ACTUALIZACIÓN EN ANTICOAGULACIÓN ORAL

Dra. Patricia Casais

AMA, 22 de agosto de 2023

CONFLICTOS DE INTERÉS

- Ensayos clínicos (ARISTOTLE- MARINER)
- Advisory Boards “ad hoc” (dabigatran, rivaroxaban)
- Actividades educativas (apixaban, rivaroxaban, edoxaban)
- Asistencia a Congresos (rivaroxaban, apixaban)

TEMAS

- Farmacocinética/dinámica
- Tromboembolismo Venoso
- Fibrilación Auricular
- Manejo Práctico

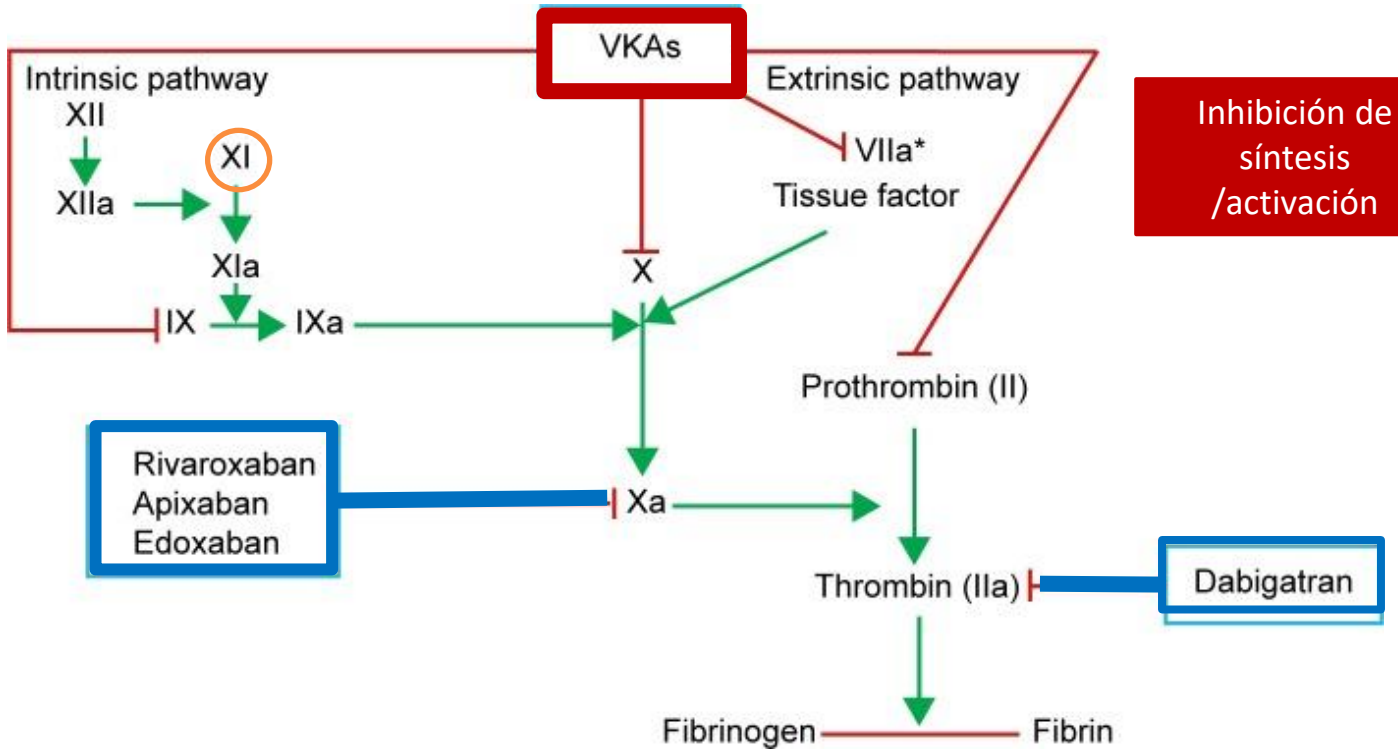
INTRODUCCIÓN

- Los DOACs son los anticoagulantes de elección en fibrilacion auricular y tromboemboliamo venoso.
- Características de los DOACs:
  - Mecanismo de acción directo
  - Respuesta “predecible”
  - Rápido comienzo del efecto anticoagulante
  - Vida media corta
  - Antídotos específicos
  - (No) requieren control de laboratorio periódico
  - Dosis fija (≠ dosis única)
- Los DOACs difieren entre sí en sus propiedades farmacocinéticas.

DROAGAS ANTICOAGULANTES ORALES
MECANISMO DE ACCIÓN

Ac. monoclonal (abelacimab) Milvexian

DOACs: Bloqueo enzimático de actividad del Factor



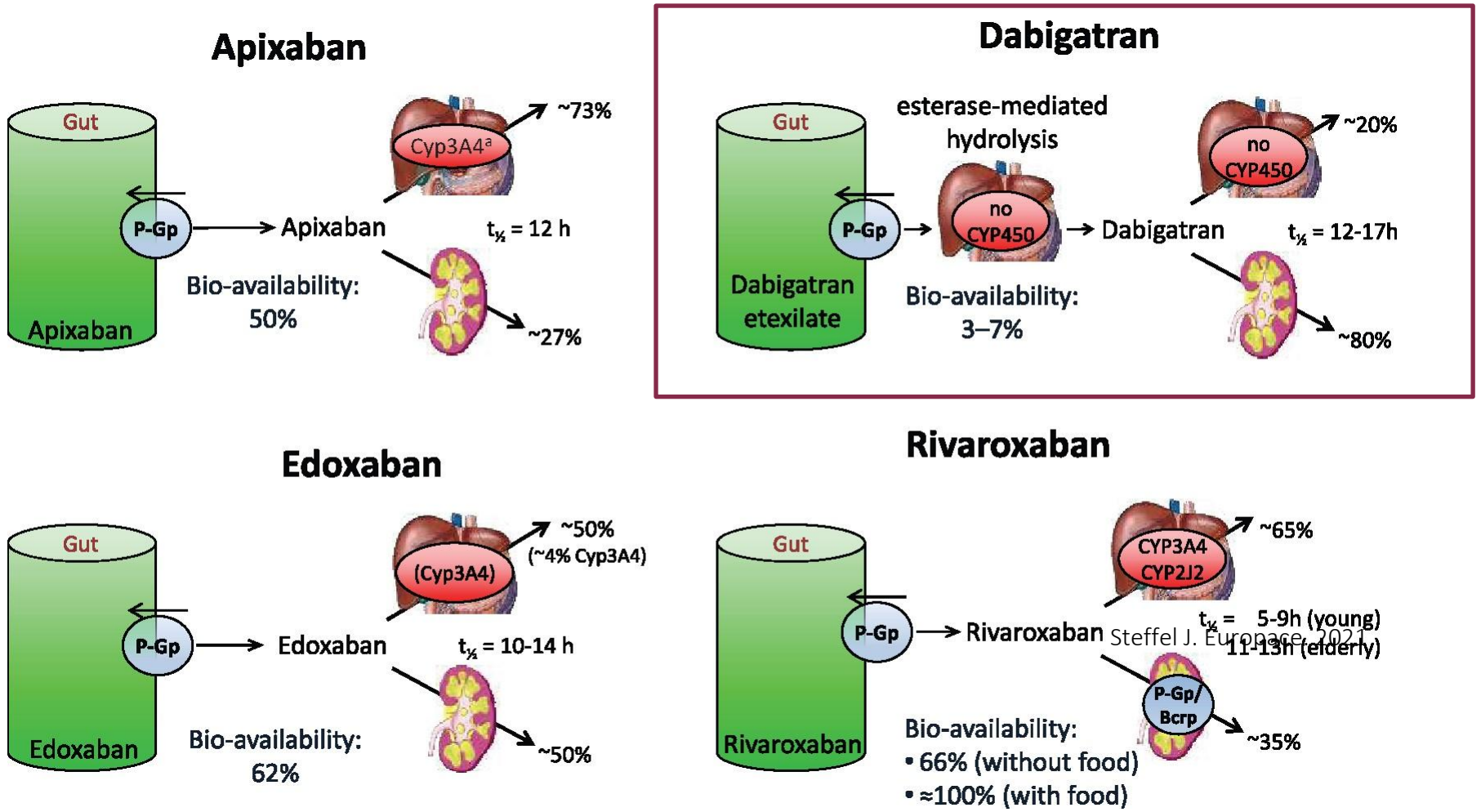
Inhibición de síntesis /activación

VKAs: antagonistas de la vitamina K (dicumarínicos: warfarina- acenocumarol)

¿QUÉ PACIENTE ES CANDIDATO A DOAC?

DROGAS	ÓRGANOS	ACTIVIDAD	CONDICIÓN	PACIENTE
• Farmacocinética • Farmacodinámica	• Función Renal • Función Hepática	• Sangrado Activo • Anemia • Adherencia	• Embarazo • Válvula Mecánica • Costos	• Peso • Preferencias del paciente

Farmacocinética



Steffel J. Europace. 2021

Steffel J..2021

FARMACOCINÉTICA DE LOS DOACS

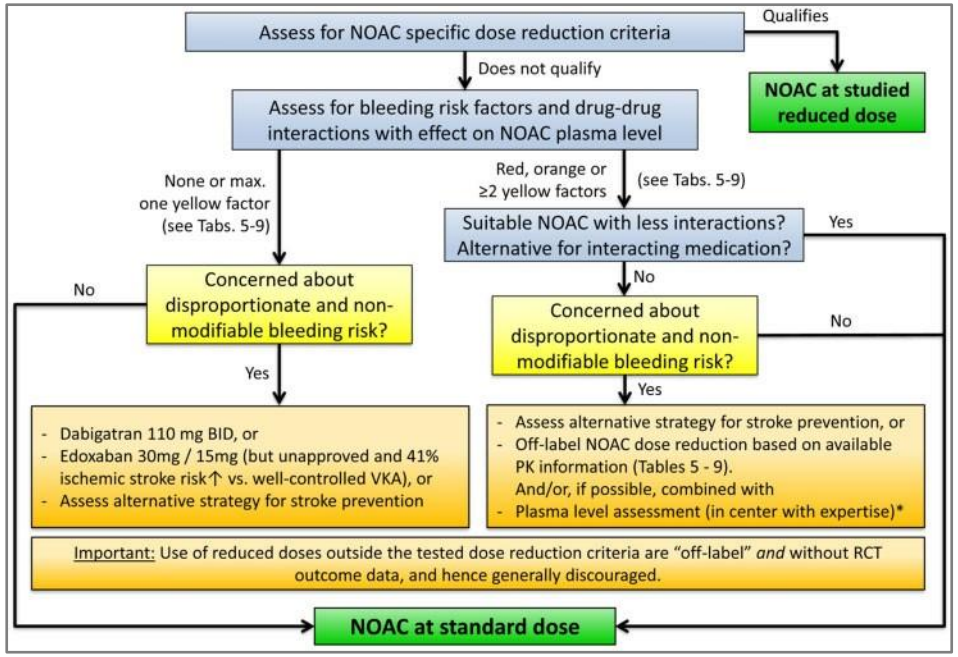
	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
Blanco	IIa	FXa	FXa	FXa
Biodisponibilidad (%)	6,5	Con alimentos, ≥ 80	50	62
T. máx (h)	0,5-2	2-4	3-4	1-2
Unión a proteínas plasmáticas (%)	35	92-95	87	55
Metabolismo por CYP P450 (%)	No	66	25	< 4
Interacción con transportadores	GP-P	GP-P, BCRP		GP-P
Eliminación renal (%)	85	66 (33 metabolito inactivo)	27	35
Vida Media (h)	12-14	5-9 (jóvenes); 11-13 (ancianos)	12	10-14
Interacciones con fármacos	Inhibidores/inductores potentes de la GP-P	Inhibidores/inductores potentes de la GP-P y del CYP3A4		Inhibidores potentes de la GP-P

T. máx: tiempo hasta alcanzar las concentraciones plasmáticas máximas- GP-P: glicoproteína P- BCRP (ABCG2): proteína de resistencia de cáncer de mama,

Ferri N. 2022- Tamargo J. 2016

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Jan Steffel[1]*, Ronan Collins[2], Matthias Antz[3], Pieter Cornu[4], Lien Desteghe[5,6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[12], Thomas Vanassche[12], Tatjana Potpara[13], A. John Camm[14], and Hein Heidbu¨chel[5,6]



	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Immune-modulating agents					
Ciclosporine	Strong-to-moderate P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	SmPC	+73% AUC (dose reduction to 30 mg once daily by label)	
Dexamethasone	Moderate CYP3A4 induction; CYP3A4 competition				
Tacrolimus	Strong-to-moderate P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition	SmPC	Consider avoiding	Consider avoiding	Consider avoiding
Prednisone	Moderate CYP3A4 induction; CYP3A4 competition				
Temsirolimus, Sirolimus	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Everolimus	CYP3A4 competition; no relevant interaction anticipated				
Tyrosine kinase inhibitors					
Imatinib, Crizotinib	Strong P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition				
Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Dasatinib	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vandetanib, Sunitinib	Strong P-gp inhibition; CYP3A4 competition				
Erlotinib, Gefitinib	CYP3A4 competition; no relevant interaction anticipated				

Europace (2021) 23, 1612–1676

INTERACCIONES MEDICAMENTOSAS

INTERACTION BETWEEN RIVAROXABAN, APIXABAN OR EDOXABAN WITH TACROLIMUS IN LUNG TRANSPLANT RECIPIENTS WITH VENOUS THROMBOEMBOLISM (VTE)

P. Olivera[1,2,3], D. Campoy[1,2,3], C. Hernández Mata[1,2], V. Cortina[2], S. Muzio[2], F. Beas[2], O. Benítez[1,2,3], F. Bosch[2,3]

[1]Thrombosis and Hemostasis Unit, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain; [2]Department of Hematology, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, Spain; [3]Vall d' Hebron Institute of Oncology, Barcelona, Catalonia, Spain.

INTRODUCTION

VTE is a major complication after lung transplantation (LT) DOACs are the standard treatment in VTE, but their use i not defined in post TL patients who require the concomitan use of DOACs with Tacrolimus due to their possible drug drug interactions.

AIM

To examine the potential interactions between Anti-Xa DOACs and Tacrolimus in lung transplantation recipient with VTE by determining the plasmatic concentrations o DOAC-Xa, Tacrolimus and the relationship with clinica events.

METHOD

- ✓ From February 2022 to March 2023, we have consecutively included 31 LT recipients treated with Tacrolimus and Anti-Xa DOACs for documented VTE.
- ✓ Plasma trough concentrations (Ctrough) of Tacrolimus were measured before and after DOAC-Xa administration.
- ✓ Blood samples were draw just before the next dose (Ctrough) and at 2-3 hours (Cpeak) after of drug intake using the Technoclone anti-Xa assay from Technoclone (Vienna-Austria) for Rivaroxaban and Apixaban, and Hyphen anti-Xa assay for Edoxaban.

CONCLUSIONS

Our results suggest that Apixaban and Edoxaban are safe with concomitant use of Tacrolimus in lung transplantation patients with VTE.

Rivaroxaban presented an increase in Ctrough and Cmax with an apparent increase in bleeding. These data should be confirmed in a prospective study

Sex: Males, n (%)	21 (67.7)
BMI, n(%)	
<20 kg/m2, n(%)	3 (9.3)
20-24.9 kg/m2, n(%)	6(19.4)
>25 kg/m2, n(%)	22 (71)
Lung transplantation	19(61.3%)
• Bilateral	12 (38.7%)
• Unilateral	
Laboratory*	
• Hemoglobin (g/dl)	12.6 (1.97)
• Platelets (x 109 /L)	261.7 (76.1)
Glomerular filtration rate (GFR) ml/min/1.73m2	
GFR >90	8 (25.8%)
GFR 60-89	14 (45.2%)
GFR 30-59	7 (22.6%)
GFR 15-29	2(6.4%)
Hemorrhagic Scales	
• VTE-BLEED, Mean (SD)	2.5 (1.5)
• RIETE, Mean (SD)	2.5 (1.8)
VTE characteristics	
• Pulmonary embolism	27 (87.1%)
• Deep venous thrombosis	4 (12.9%)
Days from start of DOAC-Xa to determination of plasma concentration, Median (SD)	35.5 (9.8)
Exposure time of tacrolimus with DOAC-Xa, days (SD)	254 (34.9)

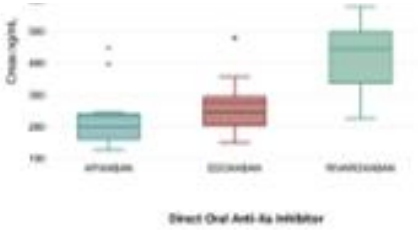


Figure 2. Plasma trough concentrations of DOAC-Xa

CONCLUSIONS

Our results suggest that Apixaban and Edoxaban are safe with concomitant use of Tacrolimus in lung transplantation patients with VTE.

Rivaroxaban presented an increase in Ctrough and Cmax with an apparent increase in bleeding. These data should be confirmed in a prospective study

ACKNOLEDGEMENTS

To all the members of the Hemostasis and Thrombosis Unit, as well as the residents who participated in this work.

REFERENCES

✓ Lam E, Bashir B, Chaballa M, Kraft WK. Drug interactions between direct-acting oral anticoagulants and calcineurin inhibitors during solid organ transplantation: considerations for therapy. Expert Rev Clin Pharmacol. 2019;12(8):781-790.

✓ Alqahtani R, Alfayez OM, Al Yami MS. Insights From Practice With Use of Direct Oral Anticoagulants in Transplantation. Prog Transplant. 2018;28(4):380-385.

CONTACT INFORMATION

Email: paveleduardo.olivera@vallhebron.cat

Twitter: @pavel_olivera

INTERACCIONES MEDICAMENTOSAS

Clinical outcomes of Direct Oral Anticoagulants in patients with concomitant use of antiepileptic drugs in the real-world registry MACACOD

C. Moret Puig[1], S. Mojal[2], M. Plaza Seijas[2], R. Acosta-Isaac[1], M. Carrasco[1]*, J. Souto[1]
[1]Hospital de la Santa Creu i Sant Pau, Barcelona. Spain
[2]Sant Pau Biomedical Research Institute, Barcelona. Spain
*Presenting author

ISTH 2023 JUNE 24-28 CONGRESS #ISTH2023 ISTH2023.ORG montréal
PB0021

INTRODUCTION

The risk of epilepsy is double in patients with atrial fibrillation (AF), possibly linked to silent stroke. Thus, a high proportion of patients with AF require the concomitant long-term administration of oral anticoagulation and antiepileptic therapy.

Antiepileptic drugs (AED) are **inductors of CYP3A4 and/or Glycoprotein-P**.

European guidelines do not recommend the concomitant use of direct oral anticoagulants (DOACs) with antiepileptic drugs because of an **increased risk of thrombotic events**.

The clinical value of this interaction is currently under study.

AIM

To assess **the incidence of thrombotic and bleeding events in patients treated with DOACs&AED** in a real-world registry.

METHODS

The patients were assessed by means of clinical records, laboratory tests, and rigorous education in the **MACACOD registry (Clinical Application Model of Direct Oral Anticoagulants, NCT04042155)** from 07/19 to 05/23.
Ethical approval and informed consent were previously obtained.

Primary outcomes:
- Major thrombotic complications: Ischemic stroke and Systemic Embolism.
- Major hemorrhagic complications: bleeding events scoring 3 or 5 points on the Bleeding Academic Research Consortium (BARC) scale.

Secondary outcomes:
- Clinically Relevant Non-Major Thrombosis (CRNMT): Superficial thrombophlebitis, peripheral venous thromboembolism, transient ischemic attack, and myocardial infarction
- Clinically Relevant Non-Major Bleeding (CRNMB): bleeding events scoring 2 points on the BARC scale.

RESULTS

Our registry included **1475 patients**, of which **1392 had at least one follow-up** (1344 AF and 48 VTE).

A total of **25 patients were on AED** (16 with levetiracetam, 3 with valproic acid, 2 with carbamazepine, 1 with phenytoin, 1 with phenobarbital, 1 with topiramate, and 1 with levetiracetam and carbamazepine) **concomitantly with DOACs** (14 with edoxaban, 4 with dabigatran, 4 with rivaroxaban, and 3 with apixaban).

Table 1. Descriptive of patient baseline characteristics (patients with at least 1 follow-up)

	DOAC		DOAC & AED	
Total follow-up (years)	2406.47		35	
N	1367		25	
Median follow-up (years); Med [P25 – P75]	1.78 [0.89 – 2.52]		1.39 [0.80 – 1.90]	
Categoric variables	**n**	**(%)**	**n**	**(%)**
Sex (male)	726	(53.1%)	11	(44.0%)
Anticoagulant therapy indication (Non-Valvular AF)	1241	(90.8%)	24	(96.0%)
Interaction drug concomitancy	228	(16.7%)	25	(100.0%)
Antiepileptic drug concomitancy	0	(0.0%)	25	(100.0%)
Antiplatelets concomitancy	108	(7.9%)	1	(4.0%)
Creatinine Clearance (Cockcroft-Gault formula) (mL/min)				
< 30	60	(4.4%)	1	(4.0%)
30 – 90	1120	(82.1%)	22	(88.0%)
> 90	185	(13.6%)	2	(8.0%)
History of previous thrombosis	211	(15.4%)	8	(32.0%)
History of previous bleeding	263	(19.2%)	2	(8.0%)
	Mean	**DS**	**Mean**	**DS**
Age	77.7	9.1	79.5	5.9
Weigh	74.7	16.1	73.7	20
BMI	27.3	5.2	27	6.4
Charlson Comorbidity Index	1.54	1.45	1.96	1.65
CHA_2DS_2-VASc scale	4	1.61	4.68	1.41
HAS-BLED scale	2.19	0.95	2.4	0.96
Creatinine Clearance (mL/min)	63.7	26.3	63.6	21.4
Anti-FXa activity TROUGH (UI/mL)	0.34	0.68	0.30	0.57
Anti-FXa activity PEAK (UI/mL)	1.41	0.61	1.19	0.53

* Comparison performed with Mann-Whitney U test or Fisher exact test as appropriate.

Table 2. Clinical Outcomes base on DOACs and AED concomitance. Incidence of complications

	DOAC		DOAC &
Total follow-up (years)	2406.47		35
N	1367		25
Median follow-up (years); Med [P25 – P75]	1.78 [0.89 – 2.52]		1.39 [0.80 –
Complications	**n**	**Inc. (IC 95%)**	**n**	**Inc.**
Major thrombotic complications	36	1.5 (1.05 - 2.07)	0	
Major haemorrhagic complications	77	3.2 (2.53 - 4)	2	5.71 (0.69 - 20.64)
Composite (MTC and MBC)	113	4.7 (3.87 - 5.65)	2	5.71 (0.69 - 20.64)
CRNMT	25	1.04 (0.67 - 1.53)	1	2.86 (0.07 - 15.92)
CRNMB	148	6.15 (5.2 - 7.22)	4	11.43 (3.11 - 29.28)
Composite (CRNMT and B)	173	7.19 (6.16 - 8.34)	5	14.29 (4.64 - 33.34)
All-cause mortality	122	5.07 (4.21 - 6.05)	1	2.86 (0.07 - 15.92)

	p
	0.412
	0.783
	0.301
	0.214
	0.123
	0.563

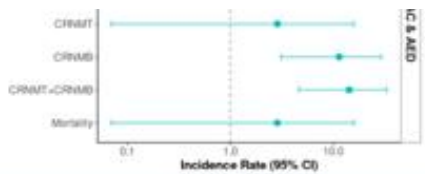
*** Comparison performed with Chi-squared test

CONCLUSIONS

In our experience, the DOACs&AED cohort has a higher risk of thromboembolism (CHA2DS2-VASc score) and incidence of previous thrombotic events. However, **no differences** were reported in **major complications, relevant non-major complications, or all-cause mortality** after 1.39 years of DOACs&AED treatment (IQ-range 0.80-1.90).

In our cohort, biological parameters were similar in both groups, including Anti-FXa activity levels, showing no effect of metabolic induction from AED in the activity levels of DOACs.

DOACs appear to be **safe and effective for patients taking AED**.



CONCLUSIONS

In our experience, the DOACs&AED cohort has a higher risk of thromboembolism (CHA2DS2-VASc score) and incidence of previous thrombotic events. However, **no differences** were reported in **major complications, relevant non-major complications, or all-cause mortality** after 1.39 years of DOACs&AED treatment (IQ-range 0.80-1.90).

In our cohort, biological parameters were similar in both groups, including Anti-FXa activity levels, showing no effect of metabolic induction from AED in the activity levels of DOACs.

DOACs appear to be **safe and effective for patients taking AED**.

REFERENCES

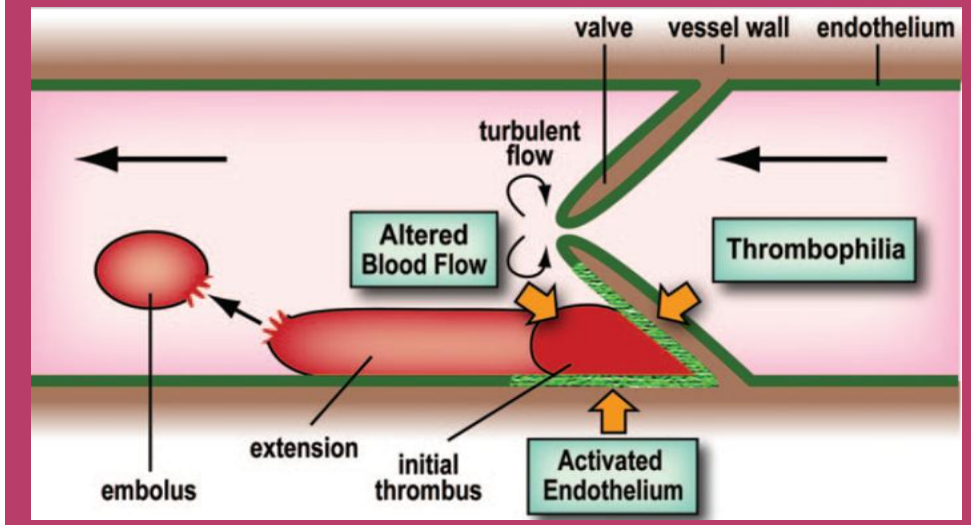
1. Hindricks G et al. 2021 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42(5):373-498. https://doi.org/10.1093/eurheartj/ehaa612 PMID: 32860505
2. SEMES. Criterios y recomendaciones generales para el uso de los anticoagulantes orales directos (ACOD) en la prevención del ictus y la embolia sistémica en pacientes con fibrilación auricular no valvular. https://www.semes.org/wp-content/uploads/2016/11/Criterios-y-recomendaciones-generales-para-el-uso-de-los-anticoagulantes-orales-directos-ACOD-en-la-prevencion-del-ictus-y-la-embolia-sistemica-en-pacientes-con-fibrilacion-auricular-no-valvular-1.pdf
3. Carrasbana M, et al. Correlation between plasma levels, anti-Xa activity and coagulation parameters in real world patients on treatment with edoxaban (abstract). Res Pract Thromb Haemost. 2021; 5 (Suppl 1). https://abstracts.isth.org/abstract/correlation-between-plasma-levels-and-the-activity-and-coagulation-parameters-in-real-world-patients-on-treatment-with-edoxaban/
4. Testa et al. Drug-Drug Interactions of Direct Oral Anticoagulants (DOACs): From Pharmacological to Clinical Practice. Pharm. 2021; 14, 1120. https://doi.org/10.3390/pharmaceutics13081120
5. Mendoza et al. Concomitant Use of Direct Oral Anticoagulants and Antiepileptic Drugs: A Prospective Cohort Study in Patients with Atrial Fibrillation. Clin. Drug Invest. 2021; 41, 41–51. https://doi.org/10.1007/s40261-020-00982-4

ACKNOLEDGEMENTS

To DAIICHI-SANKYO Spain for its support

CONTACT INFORMATION

Carla Moret Puig, Hematology MD.
CMoret@santpau.cat



TROMBOEMBOLISMO VENOSO

Caso Clínico

Paciente de 35 años, sexo femenino.

Trombosis venosa profunda íleo-femoral derecha.

Anovulatorios desde hace 3 meses.

Juega al hockey.

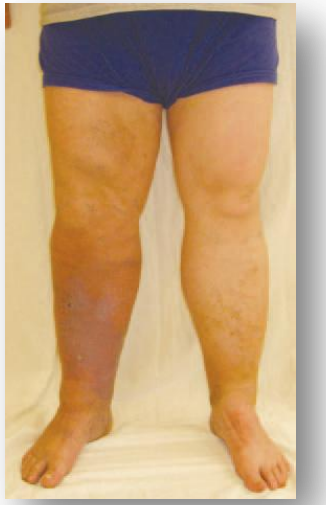
Peso: 50 kg

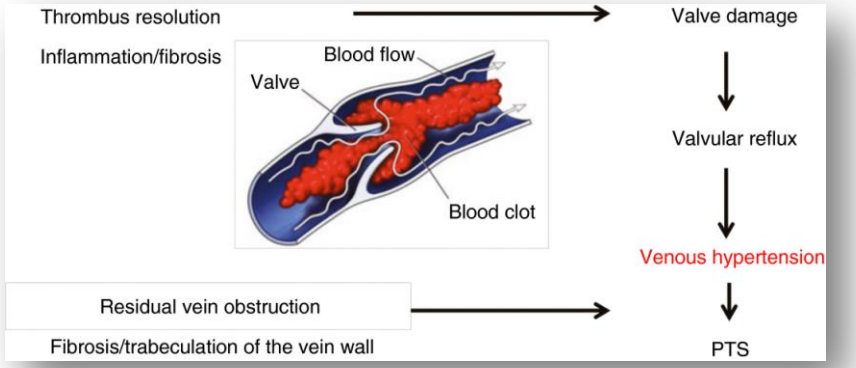
Tratamiento TEV

	DOSIS INICIAL	DOSIS A LARGO PLAZO
Dabigatran	**(Heparina)** + 150 mg c/ 12 hs.	
Rivaroxaban	15 mg c/12 hs. x 3 sem.	20 mg/d
Apixaban	10 mg c/ 12 hs. x 7días	5 mg c/12 hs.
Edoxaban	**(Heparina)** + 60 mg/d **(Heparina)** + 30 mg/d si ClCr 30-50 mL/min, ≤ 60 kg o inhibidores GP-P	

Sme. Postrombótico (SPT)

- 3-6 meses hasta 2 años luego de TVP aguda (5-10 años)
- Incidencia: 20-50% a 2 años.
- Hipertensión venosa secundaria al reflujo valvular causado por daño y/o obstrucción venosa por trombo residual, fibrosis venosa. Respuesta inflamatoria a trombosis aguda.
- Anticoagulación subterapéutica ↑ 2-3 veces riesgo SPT.





¿En TVP proximal, el tratamiento con DOACs, sin HBPM se asocia con mayor SPT o trombosis venosa residual (TVR)?

HBPM: heparina de bajo peso molecular

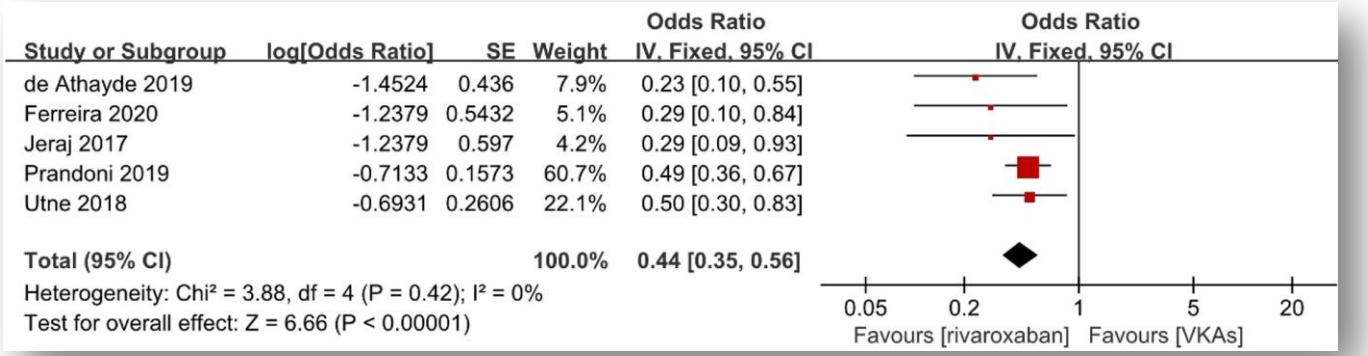
Søgaard M.2018-Li R. 2020-Karathanos C. 2021- ten Cate-Hoek AJ. 2018

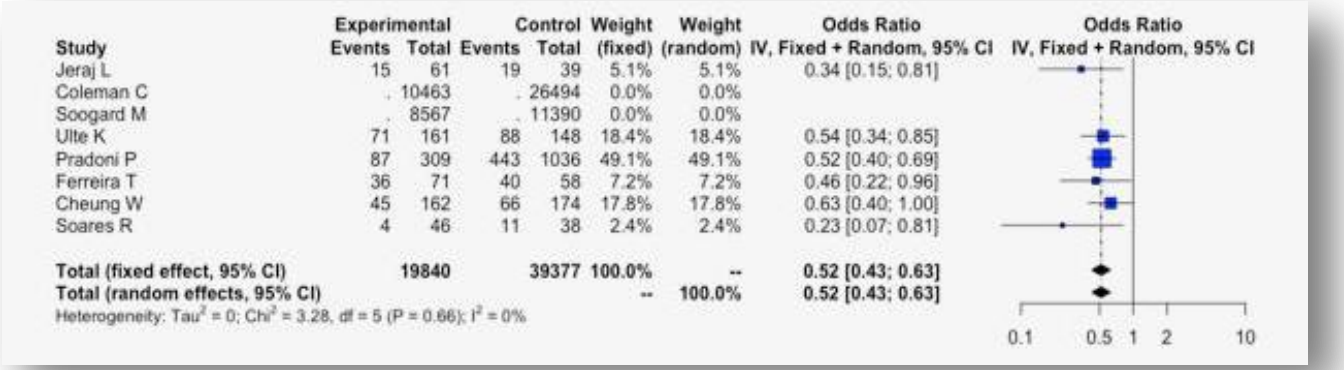
DOACs y Sme. Postrombótico

META-ANÁLISIS:

- 7 estudios (2016–20): N= 2364 pac (833 con rivaroxaban y 1531 con AVK) -3 cross-sectional, 3 cohortes prospectivas y 1 RCT. Score de Villalta.

- 8 estudios (hasta junio 2020): N= 59.119 pac. (19.840 (33.5%) con rivaroxaban y 39.377 pac (66.5%) con LMWH + warfarina)- 2 RCT- 6 retrospectivos. Score de Villalta.





Li R. 2020-Karathanos C. 2021

DOACs y Sme. Postrombótico

Registro Danés: incidencia SPT en cohorte de pacientes con TVP anticoagulados con rivaroxaban vs. warfarina. Registros nacionales daneses (diciembre 2011-marzo 2017).

	N (%)	Seguimiento (años)	Edad	Sexo femenino	TVP/TEP	TEV Provocado	SPT a 3 años (100 pac/año)	HR (95% IC)
Warfarina	11.390 (57)	2.6 (IQR 1.3-3.9)	64.2±17.2	5504 (48.3)	6231 (54.7)/ 5159 (45.3)	2747 (24.1)	0.55	0.88 (0.66-1.17)
Rivaroxaban	8567 (43)	1.8 (IQR 1.0-2.9)	64.4±17	4000 (46.7)	54.3 (4654)/ 45.7 (3913)	1670 (19.5)	0.53	

Cohorte prospectiva: 309 pac ambulatorios con TVP proximal, tratados con DOACs (84% rivaroxaban, 12% apixaban, 4% dabigatran). Seguimiento: 3 años. Comparados con cohorte histórica (N=1036 pac. AVK- 2003-09)

	SPT	SPT en TVR	OR (95% CI)
Cohorte prospectiva DOACs	87 (28.2%)	43.8%	0.60 (0.40- 0.88).
Cohorte histórica (AVK)	443 (42.8%)	56.5%	

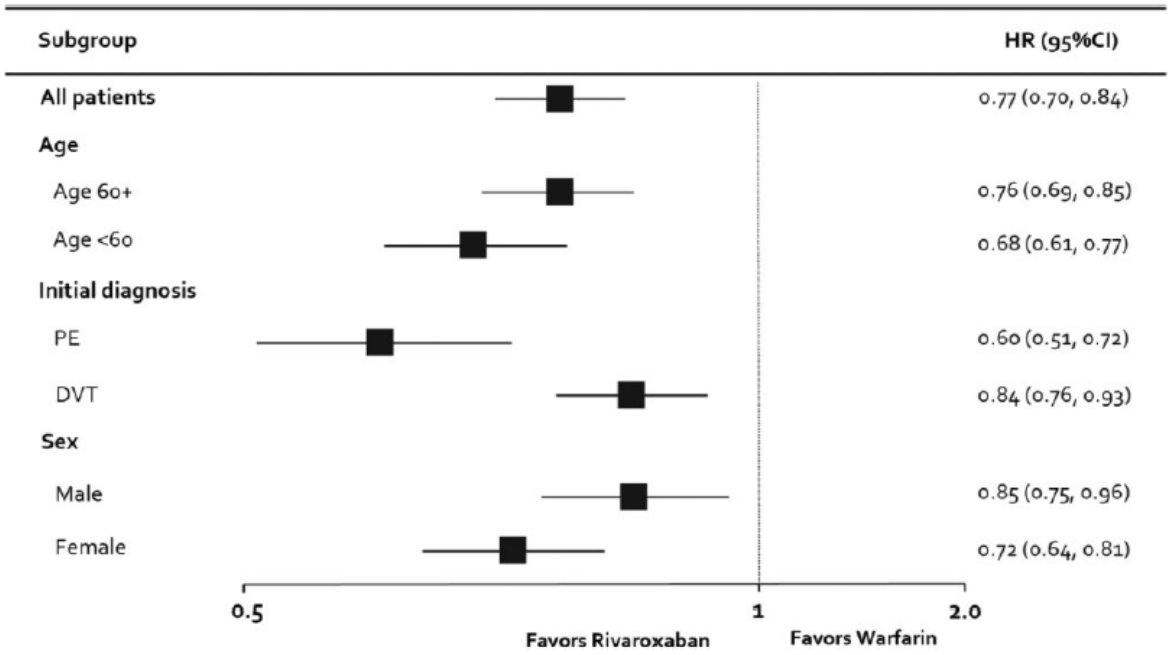
TVR en TVP proximal: DOACs vs. AVK: OR 0.63 (95% CI 0.48–0.81) a 3 meses y 0.17 (95% CI 0.11–0.26) a 6 meses.

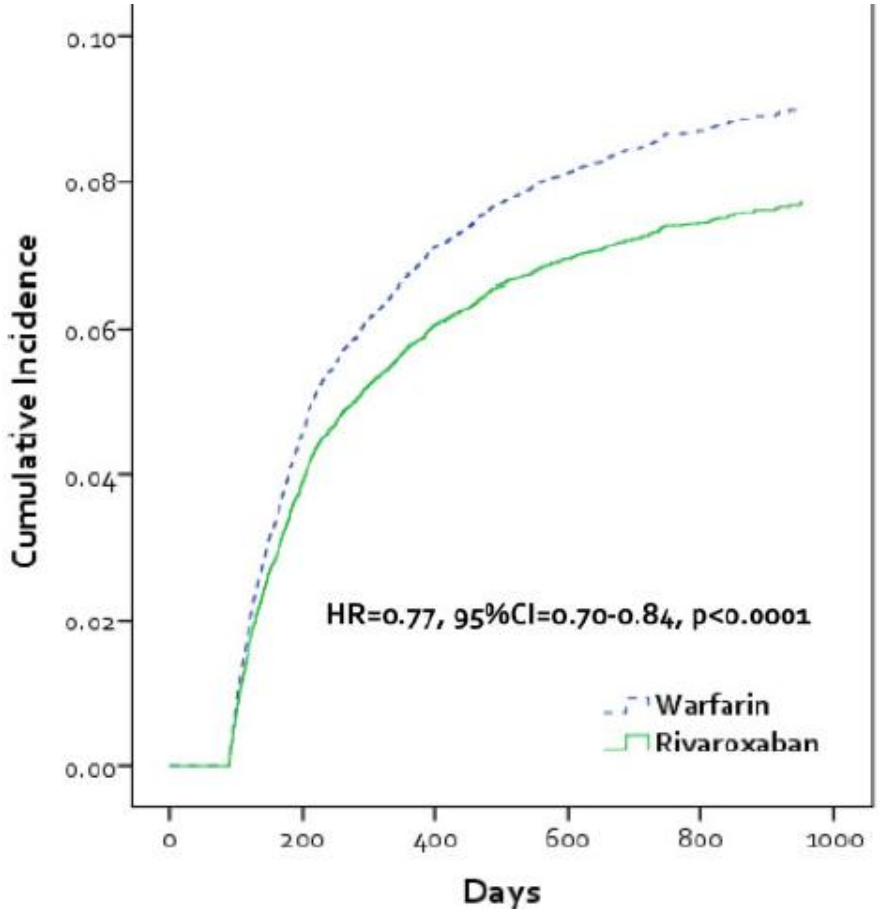
TVR: Trombosis venosa residual

Søgaard M. 2018- Prandoni P. 2019- Prandoni P. 2017

DOACs y Sme. Postrombótico

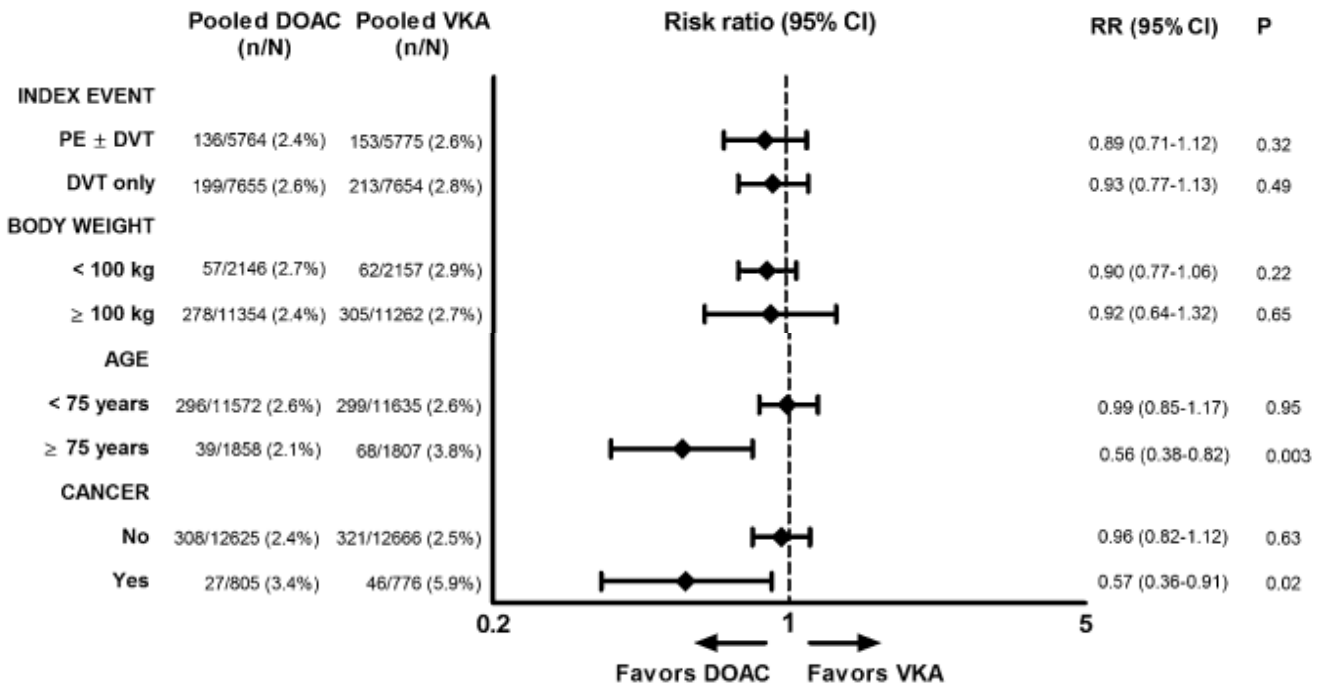
- **US MarketScan (base datos comercial + Medicare)**
- N= 10.463 TVP tratados con rivaroxaban
- N= 26.494 pacientes con TVP tratados con AVK
- Rivaroxaban: ↓ 23% incidencia de SPT





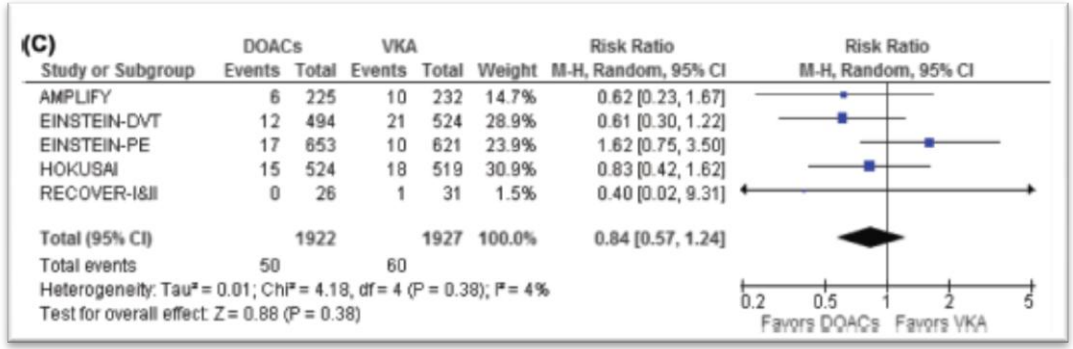
Coleman CI. 2018

DOACs en Poblaciones “Especiales”

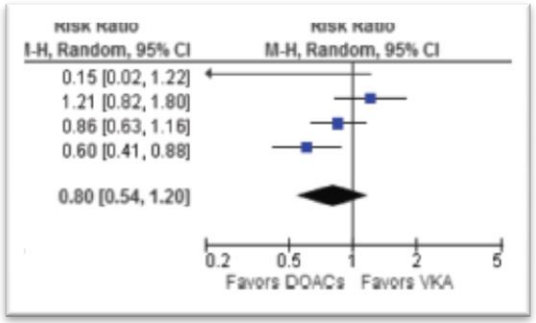


Bajo peso

EFICACIA



SEGURIDAD



Van Es N.. 2014-Di Minno MND. 2015

DOACS EN MUJERES

¿ Se deben suspender los AO/TRH en una mujer que tiene TEV asociada a terapia hormonal?

TEV intra-terapia hormonal

TEV asociada a AO/TRH: continuar durante anticoagulación

Sub-análisis EINSTEIN: Mujeres $\leq$ 60 años- AO/TRH a elección:

	TEV recurrente (% /año)	
	No T. hormonal	T. Hormonal
Rivaroxaban	5.4 (3.3-8.2)	3.1[#] (0.6-8.9)
Enoxaparina-AVK	4.0 (2.4-6.5)	4.5[#] (1.2-11.5)

[#] 3/98 vs. 4/89 eventos/años-paciente

AO: anovulatorios- TRH: terapia reemplazo hormonal

Cohen H. 2016 - Martinelli I. 2016

METRORRAGIA

Sub-estudio de pacientes mujeres de los EINSTEN DVT/PE:

- Rivaroxaban: HR 2.13, IC 95% 1.57-2.89; independiente de tratamiento hormonal concomitante
- Período de tratamiento de 30 mg/d.
- Anemia previa y/o patología ginecológica > riesgo

AMPLIFY VTE:

- Menstruaciones más prolongadas (OR 2.3 IC95% 0.5-11) no más abundantes y sangrado vaginal más frecuente (x 3) con apixaban.

RECOVER:

- Sangrado uterino anormal 5.9% (vs. 9.6% con warfarina. OR 0.59 95%CI 0.39-0.90)

HOKUSAI-VTE

- Edoxaban 628 8 (1.3%) vs Warfarin 665 3 (0.9%)

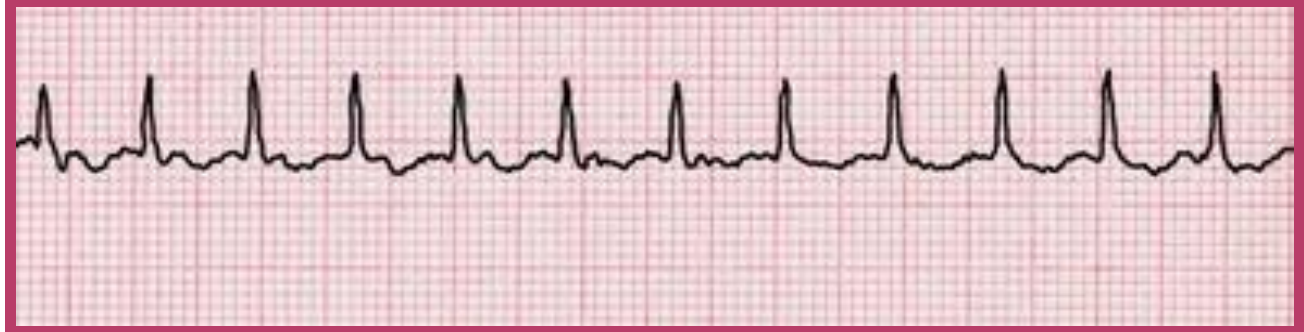
Beyer-Westendorf J. 2020- Boonyawat K. 2020

DOACS EN MUJERES

EMBARAZO Y LACTANCIA	**CONTRAINDICADOS** Suspender DOAC – Rotar a HBPM Abortos/malformaciones ~ población general No es indicación de terminación
EDAD FÉRTIL	Informar riesgos y modo de proceder si embarazo ¿Test embarazo previo a inicio? Interrogar sobre patología ginecológica (metrorragia), anemia
MENSTRUACIÓN	Anovulatorios- ácido tranexámico- DIU levonorgestrel- Cambio de DOAC?

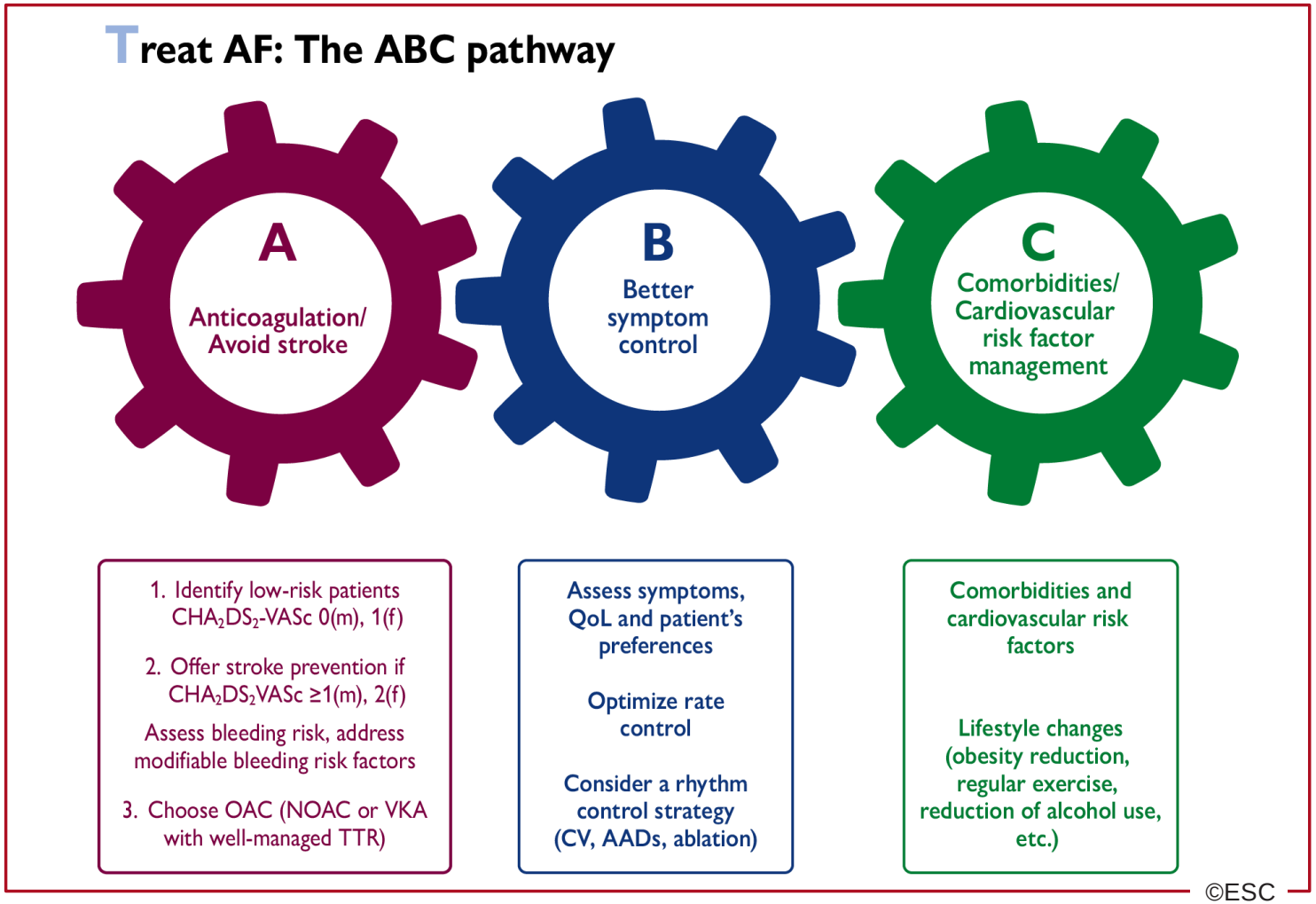
AO: anovulatorios- TRH: terapia reemplazo hormonal

Cohen H. 2016 - Martinelli I. 2016



FIBRILACIÓN AURICULAR

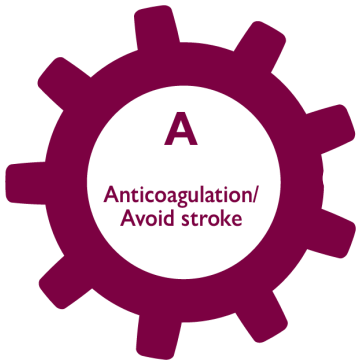
MANEJO DEL PACIENTE CON FA



Hindricks G. 2020- Gorog DA. 2022

ANTICOAGULACIÓN EN EL PACIENTE CON FA

EVALUACIÓN DEL RIESGO DE SANGRADO



1. Identify low-risk patients CHA_2DS_2-VASc 0(m), 1(f)
2. Offer stroke prevention if CHA_2DS_2VASc ≥1(m), 2(f)
   Assess bleeding risk, address modifiable bleeding risk factors
3. Choose OAC (NOAC or VKA with well-managed TTR)

EVALUACIÓN FORMAL DEL RIESGO (HASBLED):

- Alta puntuación no contraindica ACO
- Historia de caídas no contraindica ACO
- > HASBLED > beneficio clínico neto
- HASBLED ≥ 3: Seguimiento: evaluación o modificación de factores de riesgo

CONTRAINDICACIONES ABSOLUTAS

- Hemorragia activa o reciente (especialmente hemorragia intracraneal, ICH)
- Trombocitopenia <50 plaquetas/L
- Anemia severa

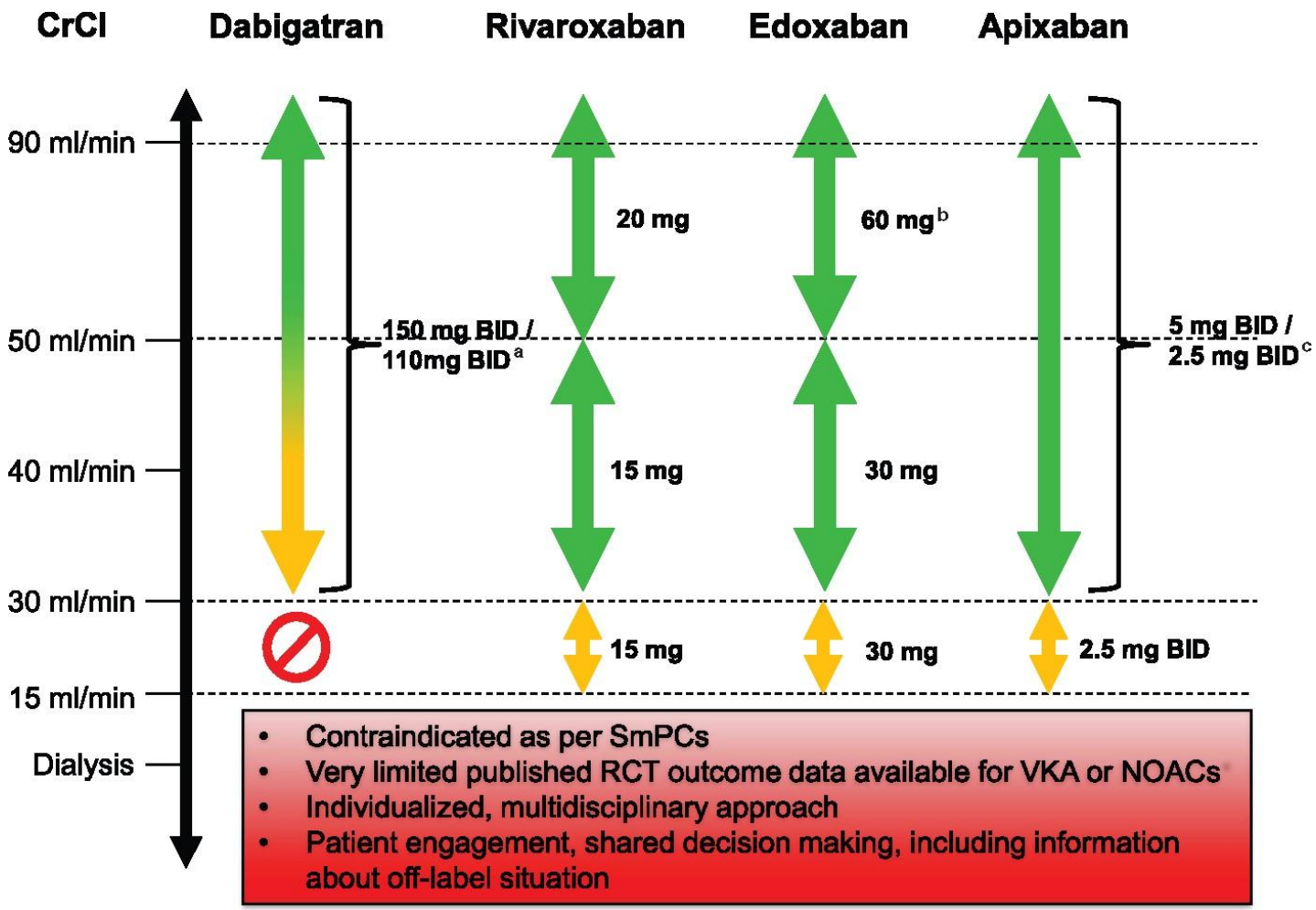
	Risk Factors
Clinical variables	History of bleeding
	Concomitant antiplatelets or NSAID use
	Excessive alcohol intake
	Uncontrolled hypertension
	Increasing age
	Cancer
	Prior stroke, small vessel disease, amyloid angiopathy
	Diabetes
	Vascular disease
Biological markers	Poor anticoagulation quality (reduced TTR)
	Liver dysfunction
	Renal dysfunction
	Anaemia
	Reduced platelet count or function

Hindricks G. 2020- Gorog DA. 2022

Dosis

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.	60 mg o.d.
Lower dose	110 mg b.i.d.			
Reduced dose		15 mg o.d.	2.5 mg b.i.d.	30 mg o.d.
Dose-reduction criteria	Dabigatran 110 mg b.i.d. in patients with: • Age ≥80 years • Concomitant use of verapamil, or • Increased bleeding risk	CrCl 15–49 mL/min	At least 2 of 3 criteria: • Age ≥80 years, • Body weight ≤60 kg, or • Serum creatinine ≥1.5 mg/dL (133 µmol/L)	If any of the following: • CrCl 15–50 mL/min, • Body weight ≤60 kg, • Concomitant use of dronedarone, ciclosporin, erythromycin, or ketoconazole

DOACs en Insuficiencia Renal



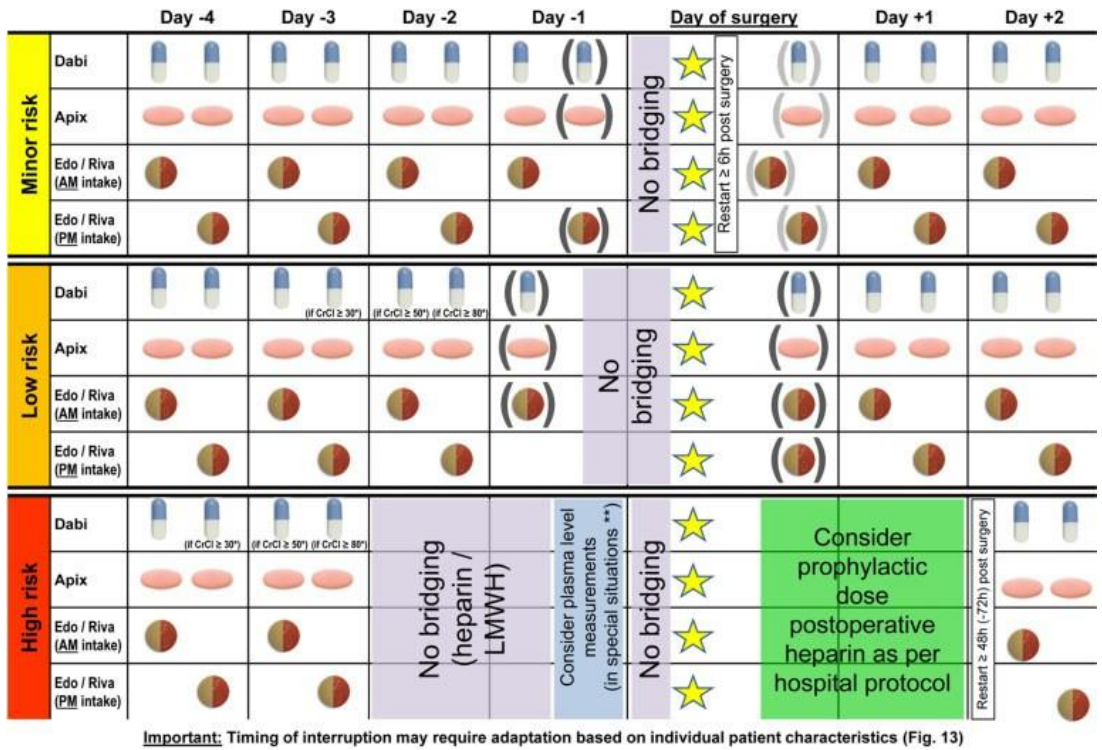
ALGUNAS CUESTIONES DE MANEJO PRÁCTICO

SUSPENSIÓN PARA CIRUGÍAS

	Dabigatran		Apixaban - Edoxaban - Rivaroxaban	
No perioperative bridging with LMWH / UFH				
Minor risk procedures: - Perform procedure at NOAC trough level (i.e., 12 h / 24 h after last intake). - Resume same day or latest next day.				
	Low risk	**High risk**	**Low risk**	**High risk**
CrCl ≥80 ml/min	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
CrCl 50-79 ml/min	**≥ 36 h**	**≥ 72 h**		
CrCl 30-49 ml/min	**≥ 48 h**	**≥ 96 h**		
CrCl 15-29 ml/min	Not indicated	Not indicated	**≥ 36 h**	
CrCl <15 ml/min	No official indication for use			

Important:

- Timing of interruption may require adaptation based on individual patient characteristics (Fig. 13)
- In patients / situations with risk of NOAC accumulation (renal insufficiency, older age, concomitant medication, see Fig. 6) pausing the NOAC 12-24 hours earlier may be considered.[207,208]
- Resume full dose of NOAC 24h after low-risk- and 48 (-72) h after high-risk interventions



Steffel J. 2021

Manejo del Sangrado: Laboratorio

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
PT/INR	✗	✓	✗	✗
aPTT	✓	✗	✗	✗
TT	✓	✗	✗	✗
dTT	✓	✗	✗	✗
ECT	✓	✗	✗	✗
Anti-FXa assays	✗	✓	✓	✓

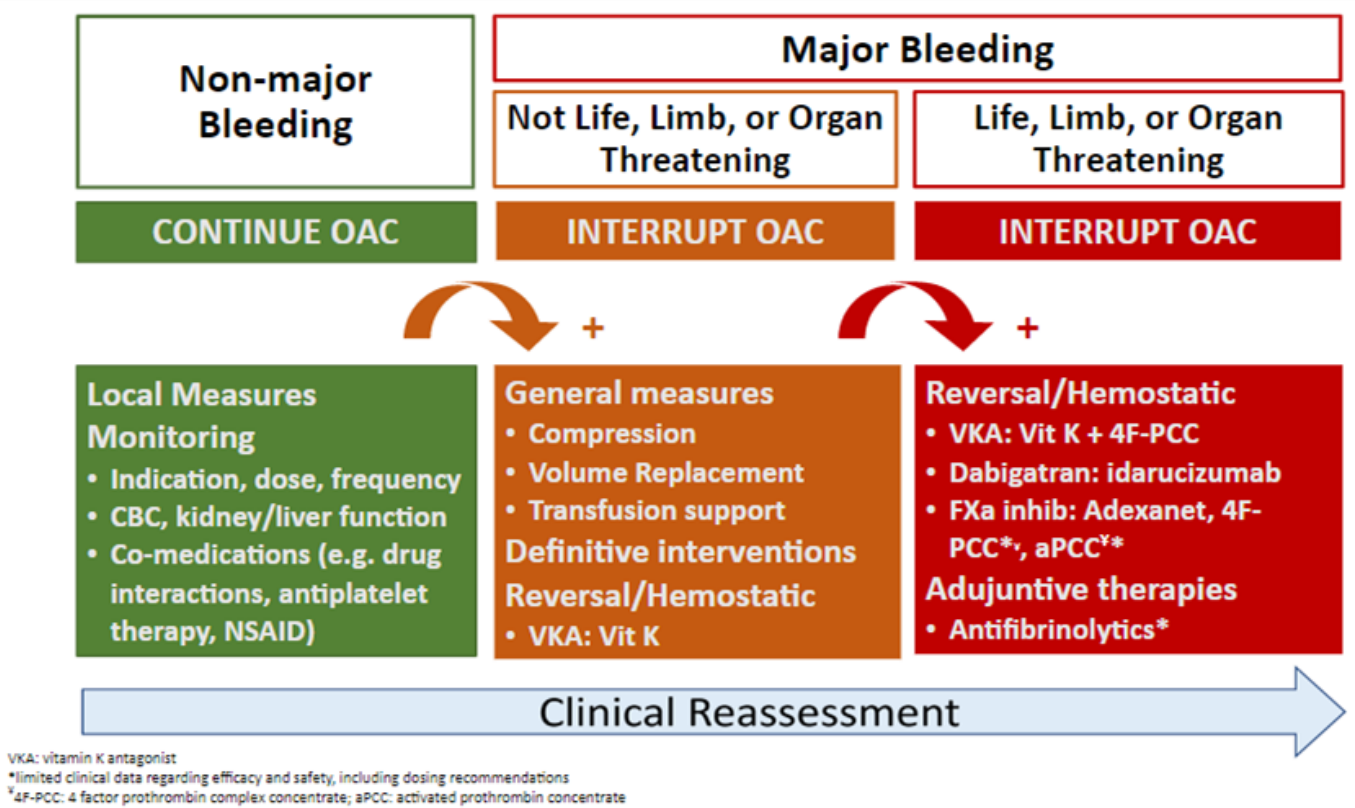
HORARIO DE LA ÚLTIMA TOMA

✗ No es útil ✓ Cualitativo ✓ Cuantitativo

MANEJO DEL SANGRADO: SEVERIDAD Y SOPORTE

EVALUAR:

1. Severidad del sangrado
2. Medidas de soporte
3. Qué DOAC toma? Cuándo tomó la última dosis?
4. Hay DOAC en circulación?
5. Requiere reversión?
6. Estrategias de Reversión
7. Re-inicio



VKA: vitamin K antagonist
*limited clinical data regarding efficacy and safety, including dosing recommendations
¥4F-PCC: 4 factor prothrombin complex concentrate; aPCC: activated prothrombin concentrate

Siegal D-& Barnes G 2021

MANEJO DEL SANGRADO: REVERSIÓN

ANTÍDOTOS

	Idarucizumab	Andexanet alfa
Structure	Humanized Fab fragment	Human rFXa variant
Target	Dabigatran	FXa inhibitors
Binding	Non-competitive	Competitive
Indication	Urgent surgery/procedure Life-threatening/uncontrolled bleeding	Reversal of apixaban or rivaroxaban for life-threatening or uncontrolled bleeding
Dose	5 g IV	Dosing dependent on FXa inhibitor and timing of last dose

Anti FXa:
Concentrado de complejo protrombínico.

Dabigatran:
FEIBA

En estudio: Ciraprantag (antídoto "universal")- VMX-C001 – CytoSorb

Siegal D-& Barnes G 2021

ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors)

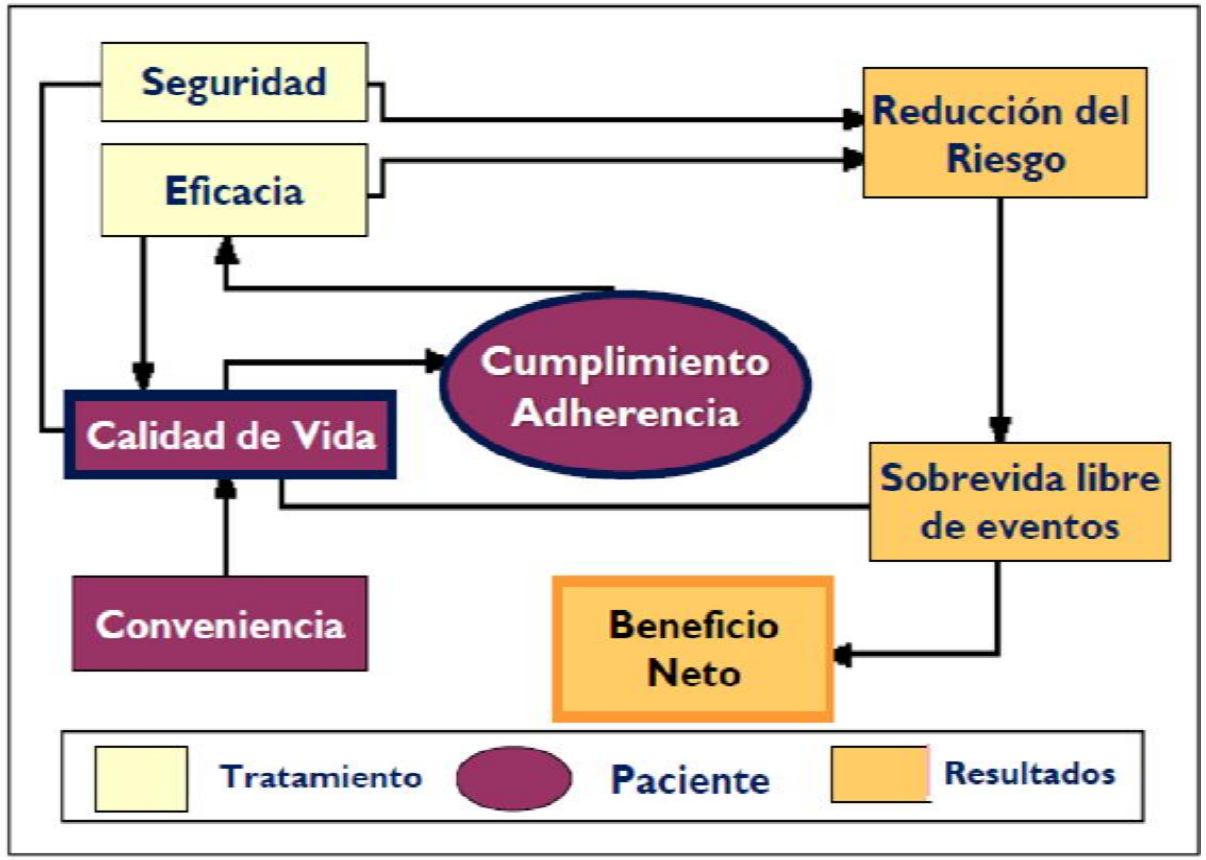
- Estudio de cohortes multicéntrico, prospectivo, de fase 3b/4 y grupo único que evaluó andexanet alfa en pacientes con hemorragia mayor aguda (HMA).
- Criterios inclusión: ≥18 años + dosis terapéuticas de DOAC o enoxaparina en las 18 horas previas.
- Hemorragia Mayor:
  - Compromiso hemodinámico.
  - Disminución de hemoglobina de ≥2 g/dL (o un hemoglobina de ≤8 g/dL).
  - Hemorragia en órgano crítico.
- Eficacia:
  1. cambio porcentual en la actividad anti-FXa respecto al valor basal
  2. % de pacientes con eficacia hemostática excelente/buena a 12 horas
- Seguridad:
  1. Muerte
  2. Trombosis
  3. Anticuerpos anti andexanet alfa o anti FX hasta ≥30 días post infusión.

- 85 centros, USA, Europa y Japón
- 479 pacientes (edad media, 78 años; 54% varones; 86% blancos). 81% fibrilación auricular.
- 245 (51%) apixabán, 176 (37%) rivaroxabán, 36 (8%) edoxabán y 22 (5%) enoxaparina.
- Mediana de tiempo desde última dosis: 11.4 horas.
- HMA: 69% ICH (n=331) y 23% digestivas (n=109)

- Disminución en actividad anti–Fxa: hasta 94%
- Eficacia hemostática clínica: 80% (95% CI 75–84)
- 50 pac (10%) evento trombótico
- 75 (15.7%) muertes en 30 días. En ICH: 16.9% (56/331 pacientes).

Truman J. 2023

LOS DOACS "SE CONTROLAN"



Control periódico

- Riesgo de sangrado
- Riesgo trombótico
- Medicación
- Función renal/hepática
- Adherencia
- Puede seguir pagándolos?
- Valores y preferencias
- Educación

Testa MA. 1996

GRACIAS!