ETEV

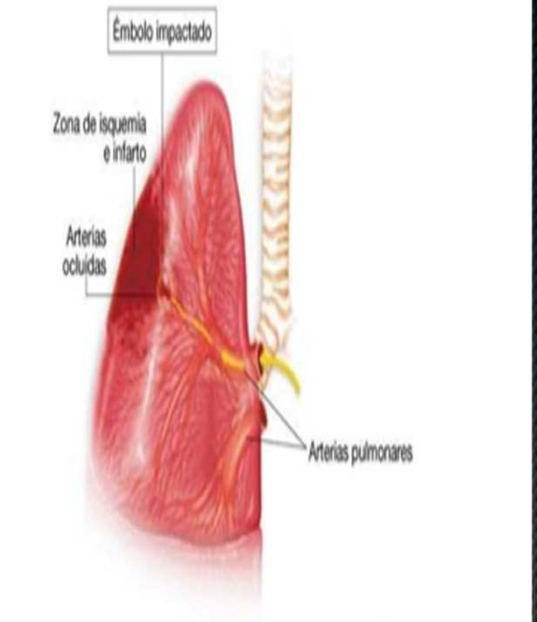
&

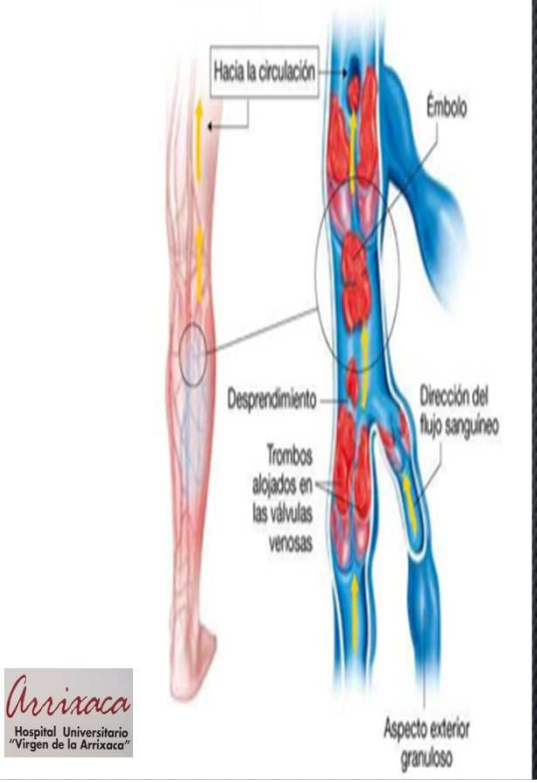
Nuevos Anticoagulantes

¿Novedades…?

Dr. Vladimir Rosa Salazar
Unidad de Corta Estancia/Trombosis.
Servicio de Medicina Interna.
Hospital Clínico Universitario Virgen de la Arrixaca, Murcia.

Novedades NACOS & ETEV





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Enfermedad Tromboembólica Venosa

Trombosis Venosa Profunda (TVP)

Embolia Pulmonar (EP)

N Engl J Med 2008;358:1037-52.

Impacto

- **En Europa, mayor mortalidad por ETEV que:**
  - ☑ Cancer de mama, próstata, SIDA y accidentes de tráfico juntos.

ÓPERA | Suspende su actuación en el Teatro Real

Plácido Domingo, ingresado por una embolia pulmonar

Plácido Domingo como Pablo Neruda.

Europa Press | Madrid

Actualizado martes 09/07/2013 **19:27 horas**

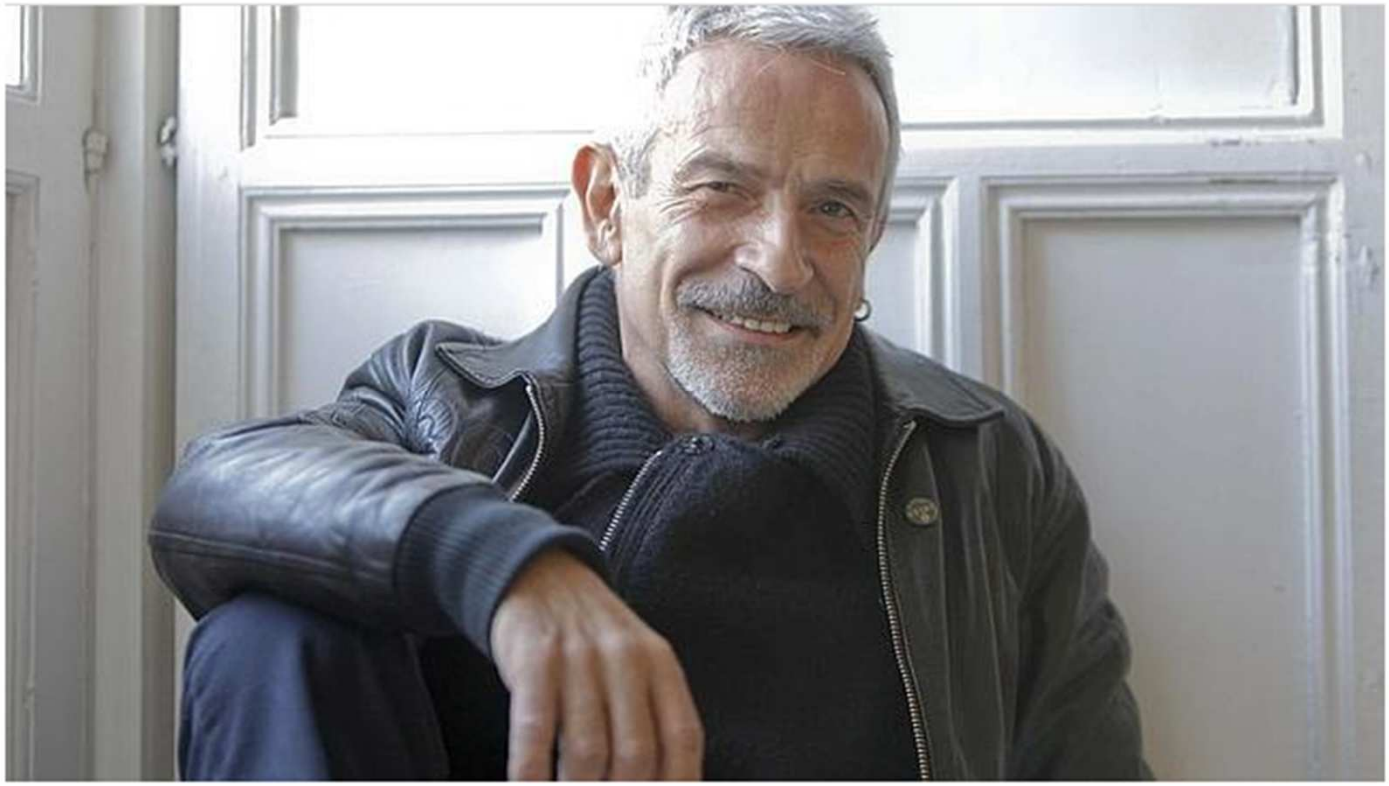
TEATRO

Víctor Ullate, hospitalizado

ABC.ES / MADRID | Día 20/05/2013 - 14.45h

TEMAS RELACIONADOS ▸ Víctor Ullate ▸ Madrid (Provincia) ▸ Ballets

▸ El bailarín y coreógrafo se recupera de varios trombos detectados en la pierna y el pulmón



BALONCESTO / BALONCESTO

Pete Mickeal, baja indefinida por un tromboembolismo pulmonar

EP | Día 25/03/2013 - 21.16h

- El mismo problema ya le obligó hace dos temporadas a abandonar la actividad competitiva

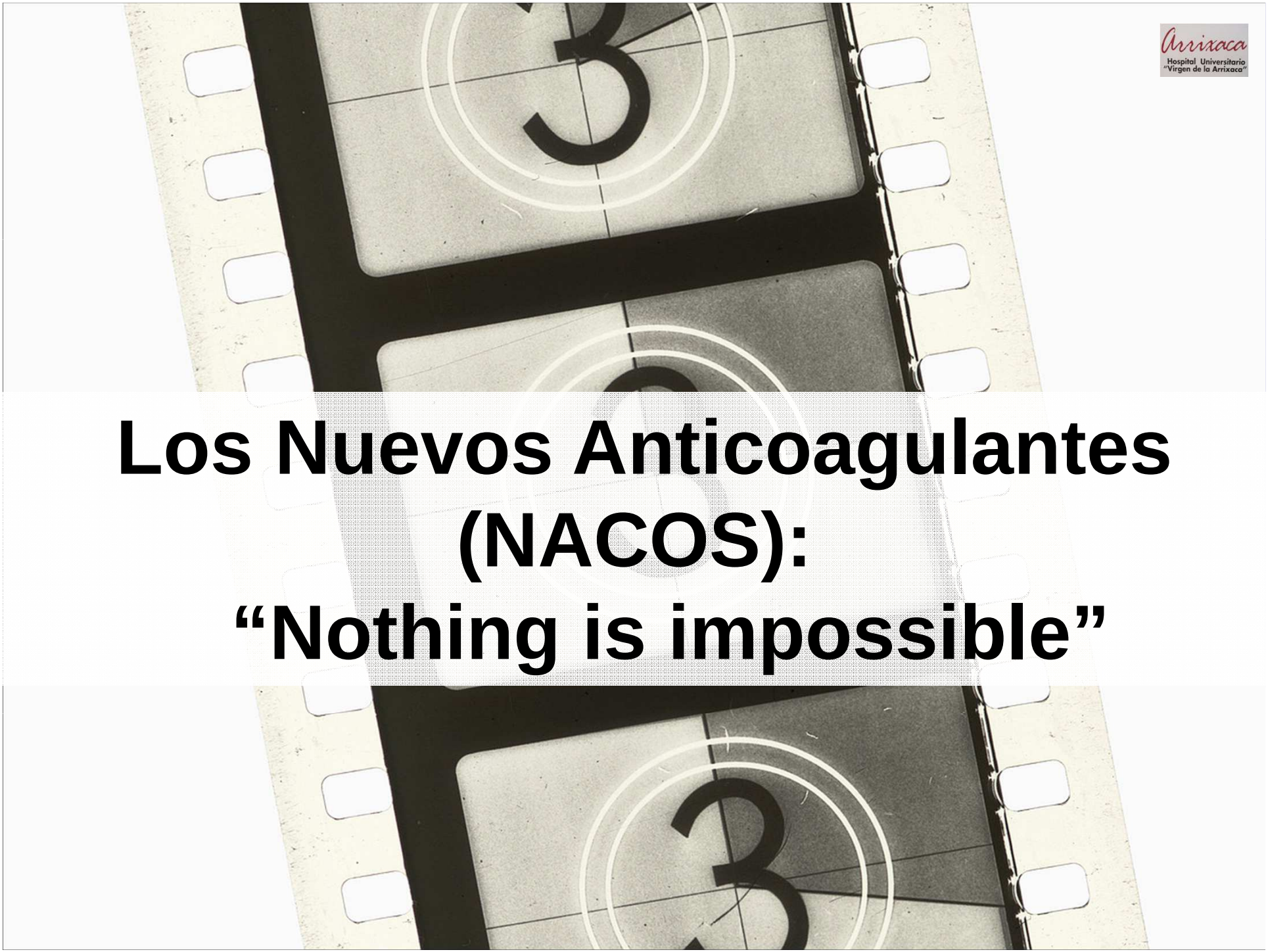
Pete Mickeal, baja indefinida por un tromboembolismo pulmonar

TENIS | Sufrió una embolia pulmonar

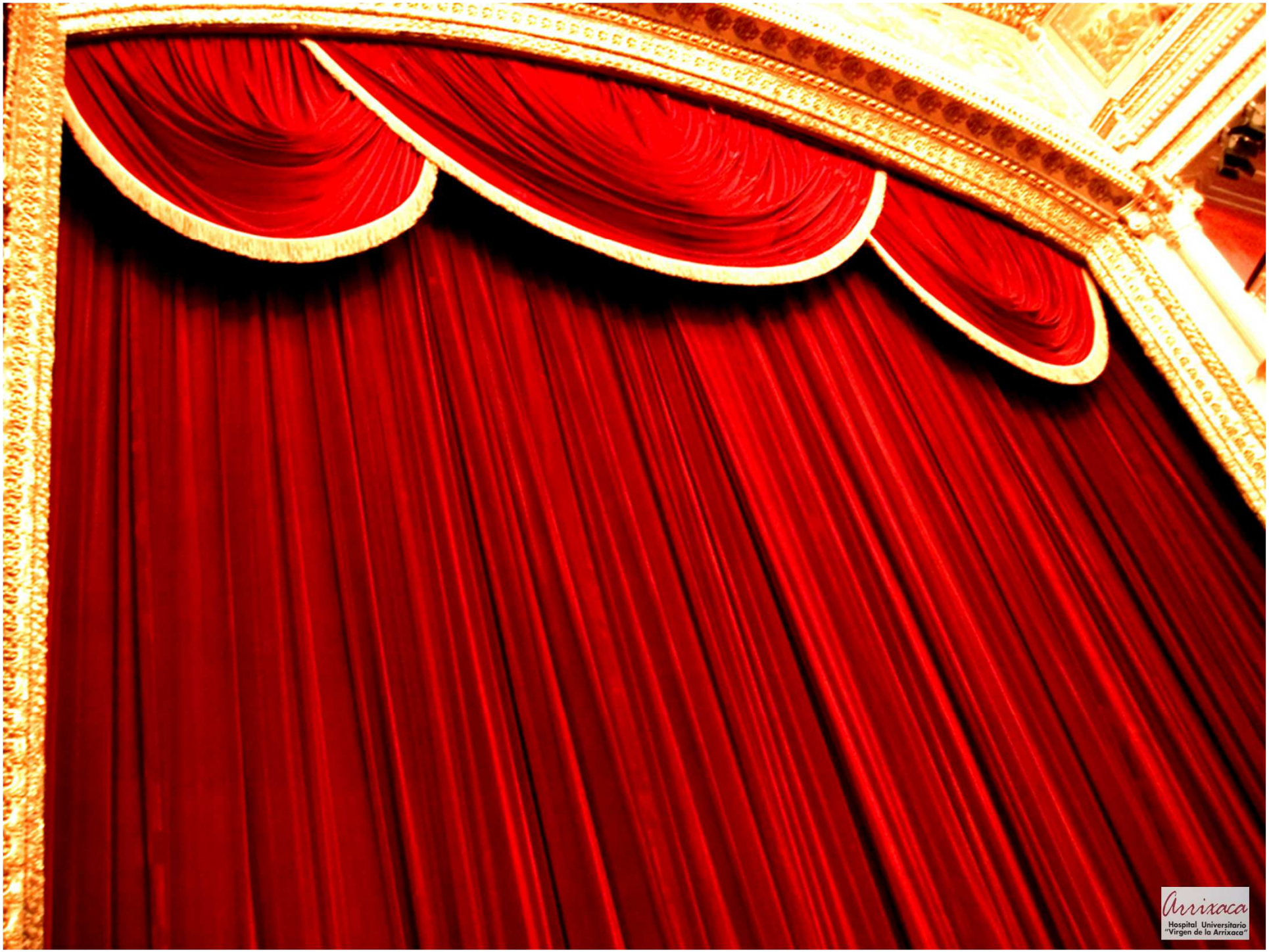
Serena, desde su casa: 'Ha sido terrible'

Williams, en un partido de Wimbledon, en 2010 (Foto: AFP).

Anticoagulación



Los Nuevos Anticoagulantes (NACOS): “Nothing is impossible”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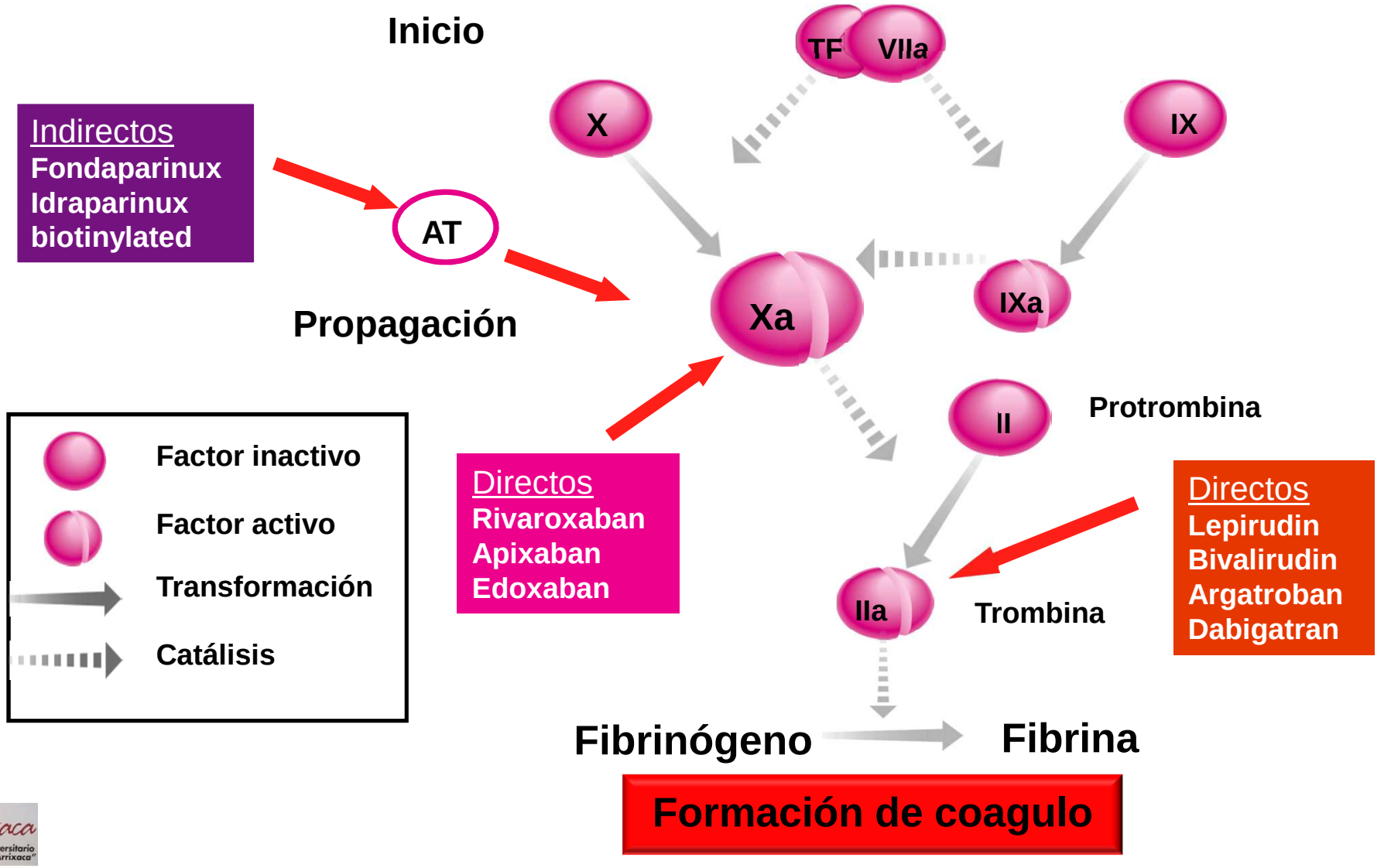
Coagulación



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Anticoagulante ideal

- Eficaz.
- Seguro.
- Cómodo.
- Barato.

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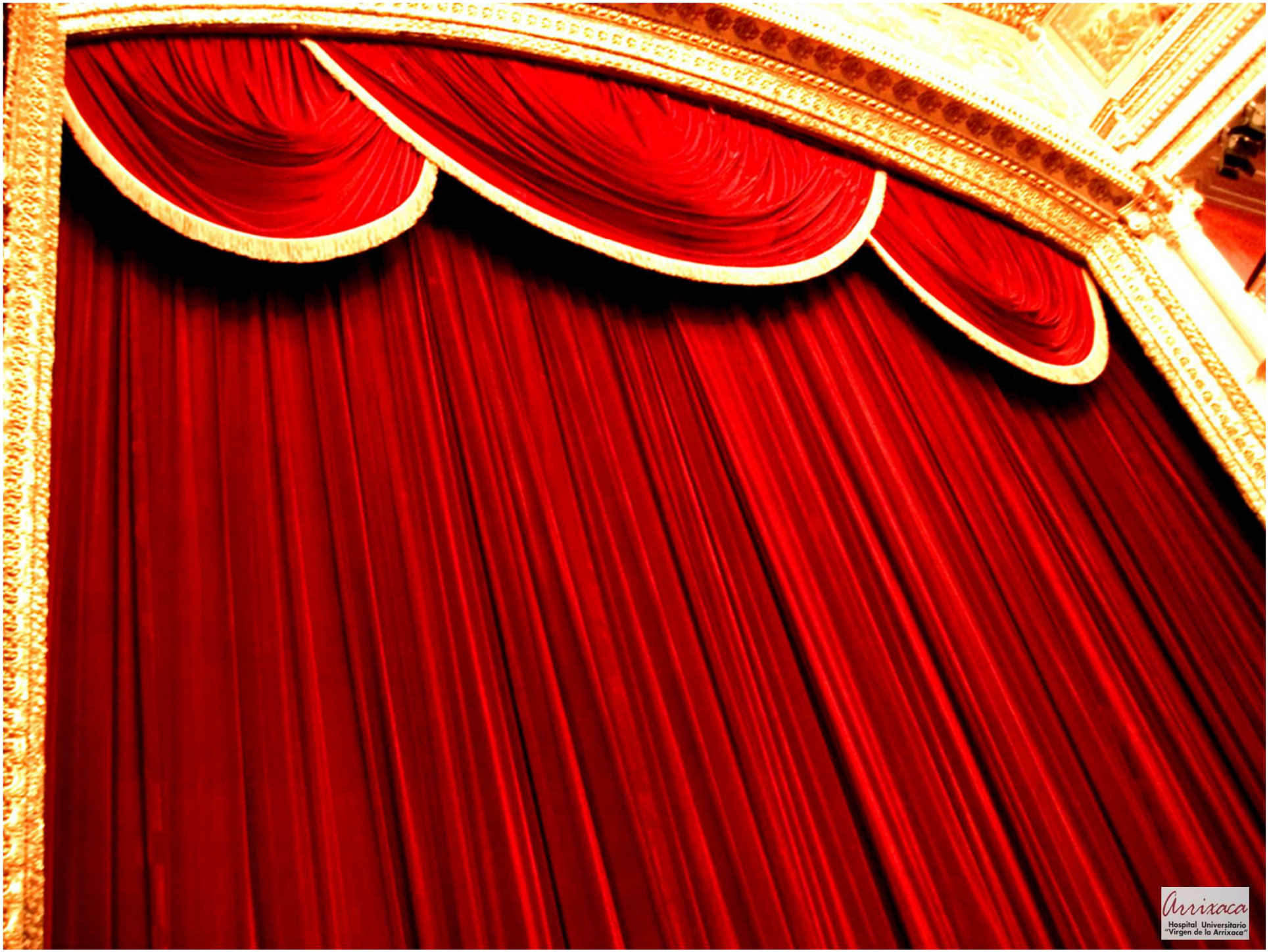
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Heparinas

HNF

HBPM

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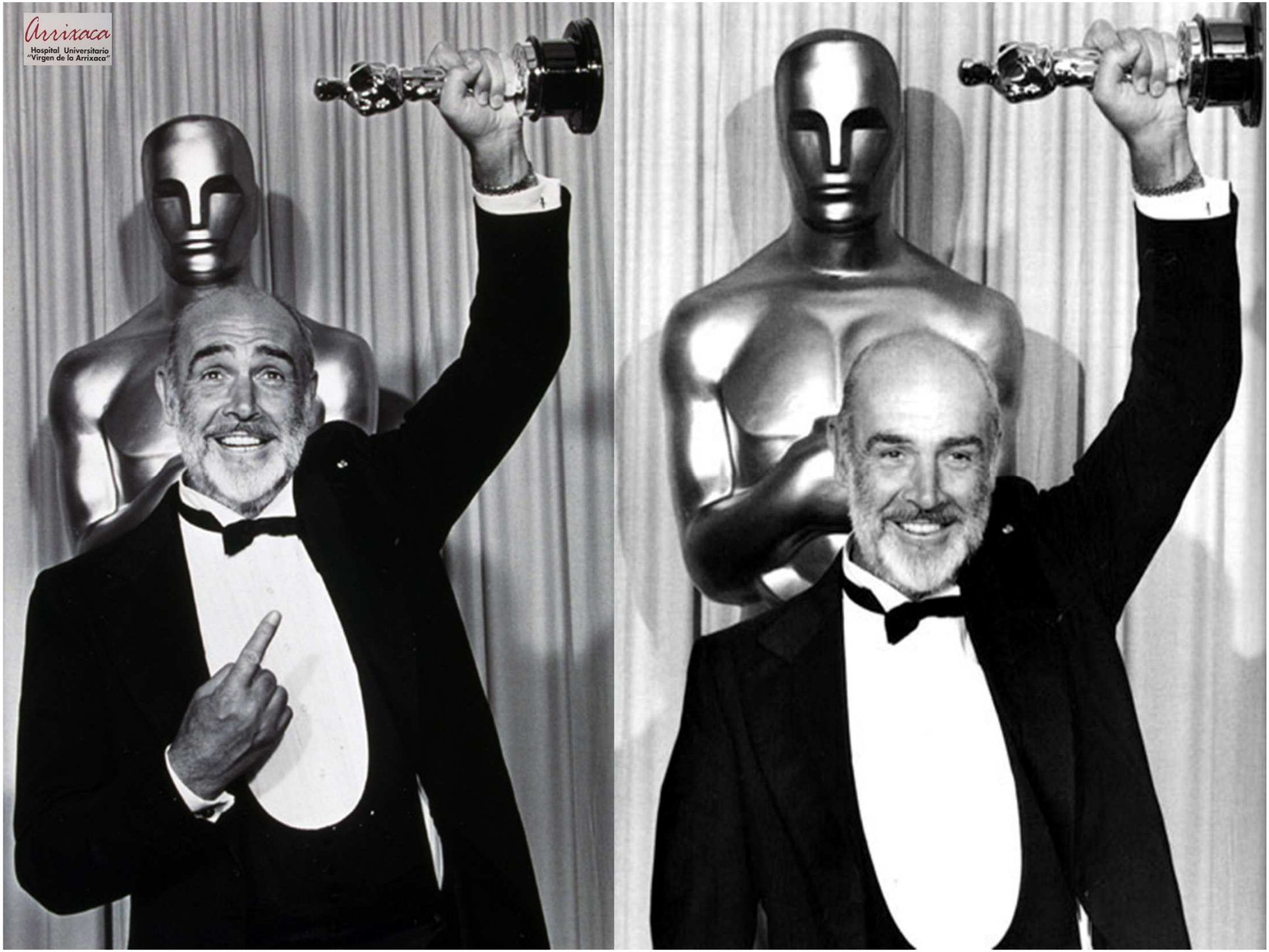

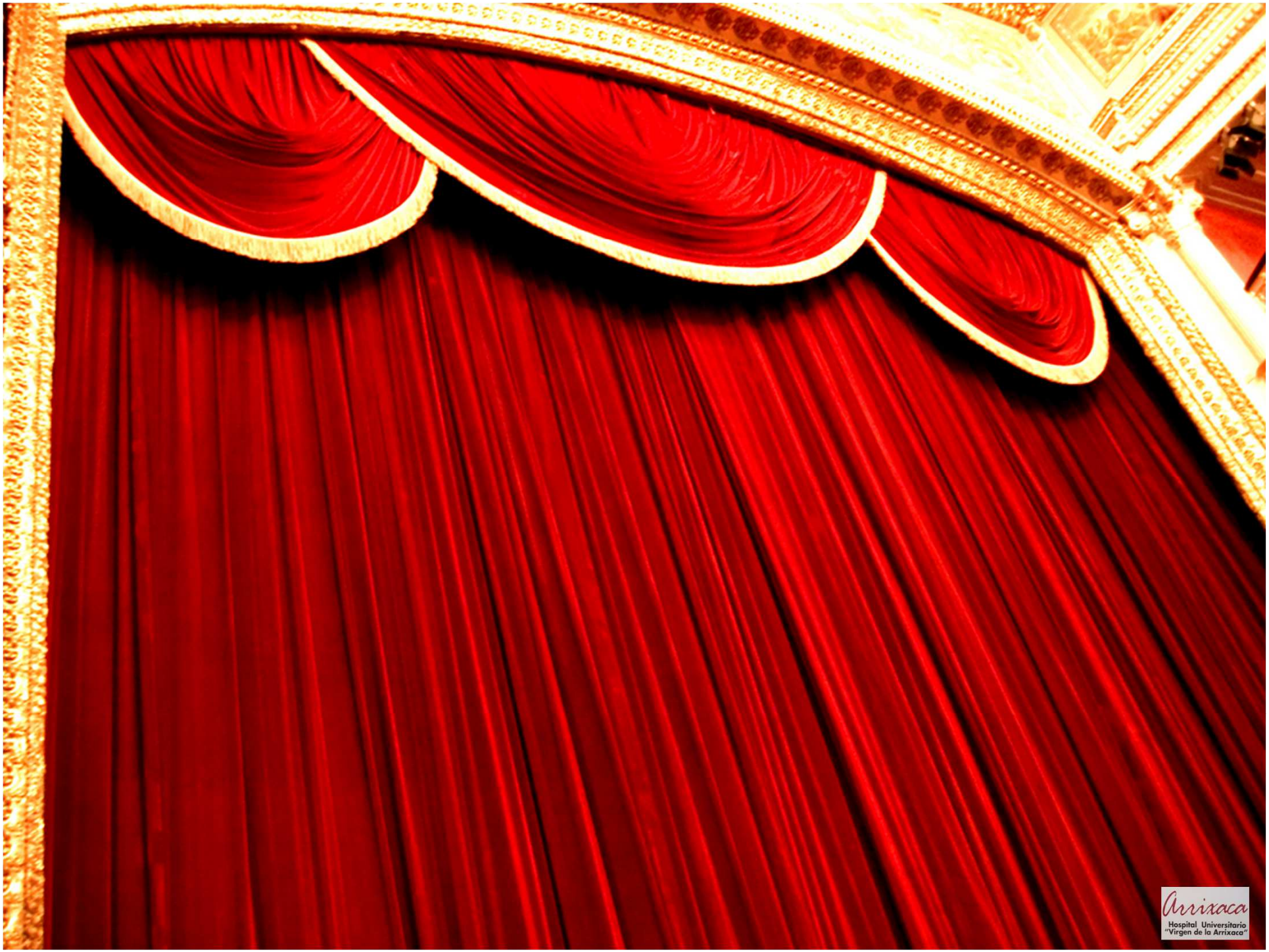
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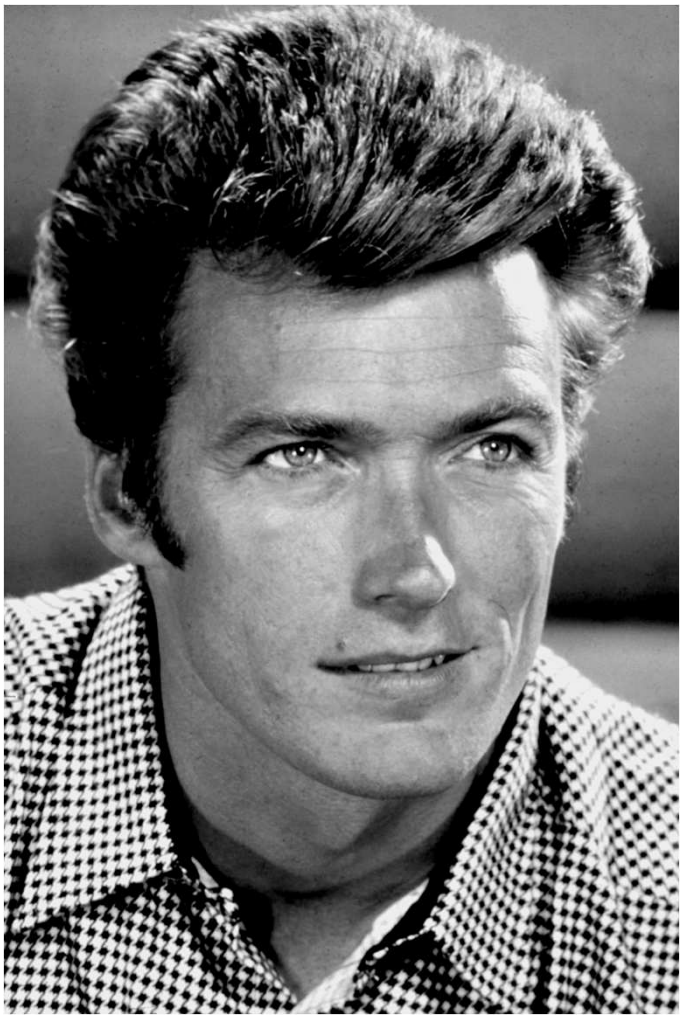
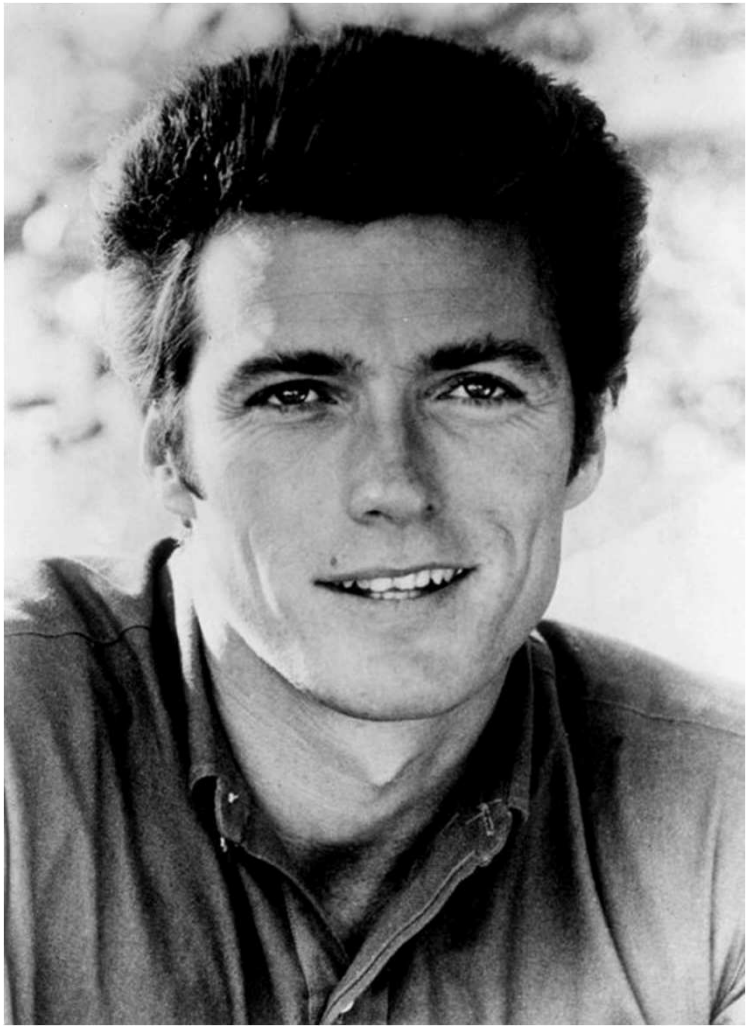
Los antivitaminas K



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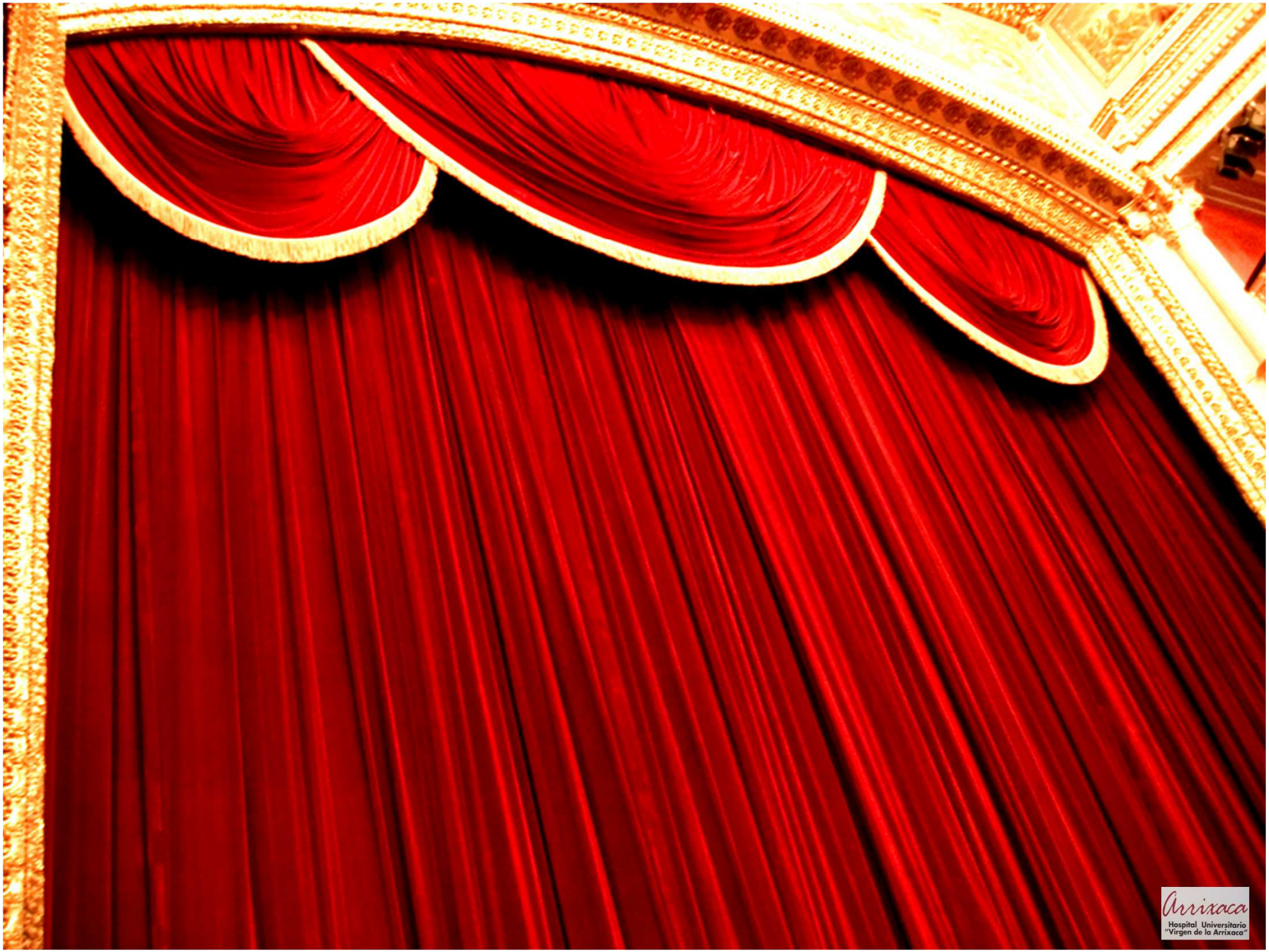
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Gatranes & Xabanes

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¿futuro?

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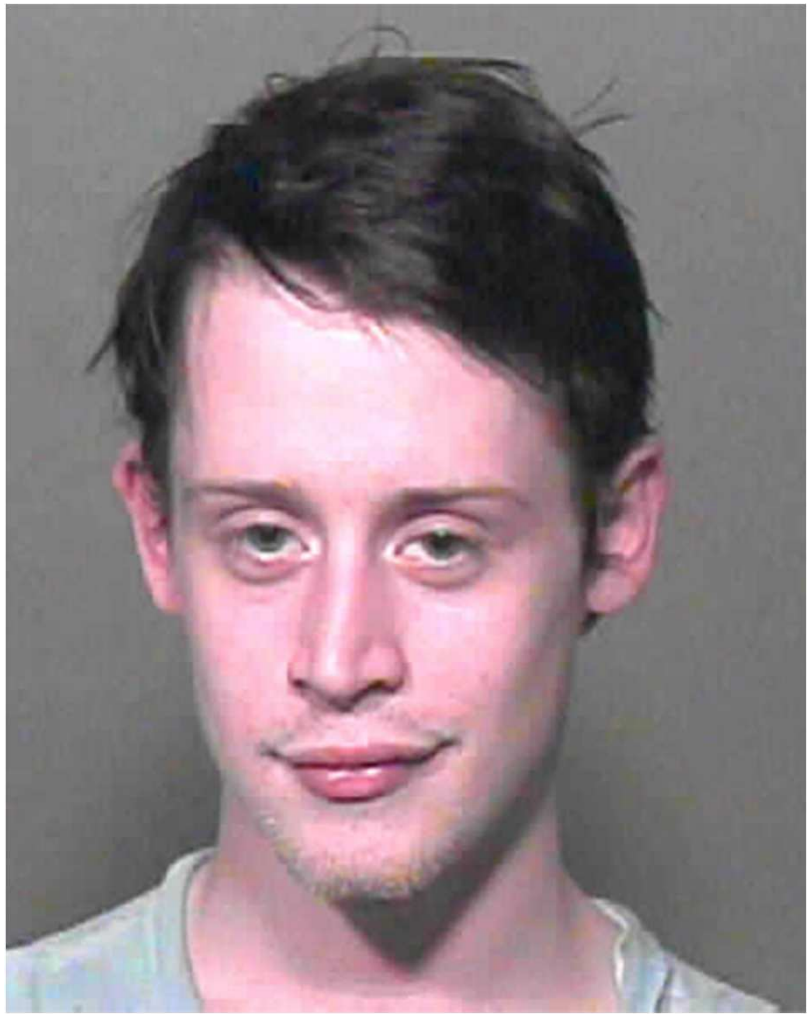

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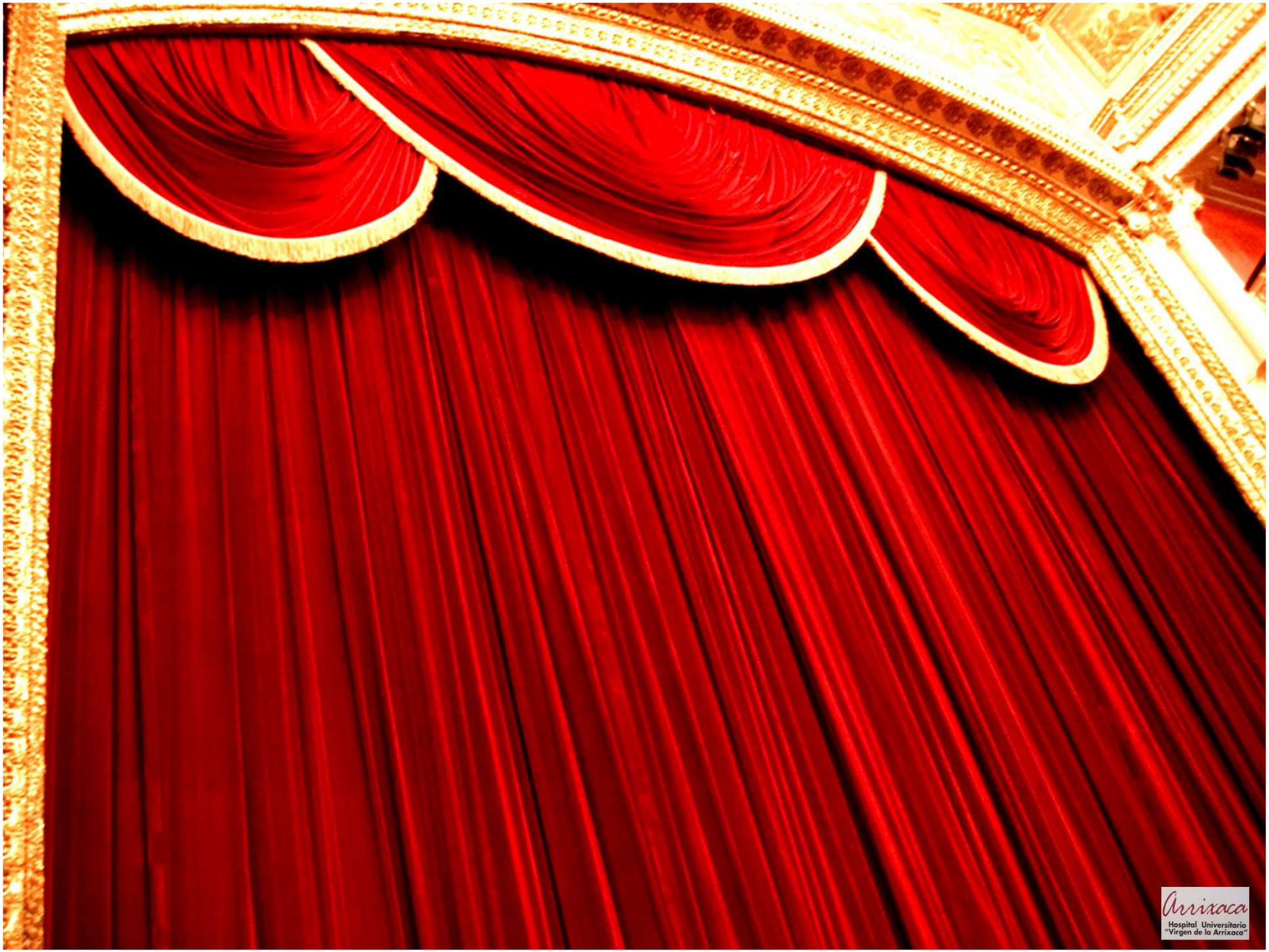
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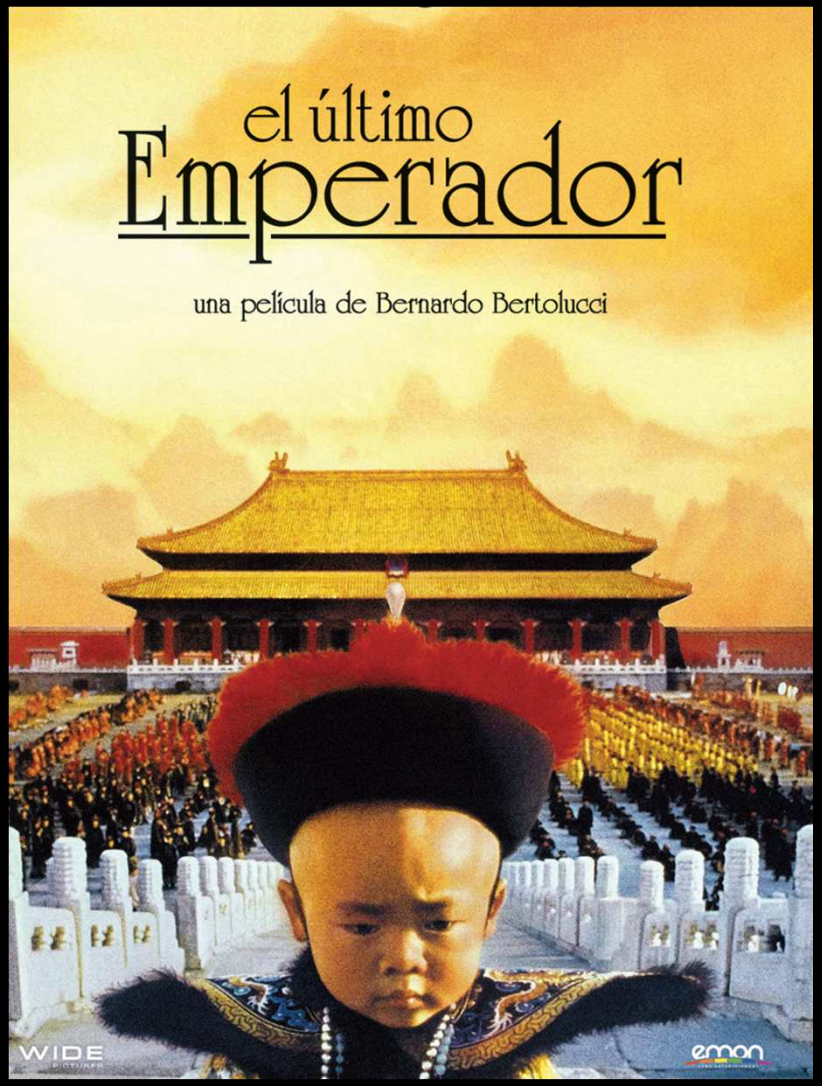
Edoxaban



Daiichi-Sankyo

HokusaiVTE

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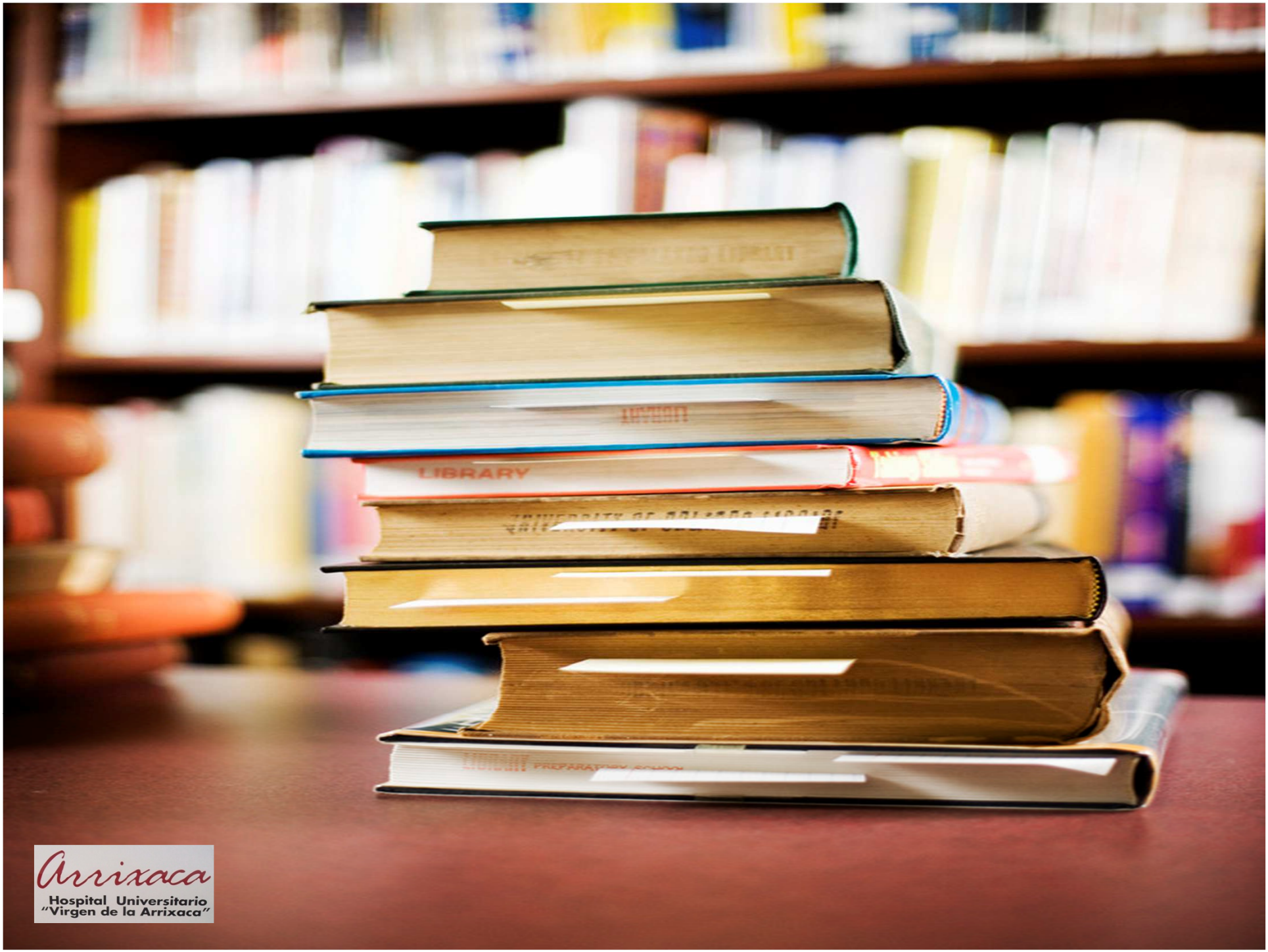
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The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D. for the RE-COVER Study Group

N Engl J Med 2009; 361:2342-2352 | December 10, 2009 | DOI: 10.1056/NEJMoa0906598

RECOVER™
Study of treatment of venous thromboembolism

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators

N Engl J Med 2010; 363:2499-2510 | December 23, 2010 | DOI: 10.1056/NEJMoa1007903

EINSTEIN DVT

ORIGINAL ARTICLE

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Urszula Masiukiewicz, M.D., Raphael Pak, Ph.D., John Thompson, Ph.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D. for the AMPLIFY Investigators

N Engl J Med 2013; 369:799-808 | August 29, 2013 | DOI: 10.1056/NEJMoa1302507

AMPLIFY

ORIGINAL ARTICLE

A Correction Has Been Published ›

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The Hokusai-VTE Investigators

N Engl J Med 2013; 369:1406-1415 | October 10, 2013 | DOI: 10.1056/NEJMoa1306638

HokusaiVTE

Ensayos clínicos

	RE-COVER I RE-COVER II	EINSTEIN-DVT EINSTEIN-PE	AMPLIFY	HOKUSAI-VTE
Fármaco	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Diseño	Doble ciego	Abierto	Doble ciego	Doble ciego
Heparina previa	NI	<48 h	<36 h	<48 h
Heparina	≥5 días	No	No	≥5 días
Dosis	150mg/12 h	15 mg/12 h, 20 mg/24 h	10 mg/12 h, 5 mg/12 h	60 mg/24 h 30 mg/24 h
Reducción dosis	No	No	No	18%
Pacientes, N	2.564 2.568	3.449 4.833	5.400	8.292
Duración	6 meses	3, 6 o 12 m.	6 meses	3 a 12 m.

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N Engl J Med 2009;361:2342–52.
N Engl J Med 2010;363:2499–10.
N Engl J Med 2012;366:1287–97.
N Engl J Med 2013;369:1406-15.

Características clínicas

	RE-COVER	EINSTEIN DVT	EINSTEIN PE	AMPLIFY	HOKUSAI
N	2.539	3.449	4.832	5.395	8.292
Edad (años)	55	56	58	57	56
Mujeres	42%	43%	47%	41%	43%
CrCl <50 mL/min	NI	7%	8%	6%	7%
TVP	69%	99%	-	65%	59%
EP	31%	0,6%	100%	35%	40%
Idiopática	NR	62%	65%	90%	65%
Cáncer	5%	6%	5%	3%	9%
TEV previo	26%	19%	19%	16%	18%

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N Engl J Med 2009;361:2342–52.
N Engl J Med 2010;363:2499–10.
N Engl J Med 2012;366:1287–97.
N Engl J Med 2013;369:1406-15.

Resultados

	RE-COVER I	EINSTEIN DVT	EINSTEIN EP	AMPLIFY	HOKUSAI
Fármaco	Dabigatran	Rivaroxaban	Rivaroxaban	Apixaban	Edoxaban
Eficacia					
Eficacia	No inferior	No inferior	No inferior	No inferior	No inferior
Seguridad					
Grave+NGCR	Mejor	NS	NS	Mejor	Mejor
Grave	NS	NS	Mejor	Mejor	NS
NGCR	NI	NS	NS	Mejor	Mejor
Cualquiera	Mejor	NI	NI	NI	Mejor

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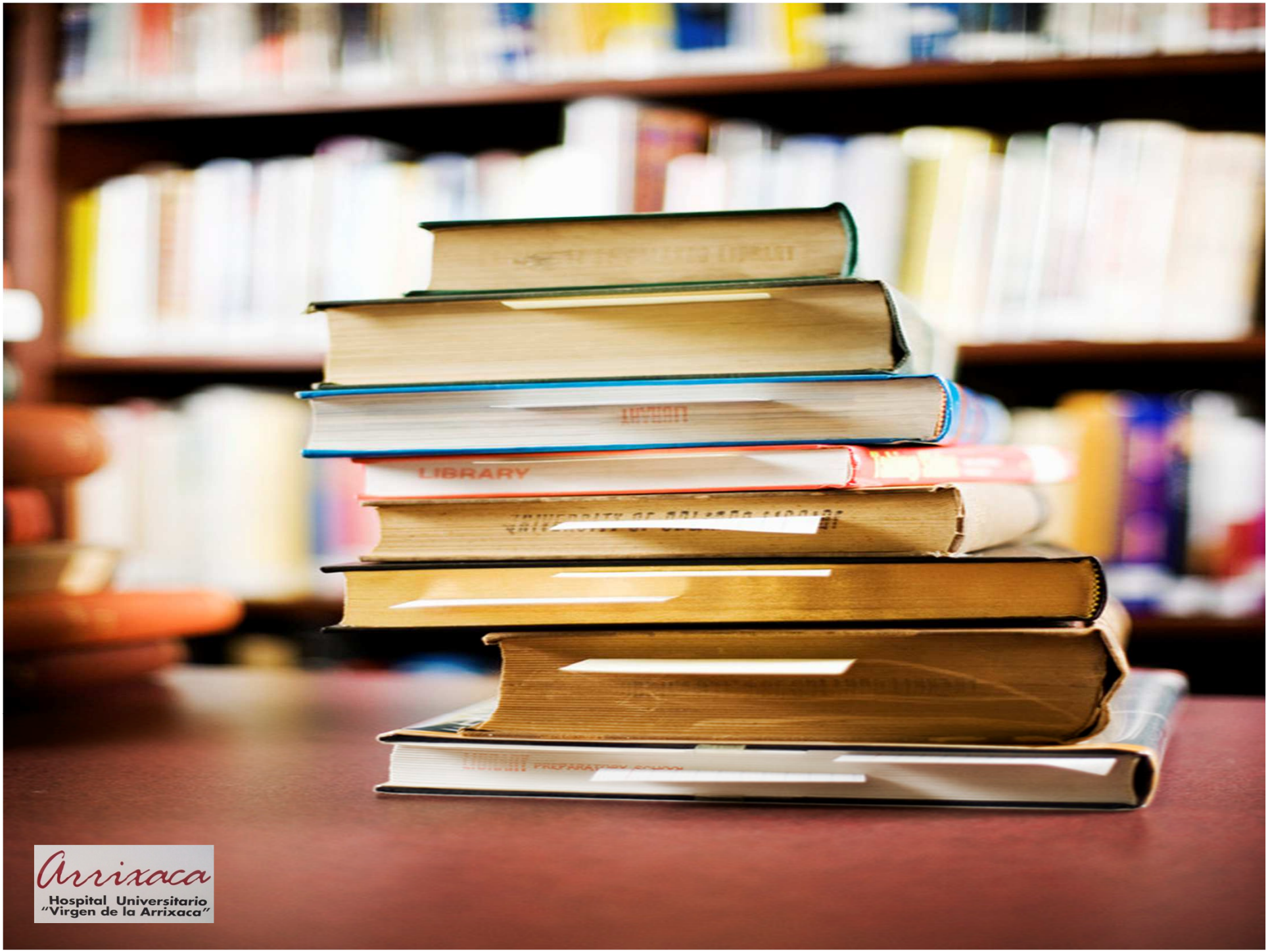
N Engl J Med 2009;361:2342–52.
N Engl J Med 2010;363:2499–10.
N Engl J Med 2012;366:1287–97.
N Engl J Med 2013;369:1406-15.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Metaanalisis

Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis

T. VAN DER HULLE,* J. KOOIMAN,* P. L. DEN EXTER,* O. M. DEKKERS,† F. A. KLOK* and M. V. HUISMAN*

**Department of Thrombosis and Hemostasis, Leiden University Medical Center; and †Departments of Clinical Epidemiology and Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, the Netherlands*

5 estudios

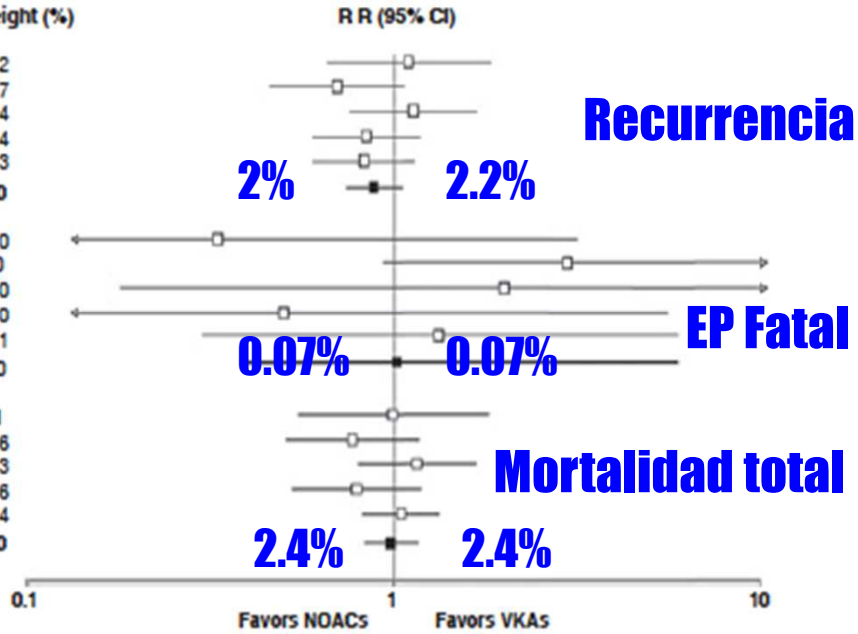
24.455 pacientes

Van Der Hulle T. *et al*.
J Thromb Haemost 2014;12:320-8.

Eficacia

Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonist in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis

Outcome Study	R R	Lower limit	Upper limit	Weight (%)
Recurrent VTE				
Re-Cover (dabigatran)	1.10	0.66	1.84	11.2
Einstein-DVT (rivaroxaban)	0.70	0.46	1.07	16.7
Einstein-PE (rivaroxaban)	1.13	0.76	1.69	18.4
Amplify (apixaban)	0.84	0.60	1.18	25.4
Hokusai (edoxaban)	0.83	0.60	1.14	28.3
Subtotal (I^2 = 0%, P = 0.46)	**0.88**	**0.74**	**1.05**	**100**
Fatal PE				
Re-Cover (dabigatran)	0.33	0.03	3.18	18.0
Einstein-DVT (rivaroxaban)	2.96	0.12	73.04	9.0
Einstein-PE (rivaroxaban)	2.00	0.18	21.99	16.0
Amplify (apixaban)	0.50	0.05	5.57	16.0
Hokusai (edoxaban)	1.33	0.30	5.96	41.1
Subtotal (I^2 = 0%, P = 0.71)	1.02	0.39	5.96	100
Overall mortality				
Re-Cover (dabigatran)	0.99	0.55	1.81	7.1
Einstein-DVT (rivaroxaban)	0.77	0.51	1.17	14.6
Einstein-PE (rivaroxaban)	1.16	0.80	1.68	18.3
Amplify (apixaban)	0.79	0.53	1.19	15.6
Hokusai (edoxaban)	1.05	0.82	1.33	44.4
Subtotal (I^2 = 0%, P = 0.50)	**0.97**	**0.83**	**1.14**	**100**



Recurrencia RR 0.88% (95% CI 0.74-1.05).

EP fatal RR 1.02% (95% CI 0.39-5.96).

Mortalidad total RR 0.97% (95% CI 0.83-1.14).

Van Der Hulle T. *et al.*
J Thromb Haemost 2014;12:320-8.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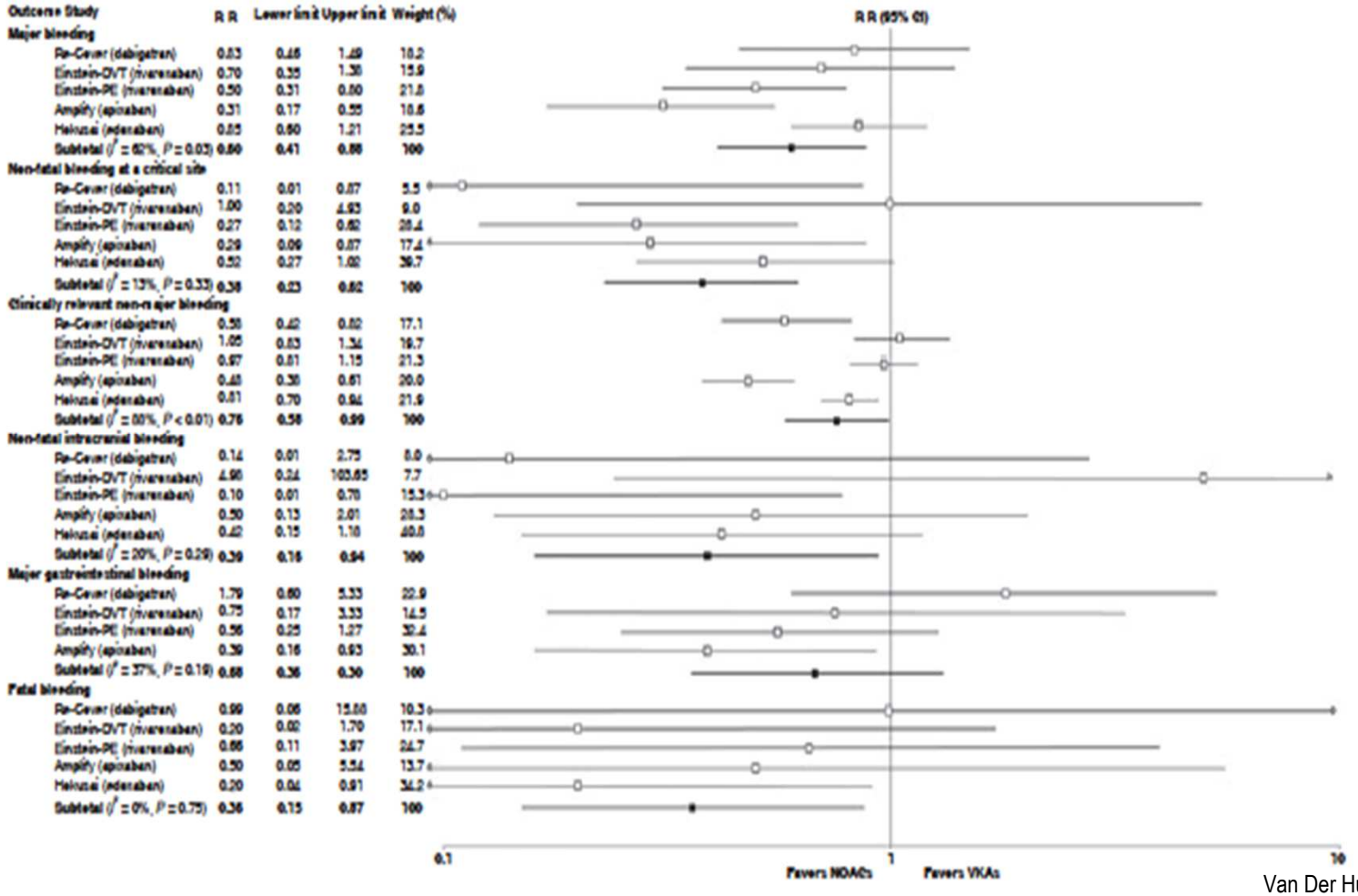
Seguridad

Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonist in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis



Van Der Hulle T. *et al.*
J Thromb Haemost 2014;12:320-8.

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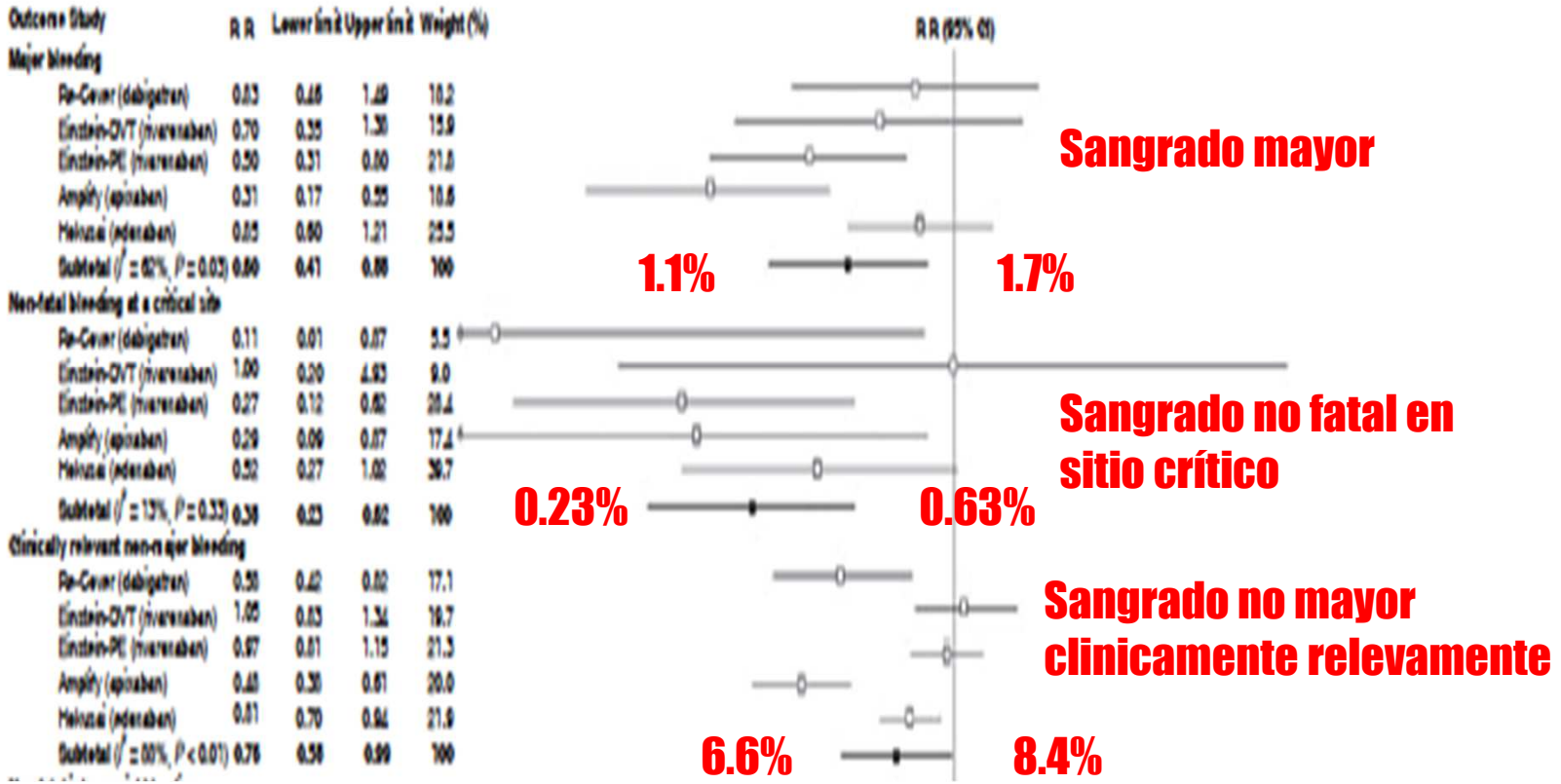

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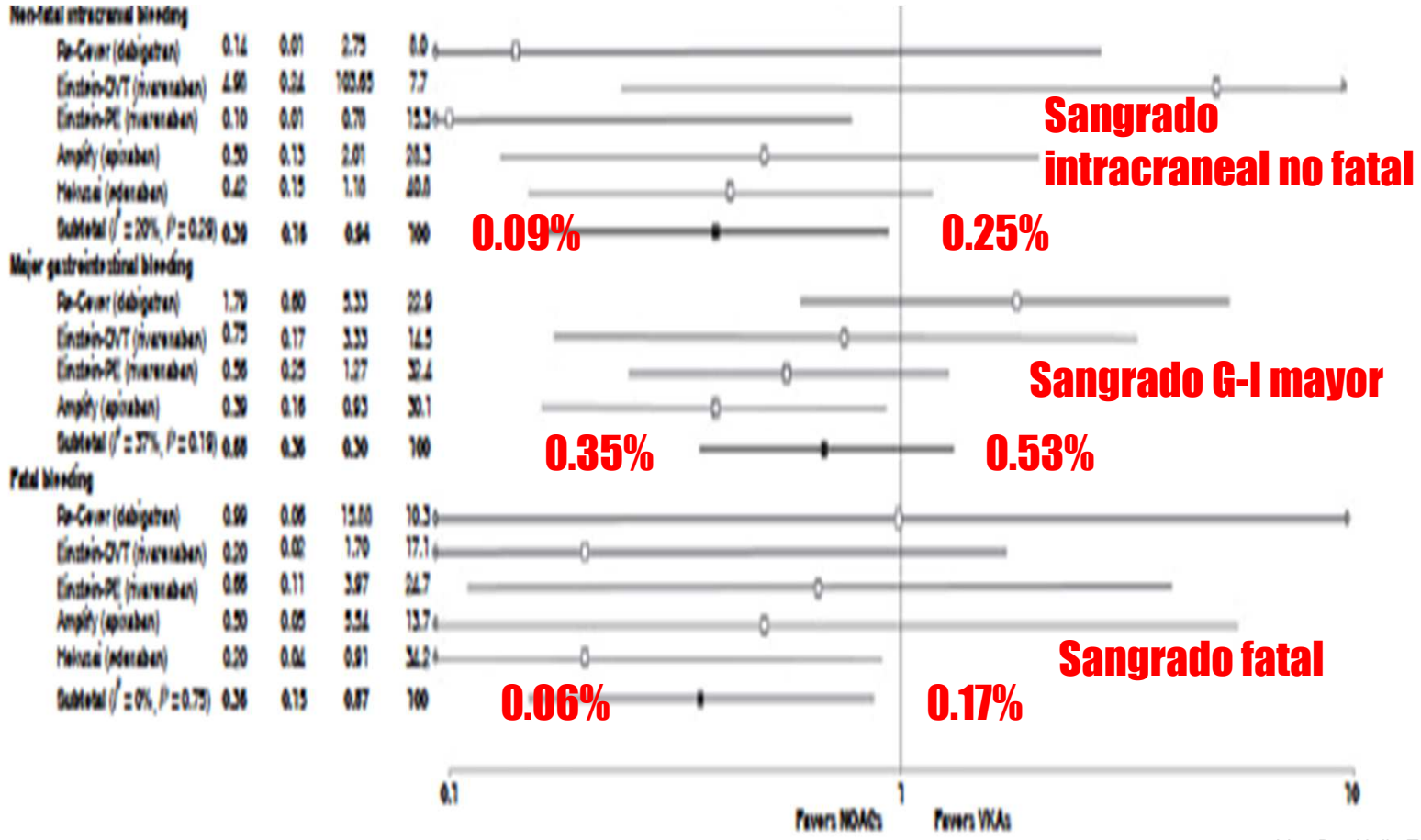


Van Der Hulle T. *et al.*
J Thromb Haemost 2014;12:320-8.

Sangrado fatal

- NNT 1111

Sangrado mayor

- NNT 149

Sangrado no mayor clínicamente relevante

- NNT 56

Van Der Hulle T. *et al*.
J Thromb Haemost 2014;12:320-8.

Sangrado intracraneal no fatal

- NNT 714

Sangrado gastro-intestinal

- NNT 625

Sangrado no fatal en sitio crítico

- NNT 263

Van Der Hulle T. *et al*.
J Thromb Haemost 2014;12:320-8.

Comparaciones indirectas

Contents lists available at ScienceDirect

Thrombosis Research

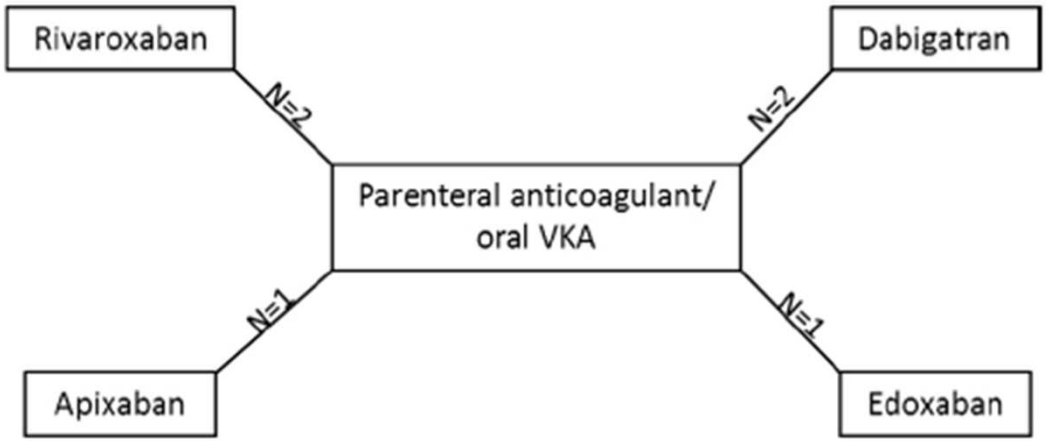
journal homepage: www.elsevier.com/locate/thromres

Regular Article

Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism

Nayon Kang, Diana M. Sobieraj *

University of Connecticut School of Pharmacy, 69 N Eagleville Rd. Unit 3092, Storrs, CT 06269, United States



Kang N *et al.*
Thrombosis Research 2014;133:1145-51.

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism

Nayon Kang, Diana M. Sobieraj *

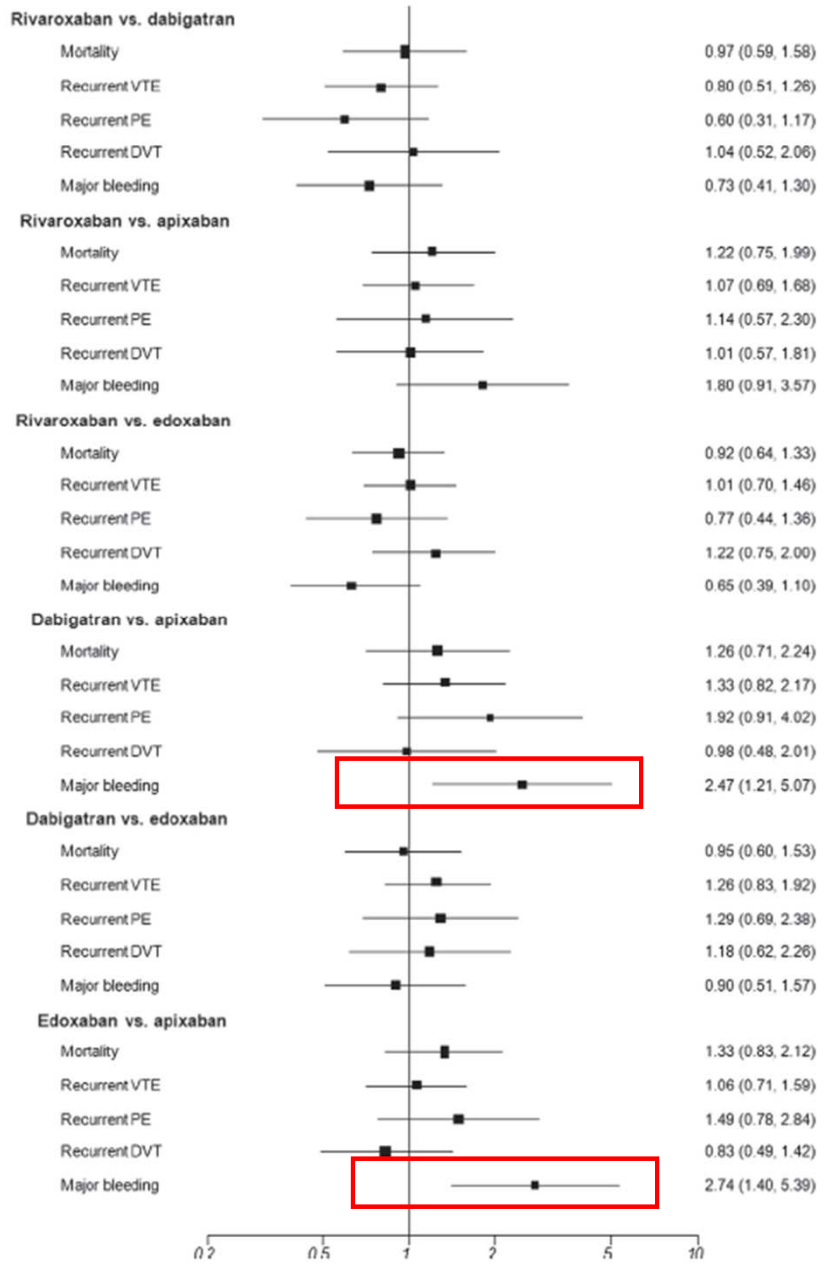
University of Connecticut School of Pharmacy, 69 N Eagleville Rd. Unit 3092, Storrs, CT 06269, United States

Table 2
Pairwise relative risks for each new oral anticoagulant versus parenteral anticoagulant plus vitamin K antagonist.*

	Morality	Recurrent VTE	Recurrent PE	Recurrent DVT	Major bleeding
Base-case analyses					
Rivaroxaban	0.97 (0.73 to 1.27)	0.90 (0.68 to 1.20)	1.08 (0.74 to 1.57)	0.70 (0.45 to 1.09)	0.55 (0.38 to 0.81)
Dabigatran	1.00 (0.67 to 1.50)	1.12 (0.79 to 1.60)	1.04 (0.59 to 1.85)	1.17 (0.70 to 1.93)	0.76 (0.49 to 1.18)
Apixaban	0.79 (0.53 to 1.19)	0.84 (0.60 to 1.18)	1.06 (0.69 to 1.65)	0.61 (0.36 to 1.06)	0.31 (0.17 to 0.54)
Edoxaban	1.05 (0.83 to 1.33)	0.89 (0.71 to 1.12)	0.88 (0.65 to 1.20)	0.91 (0.64 to 1.29)	0.85 (0.60 to 1.21)
Sensitivity analysis					
Rivaroxaban	0.95 (0.64 to 1.42)	0.90 (0.56 to 1.43)	1.07 (0.73 to 1.58)	0.71 (0.40 to 1.24)	0.56 (0.38 to 0.82)

* Values represent relative risks and 95% confidence intervals.

Kang N *et al.*
Thrombosis Research 2014;133:1145-51.



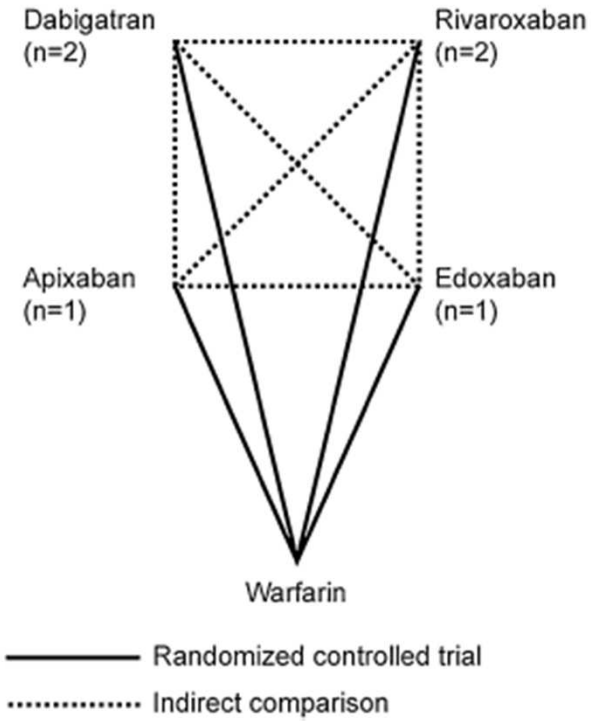
Kang N *et al.*
Thrombosis Research 2014;133:1145-51.

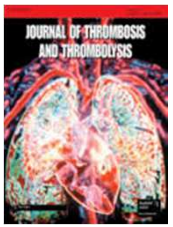
Comparaciones indirectas

J Thromb Thrombolysis
DOI 10.1007/s11239-014-1102-5

Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism

Simon Mantha · Jack Ansell





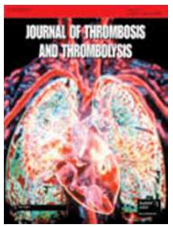
Mantha S. et al.
J Thromb Thrombolysis 2014.

J Thromb Thrombolysis
DOI 10.1007/s11239-014-1102-5

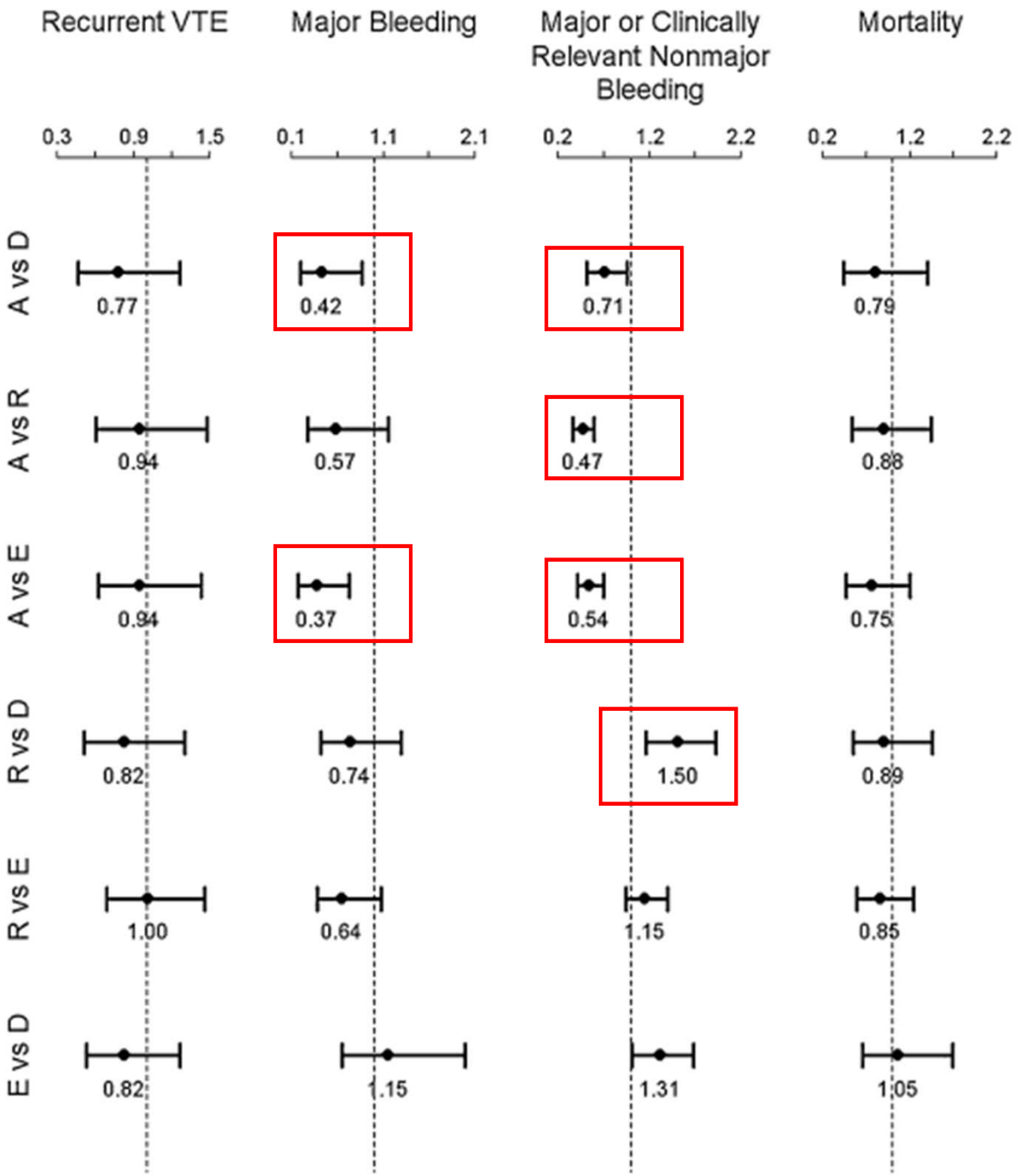
Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism

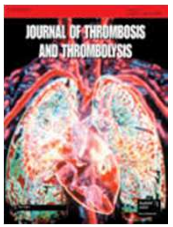
Simon Mantha · Jack Ansell

	Dabigatran (RE-COVER I and RE-COVER II combined)[a]			Rivaroxaban (EINSTEIN-DVT and EINSTEIN-PE combined)[b]			Apixaban (AMPLIFY)[b]			Edoxaban (Hokusai-VTE)[c]		
	HR	95 % CI	*p*	HR	95 % CI	*p*	RR	95 % CI	*p*	HR or OR[e]	95 % CI	*p*
Recurrent VTE	1.09	0.76–1.57	NA	0.89	0.66–1.19	0.41	0.84	0.60–1.18	<0.001[d]	0.89	0.70–1.13	<0.001[d]
Major bleeding	0.73	0.48–1.11	NA	0.54	0.37–0.79	0.002	0.31	0.17–0.55	<0.001	0.84	0.59–1.21	0.35
Major or clinically relevant nonmajor bleeding	0.62	0.50–0.76	NA	0.93	0.81–1.06	0.27	0.44	0.36–0.55	<0.001	0.81	0.71–0.94	0.004
Death	1.0	0.67–1.51	NA	0.89	0.67–1.18	0.43	0.79	0.53–1.19	NA	1.05[e]	0.82–1.35[e]	0.70[e]



Mantha S. et al.
J Thromb Thrombolysis 2014.





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Subgrupos

Subgrupo Hokusai

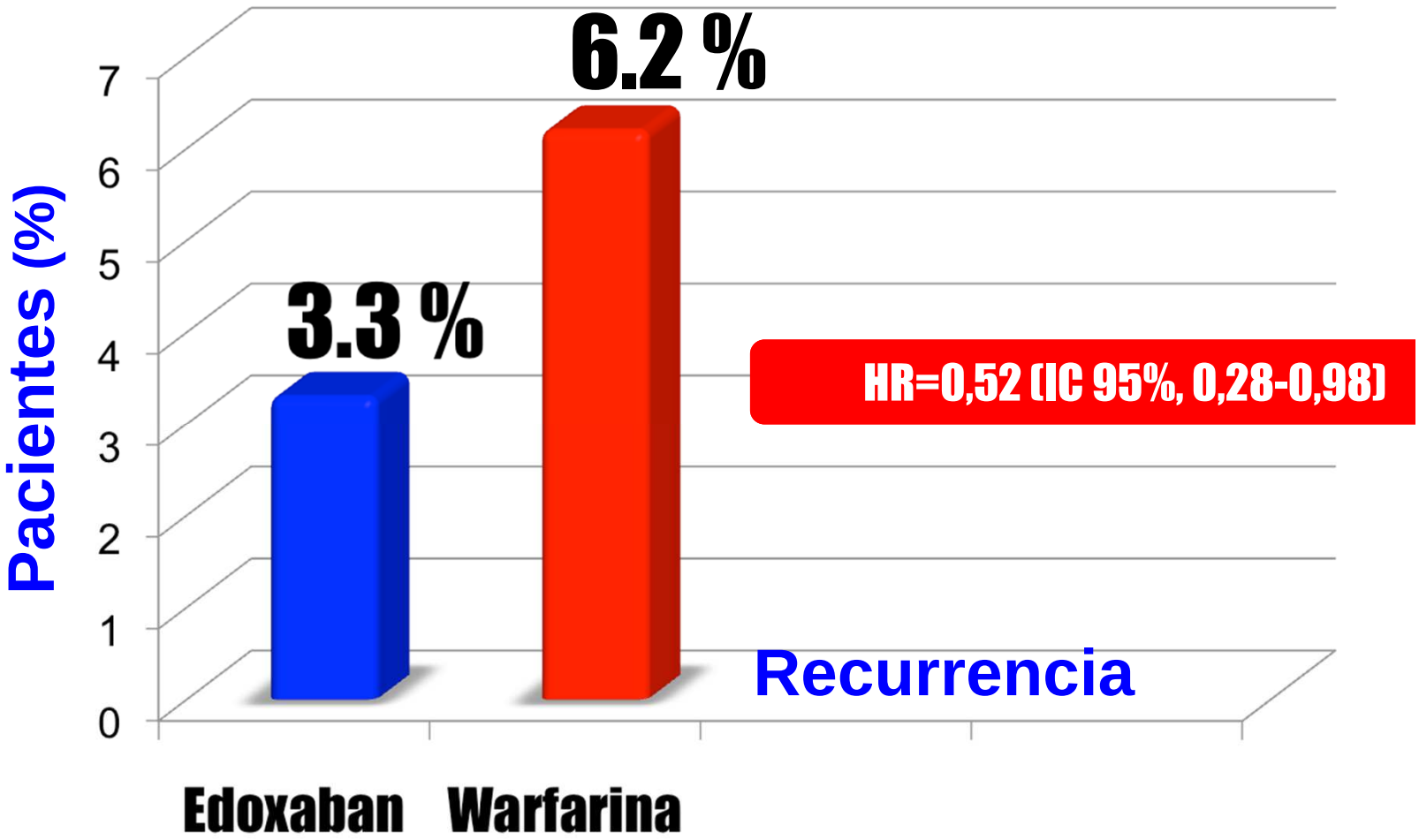
EP grave

NT-proBNP ≥ 500

HokusaiVTE

N Engl J Med 2013;369:1406-15.

EP grave



HokusaiVTE

N Engl J Med 2013;369:1406-15.

Conclusiones

- NACOS ya son una realidad.
- Edoxaban el último en llegar.
- Ya están estudiados en ETEV.
- Similar eficacia que AVK.
- Menos complicaciones hemorrágicas.
- Un futuro prometedor.

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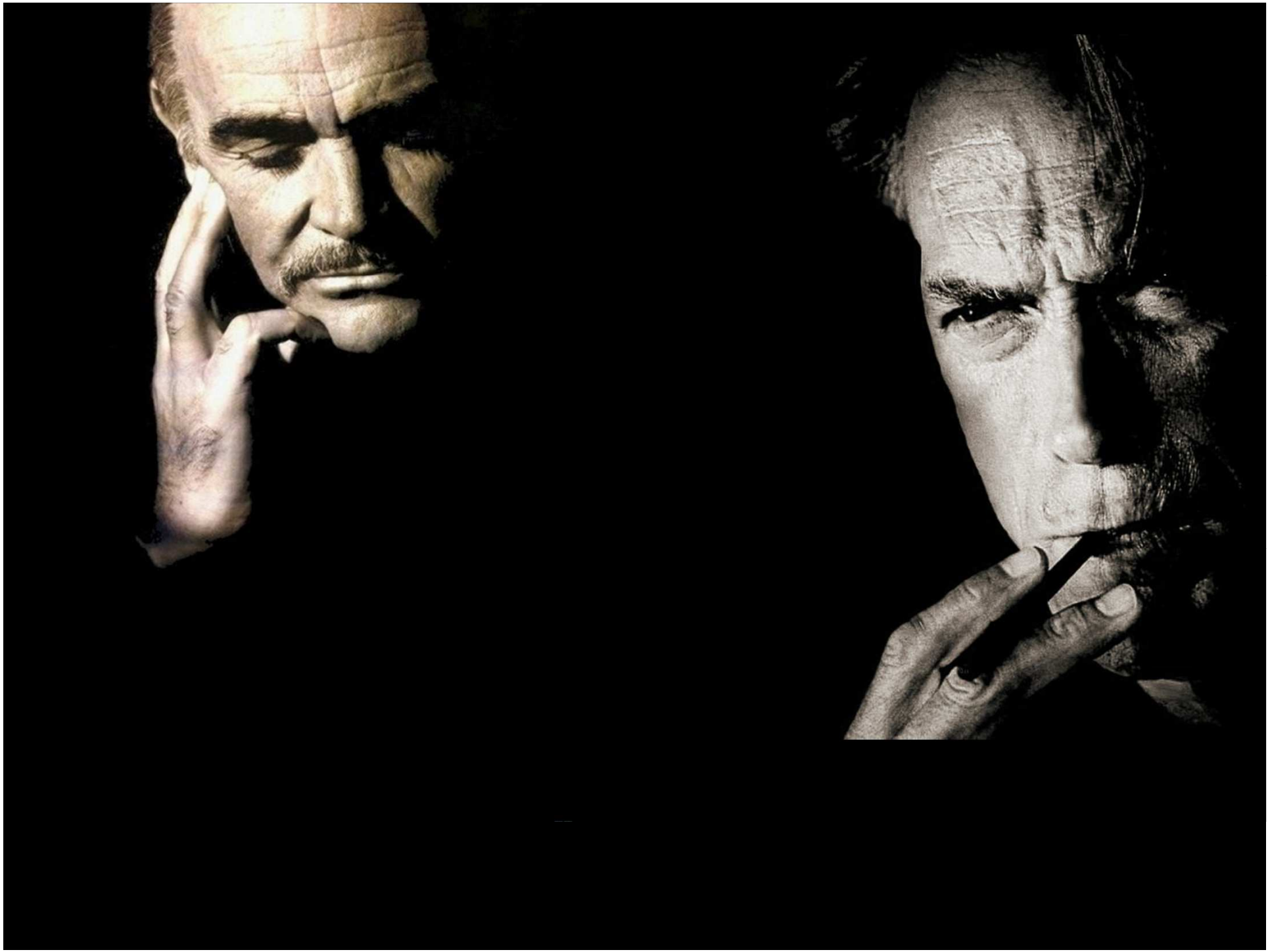


Muchas gracias
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Comodidad

RE-LY

	Warfarina	Dabigatran 110 mg	Dabigatran 150 mg
Tasa abandono 1er año.	10%	15%	16%
Tasa abandono 2º año	17%	21%	21%

RELY®
Study of stroke prevention in atrial fibrillation

Ezekowitz et al. **N Engl J Med 2009;361:1139-51.**

Adverse Events and Discontinuation

	Rivaroxaban (N=7111)	Warfarina (N=7125)
Any Adverse Event	82.4	82.2
Any Serious Adverse Event	37.3	38.2
AE leading to study drug discontinuation	15.7	15.2
Study drug discontinuation	**23.7**	**22.2**

Values are N (%)

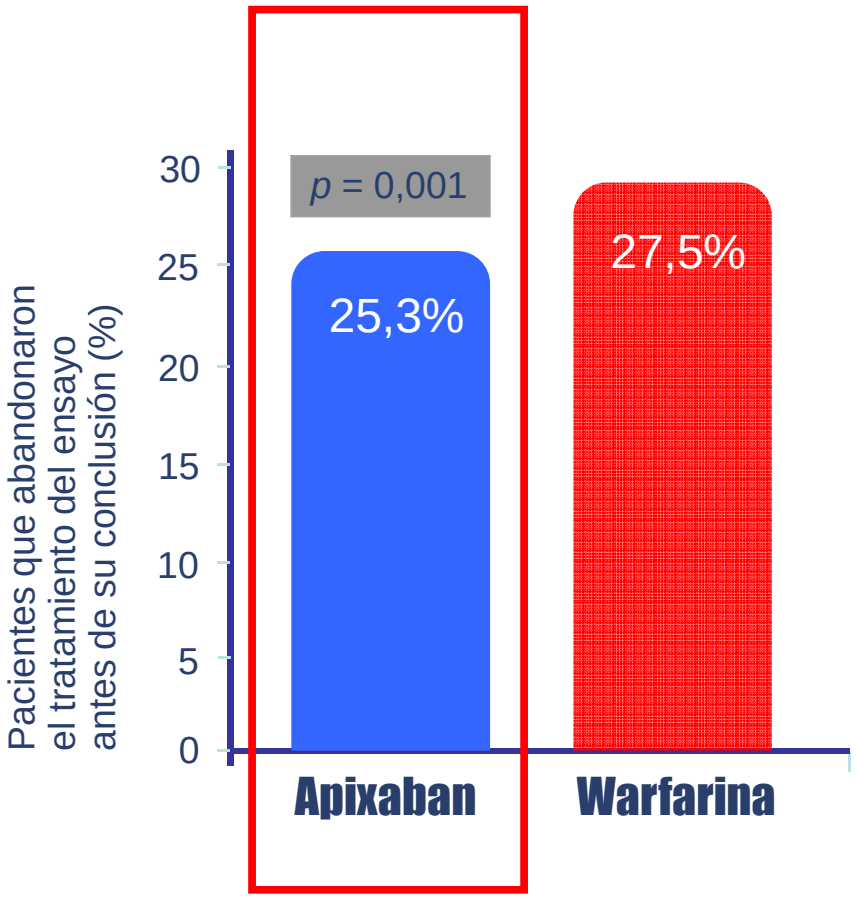
ROCKET AF

Patel et al. **N Engl J Med 2011;365:883-91**.

Abandono tratamiento

- Media del seguimiento: **1,8 años**
- Media del TRT con warfarina: **62,2%**
- **Apixaban menos abandonos con warfarina**

TRT: tiempo en rango terapéutico.



Granger et al. **N Engl J Med 2011;365:981-92.**

“Poderoso caballero es don dinero”

Quevedo.

Antivitaminas K: 0,12 € /día.

Nuevos ACO: 2 € /día.

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500.000 anticoagulados en España x 1,88 € al día =

940.000 €/día.

156 millones ptas/día.

28.200.000 €/mes.

4.700 millones ptas/mes.

NACOS

Aportarían beneficios en término de reducción de: ictus, embolismos, hemorragias y muertes evitadas frente a dicumarínicos y AAS.

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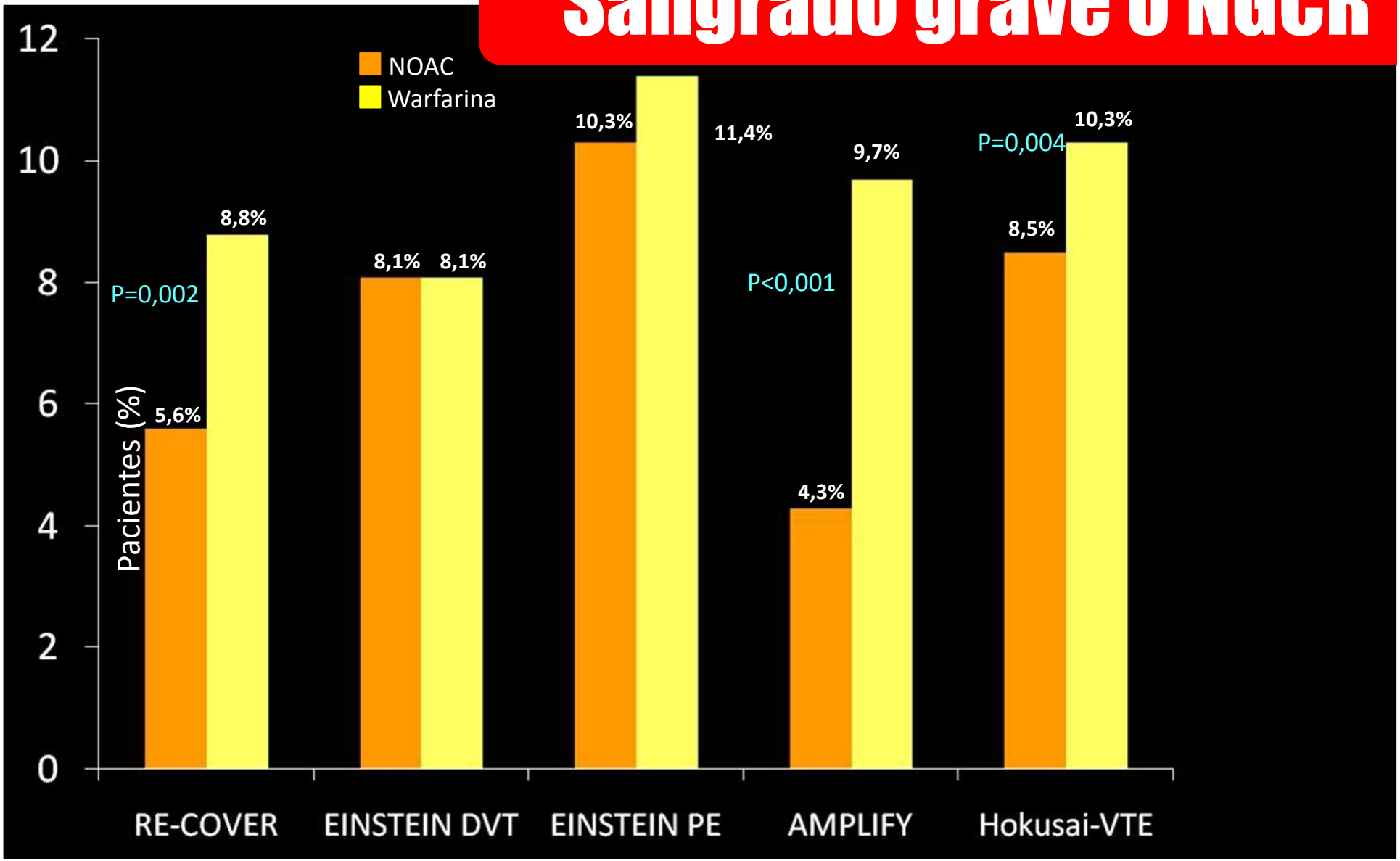
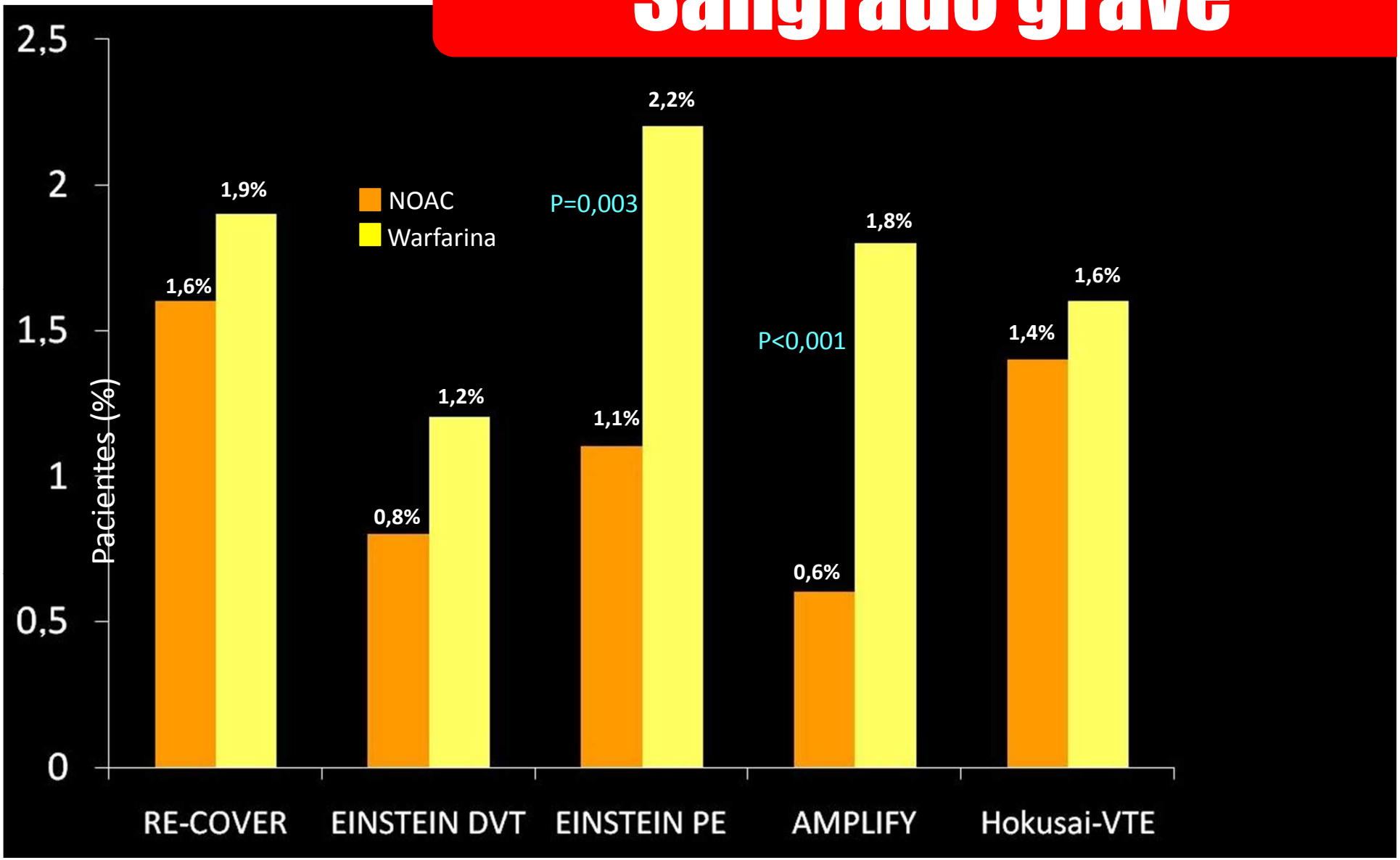
Sangrado grave o NGCR



N Engl J Med 2009;361:2342–52.
N Engl J Med 2010;363:2499–10.
N Engl J Med 2012;366:1287–97.
N Engl J Med 2013;369:1406-15.

Sangrado grave



N Engl J Med 2009;361:2342–52.
N Engl J Med 2010;363:2499–10.
N Engl J Med 2012;366:1287–97.
N Engl J Med 2013;369:1406-15.

Cronología AVK

1921	Epidemia en el ganado de EEUU.
1941	Patente del Dicumarol.
1948	Raticida Warfarina.
1951	Intento de suicidio de un soldado con W.
1954	Se aprueba su uso en humanos.
1978	Se descubre interferencia con la vitamina K.

Cronología Heparina

1922	William Howell aísla la heparina.
1933	Preparados de heparina de pulmón bovino.
1937	Primara inyección de heparina profiláctica.
1960	Descubrimiento de la parte antiXa.
1980	Síntesis y uso de HBPM.