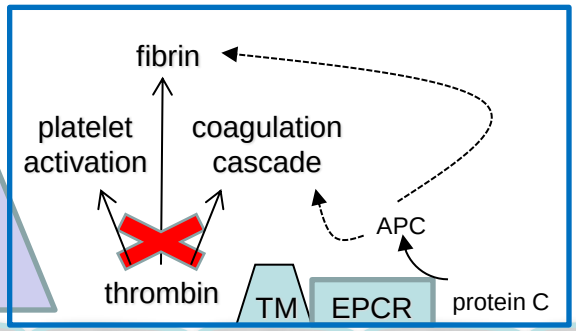
Tissue damage, hypoperfusion and bleeding

HAEMORRHAGIC PHENOTYPE (consumptive) ⟷ **THROMBOTIC PHENOTYPE** (hypercoagulable)

DIC(?)

1

ACoTS



Circulating dysfunctional platelets

3

Platelets sequestration:
← outer SHELL (dysfunctional)
←inner CORE (functional)

4

EGL shedding
↑ Syn1, HA, HS, CS

Degranulation of WPBs
↑ tPA, Ang2

…modified and worsened by:
Exogenously-induced secondary pathologies

a) HYPOTHERMIA

b) METABOLIC ACIDOSIS

c) ANAEMIA and HAEMODILUTION

d) EXOGENOUS ANTICOAGULATION

↓ platelet function
↓ coagulation factors
↑ breakdown rate

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TROMBOCITOPENIA INDOTTA DA EPARINA

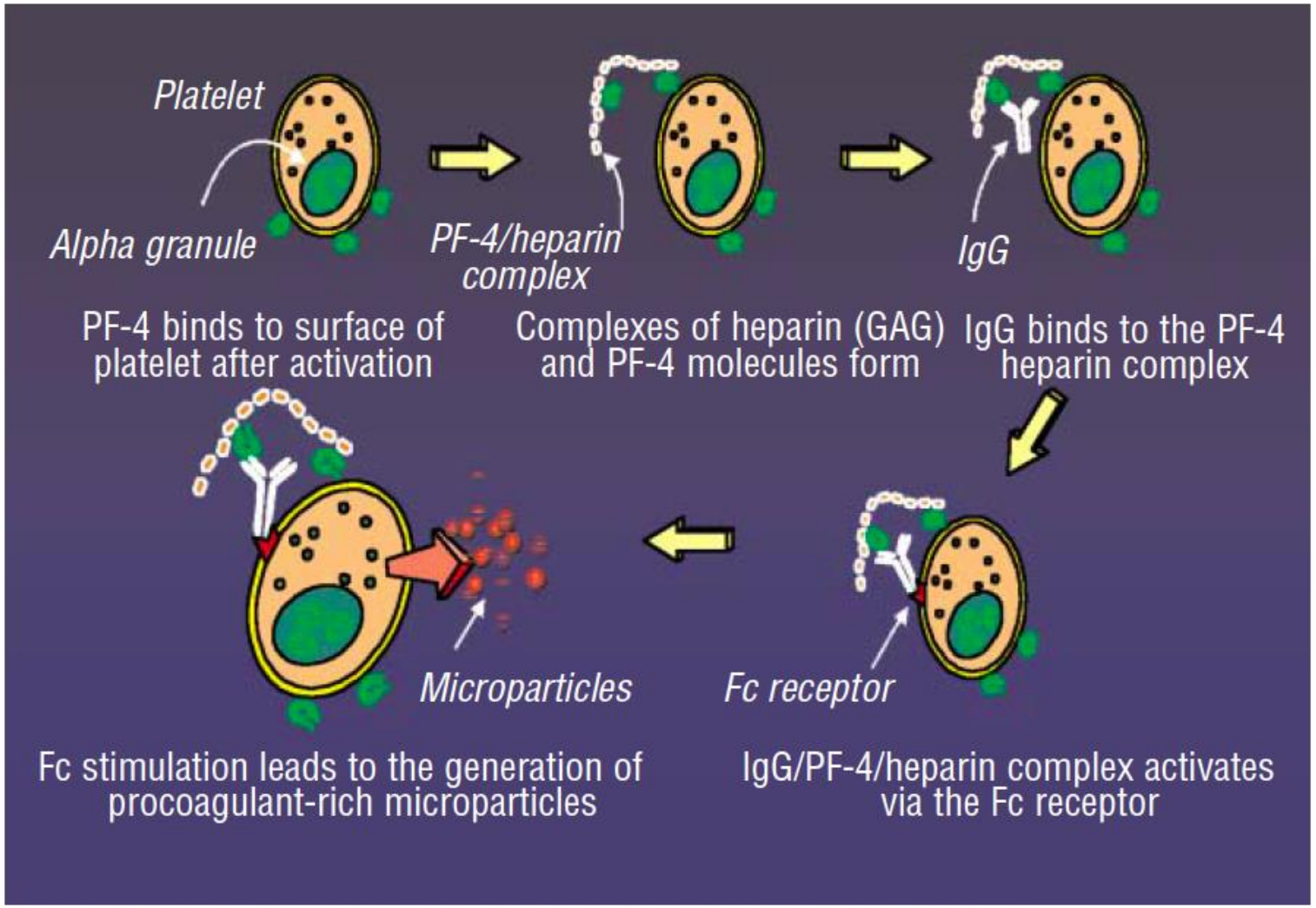

Figure 1 Pathophysiology of heparin-induced thrombocytopenia.

From Kelton JG. The pathophysiology of heparin-induced thrombocytopenia: biological basis for treatment. *Chest*. 2005;127(2 suppl):9S-20S. Used with permission.

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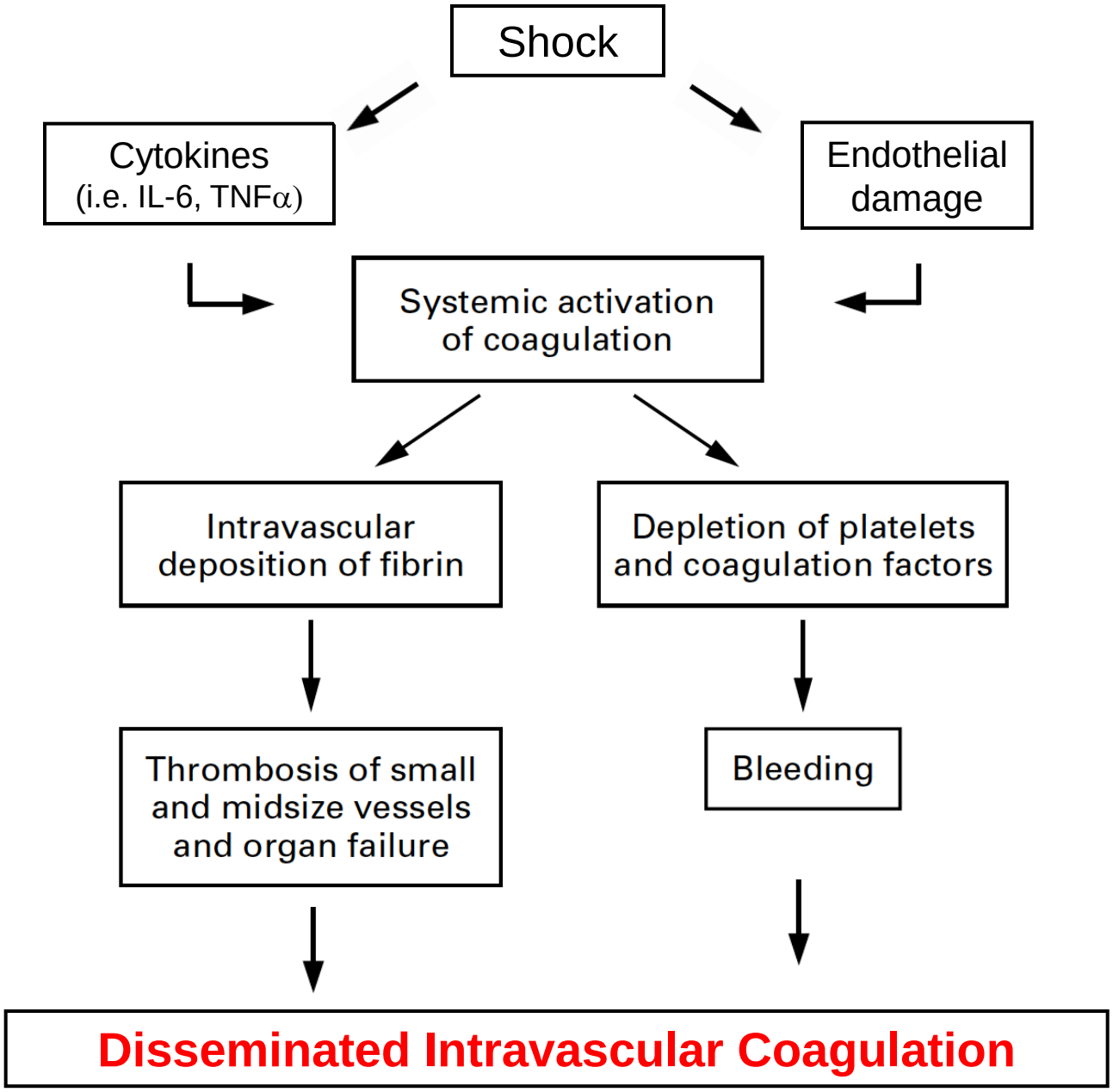

modified from Levi M & Ten Cate H, NEJM 1999

Laboratory findings in acute DIC

Platelet count		↓
Fibrinogen		↓
PT (INR)	↑	
PTT	↑	
D-dimer	↑	
Peripheral smear	Schistocites, helmet cells	

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Coagulation changes in liver cirrhosis

Hemostasis phase	Procoagulant changes	Prohemorragic changes
Primary hemostasis (vessel wall-platelets)	- High vWF - Low ADAMTS 13	- Low platelets count
Blood coagulation (thrombin generation and inhibition)	- Low anticoagulant factors (PC and AT) - High factor VIII	- Low fibrinogen, II, V, VII, IX, X, XI
Fibrinolysis (clot dissolution)	-Low plasminogen - High PAI	- High t-PA - Low TAFI - Low α_2-antiplasmin

Adapted from Tripodi and Mannucci NEJM 2011

Cirrhosis hemostatic balance