Nuevos anticoagulantes orales

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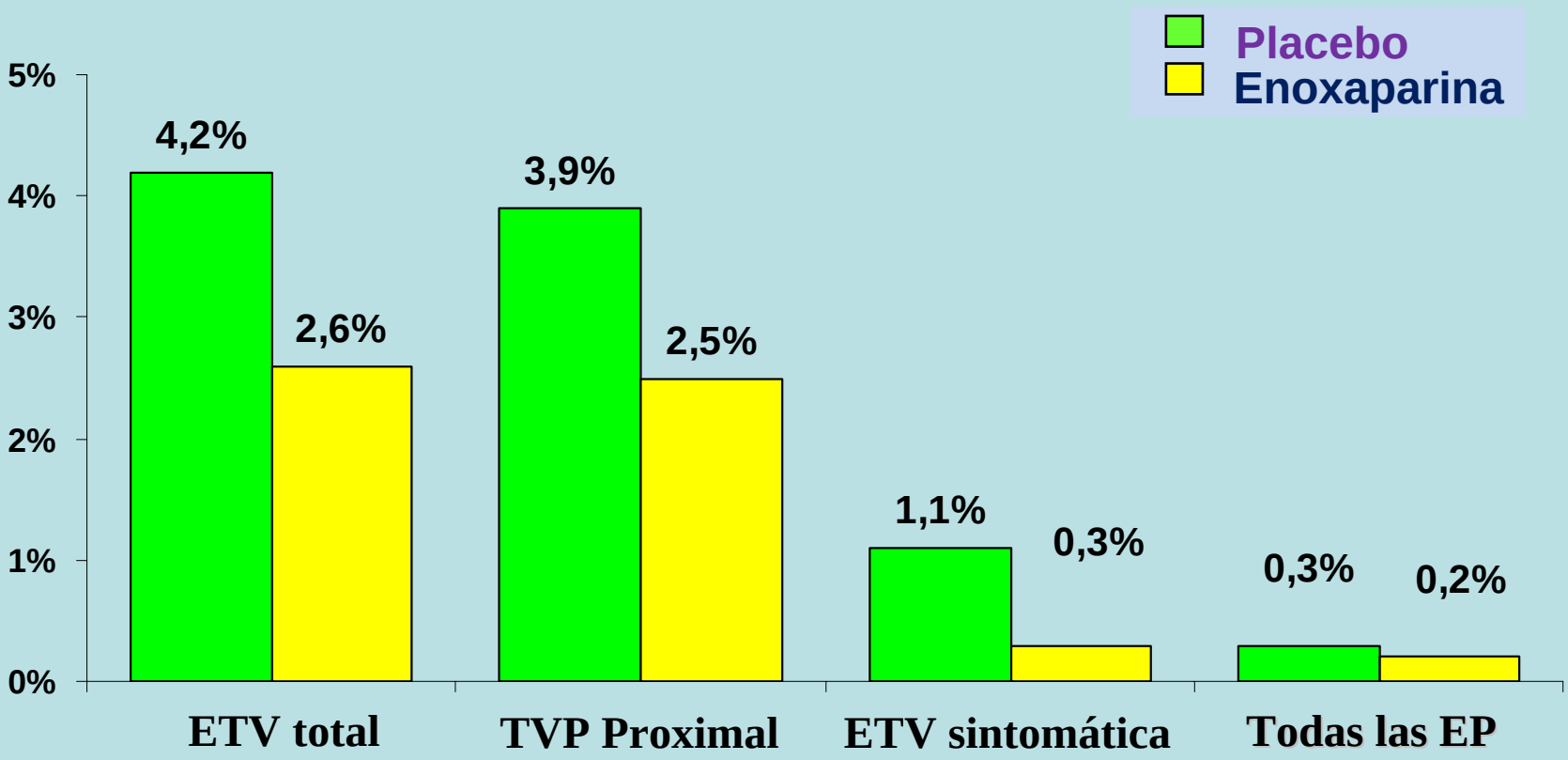
Extended-Duration Venous Thromboembolism Prophylaxis in Acutely Ill Medical Patients With Recently Reduced Mobility

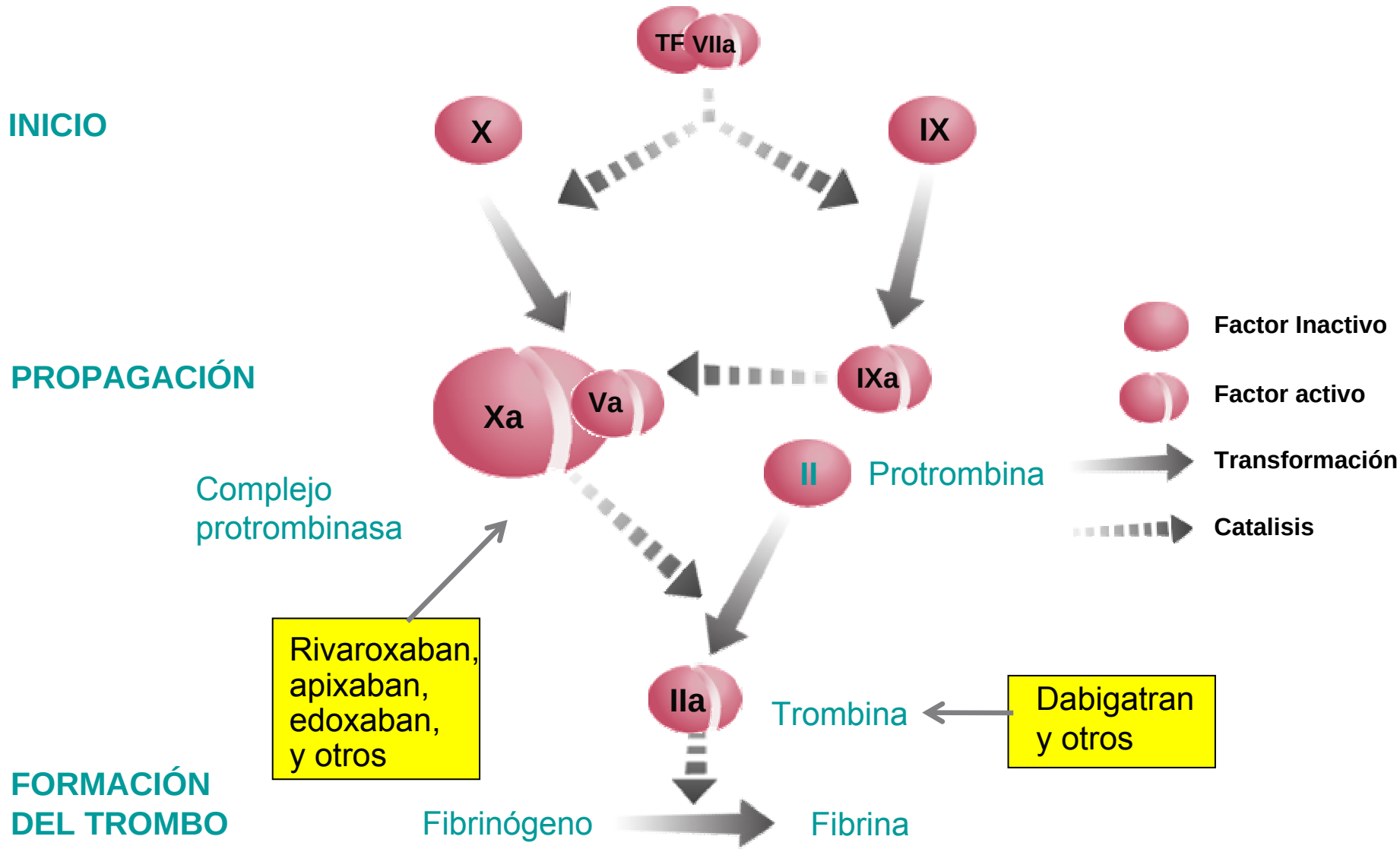
A Randomized Trial

Russell D. Hull, MBBS; Sebastian M. Schellong, MD; Victor F. Tapson, MD; Manuel Monreal, MD; Meyer-Michel Samama, MD, PharmD; Philippe Nicol, PhD; Eric Vicaut, MD, PhD; Alexander G.G. Turpie, MD; and Roger D. Yusen, MD, MPH, for the EXCLAIM (Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization) study*



Ann Intern Med. 2010;153:8-18.

Nuevos anticoagulantes en Fase III



Adaptado de: Kubitza D and Haas S. *Expert Opin Investig Drugs* 2006;15:843–855

VTE treatment: clinical studies

	Phase II	Phase III
Dabigatran Oral, direct thrombin inhibitor		**RE-COVER & RE-COVER II** 5–10 days pre-treatment with LMWH bridging to dabigatran or VKA for 6 months **RE-MEDY** 3–6 months' treatment with approved anticoagulant; switch to dabigatran or VKA **RE-SONATE** 6–18 months' VKA treatment followed by 6 months dabigatran or placebo
Rivaroxaban Oral, direct Factor Xa inhibitor	**EINSTEIN DVT** Rivaroxaban vs LMWH/UFH followed by VKA **ODIXa-DVT** Rivaroxaban vs enoxaparin followed by VKA	**EINSTEIN DVT/PE** Rivaroxaban for 3, 6 or 12 months vs enoxaparin for ≥5 days followed by VKA for 3, 6, or 12 months **EINSTEIN EXT** Pre-treatment with rivaroxaban or VKA for 6 or 12 months followed by rivaroxaban or placebo for 6 or 12 months
Apixaban Oral, direct Factor Xa inhibitor	**Botticelli-DVT** Apixaban vs LMWH or fondaparinux followed by VKA	**AMPLIFY** Apixaban 10 mg bid followed by 5 mg bid for 6 months vs enoxaparin followed by VKA **AMPLIFY-EXT** Apixaban 2.5 mg bid or 5 mg bid for extended 12 months period vs placebo

	Dabigatran	Rivaroxaban	Apixaban
Mechanism of action	Direct Thrombin inhibitor	Direct FXa inhibitor	Direct FXa inhibitor
Oral availability	6.5 %	80 %	~50 %
Route of administration	Oral	Oral	Oral
Dosing	OD	OD	BID
Pro-drug	Yes	No	No
Food effect	No	No	No
Renal Clearance	85 %	36 %	~27 %
Mean Half-Life (T1/2)	14–17 h (patients)	7–11 h	~12h
Tmax	0.5–2 h	2–4 h	3 h
Drug interactions	P-gp inhibitors P-gp inducers Amiodarone	CYP 3A4 and P-gp inhibitors CYP 3A4 inducers	CYP 3A4 and P-gp inhibitors CYP 3A4 inducers

DABIGATRAN

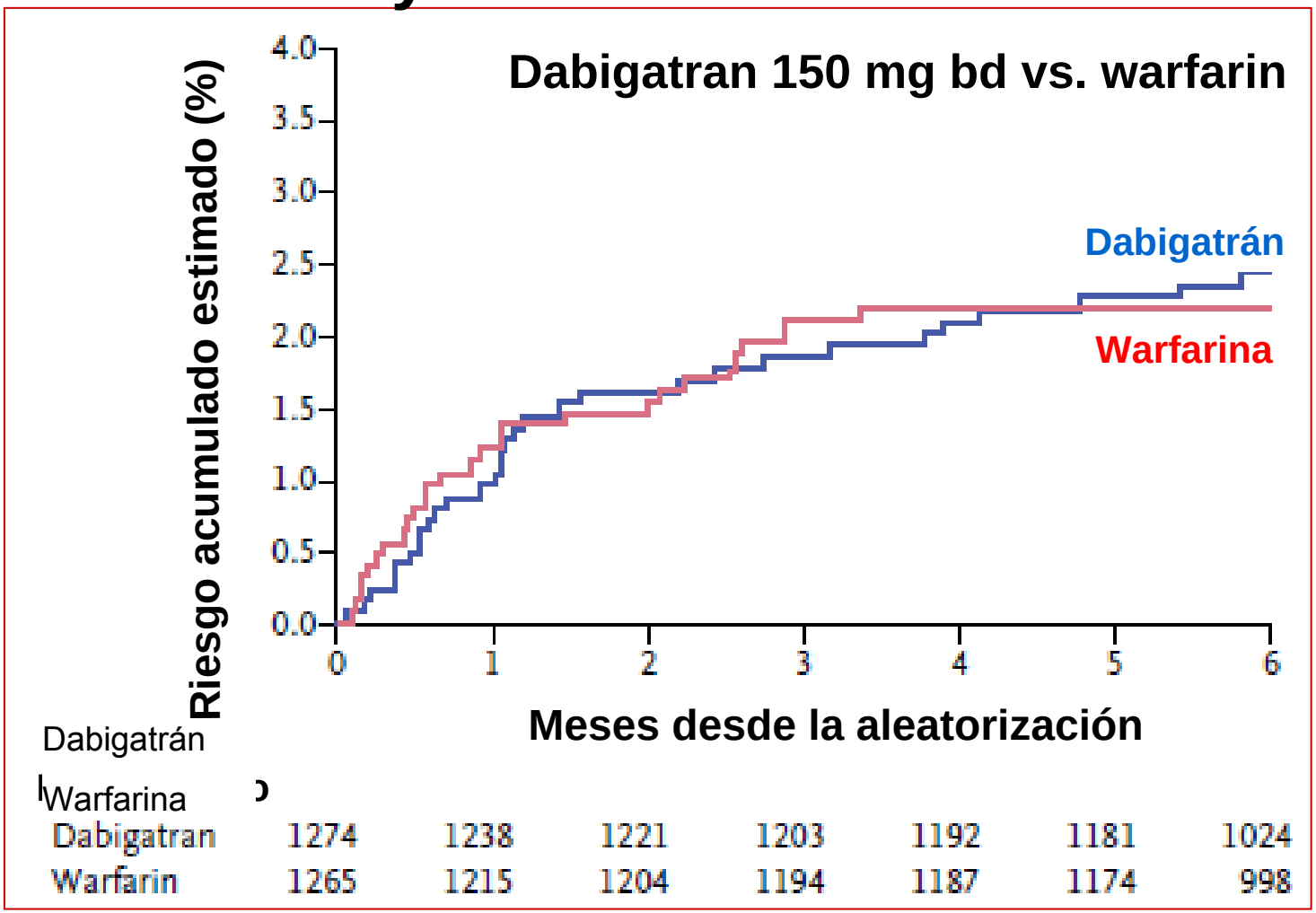
- Oral prodrug, converted to dabigatran, a potent reversible direct **thrombin** inhibitor (DTI)
- Rapid onset of action
- Half life of 12-17 h,
- ~ 80% renally excreted
- Predictable and consistent anticoagulant effects
- Low potential for drug-drug interactions, no drug-food interactions
- No requirement for routine coagulation monitoring

Cirugía ortopédica mayor:

- **ClCr <30 mL/min: NO**
- **ClCr 30-50 mL/min: OJO**
- **Catéter epidural: NO**
- **Edad >75 años: 150 mg/día**
- **GOT/GPT >2 veces: NO**
- **Amiodarona: 150 mg día**
- **Verapamilo o rifampicina: OJO**
- **Clopidogrel, AINEs: NO**

RECOVER™
Study of treatment of venous thromboembolism

Riesgo acumulado de recurrencias y muerte relacionada



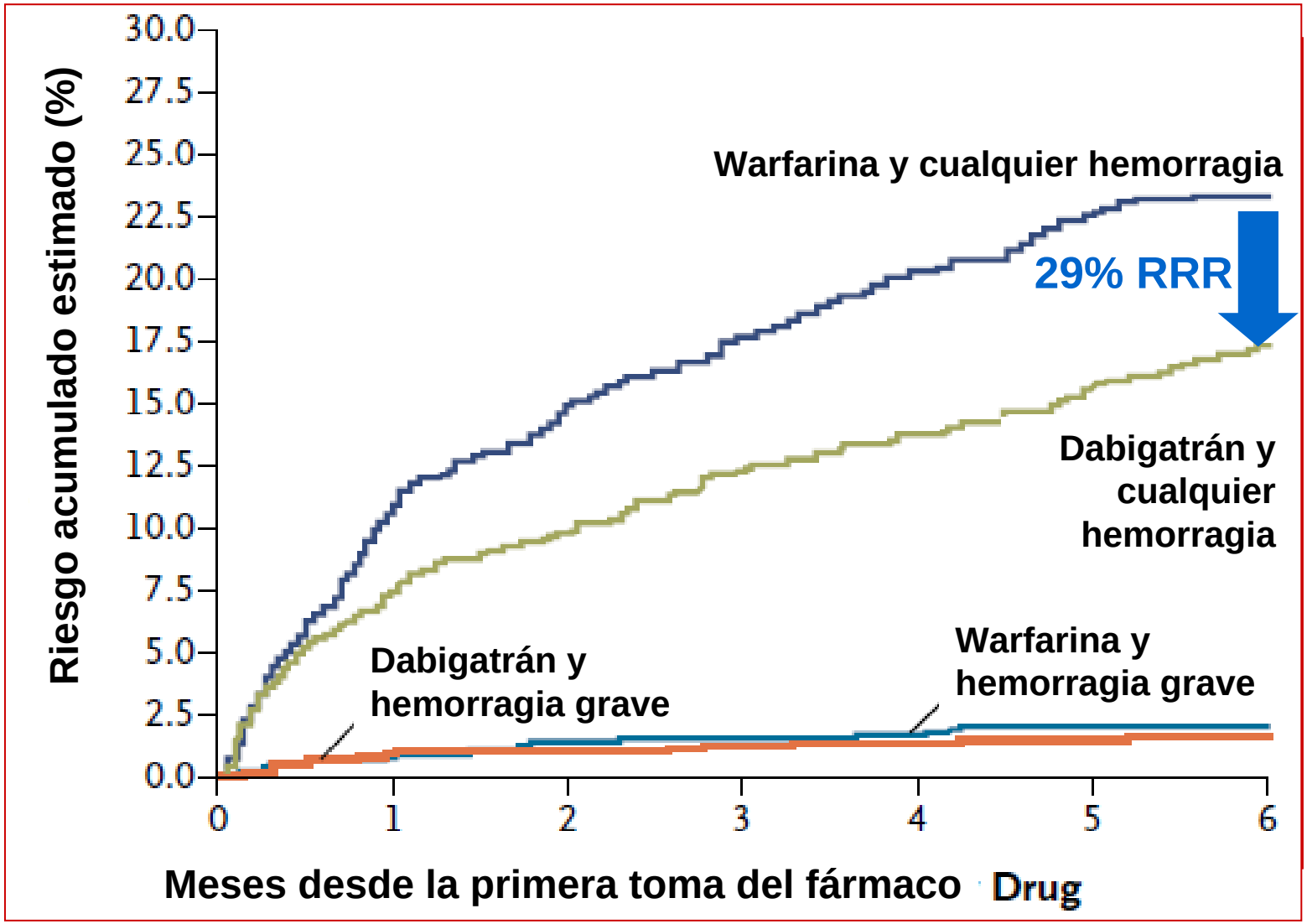
Schulman S, et al. N Engl J Med 2009;361:2342–2352

Criterios de valoración secundarios de la eficacia

	Dabigatrán 150 mg bid n = 1274	Warfarina n = 1265	Cociente de riesgos instantáneos ($IC_{95\%}$)
TVP sintomática (%)	16 (1,3)	18 (1,4)	0,87 (0,44-1,71)
EP sintomática no mortal (%)	13 (1,0)	7 (0,6)	1,85 (0,74-4,64)
Mortalidad relacionada con TEV	1 (0,1)	3 (0,2)	0,33 (0,03-3,15)
Mortalidad total	21 (1,7)	21 (1,7)	0,98 (0,53-1,79)

RECOVER™
Study of treatment of venous thromboembolism

Riesgo acumulado de hemorragia



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Localizaciones de hemorragia grave

	Dabigatran n = 1273	Warfarina n = 1266
Hemorragia mortal	1	1
Hemorragia en órganos críticos	1	9
Intracraneal	0	3
Hemartrosis	1	5
Hemoptisis	0	1

RELY®
Study of stroke prevention in atrial fibrillation

Net clinical benefit

Characteristics	Dabi 110 mg	Dabi 150 mg	Warfarin
Number of patients (n)	6015	6076	6022
Net Clinical Benefit	7.09	6.91	7.64
- Stroke / SSE	1.53	1.11	1.69
- Death	3.75	3.64	4.13
- Major bleeding	2.71	3.11	3.36
- Pulmonary embolism	0.12	0.15	0.09
- Myocardial infarction	0.72	0.74	0.53

All data represents %/year

RELY®
Study of stroke prevention in atrial fibrillation

Net clinical benefit

Characteristics	Dabi 110 mg	Warfarin	P-value 110 vs. W
Number of patients (n)	6015	6022	
- Stroke / SSE	1.53	1.69	<0.001 (NI)
- Death	3.75	4.13	0.13
- Major bleeding	2.71	3.36	0.003
- Myocardial infarction	0.72	0.53	0.07

All data represents %/year

RELY®
Study of stroke prevention in atrial fibrillation

Net clinical benefit

Characteristics	Dabi 150 mg	Warfarin	P-value 150 vs. W
Number of patients (n)	6076	6022	
Net Clinical Benefit	6.91	7.64	0.04
- Stroke / SSE	1.11	1.69	<0.001 (NI) <0.001 (sup)
- Death	3.64	4.13	0.051
- Major bleeding	3.11	3.36	0.31
- Myocardial infarction	0.74	0.53	0.048

All data represents %/year

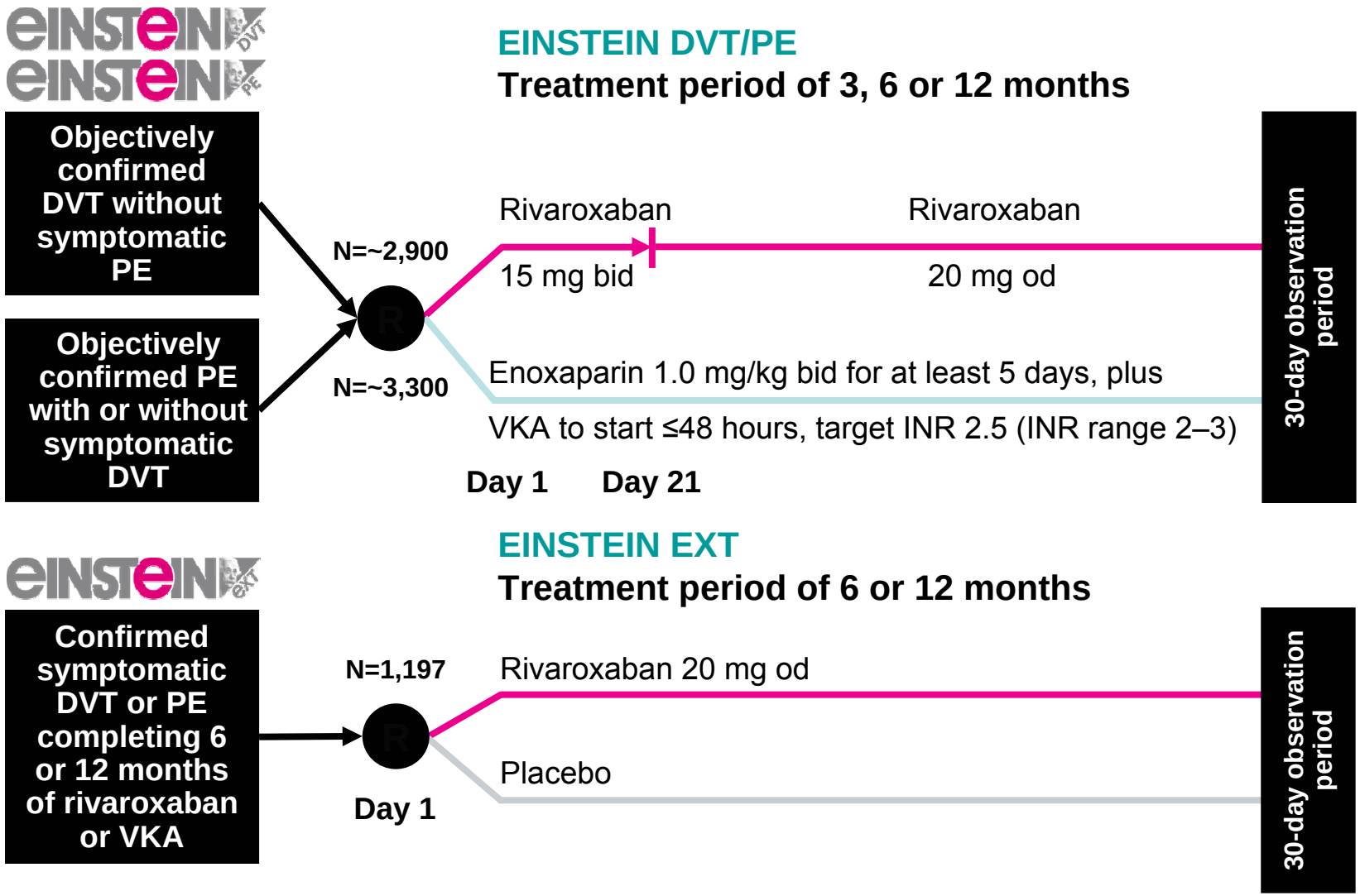
RIVAROXABAN

- Direct, specific, competitive **Factor Xa** inhibitor
- Rapid onset of action
- Half-life: 7–11 hours
- Dual mode of elimination:
  - 1/3 of drug excreted unchanged by the kidneys
  - 2/3 of drug metabolized by the liver: half excreted renally; half excreted by the fecal route
- No dietary restrictions

Cirugía ortopédica mayor:

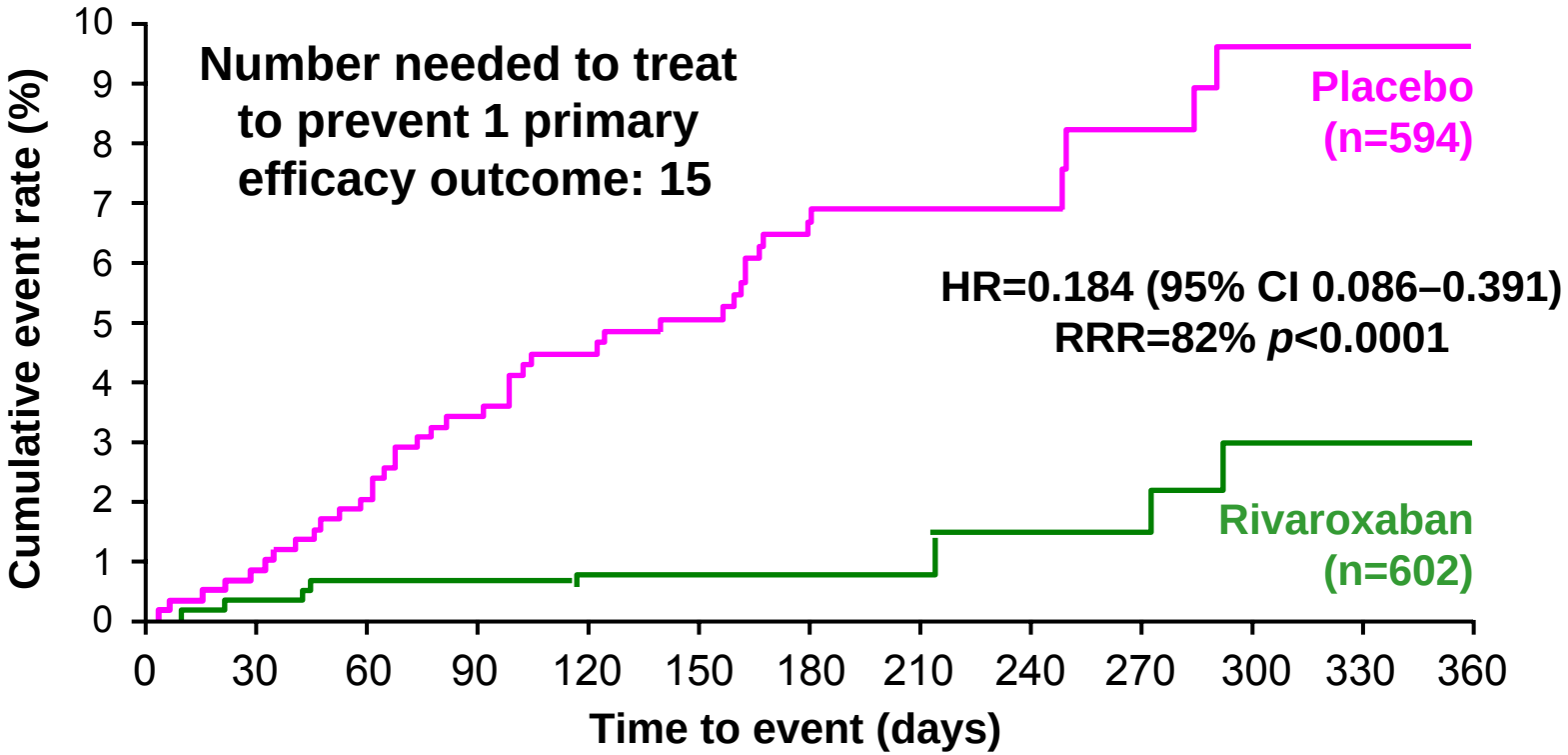
- **ClCr <15 mL/min: NO**
- **ClCr 15-30 mL/min: OJO**
- **Edad >75 años: misma dosis**
- **Insuf. hepática moderada: OJO**
- **Ketoconazol, ritonavir: NO**
- **AINEs, AAS, clopidogrel: OJO**

EINSTEIN phase III: study designs



EINSTEIN DVT, PE, Extension Evaluation Study Information available at: http://clinicaltrials.gov

Primary efficacy outcome analysis (time to first event)



Number of subjects at risk													
Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	554	521	467	444	164	138	133	110	93	85

ITT population; CI, confidence interval; HR, hazard ratio; RRR, relative risk reduction

Primary efficacy outcome and individual components

	Placebo (n=594)		Rivaroxaban (n=602)	
Symptomatic recurrent VTE*	**42**	**(7.1%)**	**8**	**(1.3%)**
Recurrent DVT	**31**	**(5.2%)**	**5**	**(0.8%)**
Non-fatal PE	**13**	**(2.2%)**	**2**	**(0.3%)**
Fatal PE	**1**	**(0.2%)**	**0**	
Unexplained death	**0**		**1**	**(0.2%)**

ITT population; *some patients experienced more than one event

Principal safety outcome: major bleeding

	Placebo (n=590)	Rivaroxaban (n=598)	
Major bleeding	**0**	**4**	**(0.7%)***
Bleeding contributing to death	**0**	**0**	
Bleeding in a critical site	**0**	**0**	
Associated with fall in Hb ≥2 g/dl and/or transfusion			
Gastrointestinal bleeding	**0**	**3**	**(0.5%)**
Menorrhagia	**0**	**1**	**(0.2%)**

*p=0.11

Number needed to harm: approximately 139

Safety population

EINSTEIN EXT

Other outcomes

	Placebo (n=594)		Rivaroxaban (n=602)	
Cardiovascular outcomes	4	(0.7%)	4	(0.7%)
STEMI	0		1	(0.2%)
Unstable angina	1	(0.2%)	3	(0.5%)
Transient ischaemic attack	1	(0.2%)	0	
Ischaemic stroke	1	(0.2%)	0	
Non-CNS systemic embolism	1	(0.2%)	0	
Total mortality	2	(0.3%)	1	(0.2%)
PE	1	(0.2%)	0	
Cancer	1	(0.2%)	0	
Unexplained death	0		1	(0.2%)

ITT population; CNS, central nervous system; STEMI, ST segment elevation myocardial infarction

Apixaban

NN®

Antikoagulans

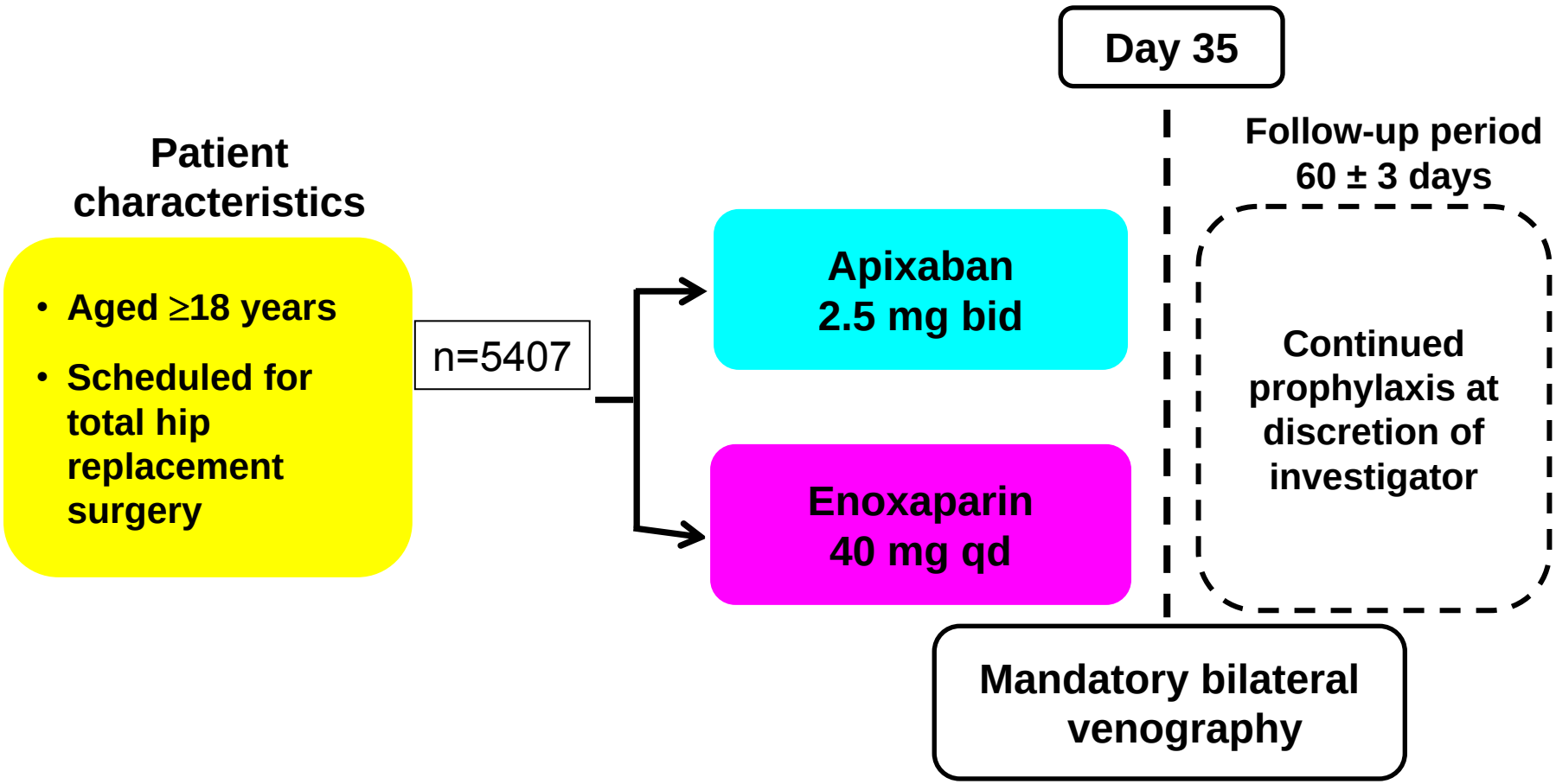
1-(4-Methoxyphenyl)-7-oxo-6- [4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro- 1H-pyrazolo[3,4-c]pyridin-3-carbamid

$C_{25}H_{25}N_5O_4$

CAS 503612-47-3

ADVANCE-3

Study design

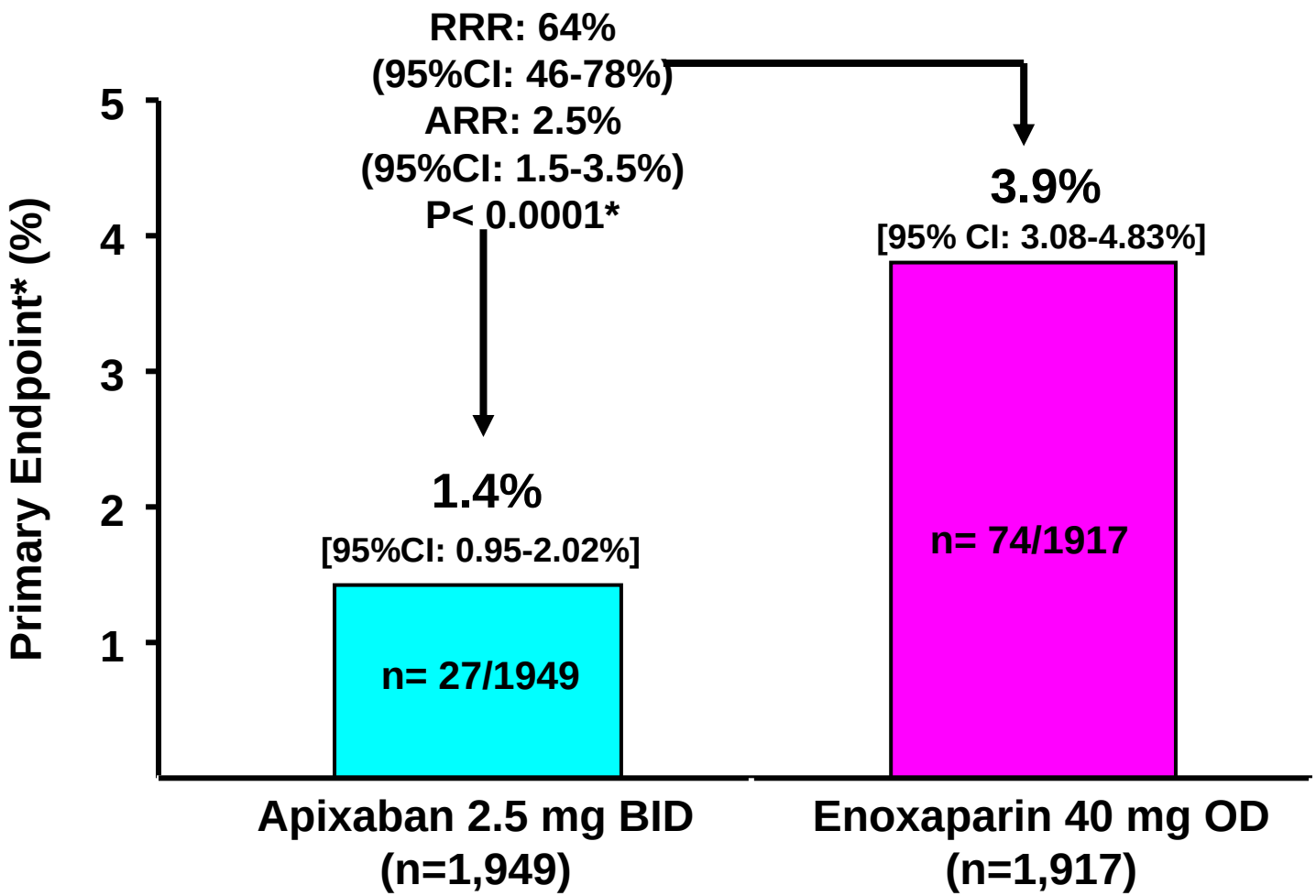


- First subcutaneous injection of study medication given 12 ± 3 hours preoperatively and resumed 12-24 hours as per investigator's standard of care
- Initial dose of oral study medication given 12-24 hours after wound closure

M R Lassen et al. Pathophysiol Haemost Thromb. 2010; 37 (suppl 1): Abstract OC356

ADVANCE-3

Primary Efficacy Results

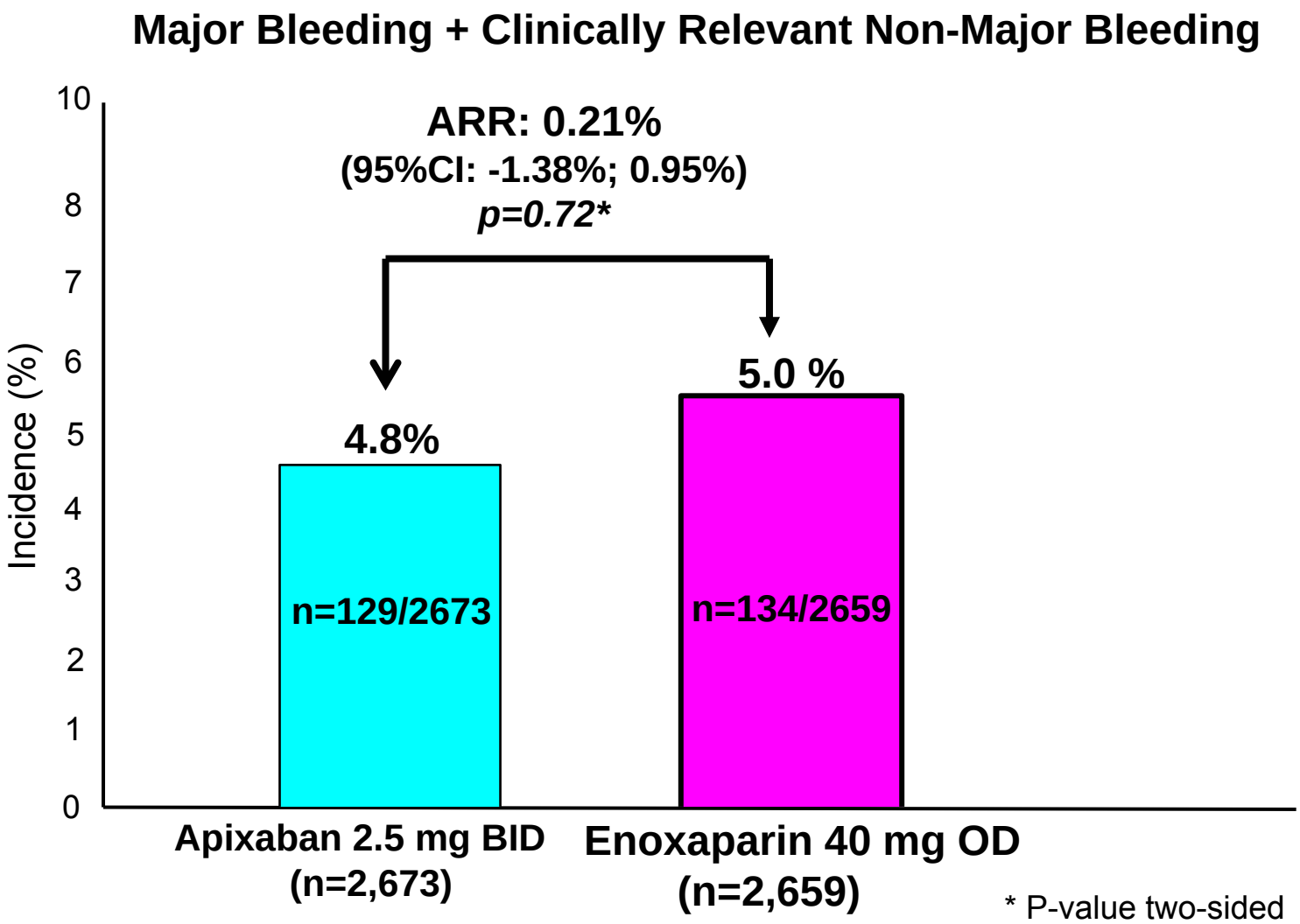


*One-sided p-value for both non-inferiority and superiority

M R Lassen et al. Pathophysiol Haemost Thromb. 2010; 37 (suppl 1): Abstract OC356

ADVANCE-3

Bleeding Results at Day 35



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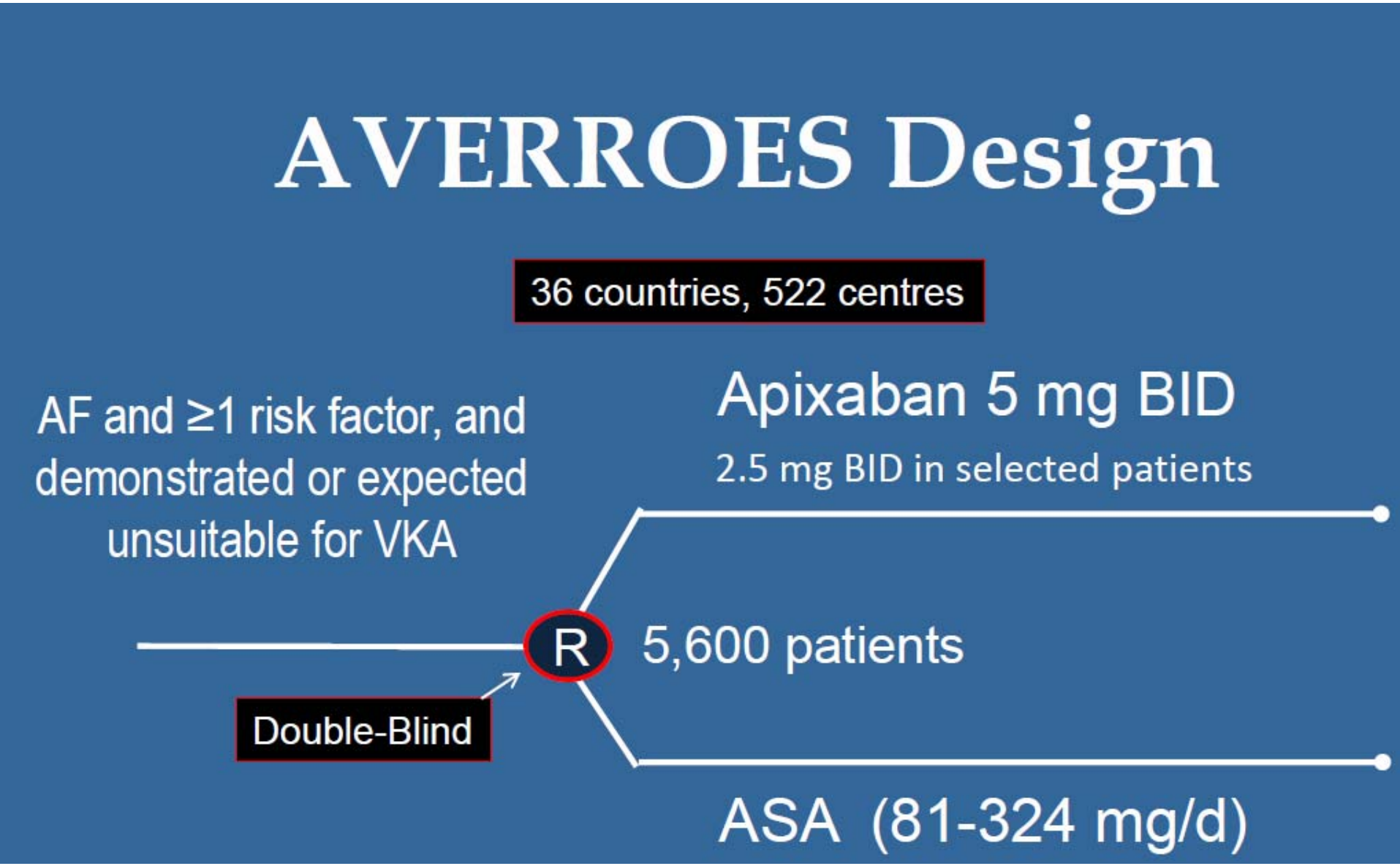
AVERROES Design



Semuloparin- AVE5026
New Hemisynthetic Ultra-LMWH

- **Indirect inhibitor of mainly coagulation factor Xa and with residual anti-IIa activity (ratio anti-Xa/anti-IIa>30)**
- **Hemisynthetic agent obtained by selective and controlled depolymerization of heparin**
  - **Oligosaccharide fragment of varying length**
  - **Molecular mass ranging 2000-3000 Da**