XXXIII Diada Pneumologia
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Nous fàrmacs en el tractament de la malaltia tromboembòlica

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AODs: farmacologia

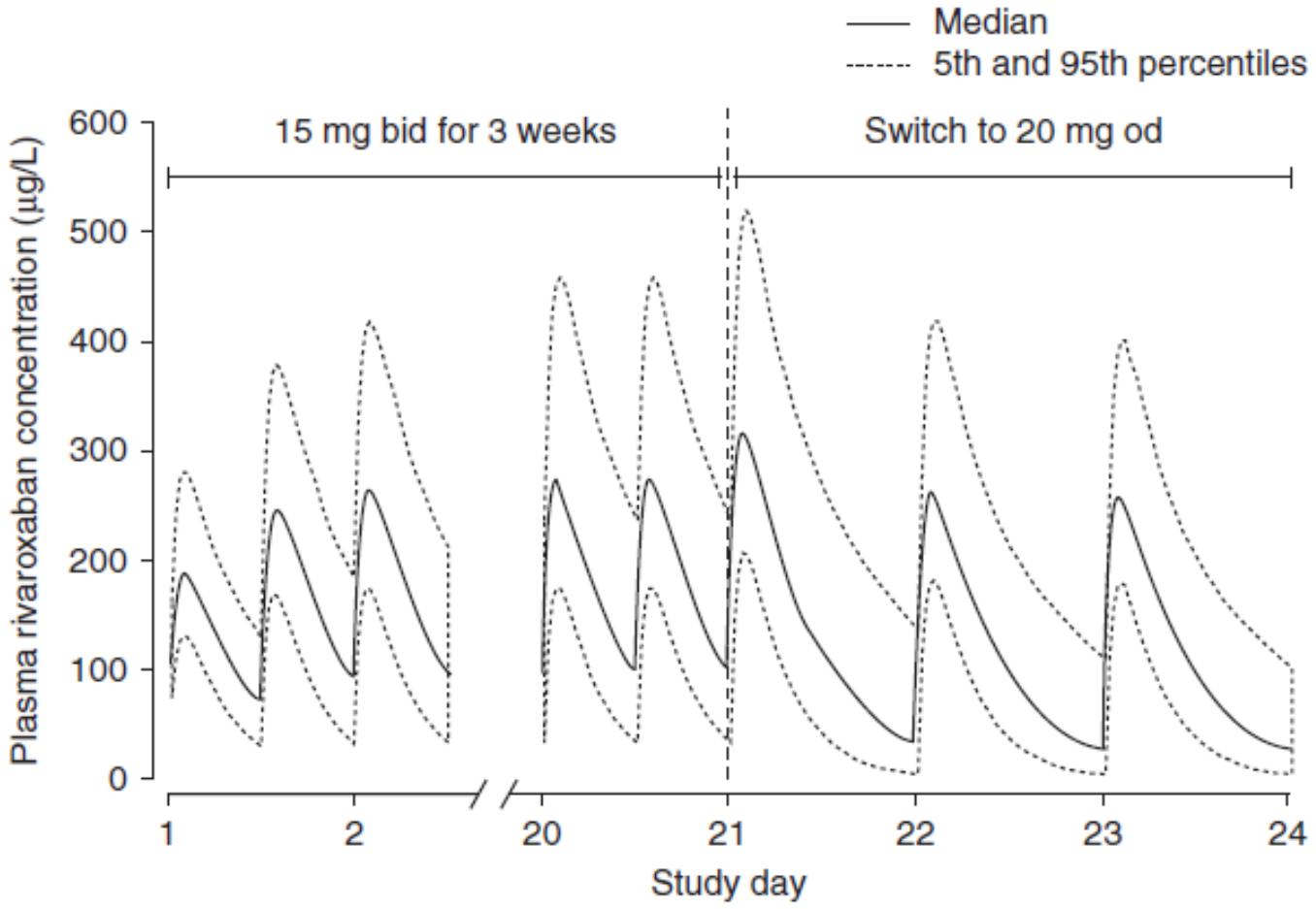
Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Drug/prodrug	Prodrug (dabigatran etexilate)	Drug	Drug	Drug
Bioavailability	6%	Almost 100% for 10 mg, less for higher doses	50%	62%
Time to maximum effect (t_{max})	1.5–2 h	2 h	3–4 h	1–2 h
Half-life (t½)	12–17 h	5–9 h*	8–15 h	9–10 h
Plasma protein binding	35%	92–95%	87%	40–59%
Renal elimination of active drug	80%	33%	25%	35–39%
Interactions mediated by	P-gp	P-gp, CYP3A4	P-gp, CYP3A4	P-gp, (CYP3A4)
Food effect	Absorption delayed, not reduced	Required for absorption of doses >10 mg	Not reported	No

- No tenen antídot

Schulman. Thromb Haemost 2014; 111:

Farmacocinètica dels AOD

Simulació, basada en els resultats acumulats d'estudis fase II, de les concentracions de rivaroxaban en les dosificacions pròpies del tractament del TEV



Mueck. Clin Pharmacokinet 2011; 50:675

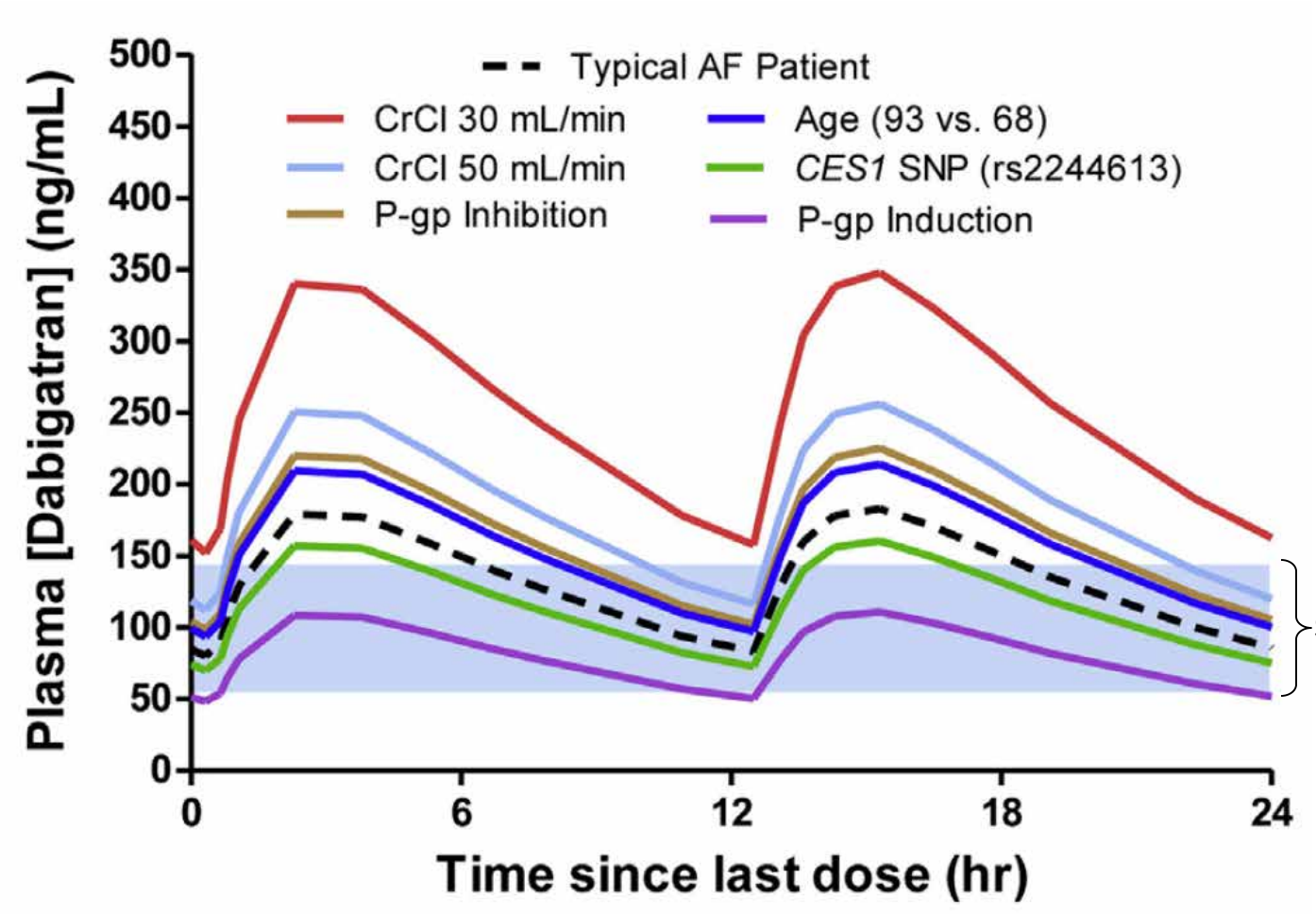
Factors que poden modificar les concentracions dels AOD

- Associació amb fàrmacs d'activitat interferent coneguda o suposada: Inhibidors o potenciadors rellevants del CYP3A4 o de la P-gp
- insuficiència renal
- insuficiència hepàtica
- edat avançada
- superfícies corporals extremes
- associació de varis factors interferents

Dabigatran:

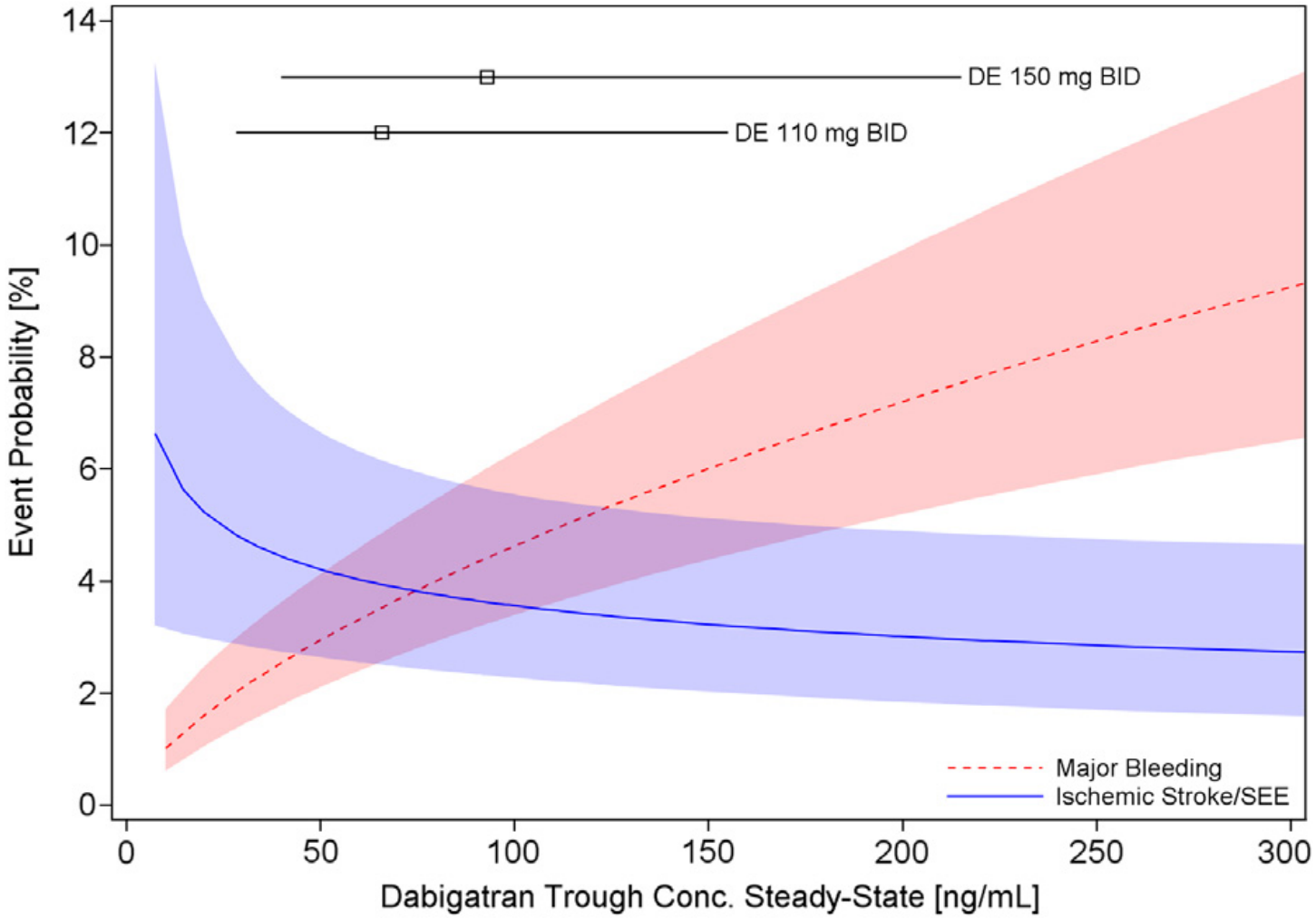
Concentracions mitjanes, steady-state, 150 mg bid

Efecte de factors interferents



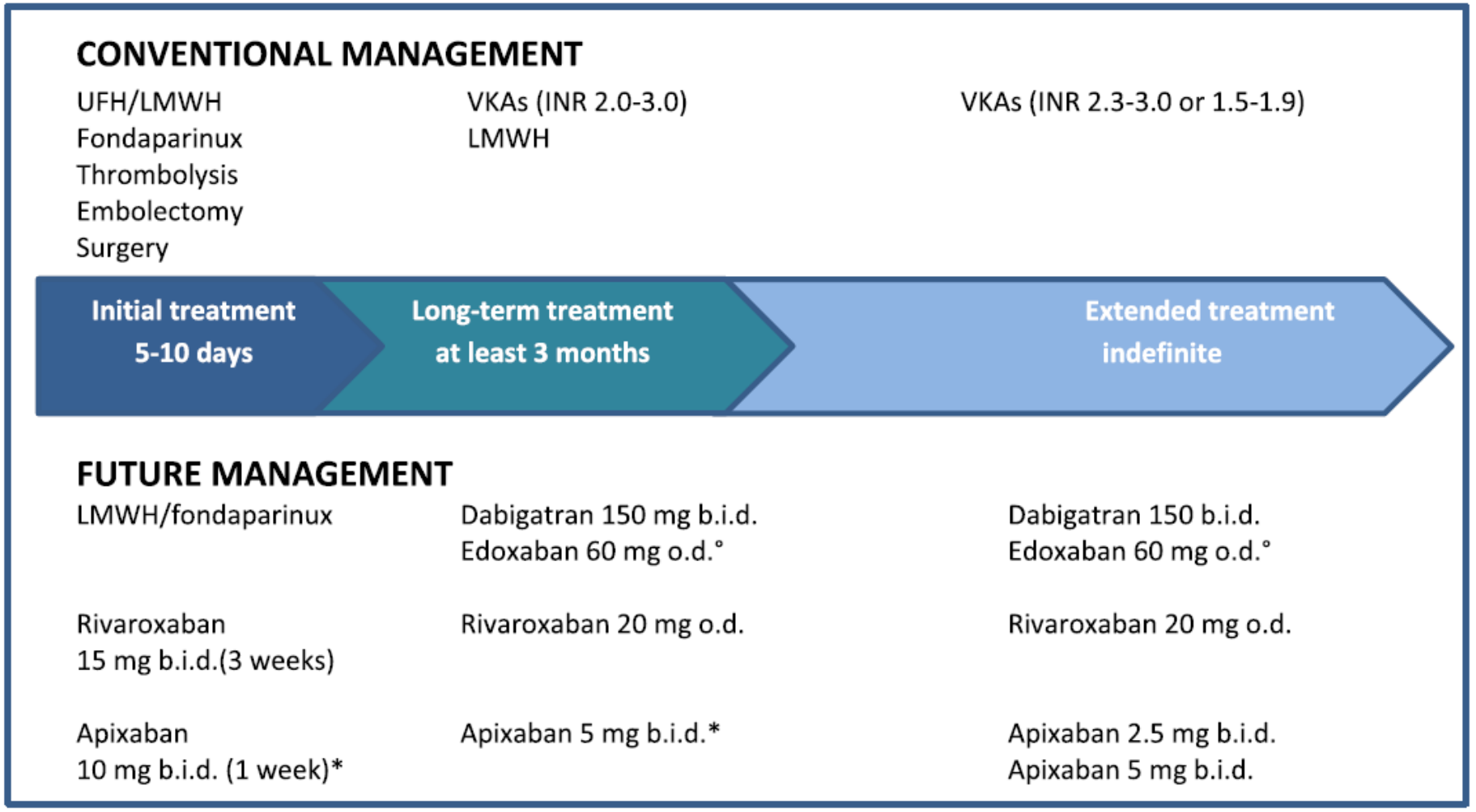
Gong. Canadian Journal of Cardiology. 2013; 29: S24

Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran



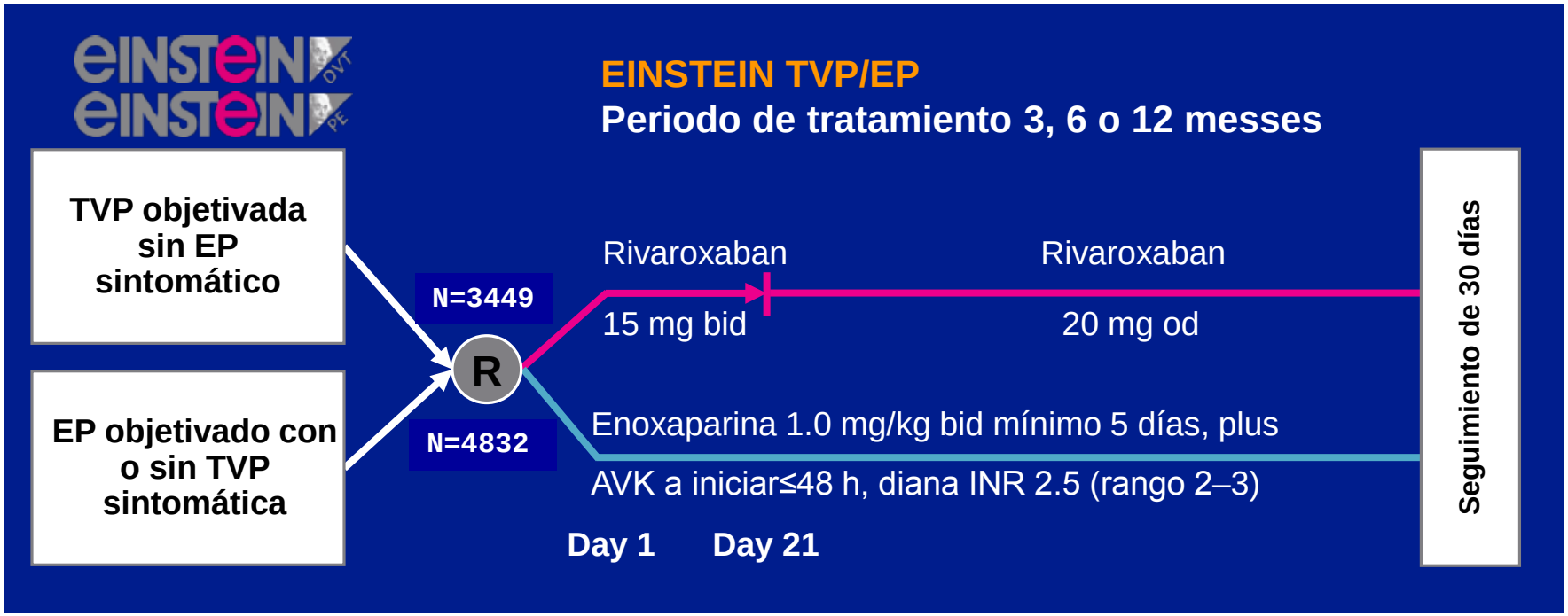
Reilly. JACC 2014; 63:321–8

Tractament del TEV



Agnelli Best Practice & Research Clinical Haematology 26 (2013) 151

Rivaroxaban en el TEV: EINSTEIN DVT i PE



Estudio abierto, valoración ciega de eventos

Metanàlisis Tractament TEV amb els AODs

Table 1: Study characteristics

Study Year Drug Class	Treatment duration in months	Patients n	Men n (%)	Mean age in years (range)	PE or PE and DVT n (%)	Isolated DVT n (%)	Unprovoked n (%)	Cancer n (%)	Previous VTE n (%)	TTR in VKA group %
Re-Cover 2009 Dabigatran DTI	6	2539	1484 (58)	55 (18-97)	786 (31)	1749 (69)	Not provided	121 (5)	649 (26)	60
Einstein-DVT 2010 Rivaroxaban FXa inhibitor	3/6/12*	3449	1960 (57)	56 (Not provided)	23 (1)	3405 (99)	2138 (62)	207 (6)	666 (19)	58
Einstein-PE 2012 Rivaroxaban FXa inhibitor	3/6/12*	4832	2556 (53)	58 (Not provided)	4832 (100)	0 (0)	3117 (65)	223 (5)	944 (20)	63
Amplify 2013 Apixaban FXa inhibitor	6	5395	3167 (59)	57 (not provided)	1836 (34)	3532 (65)	4845 (90)	143 (3)	872 (16)	61
Hokusai 2013 Edoxaban FXa inhibitor	3/6/12*	8240	4716 (57)	56 (Not provided)	3319 (40)	4921 (60)	5410 (66)	771 (9)	1520 (18)	64

Hulle. J Thromb Haemost. 2014

Metanàlisis Tractament TEV amb els AODs

Table 2: Efficacy and safety outcomes

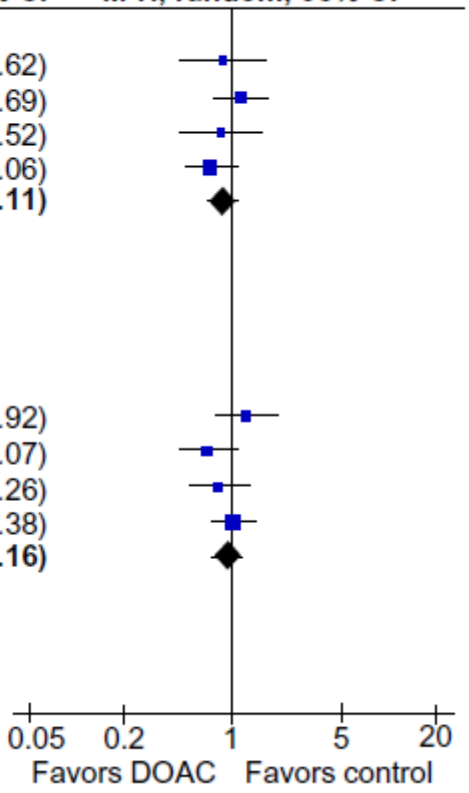
Outcome	NOACs n % Range	VKA n % Range	Pooled absolute risk difference % (95% CI)	NNT with NOACs to prevent 1 event (95% CI)
Recurrent VTE	241/12,151 2.0 1.6-2.4	273/12,153 2.2 1.8-3.0	-0.24 (-0.60 to 0.11)	417 (167 to -909)
Fatal PE	9/12,151 0.07 0.04-0.10	9/12,153 0.07 0.00-0.24	0.01 (-0.06 to 0.08)	10,000 (1667 to -1250)
Overall mortality	290/12,197 2.4 1.5-3.2	298/12,193 2.4 1.7-3.1	-0.10 (-0.47 to 0.28)	1,000 (213 to -357)
Major bleeding	131/12,197 1.1 0.6-1.6	211/12,193 1.7 1.2-2.2	-0.67 (-1.13 to -0.21)	149 (88 to 476)
Non-fatal bleeding at a critical site	28/12,179 0.23 0.08-0.32	77/12,193 0.63 0.18-1.08	-0.38 (-0.65 to -0.10)	263 (153 to 1000)
Clinically relevant non-major bleeding	806/12,179 6.6 3.9-9.5	1024/12,193 8.4 6.9-9.8	-1.77 (-3.40 to -0.15)	56 (29 to 667)
Non-fatal intracranial bleeding	11/12,179 0.09 0.00-0.12	31/12,193 0.25 0.00-0.42	-0.14 (-0.31 to 0.03)	714 (323 to -3,333)
Major gastrointestinal bleeding	28/8,079 0.35 0.17-0.71	43/8,071 0.53 0.23-0.67	-0.16 (-0.42 to 0.11)	625 (238 to 909)
Fatal bleeding	7/12,179 0.06 0.04-0.08	21/12,193 0.17 0.07-0.29	-0.09 (-0.17 to 0.00)	1,111 (588 to 0)

Hulle. J Thromb Haemost. 2014

Subgroup analysis of recurrent VTE depending on index event (PE or DVT) in clinical trials with DOAC in the treatment of VTE.

A

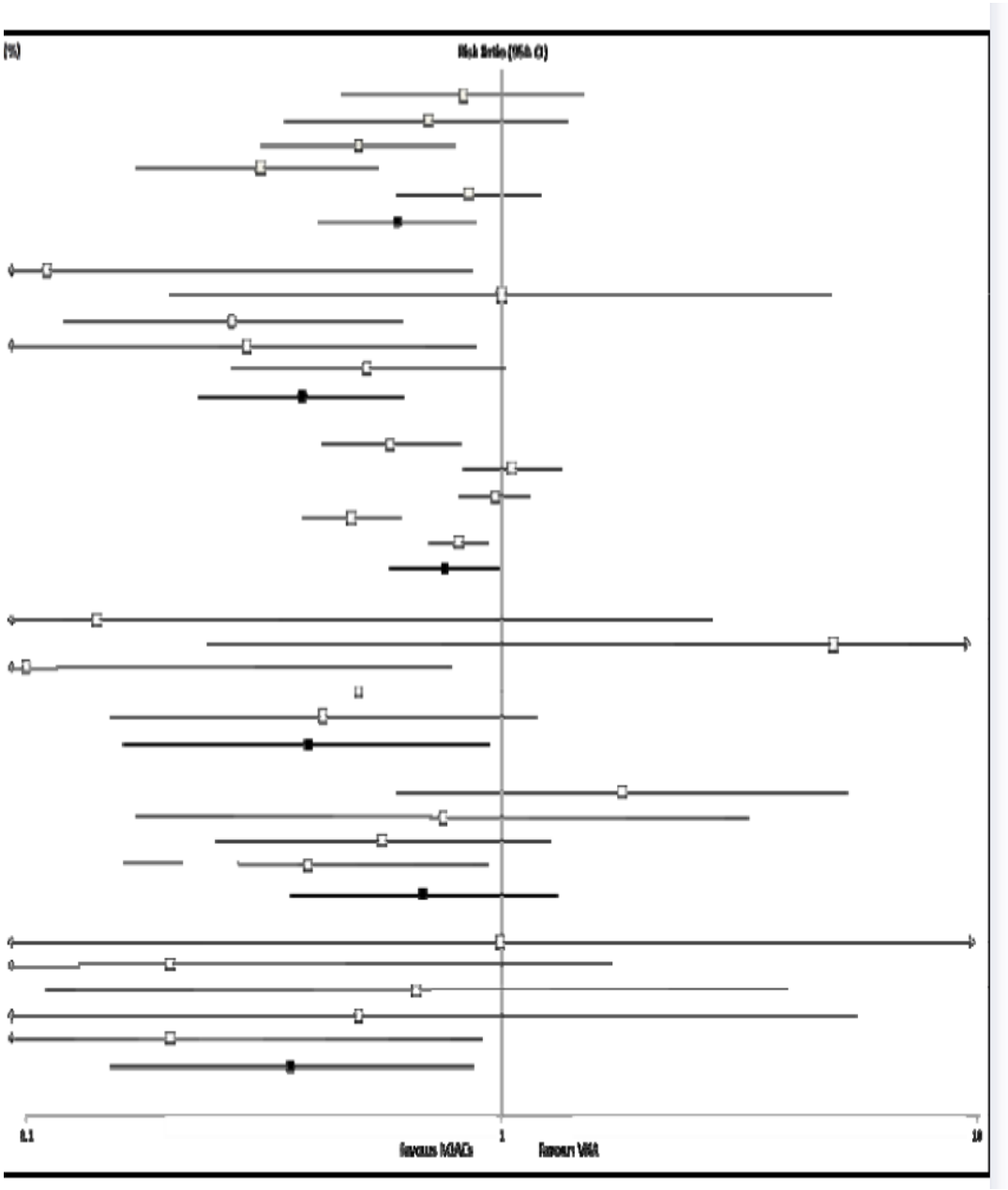
Study or subgroup	DOAC Events	DOAC Total	Standard treatment Events	Standard treatment Total	Weight	Risk ratio M-H, random, 95% CI
1 Index PE						
0102. POOL RE-COVER I–II	18	795	21	807	5.6%	0.87 (0.47, 1.62)
04. EINSTEIN PE	50	2,419	44	2,413	13.4%	1.13 (0.76, 1.69)
05. AMPLIFY	21	930	24	906	6.4%	0.85 (0.48, 1.52)
06. HOKUSAI-VTE	47	1,650	65	1,669	15.8%	0.73 (0.51, 1.06)
Subtotal (95% CI)		**5,794**		**5,795**	**41.2%**	**0.88 (0.70, 1.11)**
Total events	136		154			
Heterogeneity: tau^2 =0.00; chi^2 =2.51, df =3 (P=0.47); I^2 =0%						
Test for overall effect: Z =1.06 (P=0.29)						
2 Index DVT						
0102. POOL RE-COVER I–II	42	1,758	34	1,747	10.8%	1.23 (0.78, 1.92)
03. EINSTEIN DVT	36	1,731	51	1,718	12.1%	0.70 (0.46, 1.07)
05. AMPLIFY	38	1,761	47	1,798	12.1%	0.83 (0.54, 1.26)
06. HOKUSAI-VTE	83	2,468	81	2,453	23.8%	1.02 (0.75, 1.38)
Subtotal (95% CI)		**7,718**		**7,716**	**58.8%**	**0.93 (0.75, 1.16)**
Total events	199		213			
Heterogeneity: tau^2 =0.01; chi^2 =3.87, df =3 (P=0.28); I^2=0%						
Test for overall effect: Z=0.64 (P=0.52)						
Test for subgroup differences: chi^2 =0.10, df =1 (P=0.76), I^2=0%						



Gomez-Outes. Vasc Health Risk Manag 2014;10:627

Metanàlisis Tractament TEV amb els AODs

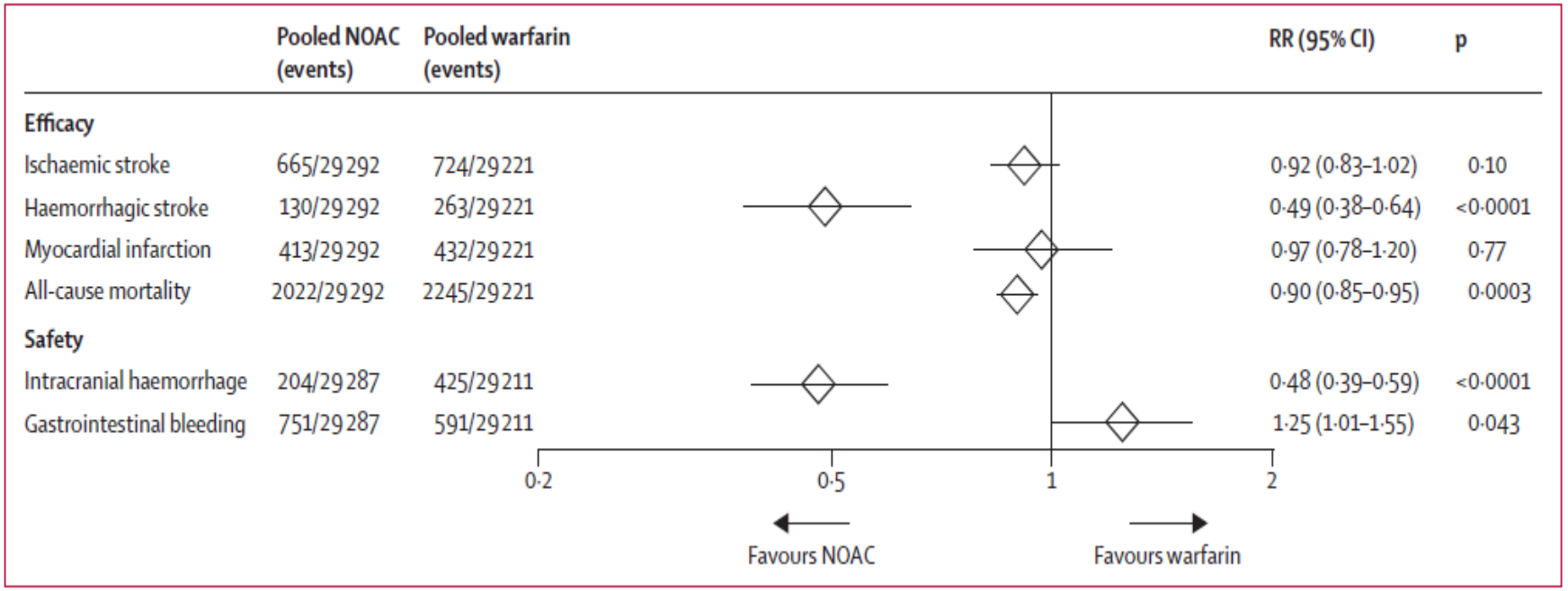
- **Major bleeding**
  - Re-Cover (dabigatran)
  - EINSTEIN DVT (rivaroxaban)
  - EINSTEIN EP (rivaroxaban)
  - Amplify (apixaban)
  - Hokusai (edoxaban)
  - Subtotal
- **Non-fatal bleeding at a critical site**
  - Re-Cover (dabigatran)
  - EINSTEIN DVT (rivaroxaban)
  - EINSTEIN EP (rivaroxaban)
  - Amplify (apixaban)
  - Hokusai (edoxaban)
  - Subtotal
- **Clinically relevant non-major bleeding**
  - Re-Cover (dabigatran)
  - EINSTEIN DVT (rivaroxaban)
  - EINSTEIN EP (rivaroxaban)
  - Amplify (apixaban)
  - Hokusai (edoxaban)
  - Subtotal
- **Non-fatal intracranial bleeding**
  - Re-Cover (dabigatran)
  - EINSTEIN DVT (rivaroxaban)
  - EINSTEIN EP (rivaroxaban)
  - Amplify (apixaban)
  - Hokusai (edoxaban)
  - Subtotal
- **Major gastrointestinal bleeding**
  - Re-Cover (dabigatran)
  - EINSTEIN DVT (rivaroxaban)
  - EINSTEIN EP (rivaroxaban)
  - Amplify (apixaban)
  - Hokusai (edoxaban)
  - Subtotal
- **Fatal bleeding**
  - Re-Cover (dabigatran)
  - EINSTEIN DVT (rivaroxaban)
  - EINSTEIN EP (rivaroxaban)
  - Amplify (apixaban)
  - Hokusai (edoxaban)



Hulle. J Thromb Haemost. 2014

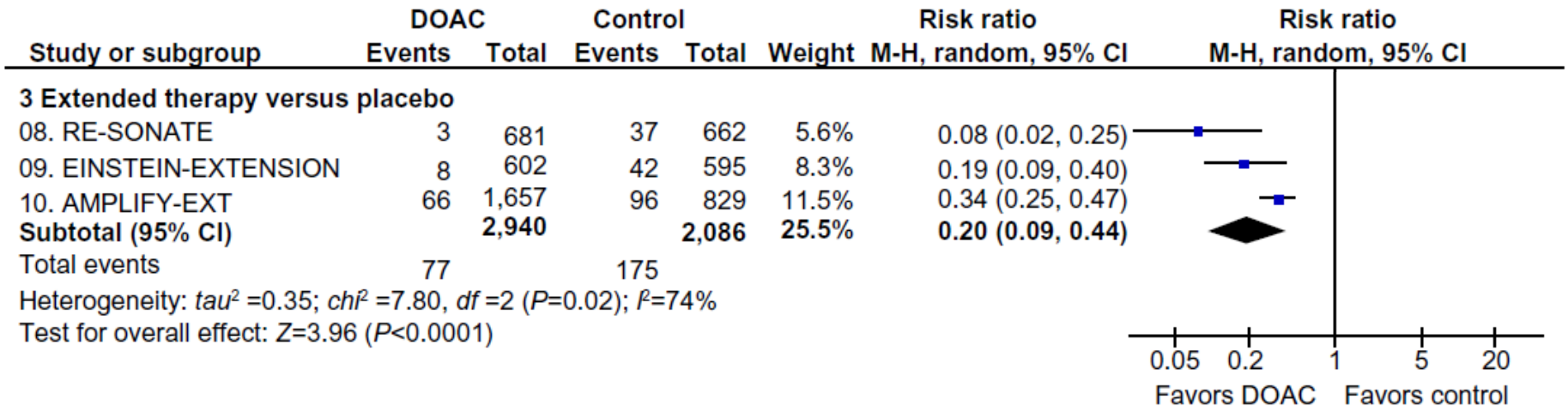
AODs en la fibril·lació auricular: un metanàlisis

Secondary efficacy and safety outcomes



Ruff. www.thelancet.com Published online December 4, 2013

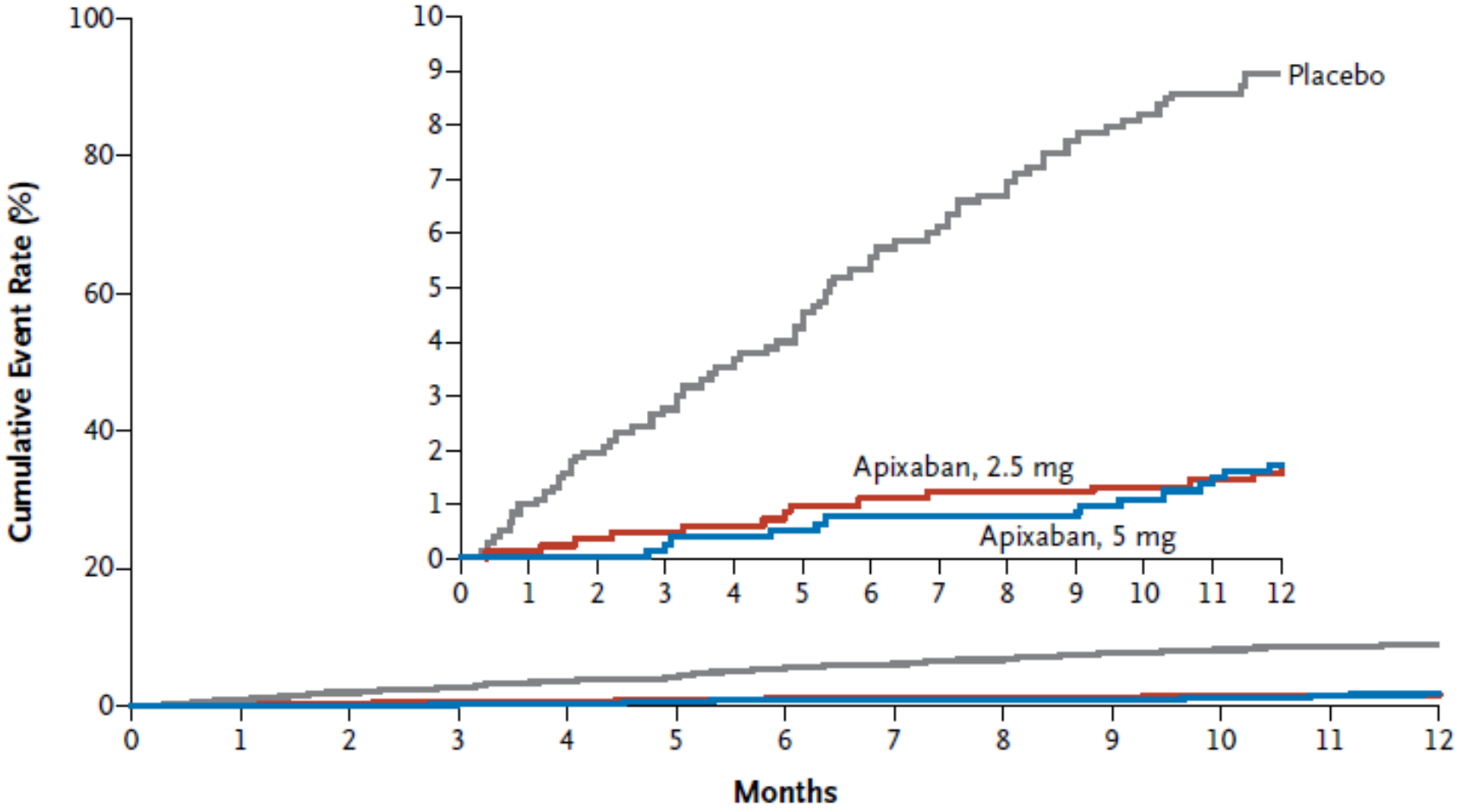
Recurrent VTEin clinical trials with DOAC in the treatment of VTE.



Gomez-Outes. Vasc Health Risk Manag 2014;10:627

Apixaban for Extended Treatment of venous Thromboembolism

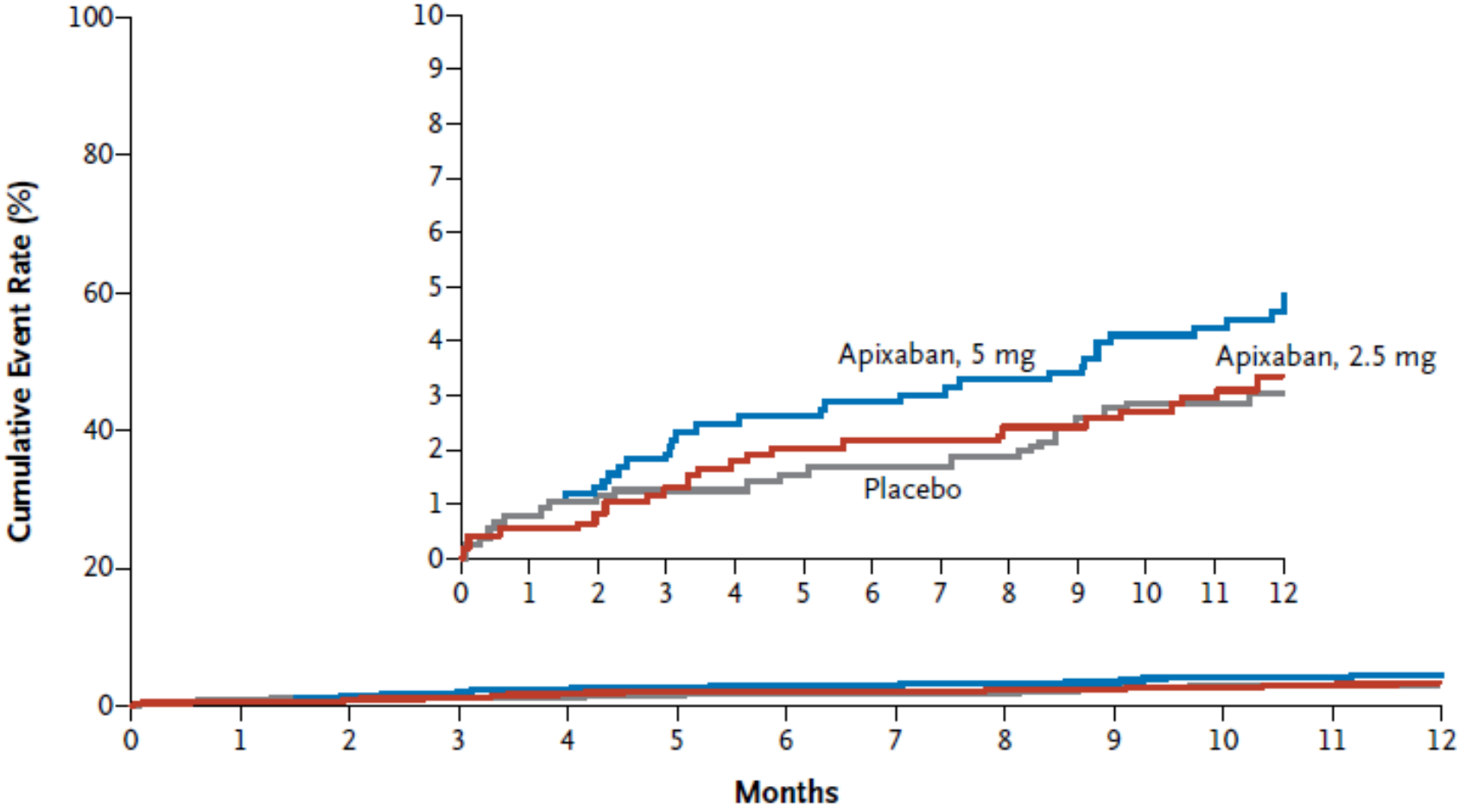
Symptomatic Recurrent VTE or VTE-Related Death



Agnelli. N Engl J Med 2013; 368:699

Apixaban for Extended Treatment of venous Thromboembolism

Major or Clinically Relevant Nonmajor Bleeding



Agnelli. N Engl J Med 2013; 368:699

EINSTEIN: criterios de exclusión

- Trombectomía, filtro VCI, o uso de trombolíticos en el tratamiento del episodio de TEV actual
- Otras indicaciones de anticoagulación
- Más de 48 horas de tratamiento pre-randomización con dosis terapéuticas de anticoagulantes o más de una dosis de AVK previa a la randomización
- Filtrado glomerular <30 ml/min
- Hepatopatía significativa (hepatitis aguda, hepatitis crónica activa, cirrosis) o ALAT >3x ULN
- Esperanza de vida <3 meses
- Sangrado activo o elevado riesgo de sangrado que contraindique el tratamiento con enoxaparina o AVK.
- Presión sistólica >180 mmHg or diastólica >110 mmHg
- Posibilidad de embarazo sin medidas anticonceptivas, embarazo o lactancia.
- Uso concomitante de inhibidores o potenciadores potentes del CYP3A4

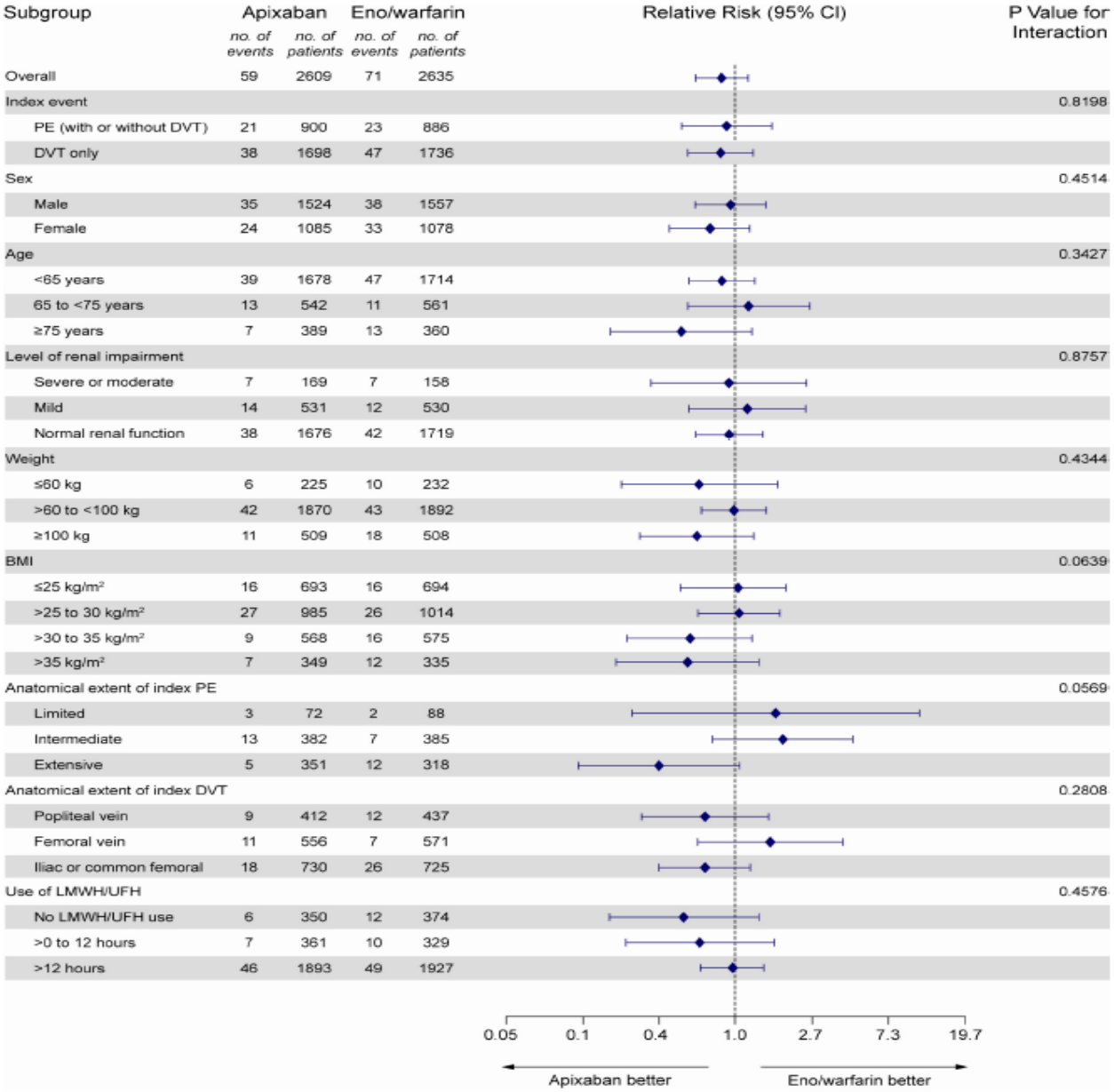
Einstein investigators. N Engl J Med 2010; 363: 2499

EINSTEIN EP – Característiques dels pacients

	Rivaroxaban (n=2419)	Enoxaparina/ AVK (n=2413)
Edat	57.9 ± 7.3	57.5 ± 7.2
Filtrat glomerular (mL/min)		
<30	4 (0.2)	2 (<0.1)
30-49	207 (8.6)	191 (7.9)
50-79	637 (26.3)	593 (24.6)
≥80	1555 (64.3)	1617 (67.0)
Pes corporal (kg)		
≤50	38 (1.6)	43 (1.8)
50-100	2034 (84.1)	2010 (83.3)
>100	345 (14.3)	359 (14.9)
Factors de risc		
TVP no provocada	64.7	64.3
càncer actiu	4.7	4.5
Antecedents previs de TEV	18.8	20.3
Extensió		
Limitada (<25% d0un lòbul)	12.8	12.4
intermèdia	57.5	59.0
Extensa (>25% vasos pulmonars)	24.7	23.9

Einstein investigators. N Engl J Med 2010; 363: 2499

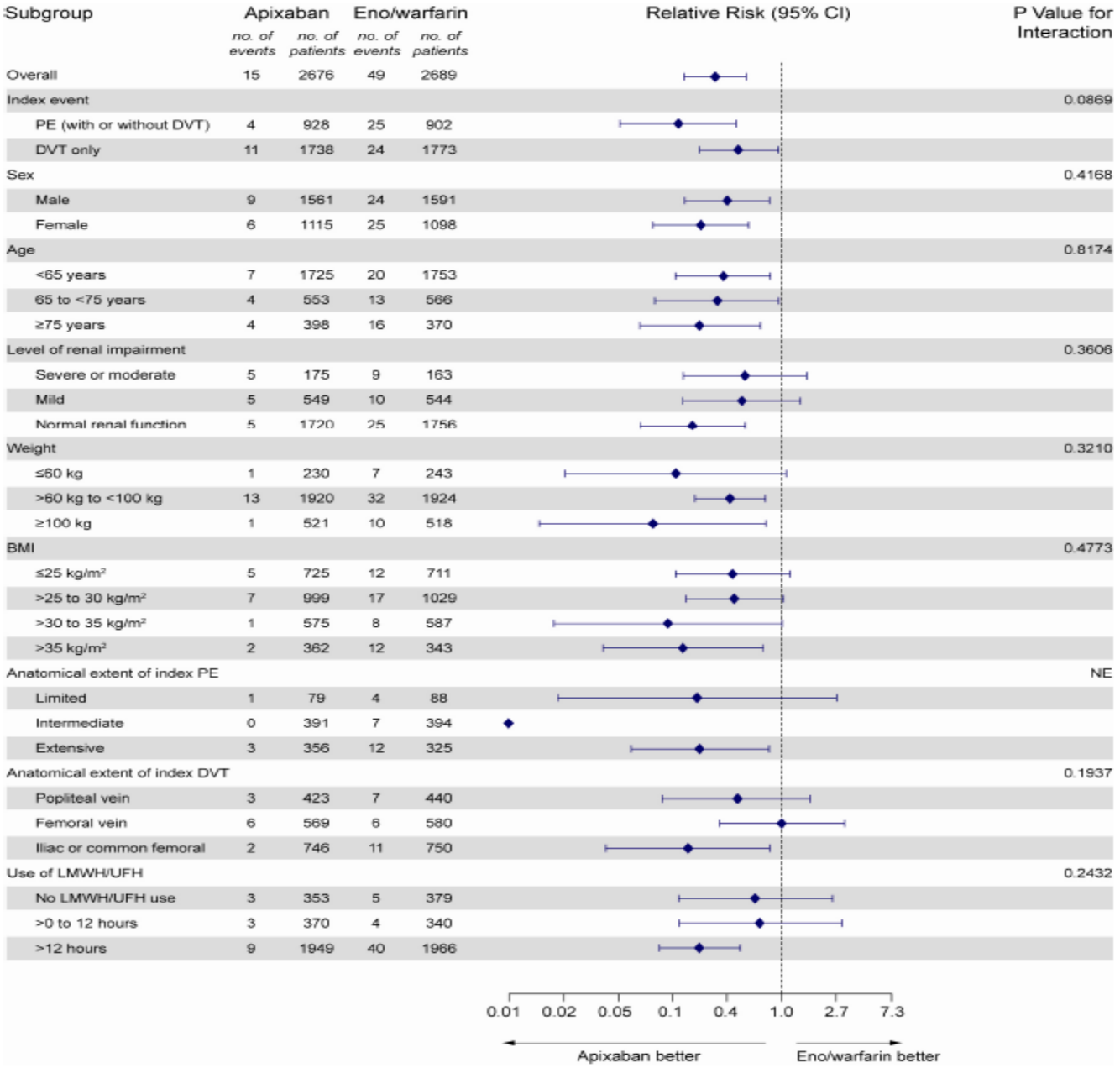
RR of the Primary Efficacy Outcomes According to Prespecified Subgroups.



Subgroup	Apixaban no. of events	Apixaban no. of patients	Eno/warfarin no. of events	Eno/warfarin no. of patients	P Value for Interaction
Overall	59	2609	71	2635	
Index event					0.8198
PE (with or without DVT)	21	900	23	886	
DVT only	38	1698	47	1736	
Sex					0.4514
Male	35	1524	38	1557	
Female	24	1085	33	1078	
Age					0.3427
<65 years	39	1678	47	1714	
65 to <75 years	13	542	11	561	
≥75 years	7	389	13	360	
Level of renal impairment					0.8757
Severe or moderate	7	169	7	158	
Mild	14	531	12	530	
Normal renal function	38	1676	42	1719	
Weight					0.4344
≤60 kg	6	225	10	232	
>60 to <100 kg	42	1870	43	1892	
≥100 kg	11	509	18	508	
BMI					0.0639
≤25 kg/m²	16	693	16	694	
>25 to 30 kg/m²	27	985	26	1014	
>30 to 35 kg/m²	9	568	16	575	
>35 kg/m²	7	349	12	335	
Anatomical extent of index PE					0.0569
Limited	3	72	2	88	
Intermediate	13	382	7	385	
Extensive	5	351	12	318	
Anatomical extent of index DVT					0.2808
Popliteal vein	9	412	12	437	
Femoral vein	11	556	7	571	
Iliac or common femoral	18	730	26	725	
Use of LMWH/UFH					0.4576
No LMWH/UFH use	6	350	12	374	
>0 to 12 hours	7	361	10	329	
>12 hours	46	1893	49	1927	

Agnelli. N Engl J Med. 2013;369:799

RR of the Primary Safety Outcomes According to Prespecified Subgroups.



Agnelli. N Engl J Med. 2013;369:799

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]	Ref[c]
PE without shock or hypotension (intermediate-or low-risk)[d]			
Anticoagulation: combination of parenteral treatment with VKA			
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is in progress.	I	C	352
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A	273, 274, 281, 353
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0).	I	B	352, 354

European Heart Journal (2014) 35, 3033–3080

Anticoagulation: new oral anticoagulants			
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B	296
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B	297
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) is recommended following acute-phase parenteral anticoagulation.	I	B[e]	293, 294
As an alternative to VKA treatment, administration of edoxaban* is recommended following acute-phase parenteral anticoagulation.	I	B	298
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.[f]	III	A	293, 295–298

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

Recommendations for acute phase treatment

Recommendations	Class[a]	Level[b]	Ref[c]
PE with shock or hypotension (high-risk)			
It is recommended that intravenous anticoagulation with UFH be initiated without delay in patients with high-risk PE.	I	C	
Thrombolytic therapy is recommended.	I	B	168
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.[d]	I	C	313
Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed.[d]	IIa	C	

European Heart Journal (2014) 35, 3033–3080

Table 4 Summary of prescribing information of the DOAC in the treatment of VTE

Characteristic	Dabigatran etexilate (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)*
Dosing				
Initial therapy	LMWH or fondaparinux for at least 5 days	Rivaroxaban 15 mg BID for 21 days (3 weeks)	Apixaban 10 mg BID for 7 days (1 week)	LMWH or fondaparinux for at least 5 days
Long-term therapy	Dabigatran 150 mg BID	Rivaroxaban 20 mg OD (15 mg OD in patients with CrCl 15–50 judged to be at high risk of bleeding) from day 22 onward	Apixaban 5 mg BID from day 8 onward	Edoxaban 60 mg OD (30 mg in patients with a CrCl 30–50 mL/min, a body weight ≤60 kg or concomitant treatment with potent Pg-p inhibitors)
Extended therapy#	Same posology as long-term therapy	Same posology as long-term therapy	Dose reduction to 2.5 mg BID is recommended following completion of at least 6 months of anticoagulation	Same as long-term therapy but no clinical experience is available beyond 12 months‡
Intake with food	Not necessary	Mandatory (39% decrease in absorption when administered without food)	Not necessary	Not necessary
Absorption with proton pump inhibitors	30% decrease (no dose-adjustment necessary)	Not significantly altered	Not significantly altered	Not significantly altered
Relevant pharmacokinetic interactions	– Potent Pg-p inhibitors (contraindicated), – Potent Pg-p inducers (not recommended)	– Potent inhibitors of both P-gp and CYP3A4 (not recommended), – Potent inducers of both P-gp and CYP3A4 (use with caution)	– Potent inhibitors or inducers of both P-gp and CYP3A4 (use with caution)	– Potent Pg-p inhibitors (dose reduction) (see long-term therapy) – Potent Pg-p inducers (no specific recommendations available)
Relevant pharmacodynamic interactions	Drugs that alter hemostasis¶	Drugs that alter hemostasis¶	Drugs that alter hemostasis¶	Drugs that alter hemostasis¶
Use in renal insufficiency	Contraindicated in severe renal insufficiency (CrCl <30 mL/min)	Not recommended if CrCl <15 mL/min Dose-adjustment in some cases (see long-term therapy above)	Not recommended if CrCl <15 mL/min	Dose adjustment in some cases (see long-term therapy above). No data available in severe renal insufficiency)

Gomez-Outes. Vasc Health Risk Manag 2014;10:627

Interval de seguretat de supressió dels AODs previ a procediments endoscòpics

(considerats fonamentalment d'elevat risc hemorràgic**)**

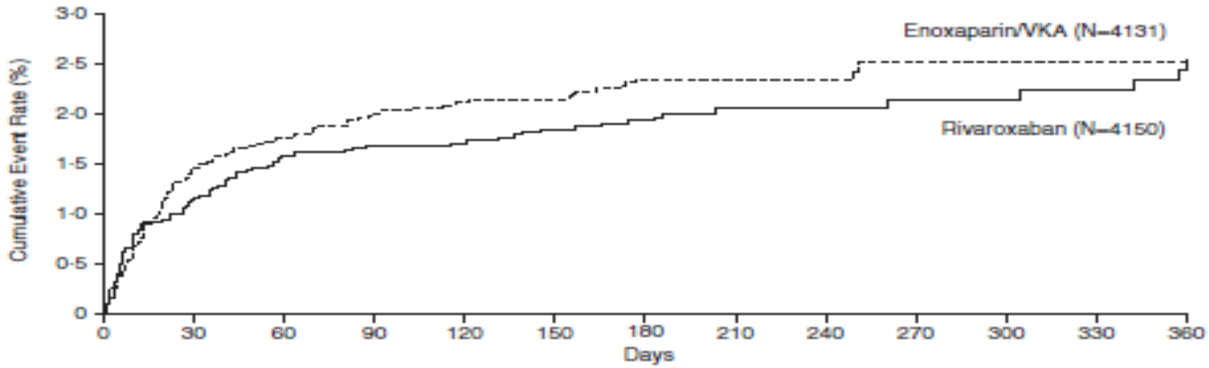
FG (mL/min)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Dabigatran (Pradaxa)
>50	2d	3d	4d
30-50	3d	4d	5d

Si elevat risc tromboembòlic cal considerar l'ús de HBPM

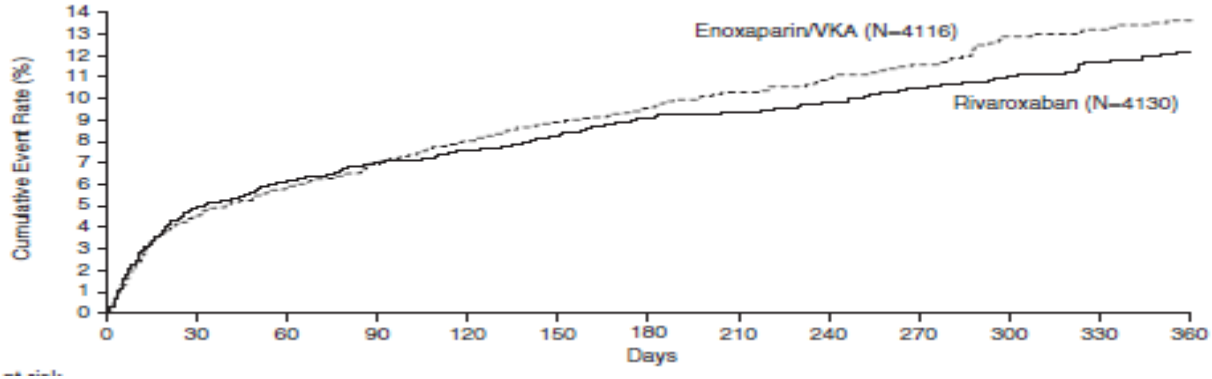
Això és tot, companys

Estudis Einstein (rivaroxaban): metanàlisis

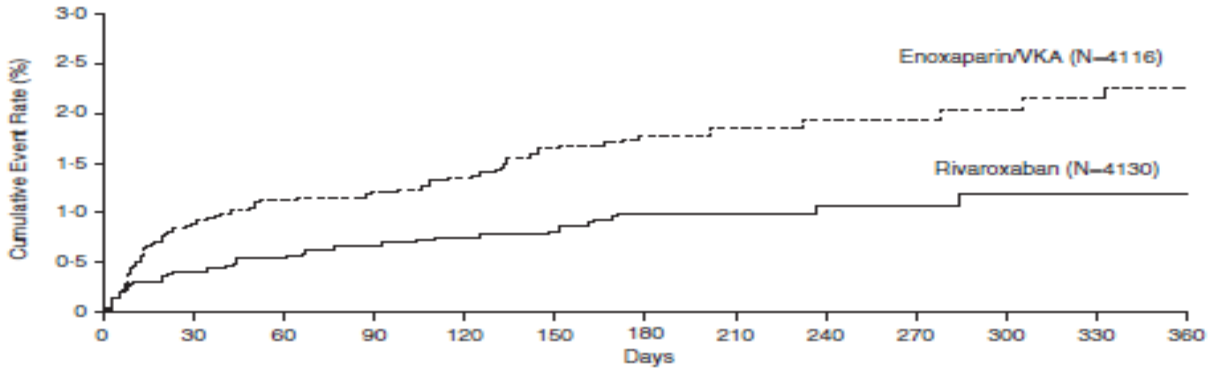
Primary efficacy outcome



Principal safety outcome



Major bleeding

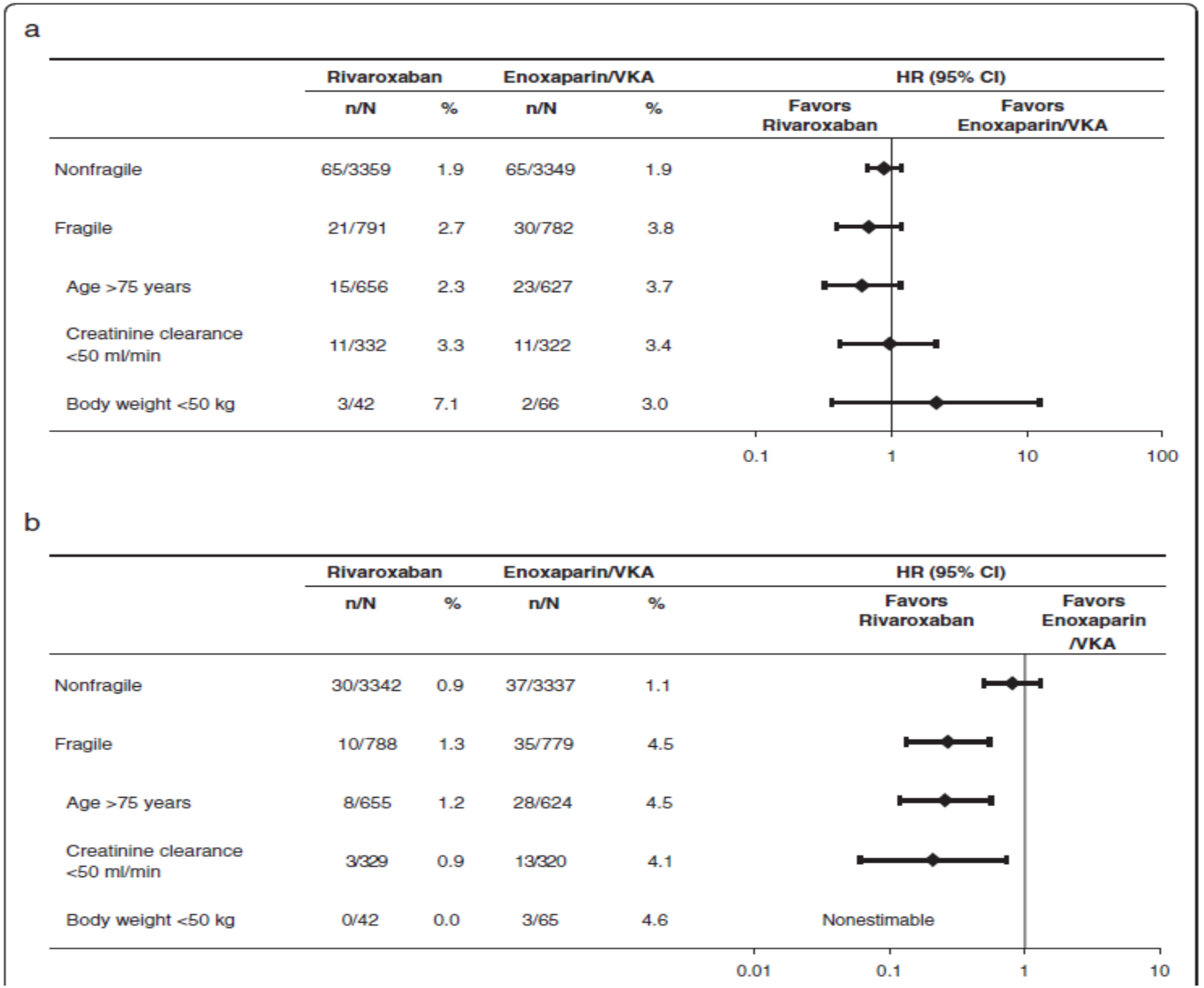


Prins. Thrombosis Journal 2013, 11:21

Estudis Einstein (rivaroxaban): metanàlisis

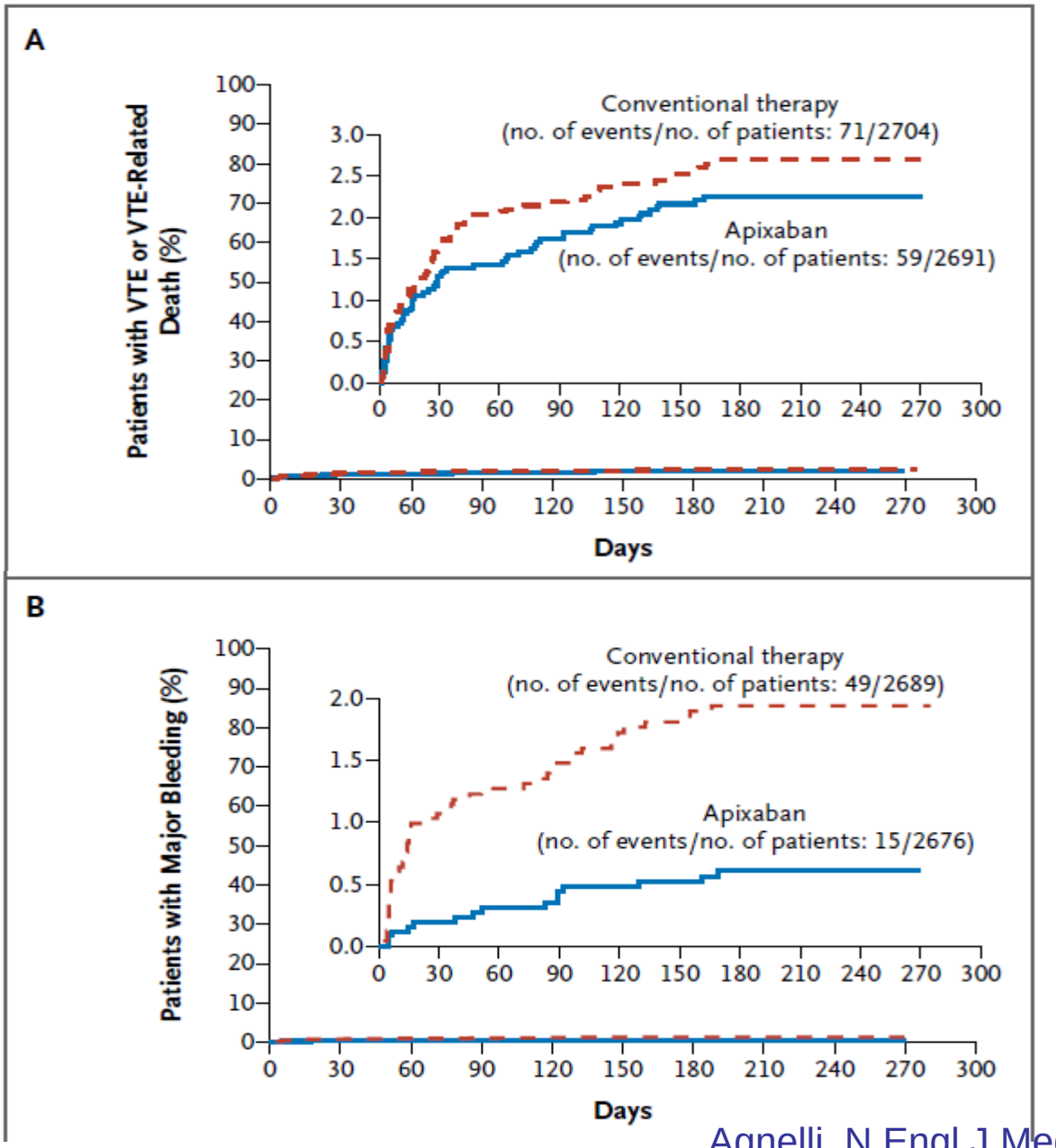
Primary efficacy

Major bleeding



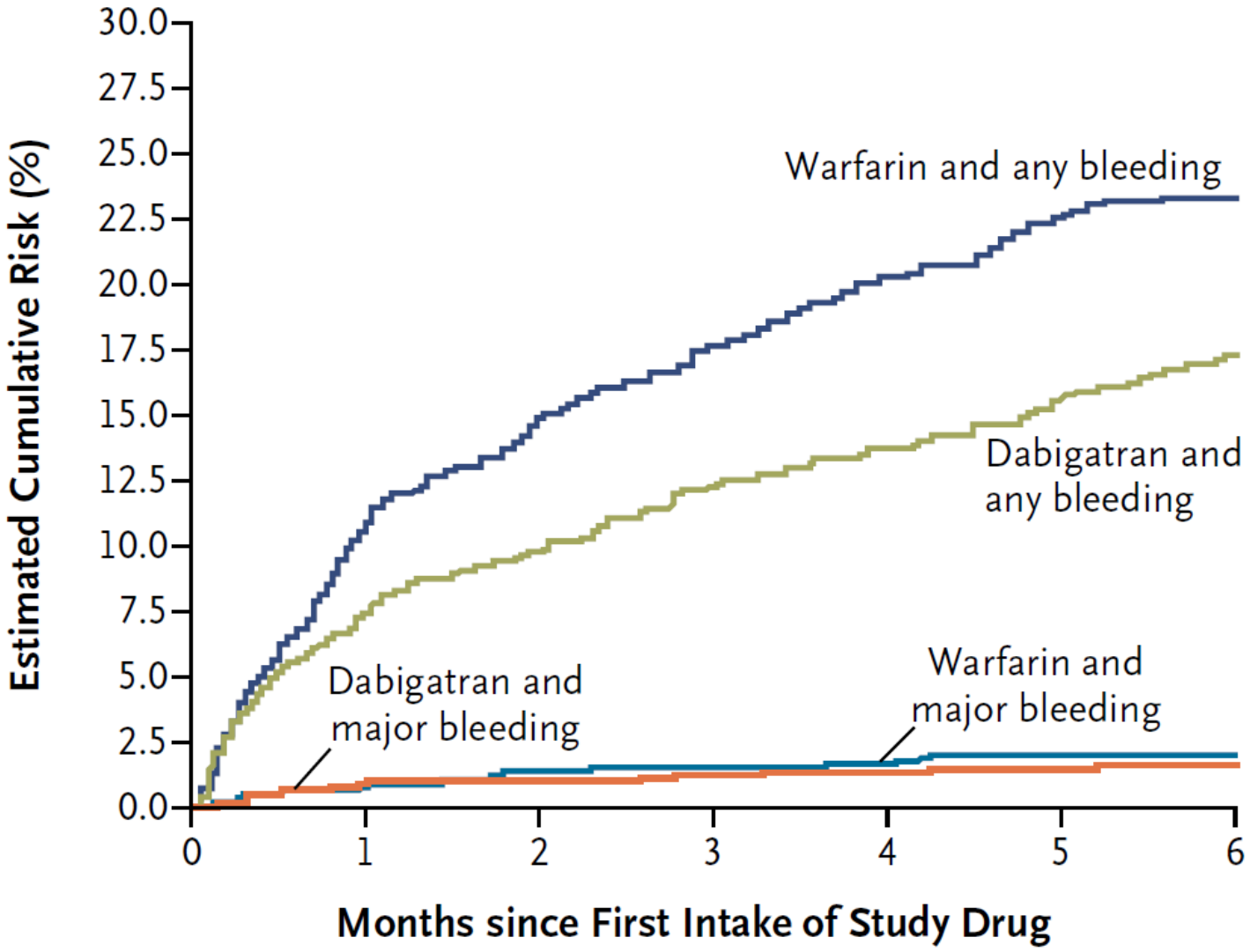
Prins. Thrombosis Journal 2013, 11:21

Estudi Amplify (Apixaban)



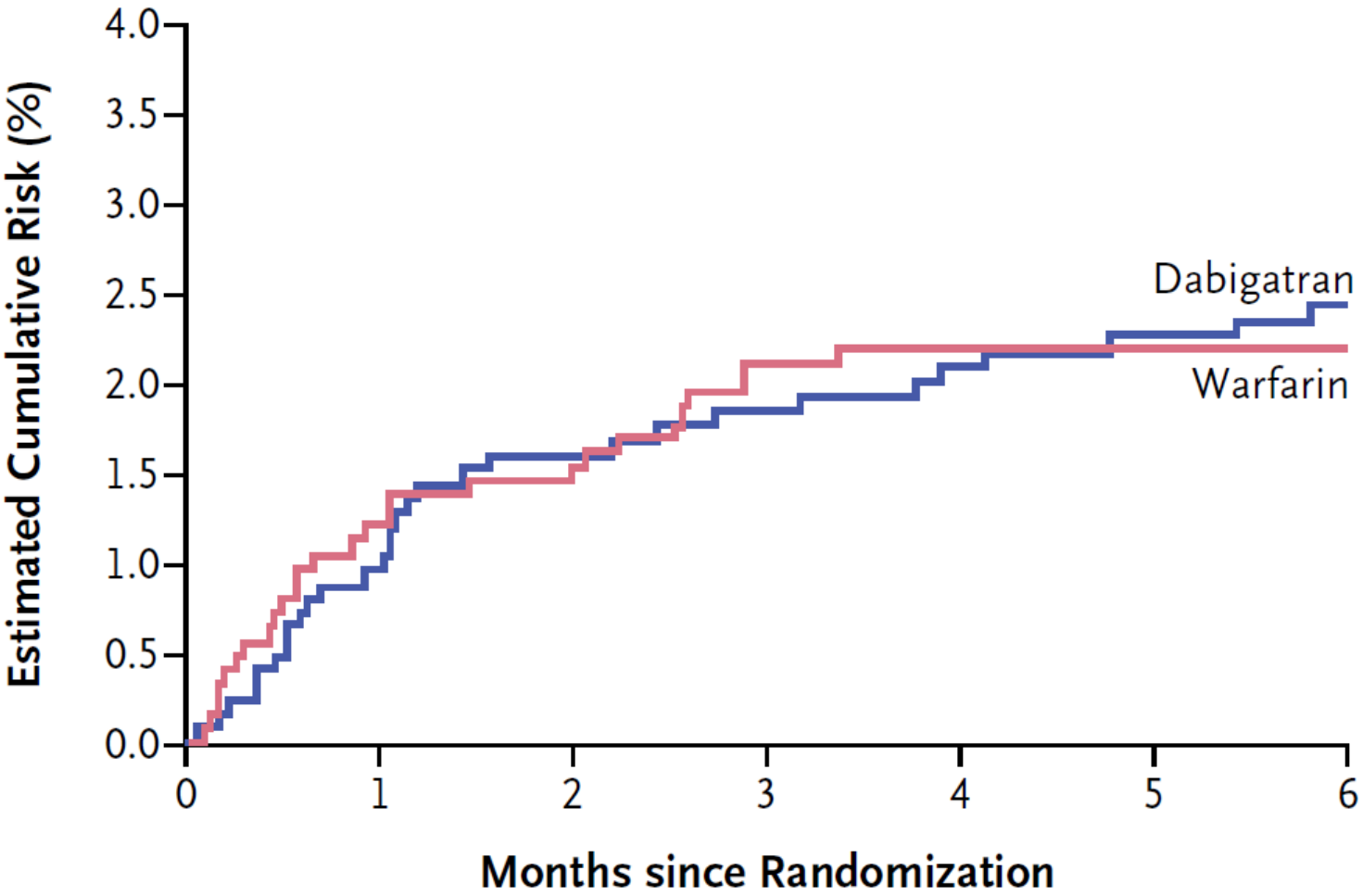
Agnelli. N Engl J Med. 2013;369:799

Estudi Re-Cover



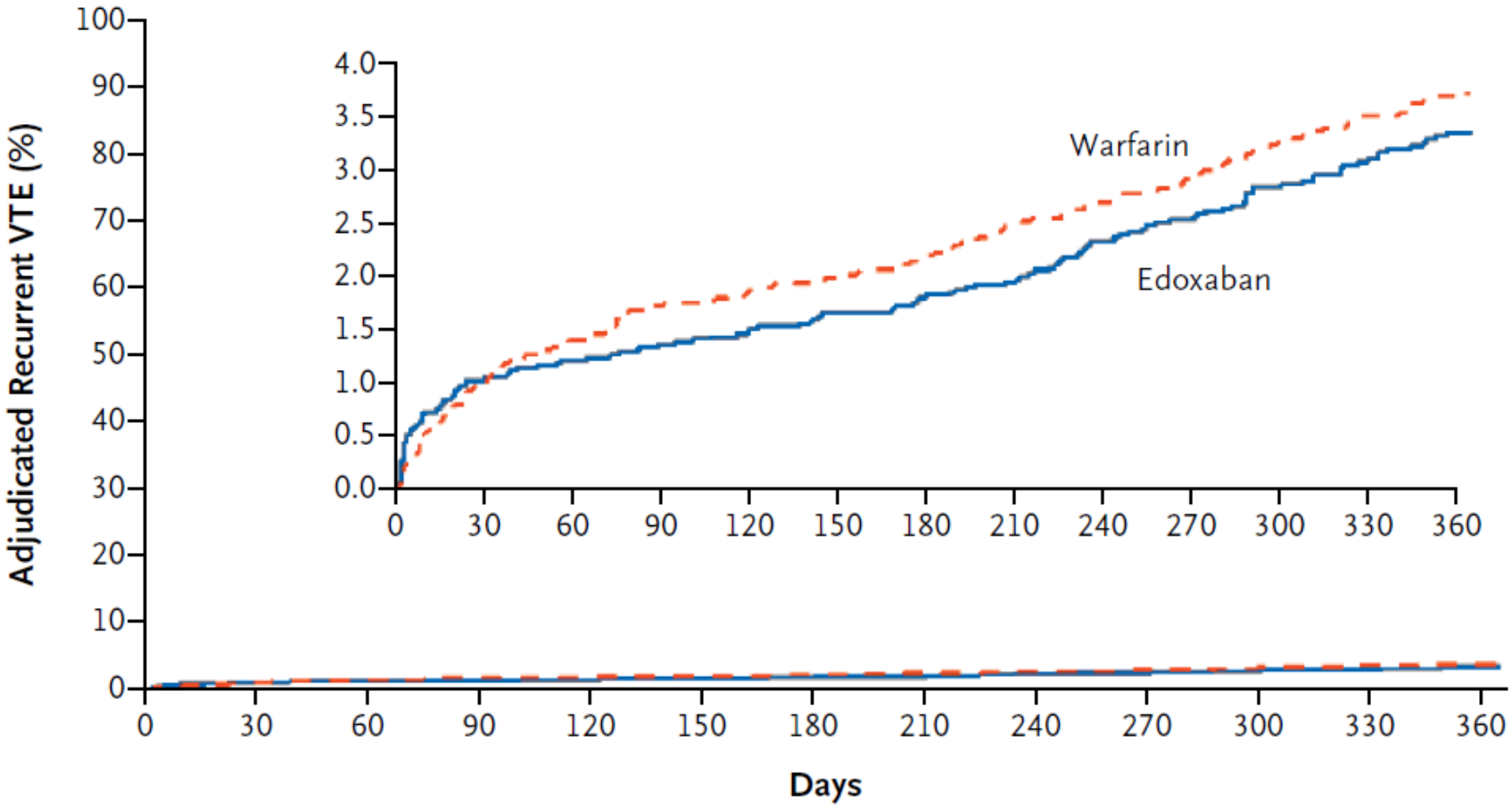
Schulman. NEMJ 2009; 361: 2342

Estudi Re-Cover



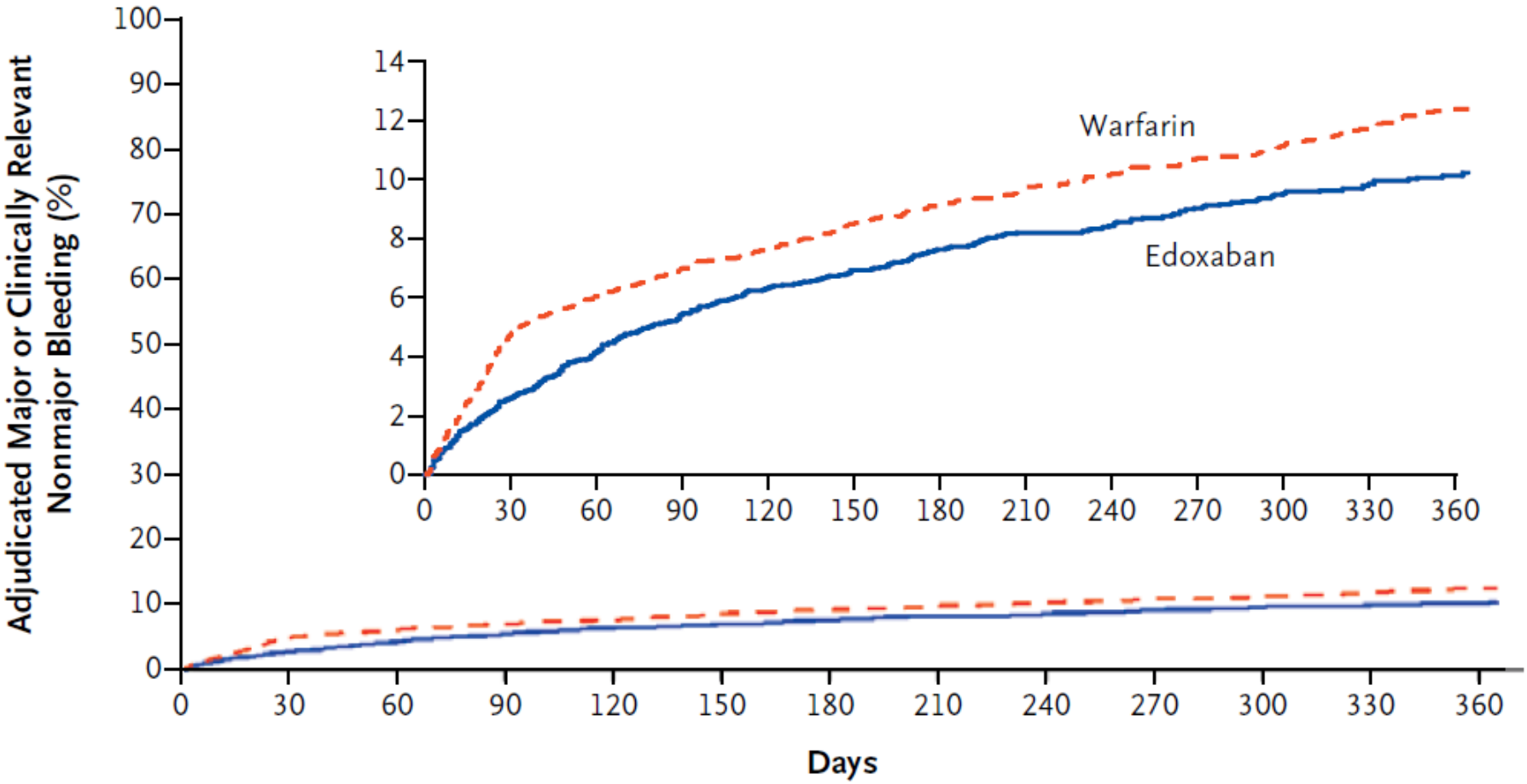
Schulman. NEMJ 2009; 361: 2342

Estudi Hokusai



Hokusai VET-investigators. NEJM 2014; 369: 1406

Estudi Hokusai



Hokusai VET-investigators. NEJM 2014; 369: 1406