V Jornadas Hematológicas del Sur

Terapia Transfusional en Medicina de Urgencia

Complicaciones del tratamiento anticoagulante.

Dr Blaz Lesina

Magnitud del problema

- Entre el 0.8 y 1.3% de la población padece de FA
- 4.000 pacientes > de 65 años x 1.000.000 de hab
  - Reg de los Rios 380.000 hab. Total 1520 pacientes
  - Riesgo de hemorragia 1-5%
  - Reg de los Rios: entre 15 y 76 pac con hemorragia/año

Wilson JA, Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. Am J Cardiol. 1999;84:R131-8.

Que anticoagulantes estamos usando

Table 1 Characteristics of study sample. Values are percentages (numbers) unless stated otherwise

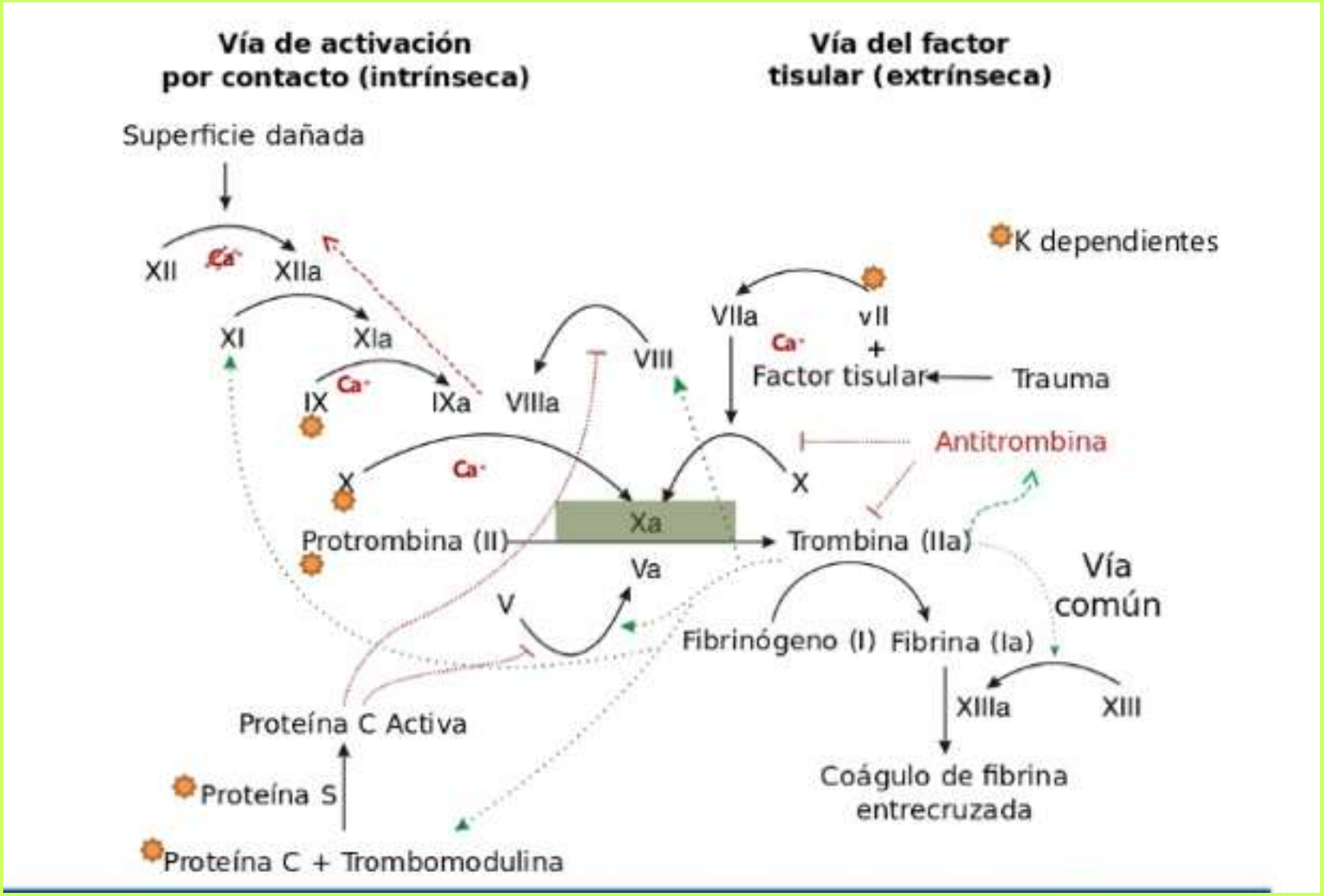
	Dabigatran (n=4907)	Rivaroxaban (n=1649)	Warfarin (n=39 607)	Total (n=46 163)
Patients' characteristics				
Mean (SD) age, years	62.0 (12.0)	57.6 (9.8)	57.4 (13.5)	57.6 (13.3)
Age group*:				
18-44	6.0 (295)	8.1 (133)	14.9 (5909)	13.7 (6337)
45-64	16.9 (827)	25.5 (420)	22.6 (8962)	22.1 (10 209)
55-64	44.4 (2178)	49.0 (808)	40.1 (15 867)	40.8 (18 853)
≥65	32.8 (1607)	17.5 (288)	22.4 (8869)	23.3 (10 764)
Female sex*	30.9 (1514)	51.5 (849)	46.9 (18 568)	45.3 (20 931)

Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *BMJ* 2015;350:h1585

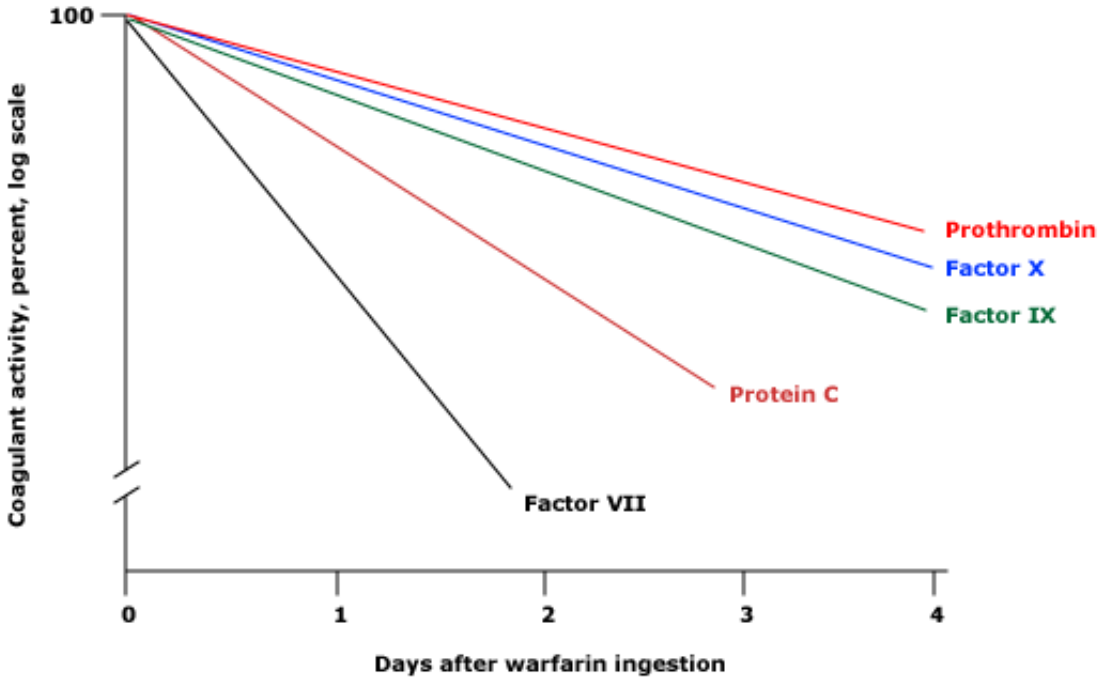
Antagonistas de vitamina K

TABLA 2. Vida media de factores de coagulación sintetizados en hígado

Factor	Vida media
Protrombina	2,8 – 4,4 días
Factor V	12-36 horas
Factor VII	2-5 horas
Factor IX	20-52 horas
Fibrinógeno	1,5-6,3 días
Factor X	32-48 horas

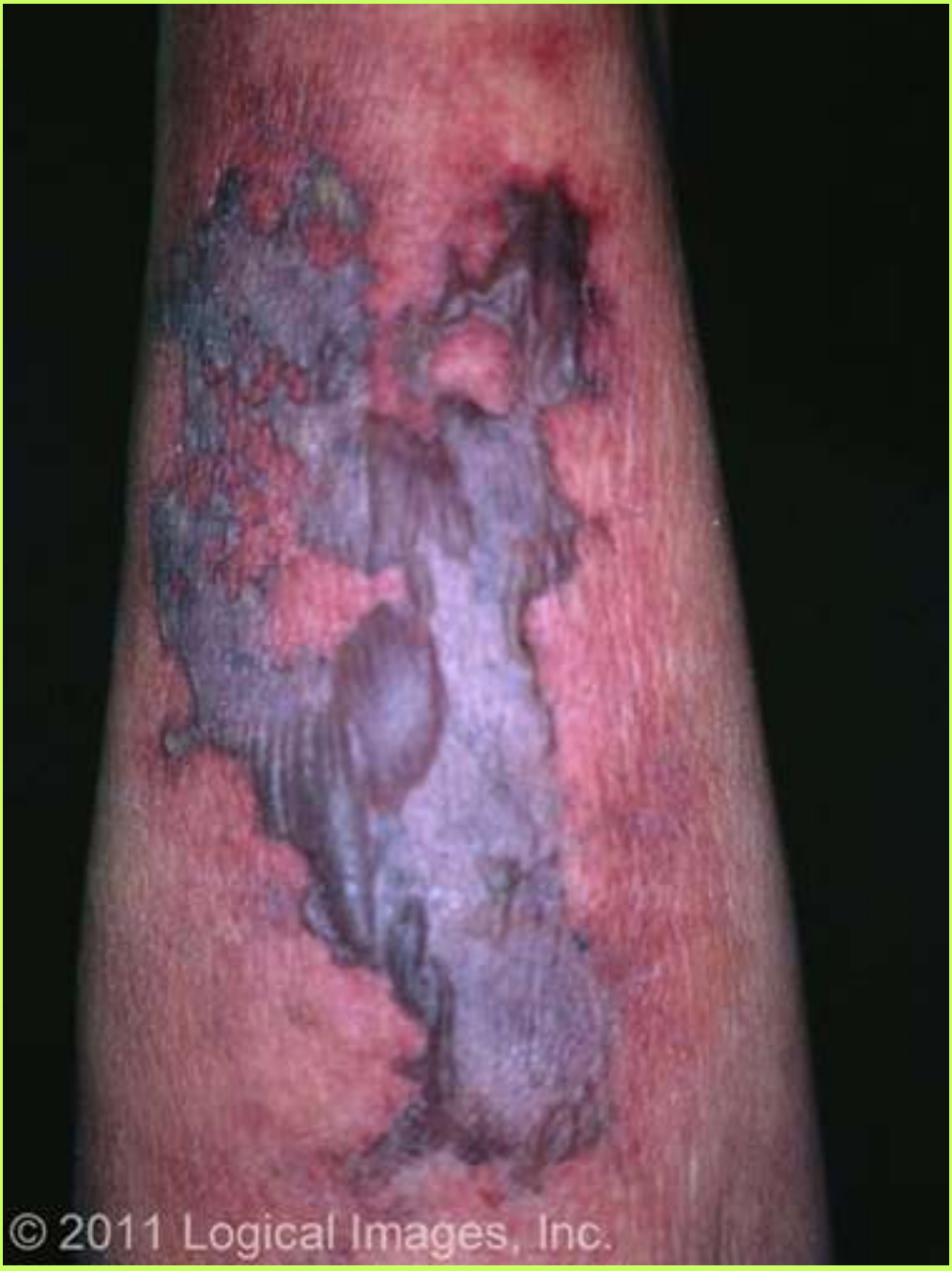

Vía de activación por contacto (intrínseca)
Vía del factor tisular (extrínseca)
Superficie dañada
XII
Ca
XIIa
XI
XIa
IX
Ca
IXa
VIIIa
VIII
K dependientes
VIIa
vII
+
Ca
Factor tisular
Trauma
Antitrombina
X
Ca
X
Xa
Protrombina (II)
Trombina (IIa)
Va
V
Vía común
Fibrinógeno (I)
Fibrina (Ia)
XIIIa
XIII
Proteína C Activa
Proteína S
Proteína C + Trombomodulina
Coágulo de fibrina entrecruzada

Effect of warfarin on blood clotting proteins

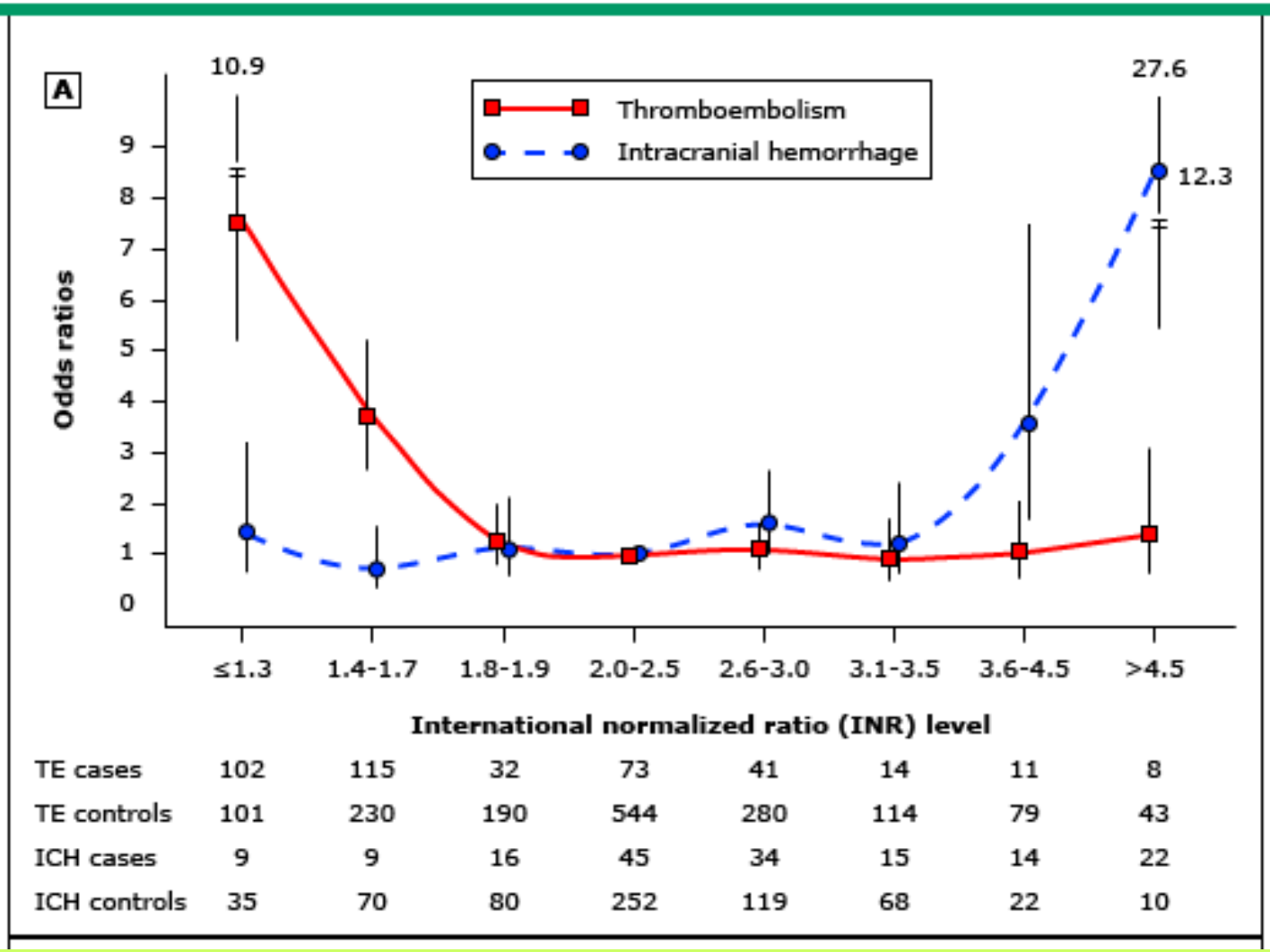


The activity of various clotting proteins (logarithmic scale) is shown here as a function of time after ingestion of warfarin (10 mg/day PO for four consecutive days) by a normal subject. Factor VII activity, to which the prothrombin time is most sensitive, is the first to decrease. Full anticoagulation, however, does not occur until factors IX, X, and prothrombin are sufficiently reduced. Protein C activity falls quickly, and, in some patients, a transient hypercoagulable state may ensue (eg, coumarin necrosis).

Redrawn from: Furie B. Oral anticoagulant therapy. In: Hematology: Basic Principles and Practice, 3rd ed, Hoffman R, Benz EJ, Shattil SJ, et al. (Eds), Churchill Livingstone, New York 2000. p.2040.


© 2011 Logical Images, Inc.

Optimal INR which minimizes both bleeding and thromboembolism in patients with atrial fibrillation



TE cases	102	115	32	73	41	14	11	8
TE controls	101	230	190	544	280	114	79	43
ICH cases	9	9	16	45	34	15	14	22
ICH controls	35	70	80	252	119	68	22	10

HEMORR$_2$HAGES SCORE

	Clinical Characteristic	Score
H	Hepatic or renal disease	1
E	Ethanol abuse	1
M	Malignancy	1
O	Older age (> 75 years)	1
R	Reduced platelet count or function	1
R	Rebleeding risk (sangrado previo)	2
H	Hypertension (uncontrolled)	1
A	Anemia	1
G	Genetic factors (CYP2C9*2 OR CYP2CP*3)	1
E	Excessive fall risk	1
S	Stroke	1

Gage BF, et al. *Am Heart J.* 2006;151:713-719.

HEMORR$_2$HAGES SCORE

Risk Score	Incidence of Major Bleeding (Bleeds per 100 patient-yrs (95% CI))
0	1.9 (0.6-4.4)
1	2.5 (1.3-4.3)
2	5.3 (3.4-8.1)
3	8.4 (4.9-13.6)
4	10.4 (5.1-18.9)
>=5	12.3 (5.8-23.1)

Gage BF, et al. *Am Heart J.* 2006;151:713-719.

Index for predicting risk of bleeding with warfarin

Age ≥65 years
History of stroke
History of gastrointestinal bleeding
One or more of the following comorbid conditions:
Recent myocardial infarction
Hematocrit <30 percent
Serum creatinine concentration >1.5 mg/dL (>133 micromol/L)
Diabetes mellitus

Low risk (no risk factors present, point score 0): 3 percent
Intermediate risk (point score 1 to 2): 12 percent
High risk (point score 3 to 4): 53 percent

Clinical characteristics comprising the HAS-BLED Bleeding Risk Score

Letter	Clinical characteristic*	Points
H	Hypertension (ie uncontrolled blood pressure)	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding tendency or predisposition	1
L	Labile INRs (for patients taking warfarin)	1
E	Elderly (age greater than 65 years)	1
D	Drugs (concomittant aspirin or NSAIDS) or alcohol abuse (1 point each)	1 or 2
		Maximum 9 points

HAS-BLED score (total points)	Bleeds per 100 patient-years•
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5 to 9	Insufficient data

TABLA 6. Riesgo anual de complicaciones trombóticas en ausencia de terapia anticoagulante

Condición	Riesgo anual de trombosis en %
Fibrilación auricular	5
Fibrilación auricular de alto riesgo	12
Prótesis valvular mecánica aórtica doble valva (St. Jude)	10-12
Prótesis valvular aórtica única valva (Shiley)	23
Fa lone	1
Válvula mitral protésica doble valva (St. Jude)	22
Prótesis múltiples (St. Jude)	91

TABLA 2. **Localización de complicaciones hemorrágicas**

Localización	Leves/moderadas	Graves	Total	%
Epistaxis	603	7	610	25,75
Gingivorragia	340	—	340	14,35
Cutánea/muscular	618	14	632	26,67
Ocular	92	2	94	3,96
Hemoptisis	53	7	60	2,53
Hemartrosis	18	1	19	0,8
Ginecológica	71	13	84	3,54
Hematuria	238	12	250	10,55
Rectorragia	101	13	114	4,81
HDA	5	38	43	1,81
Melena	27	36	63	2,65
Hemorragia interna		4	4	0,16
Cerebral	2	43	45	1,9
Otros	11		11	0,46
Total	2.179 (91,98%)	190 (8,02%)	2.369	
Muertes	—	20	20	0,84

Hemorragia.

- <u>Siempre investigar la causa</u>
- Hemorragia digestiva
  - EDA:
    - Identifica la causa en > 50%
    - Consigue hemostasia en >90%
- Hematuria:
  - 3.2% de pac. Con TACO vs 4.8% grupo control
  - Si se estudia > 70% se encuentra dg de base

W olf A T, W asan S K, S altzman J R. I mpact of anticoagulation on rebleeding following endoscopic therapy for nonvariceal upper gastrointestinal hemorrhage . Am J Gastroenterol .2007 ; 102 (2): 290 - 296 .
Culclasure TF , Bray VJ , Hasbargen JA . The signifi cance of hematuria in the anticoagulated patient . Arch Intern Med .1994 ; 154 (6): 649 - 652 .
Schuster GA , Lewis GA . Clinical signifi cance of hematuria in patients on anticoagulant therapy . J Urol . 1987 ; 137 (5):923 - 925 .
Van Savage JG , Fried FA . Anticoagulant associated hematuria:a prospective study . J Urol . 1995 ; 153 (5): 1594 - 1596 .

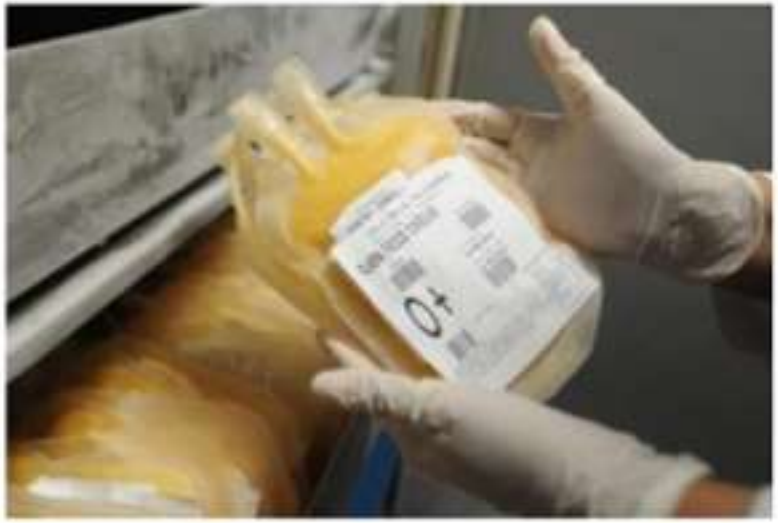
INR	HEMORRAGIA	ACCION RECOMENDADA
Alrededor de 5	NO	Disminuir dosis/omitir una dosis
Entre 5 y 9	NO	Omitir una dosis/omitir una dosis + vit K 1 - 2.5 mg vo
Mayor a 9	NO	Susp dosis + vit K 2.5 -5 mg VO
Cualquiera	Hemorragia mayor	Susp + vit K 10 mg EV+ complejo protrombina o PFC

Vitamina K

- K1: derivada de plantas
  - V.O.: disminuyen INR de 8 a 4 en 1.4 días
  - EV. Inicio de acción en 2 horas y normalización en 24 horas
  - EV. Reacción anafiláctica en 3 de 10000 dosis
    - aceite de castor polietoxilado
  - Diluir: 50 ml suero adm en 20 min.
  - Se usa para disminuir el riesgo de rebote.

Plasma fresco congelado

- El de uso más común
- 60% se usa para revertir HIC por ACOr.
- Producto sanguíneo que contiene todos los factores de coagulación
- Concentración de factores no es estándar.
- Depende de la variabilidad genética del donador.



Pueden ser necesarios amplios volúmenes para corregir el déficit de coagulación
Según INR objetivo (1,5 – 1,7 = 2 L plasma)

Demora en inicio de acción por:
- Requerimiento de pruebas de compatibilidad
- Paso de infusión lenta

Concentrados de complejo de protrombina

Product	Availability	Clotting Factors				Anticoagulant Proteins			
		FII	FVII	FIX	FX	Protein C	Protein S	AT	Heparin*
Three-factor PCCs									
Bebulin VH[10]	U.S.	24–38 IU/ml	<5 IU/ml	24–38 IU/ml	24–38 IU/ml	NA	NA	NA	<0.15 IU/IU FIX
Profilnine SD[11]	U.S.	NMT 150 U/100 FIX units	NMT 35 U/100 FIX units	100 U	100 U/100 FIX units	NA	NA	NA	None
Four-factor PCCs									
Beriplex P/N[12]	Europe, Canada, U.S. (as Kcentra)	20–48 IU/ml	10–25 IU/ml	20–31 IU/ml	22–60 IU/ml	15–45 IU/ml	12–38 IU/ml	0.2–1.5 IU/ml	0.4–2 IU/ml
Octaplex[13]	Europe, Canada	14–38 IU/ml	9–24 IU/ml	25 IU/ml	18–30 IU/ml	13–31 IU/ml	12–32 IU/ml	NA	5–12.5 IU/ml
rFVIIa									
NovoSeven[14]	None†	None	0.6 mg/ml	None	None	None	None	None	None
Activated PCC									
FEIBA NF[15]	U.S., Europe	1.3 U/U	0.9 U/U‡	1.4 U/U	1.1 U/U	1.1 U/U	NA	NA	None

Bebulin (Baxter BioScience, Westlake Village, CA); Beriplex (CSL Behring, Marburg, Germany); FEIBA (Baxter AG, Vienna, Austria); NovoSeven (NovoNordisk, Bagsværd, Denmark); Octaplex (Octapharma AG, Lachen, Switzerland); Profilnine (Grifols Biologicals Inc., Los Angeles, CA).

* Reported as anti-Xa levels in IU/ml. † Not approved in any country for this indication. ‡ Factor VII is mainly in the activated form.

AT = antithrombin; FEIBA = Factor Eight Inhibitor Bypassing Activity; FIX = factor IX; NA = information not available in product label; NMT = not more than; PCC = prothrombin complex concentrate; rFVIIa = recombinant activated factor VII; U.S. = United States.

Concentrados de complejo de protrombina

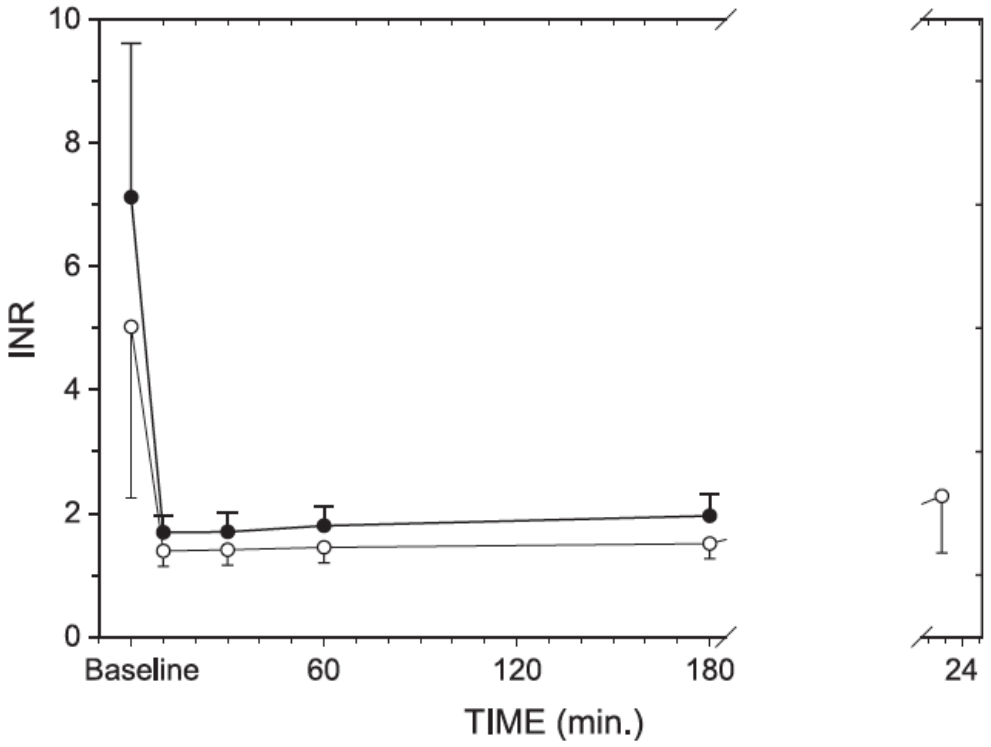


Fig. 1 Change of INR after administration of Octaplex during 24 h follow-up in bleeding (full symbols) and surgical patients (open symbols). Except for baseline, all INR values were significantly higher in bleeding patients. Values represent mean ± S.D.

Efficacy and safety of a prothrombin complexconcentrate (OctaplexR) for rapid reversal of oral anticoagulation
A. Lubetsky et al. Thrombosis Research 113 (2004) 371--378

Vitamina K evita el rebote

Variable evaluada en el estudio	Concentrado protrombina+Vit K	Concentrado de protrombina	Vitamina K
N= número de pacientes	N = 11	N = 2	N = 4
INR inicial (mediana)	2,70 (2,70->10)	6,23	2,69 (2,03-3,35)
INR 10 min tras admón.	1,13 (0,91-1,36) p<0,01	1,36	No cambio
INR 12 a 24 horas tras admón.	1,06 p<0,01	2,07	1,28 (1,25-1,44) p=0,07

p respecto al INR inicial

Masahiro Yasaka, Ttosiyuki Sakata, Kazuo Minematsu, Hiroaki Naritomi.Correction of INR by prothrombin complex concentrate and vitamin K in patiens with warfarin related hemorragic complication.Thrombosis research 108 (2003)25-30

Table 3. Adverse Events and Secondary Outcomes

Adverse Event (%)	Frozen Plasma (N=149)	Octaplex (N=165)	p-value
Any Adverse Event	29 (19.5)	16 (9.7)	0.014
Death	22 (14.8)	15 (9.1)	0.120
Ischemic Stroke	0 (0)	0 (0)	-
Myocardial Infarction	2 (1.3)	1 (0.6)	0.606
Heart Failure	4 (2.7)	0 (0)	0.0496
Pulmonary Embolism	0 (0)	0 (0)	-
Deep Venous Thrombosis	1 (0.7)	0 (0)	0.475
Arterial Thromboembolism	0 (0)	0 (0)	-
Any Adverse Event Excluding Death	7 (4.7)	1 (0.6)	0.029
Secondary Outcomes			
Time to INR reversal (hours) (Median, Q1-Q3)	11.8 (8.3–17.5)	5.7 (3.4–11.0)	<0.0001
Hospital length of stay (days) (Median, Q1-Q3)	5 (2–12)	4 (2–11)	0.245
Mean units of packed red blood cells (Mean, SD)	3.2 (1.8)	1.4 (1.7)	<0.0001

Outcomes of Urgent Warfarin Reversal With Frozen Plasma Versus Prothrombin Complex Concentrate in the Emergency Department Michael Hickey et al Circulation. 2013;128:360-364.

Dosis de octaplex

INR inicial	2-2.5	2.5-3	3-3.5	> 3.5
mL/kg	0.9 -1.3	1.3-1.6	1.6-1.9	> 1.9

Frasco 20 ml

Hemorragia Intracraneal por antagonistas de vit K

NIKE

N	Normalize INR
I	Inmediate coagulophaty reversal
K	Vit K, para evitar rebotes
E	Elevation of INR , all level require urgent correction


TERAPIA
INTENSIVA
zzzZZ
NESTOR MARTIN
2003

Hemorragia intracraneal por antagonistas de vitamina K

- Tratamiento:
  - Suspender la droga
  - Dg por TAC
  - 10 mg vit K c/12 horas
  - Complejo de protrombina ev
  - Si no hay : PFC
  - Control INR a los 30 minutos y cada 6 horas primeras 24 horas: meta < 1.4
  - Luego control INR diario.

Hemorragia asociada a los nuevos anticoagulantes

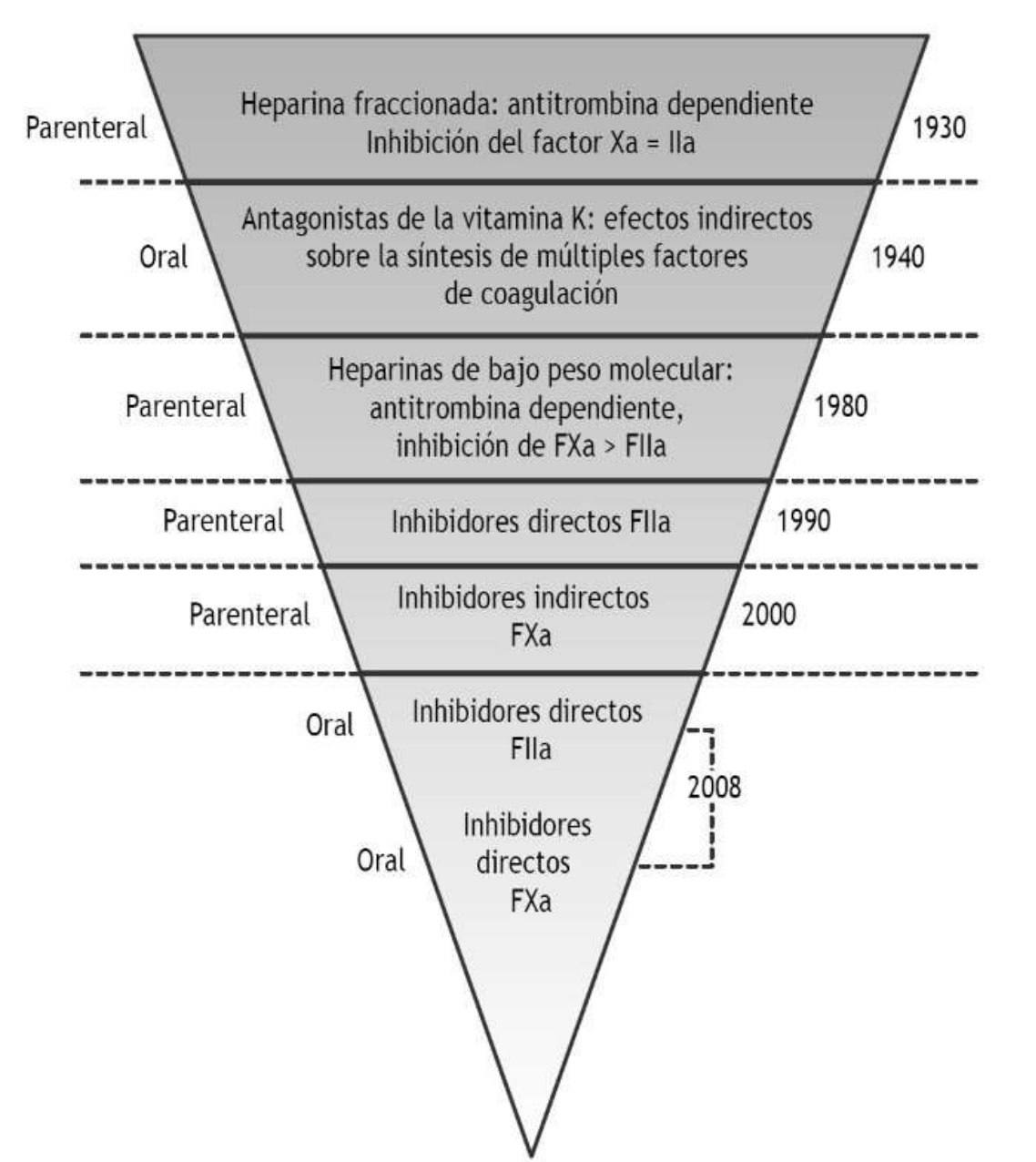
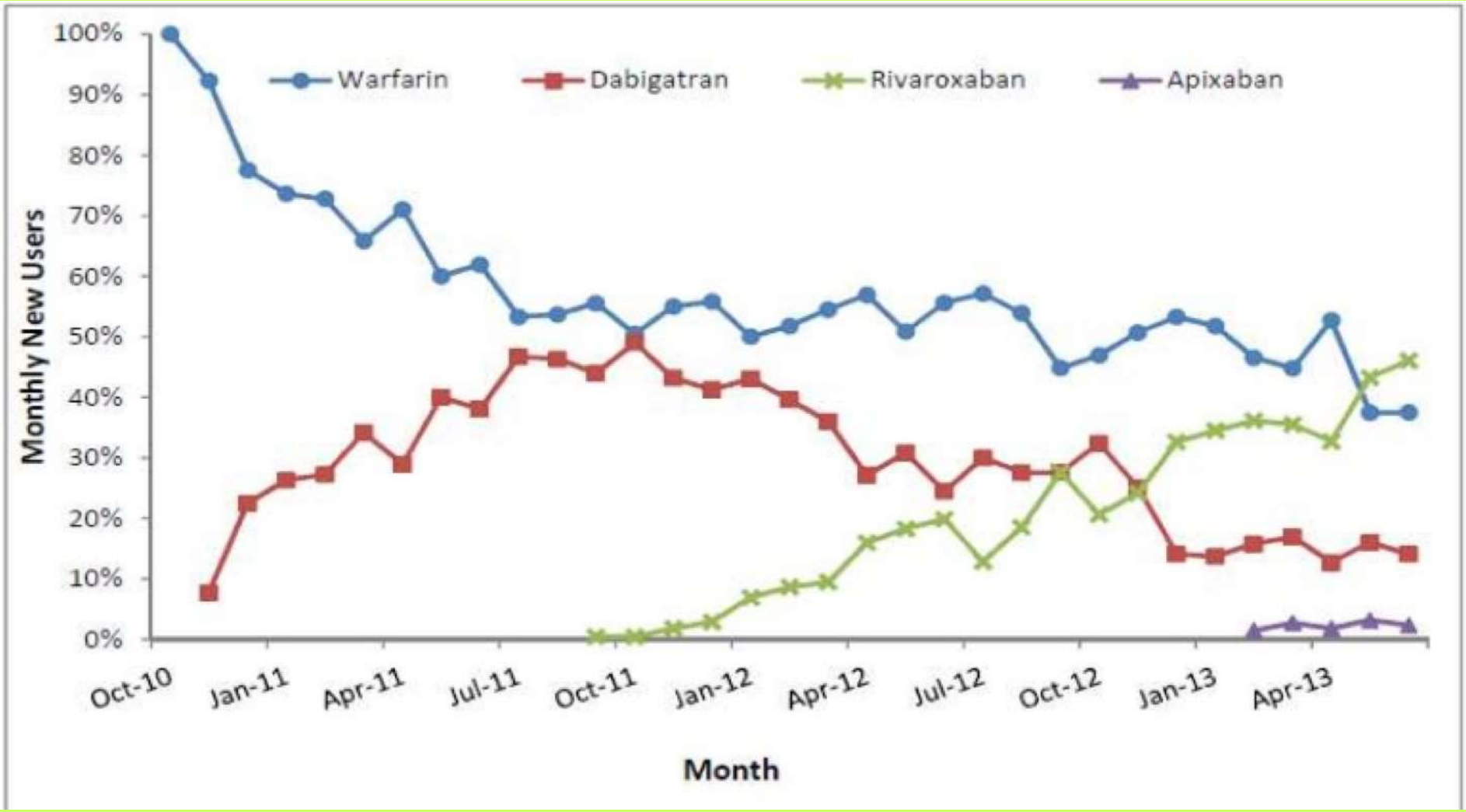
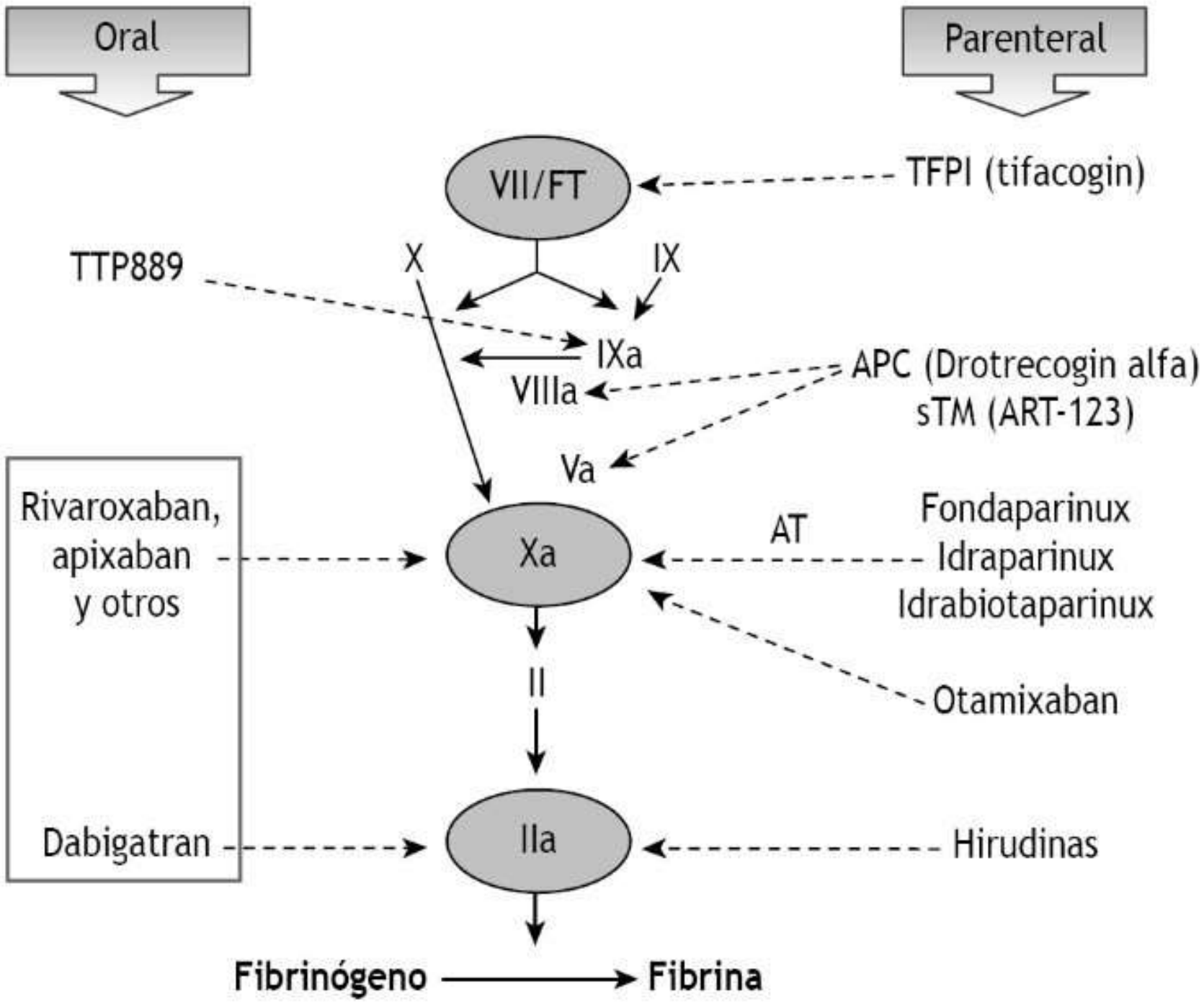


Table 1. Approved indications for use of novel oral anticoagulants

Drug/region	Prevention of stroke/systemic embolism in nonvalvular atrial fibrillation	Prevention of VTE after hip/knee replacement surgery	Treatment of acute VTE	Prevention of VTE recurrence
Dabigatran				
United States	✓			
Canada	✓	✓		
Europe	✓	✓		
Rivaroxaban				
United States	✓	✓	✓	✓
Canada	✓	✓	✓	✓
Europe	✓	✓	✓	✓
Apixaban				
United States	✓			
Canada	✓	✓		
Europe	✓	✓		

VTE, venous thromboembolism.


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Monthly New Users
Warfarin
Dabigatran
Rivaroxaban
Apixaban
Oct-10
Jan-11
Apr-11
Jul-11
Oct-11
Jan-12
Apr-12
Jul-12
Oct-12
Jan-13
Apr-13
Month


Oral
Parenteral
VII/FT
TFPI (tifacogin)
TTP889
X
IX
IXa
VIIIa
APC (Drotrecogin alfa)
sTM (ART-123)
Va
Rivaroxaban,
apixaban
y otros
Xa
AT
Fondaparinux
Idraparinux
Idrabiotaparinux
Otamixaban
II
Dabigatran
IIa
Hirudinas
Fibrinógeno
Fibrina

Propiedad	Rivaroxaban	Apixaban	Dabigatran
Diana	Factor Xa	Factor Xa	Factor IIa
Pro-fármaco	No	No	Sí
Administración	Oral	Oral	Oral
Dosis profiláctica	Fija, 1/día	Fija, 2/día	Fija, 1/día
Biodisponibilidad	80%	50%	6%
Control analítico	No	No	No
Pico	3 h	3 h	2 h
Vida media	7-11 h	9-14 h	12-17 h
Eliminación			
Renal	66%	25%	80%
Biliar	33%	75%	20%
Interacciones	(1)	(1)	(2)
Seguridad en el embarazo	No	No	No
Antídoto	No	No	No

(1) Potente CYP3A4 e inhibidores de las P-glucoproteínas.
(2) Inhibidores de la bomba de protones.
Modificada de Francis[4], Gross y Weitz[5], Bounameaux[10] y Eikelboom y Weitz[15].

Escépticos

Los hay en todos lados

Table 3. **Summary of the Strength of Evidence for Adverse Effects for Atrial Fibrillation and Venous Thromboembolism Combined**

Outcome	Strength of Evidence	Summary
Fatal bleeding	Moderate	The risk for fatal bleeding was lower with NOACs (RR, 0.60 [95% CI, 0.46 to 0.77]). Risk difference was 1 fewer death per 1000 patients.
Major bleeding	Low	The risk for major bleeding was lower with NOACs (RR, 0.80 [CI, 0.63 to 1.01]), but the CI included no effect. In 2011, the FDA issued a notice that it was evaluating reports of serious bleeding with dabigatran.
Gastrointestinal bleeding	Low	The risk for gastrointestinal bleeding was increased with NOACs (RR, 1.30 [CI, 0.97 to 1.73]).
Myocardial infarction	Low	The risk for myocardial infarction was not different with NOACs (RR, 0.95 [CI, 0.81 to 1.11]). In a subgroup analysis, the risk was increased with dabigatran (RR, 1.35 [CI, 0.99 to 1.85]) compared with FXa inhibitors (RR, 0.84 [CI, 0.70 to 1.01]) ($P = 0.010$).
Discontinuation due to adverse effects	Low	Discontinuation due to adverse effects was higher with NOACs (RR, 1.23 [CI, 1.05 to 1.44]), but the CI was large and included no effect. In subgroup analysis, rates of discontinuation were higher for dabigatran than for FXa inhibitors.
Liver dysfunction	Low	The risk for liver dysfunction was not different with NOACs (RR, 0.82 [CI, 0.56 to 1.18]).

FDA = Food and Drug Administration; FXa = factor Xa; NOAC = new oral anticoagulant; RR = risk ratio.

SUSPENSIÓN Y REINICIO

- PORCENTAJES MEDICACION SEGÚN VIDA MEDIA:

VIDAS MEDIAS	% MEDIACMENTO	% ELIMINACION
1	50%	50%
2	25	75
3	12	87.5
4	6.2	93.8
5	3-1	96.9
6	1.6	

VIDAS MEDIAS

Recommendations of the Working Group on Perioperative Hemostasis and the French Study Group on Thrombosis and Haemostasis. Arch. Cardiovasc. Dis 2011; 104: 669–76

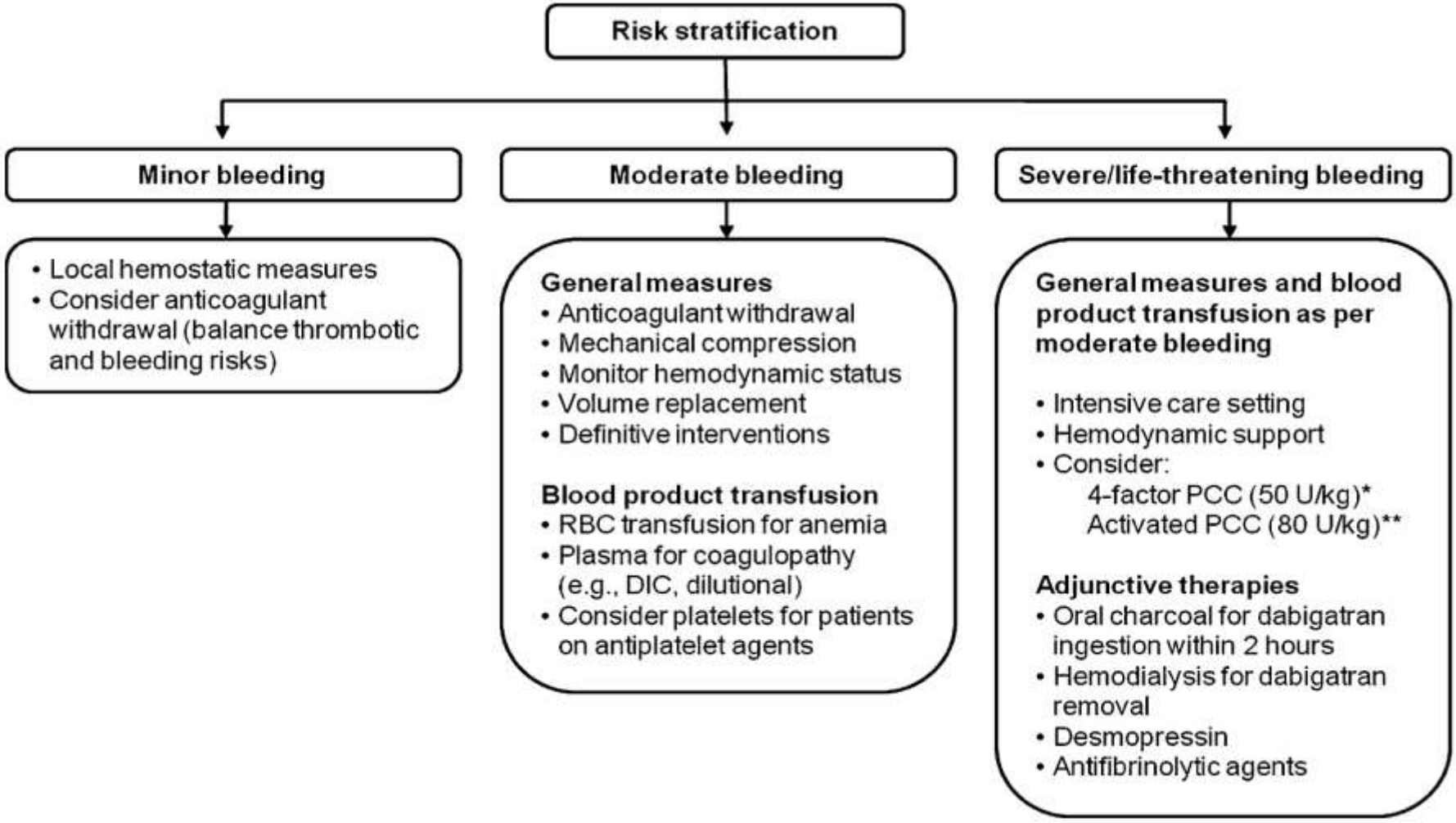
¿Cuanto tiempo suspendo antes de la cirugía?

Drug	Metabolism, renal, and faecal/biliary elimination*	Elimination half-life	Five half-lives	Baron and colleagues:[12] recommendations
Dabigatran	Renal 80%, faecal 20%	12–17 h 28 h (end-stage renal disease)	85 h (4 days) 140 (6 days) (end-stage renal disease)	1–2 days with CrCl ≥50 ml min^{-1}; 3–5 days with CrCl <50 ml min^{-1}
Rivaroxaban	Metabolism 33%, renal 33% (33% inactive metabolites)	9–13 h	65 h (3 days)	≥1 day with normal renal function; 2 days with CrCl 60–90 ml min^{-1}; 3 days with CrCl 30–59 ml min^{-1}; 4 days with CrCl 15–29 ml min^{-1}
Apixaban	Renal 25%, metabolism and faecal elimination 75%	15.2 (8.5)	75 h (3–4 days)	1 or 2 days with CrCl >60 ml min^{-1}; 3 days with CrCl 50–59 ml min^{-1}; 5 days with CrCl<30–49 ml min^{-1}

Interpretation of Laboratory Tests in Setting of NOAC Administration

	PT	aPTT	TT	dTT	ECT	Anti-Factor Xa	SMC Anti-Factor Xa
Direct Thrombin Inhibitors	⇔/⇑	⇔/⇑	⇑	⇑	⇑	⇑	⇔
Factor Xa Inhibitors	⇔/⇑	⇔/⇑	⇔	⇔	⇔	⇑	⇑

PT=prothrombin time, aPTT=activated partial thromboplastin time, TT=thrombin time, dTT=dilute thrombin time, ECT=ecarin clotting time, SMC=specific modified chromogenic


Risk stratification
Minor bleeding
Moderate bleeding
Severe/life-threatening bleeding
• Local hemostatic measures
• Consider anticoagulant withdrawal (balance thrombotic and bleeding risks)
General measures
• Anticoagulant withdrawal
• Mechanical compression
• Monitor hemodynamic status
• Volume replacement
• Definitive interventions
Blood product transfusion
• RBC transfusion for anemia
• Plasma for coagulopathy (e.g., DIC, dilutional)
• Consider platelets for patients on antiplatelet agents
General measures and blood product transfusion as per moderate bleeding
• Intensive care setting
• Hemodynamic support
• Consider:
4-factor PCC (50 U/kg)*
Activated PCC (80 U/kg)**
Adjunctive therapies
• Oral charcoal for dabigatran ingestion within 2 hours
• Hemodialysis for dabigatran removal
• Desmopressin
• Antifibrinolytic agents


¿QUÉ SERÁ PEOR? ¿ESTE PRESENTE QUE ESTAMOS VIVIENDO O EL FUTURO QUE NOS ESPERA?
EL PASADO, QUE QUIERE VOLVER.
berlich@gmail.com

En camino……

- Humanized monoclonal antibody fragment against dabigatran

- Inactive factor Xa derivatives.

V Jornadas Hematológicas del Sur

Terapia Transfusional en Medicina de Urgencia