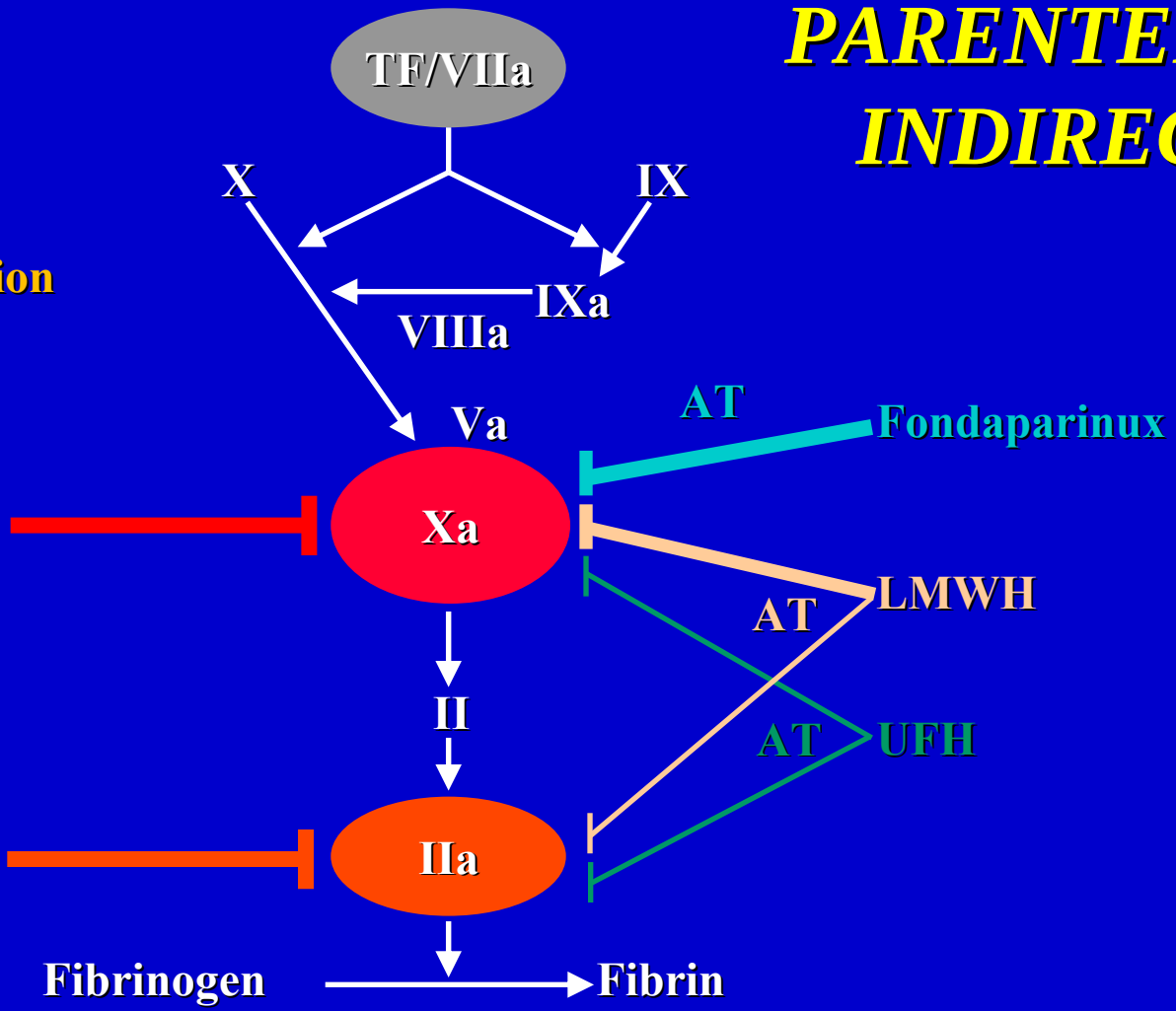
New Oral Anticoagulant Drugs in the Prevention of DVT

Targets for Anticoagulants

ORAL DIRECT

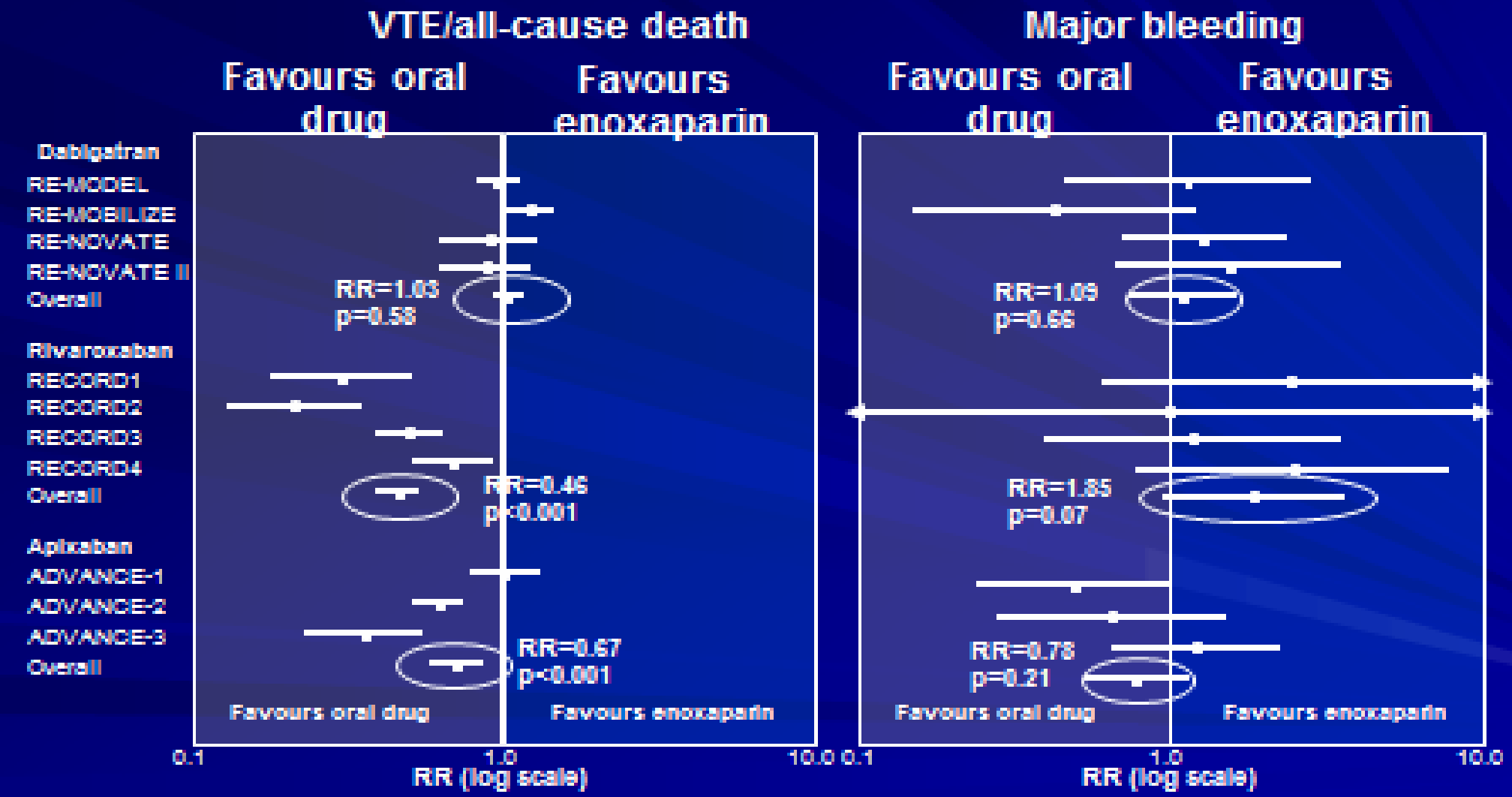
VKAs inhibit the hepatic synthesis of several coagulation factors

PARENTERAL INDIRECT



Adapted from Weitz *et al*, 2005; Weitz *et al*, 2008

Pooled estimates of the results of RCTs comparing oral anticoagulants *vs.* enoxaparin in THR or TKR



No head-to-head randomised clinical trials comparing apixaban, rivaroxaban and dabigatran have been performed. Results of indirect comparisons need to be interpreted with caution.

Adapted from Eriksson et al. Annu Rev Med 2011;62:41-57

Rivaroxaban Status

- Approved by Canadian, American (FDA) and European regulatory agencies for prophylaxis after TKR and THR

Dabigatran Status

- Approved by European and Canadian regulatory agencies for prophylaxis after THR and TKR
- In November 2011, Boehringer Ingelheim confirmed 260 fatal bleeding events worldwide between March 2008 and October 2011.
- On December 7, 2011, the FDA initiated an investigation into serious bleeding events associated with dabigatran

Recommendations for Elective Hip Replacement

Fondaparinux	Grade A (Most effective)
LMWH	Grade A
IPC + GEC	Grade A (Equivalent to LMWH)
IPC+GEC+LMWH	Grade A (More effective than either)
Rivaroxaban, Dabigatran	Grade A

Initiation

LMWH: before or after operation (Grade A)
Fondaparinux: at least 6 hours after operation

Duration of prophylaxis

LMWH: 4-6 weeks (Grade A)
Fondaparinux: 4-6 weeks (Grade B; extrapolated from Hip fracture)

Recommendations for Elective Knee Replacement

Fondaparinux	Grade A (Most effective)
LMWH	Grade A
IPC + GEC	Grade B (One small study)
IPC+GEC+LMWH	Grade A (More effective than either)
Rivaroxaban, Dabigatran	Grade A

Initiation

LMWH: before or after operation (Grade A)
Fondaparinux: at least 6 -8 hours after operation

Duration of prophylaxis

LMWH: 4-6 weeks (Grade A)
Fondaparinux: 4-6 weeks (Grade B; extrapolated from Hip fracture)

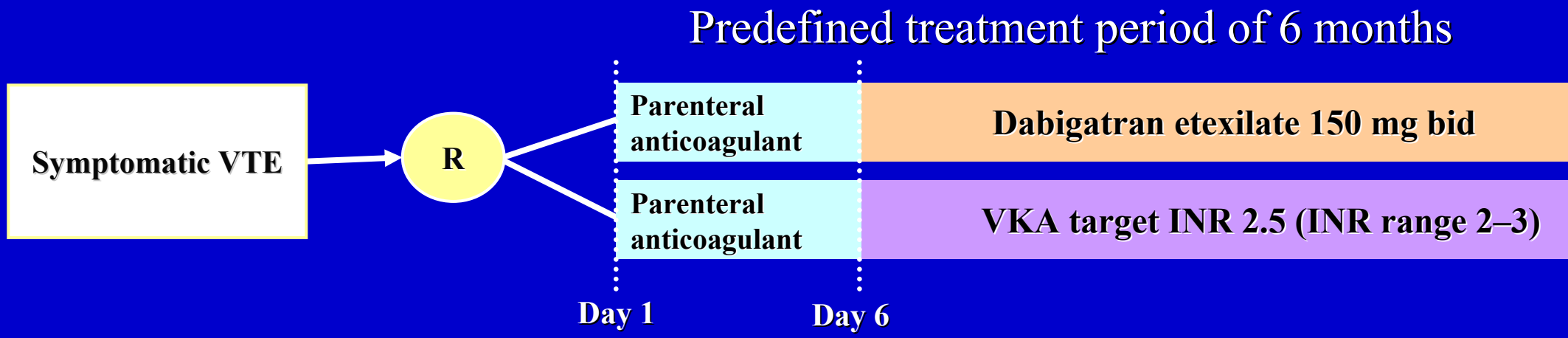
New Oral Anticoagulant Drugs in the Treatment of DVT

VTE treatment: clinical studies[1]

	Phase II	Phase III
Rivaroxaban Oral, direct Factor Xa inhibitor	**EINSTEIN DVT** Rivaroxaban vs LMWH/UFH followed by VKA[2] **ODIXa-DVT** Rivaroxaban vs enoxaparin followed by VKA[3]	**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 -12 months followed by rivaroxaban or placebo for 6 or 12 months
Dabigatran Oral, direct thrombin inhibitor		**RE-COVER**[5] 5–10 days pre-treatment with LMWH bridging to dabigatran or VKA for 6 months **RE-MEDY** 3–12 months' treatment with approved anticoagulant; switch to dabigatran or VKA **RE-SONATE** 6–18 months' VKA treatment followed by 6 months dabigatran or placebo
Apixaban Oral, direct Factor Xa inhibitor	**Botticelli-DVT** Apixaban vs LMWH or fondaparinux followed by VKA[4]	**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

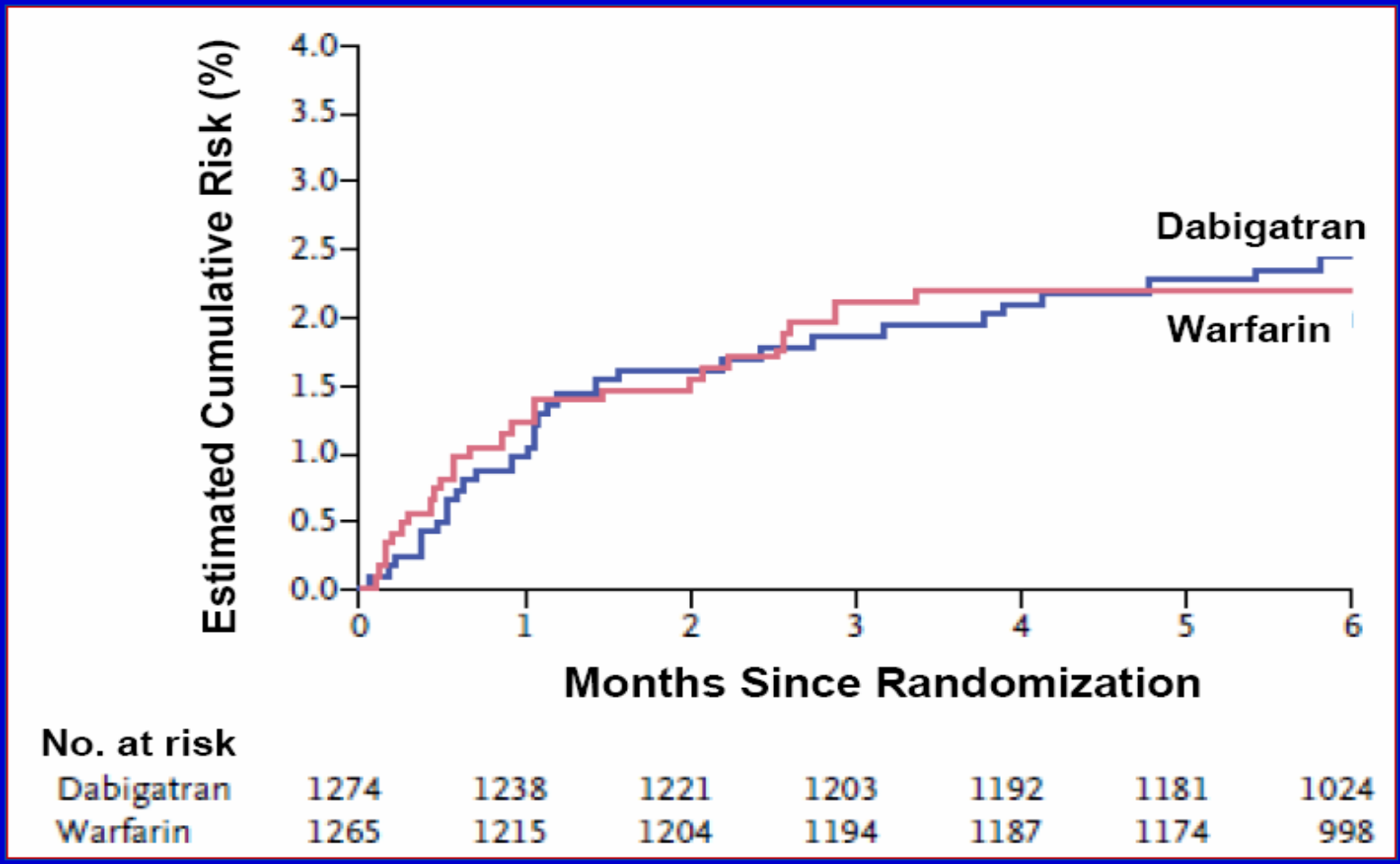
1. http://clinicaltrials.gov; 2. Büller HR *et al. Blood* 2008;112:6:2242–2247; 3. Agnelli GA *et al. Circulation* 2007; 116:180–187; 4. Büller HR *et al. J Thromb Haemost* 2008;6;1313–1318; 5. Schulman S *et al. N Engl J Med* 2009; 361:2342–2352

Dabigatran: RE-COVER



1. Schulman S, *et al*. *N Engl J Med* 2009;361:2342–2352; 2. RE-COVER-II Study Information. Trial ID: NCT00680186 Available at: http://clinicaltrial.gov/ct2/show/NCT00680186

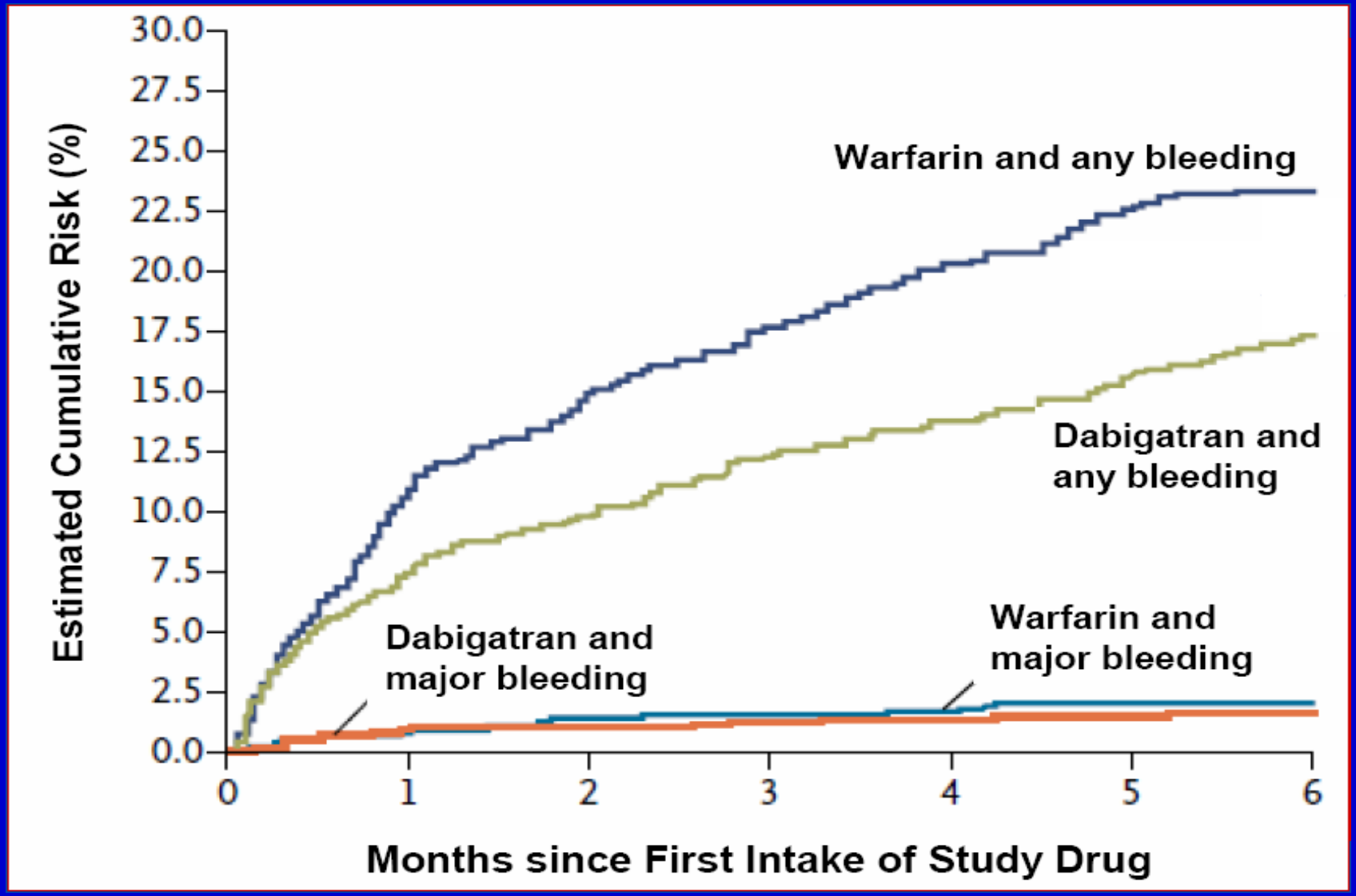
Primary Outcome: Cumulative Risk of Recurrent VTEand Related Death



Dabigatran was non-inferior to warfarin for prevention of recurrent or fatal VTE ($P<0.001$ for both hazard ratio and risk difference criteria).

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

Major and Any Bleeding



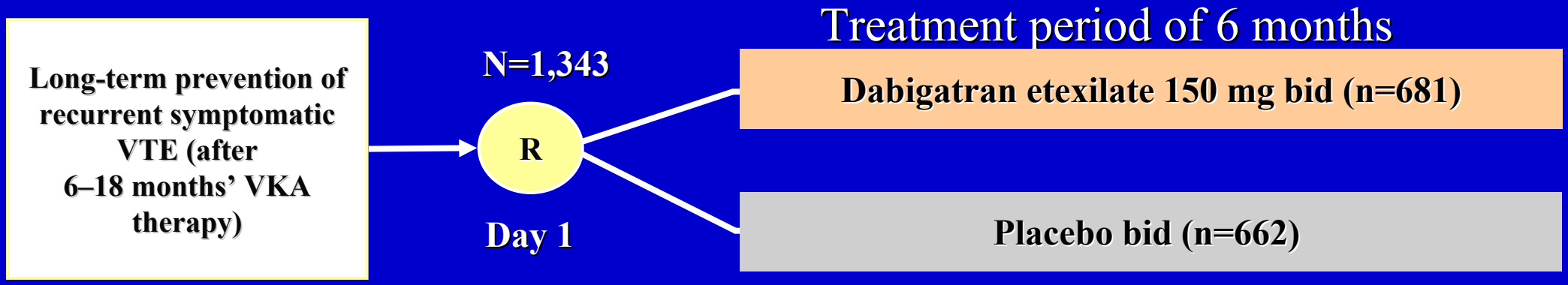
Schulman S, *et al. N Engl J Med* 2009;361:2342–2352

RE-COVER:– Adverse Events

Event	Dabigatran		Warfarin		p value
	Double-dummy phase (N=1,226)	Total treatment period (N=1,273)	Double-dummy phase (N=1,214)	Total treatment period (N=1,266)	
Any, n (%)	770 (62.8)	844 (66.3)	792 (65.2)	856 (67.6)	0.51
Serious event, n (%)	147 (12.0)	165 (13.0)	133 (11.0)	150 (11.8)	0.43
Event leading to stop of study drug, n (%)	97 (7.9)	115 (9.0)	79 (6.5)	86 (6.8)	0.05
Diarrhoea, n (%)*	46 (3.8)	57 (4.5)	34 (2.8)	38 (3.0)	0.06
Dyspepsia, n (%)*	36 (2.9)	39 (3.1)	7 (0.6)	9 (0.7)	<0.001
Acute coronary syndrome, any, n (%)	4 (0.3)	5 (0.4)	3 (0.2)	3 (0.2)	0.73
Myocardial infarction, n (%)	3 (0.2)	4 (0.3)	2 (0.2)	2 (0.2)	0.69
ALT >3 ×ULN plus bilirubin >2 ×ULN, n/N (%)	2/1195 (0.2)	2/1055 (0.2)	4/1182 (0.3)	4/1106 (0.4)	0.69

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

Dabigatran vs Placebo for Extended Maintainance Therapy of VTE: RE-SONATE



Primary efficacy outcome: recurrent symptomatic VTE (composite DVT, fatal and non-fatal PE) during treatment

Primary safety outcome: Major bleeding

1. RE-SONATE Study Information. Trial ID: NCT00558259. Available at: http://clinicaltrials.gov/ct2/show/NCT00558259
2. Abstract ISTH Kyoto 2011 O-MO-037

Dabigatran study programme in prevention of secondary VTE: RE-SONATE

	Dabigatran n=681	Placebo n=662	HR (95% CI)	P
Recurrent VTE	3 (0.4%)	37 (5.6%)	0.08 (0.02 to 0.25)	< 0.0001
Major bleeds	2 (0.39%)	0		
Clinically Relevant bleeds	36 (5.3%)	12 (1.8%)	2.9 (1.5 to 5.6)	0.001
Cardiovascular Events	3 (0.4%)	2 (0.3%)		
Deaths	0	1		

Abstract ISTH Kyoto 2011 O-MO-037

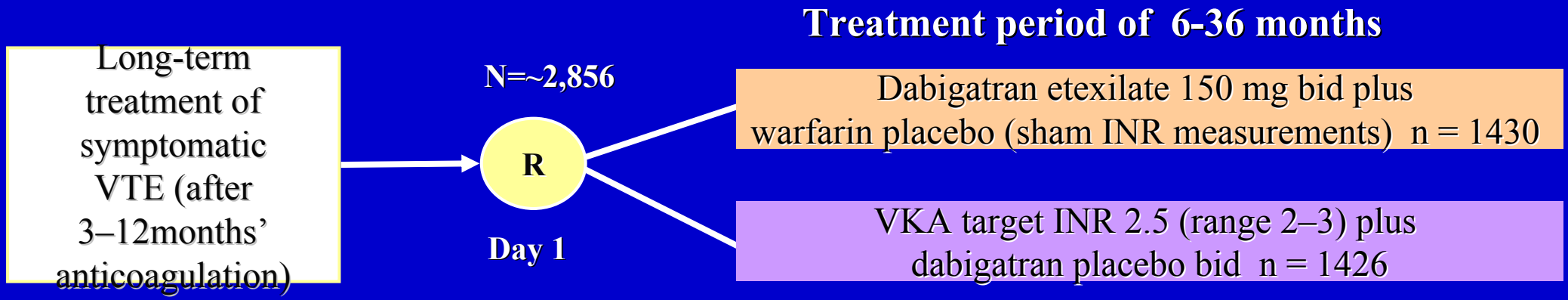
Dabigatran study programme in prevention of secondary VTE: RE-SONATE

Conclusion:

Extended treatment with dabigatran was associated with a 92% relative risk reduction for recurrent VTE and a low risk for major bleeding

Abstract ISTH Kyoto 2011 O-MO-037

Dabigatran or Warfarin for Extended Maintainance Therapy of VTE: RE-MEDY



Primary efficacy outcome: composite of recurrent symptomatic VTE (DVT and PE) and deaths related to VTE during the treatment period

Secondary outcome: bleeding events during treatment

1. RE-MEDY Study Information. Trial ID: NCT00329238 Available at: http://www.clinicaltrials.gov/ct2/show/NCT00329238?term=NCT00329238&rank=1
2. Abstract ISTH Kyoto 2011 O-TH-033

Dabigatran or Warfarin for Extended Maintainance Therapy of VTE: RE-MEDY

	Dabigatran n=1430	Warfarin n=1426	HR (95% CI)	P
Recurrent VTE	26 (1.8%)	18 (1.3%)	1.44 (0.78 to 2.64)	0.03 (non-inferiority)
Major bleeds	13 (0.9%)	25 (1.8%)	0.52 (0.27 to 1.01)	0.047
Any bleeds	277 (19%)	373 (26%)	0.71 (0.61 to 0.83)	< 0.0001
ACS	13 (0.9%)	3 (0.2%)		0.02
Deaths	17	19		

Abstract ISTH Kyoto 2011 O-TH-033

Dabigatran or Warfarin for Extended Maintainance Therapy of VTE: RE-MEDY

Conclusions:

1. Dabigatran was as effective as warfarin in the extended treatment of VTE
2. Dabigatran was associated with a reduced risk for bleeding, but an increased incidence of acute coronary events

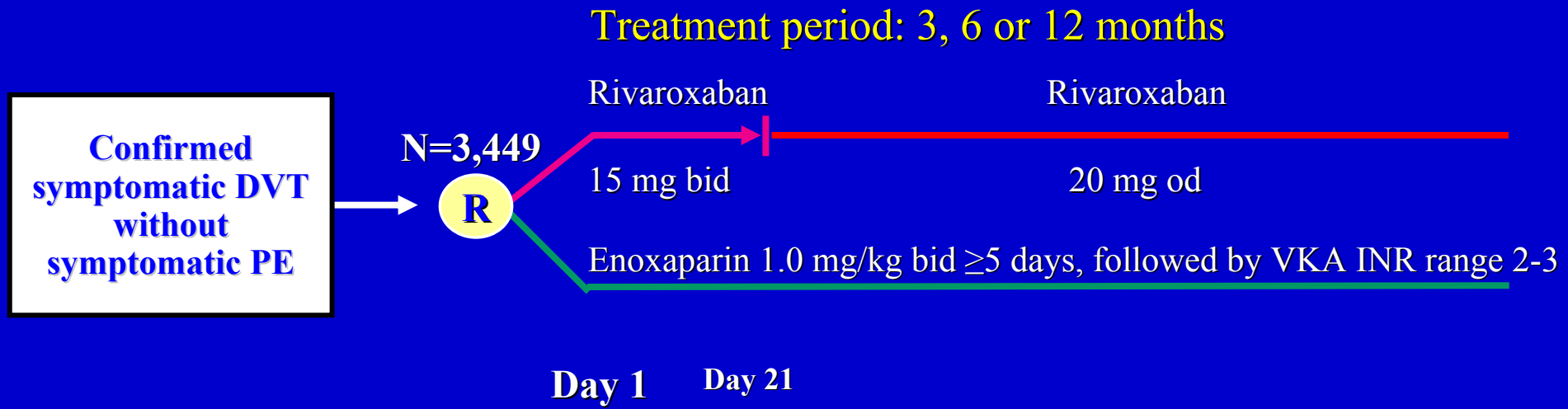
Abstract ISTH Kyoto 2011 O-MO-037

The EINSTEIN DVT study

Oral rivaroxaban versus standard therapy for the acute treatment of symptomatic DVT

EINSTEIN DVT: study design

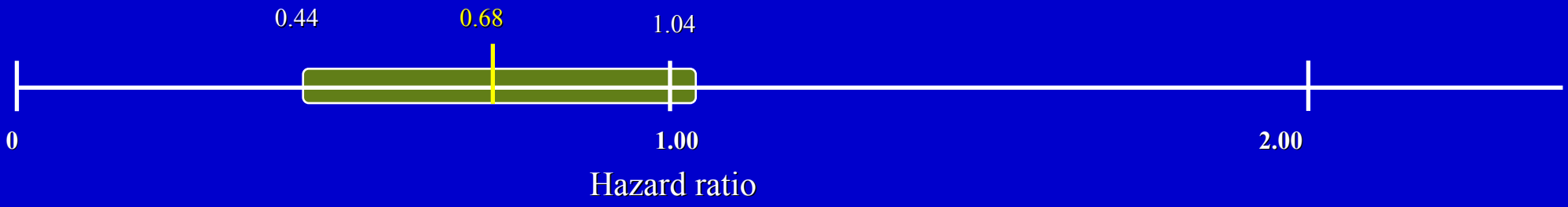
- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- Randomized, open-label, event-driven, non-inferiority study
- 88 primary efficacy outcomes needed



EINSTEIN DVT trial ID: NCT00440193

Primary efficacy outcome analysis

	Rivaroxaban (n=1,731)		Enoxaparin/VKA (n=1,718)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**36**	**(2.1)**	**51**	**(3.0)**
Recurrent DVT	14	**(0.8)**	28	**(1.6) (p=0.035)**
Recurrent DVT + PE	1	**(<0.1)**	0	**(0)**
Non-fatal PE	20	**(1.2)**	18	**(1.0)**
Fatal PE/unexplained death where PE cannot be ruled out	4	**(0.2)**	6	**(0.3)**



Rivaroxaban superior

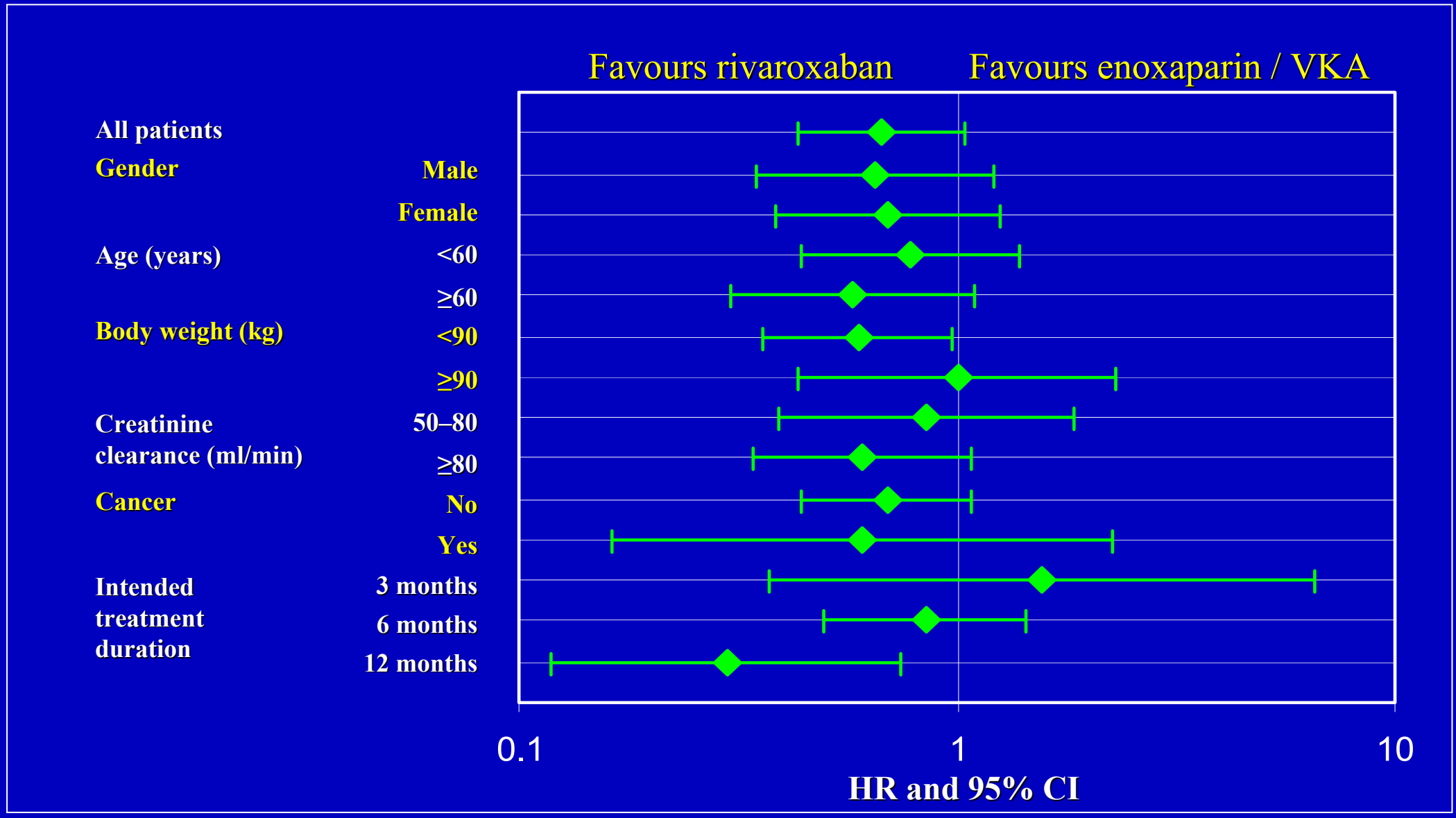
Rivaroxaban non-inferior

Rivaroxaban inferior

p=0.076 for superiority (two-sided)

p<0.0001 for non-inferiority (one-sided)

Primary efficacy outcome by subgroup



Principal safety outcome analysis

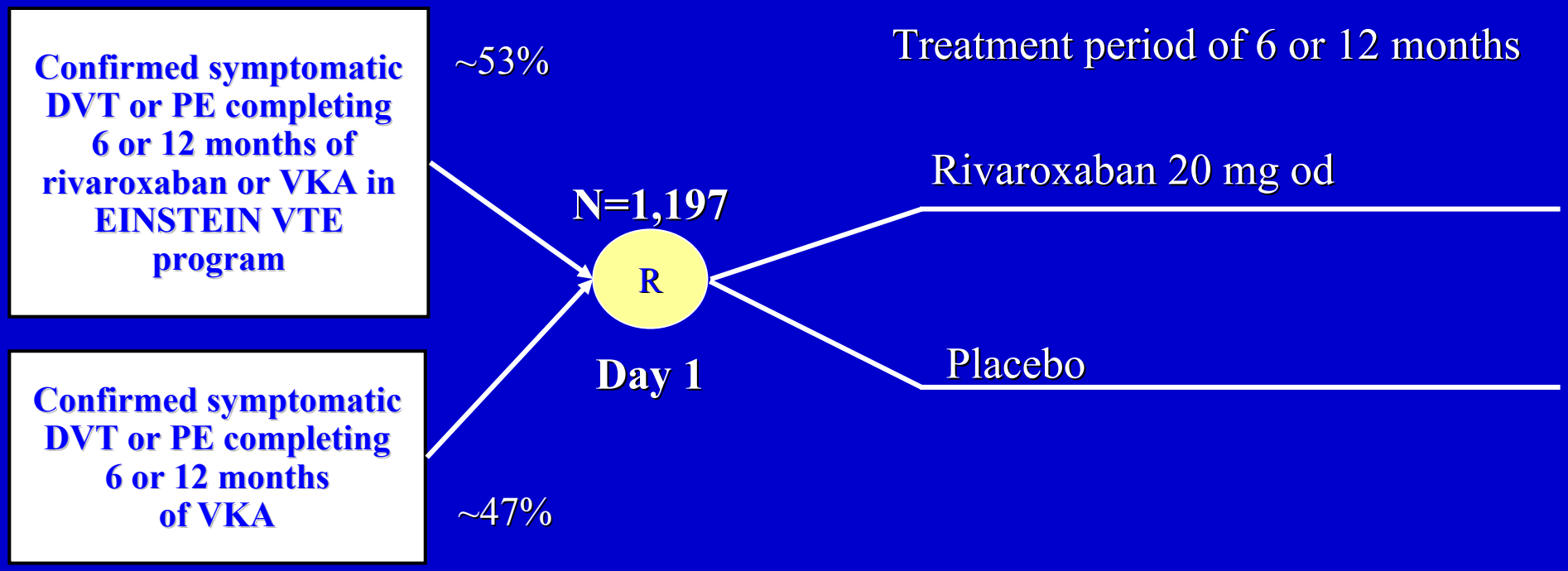
	Rivaroxaban (n=1,718)		Enox / VKA (n=1,711)		HR (95% CI)
	n	(%)	n	(%)	*p* value
First major or clinically relevant non-major bleeding	139	(8.1)	138	(8.1)	0.97 (0.76–1.22) *p*=0.77
Major bleeding	14	(0.8)	20	(1.2)	
Contributing to death	1	(<0.1)	5	(0.3)	
In a critical site	3	(0.2)	3	(0.2)	
Associated with fall in Hb ≥ 2 g/dl and/or transfusion of ≥ 2 units	10	(0.6)	12	(0.7)	
Clinically relevant non-major bleeding	129	(7.5)	122	(7.1)	

Conclusion

Oral rivaroxaban, 15 mg twice-daily for 3 weeks followed by 20 mg once daily, could provide clinicians and patients with a simple, single-drug approach for the acute and continued treatment of DVT that potentially improves the benefit–risk profile of anticoagulation

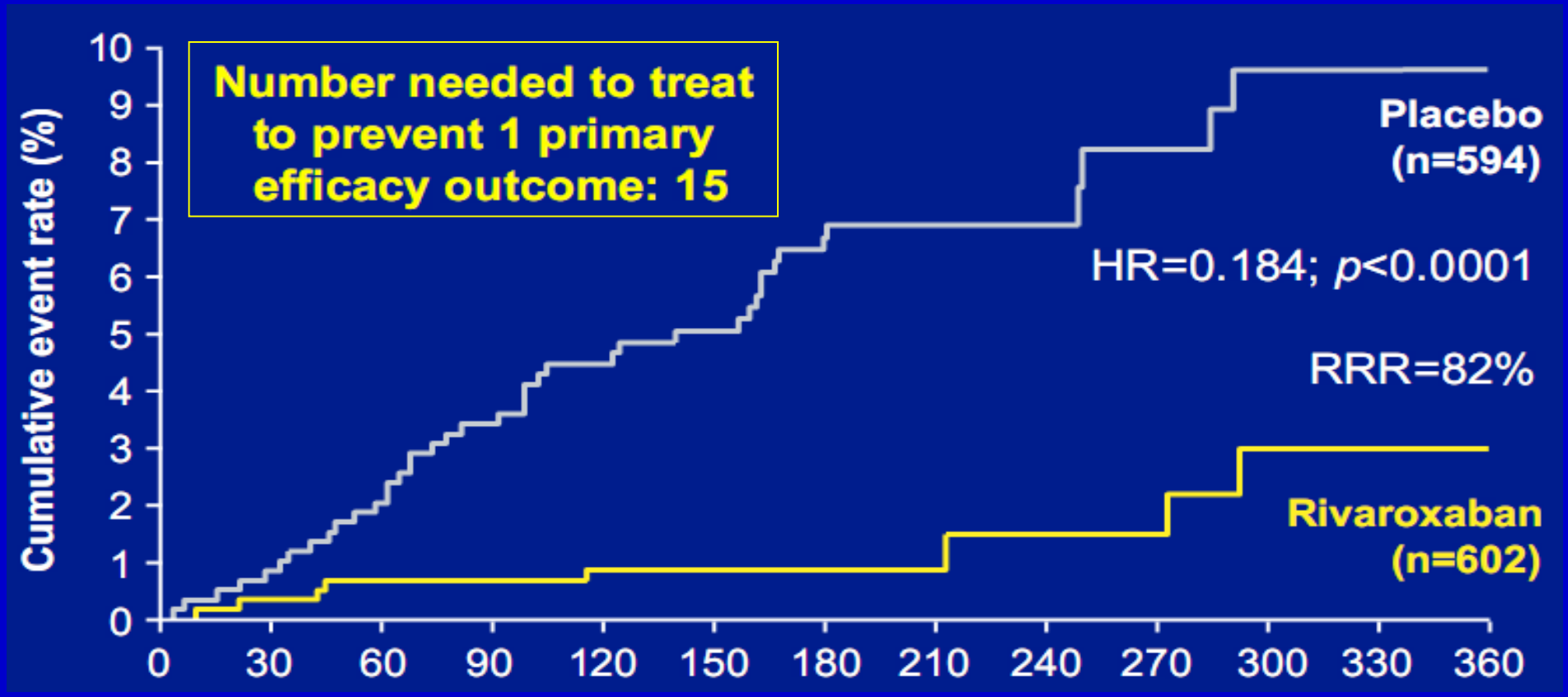
The EINSTEIN Extension study

Randomized, double-blind, placebo-controlled, event-driven (n=30), superiority study



EINSTEIN Extension Trial ID: NCT00439725

Primary efficacy outcome analysis



The EINSTEIN Extension study. *Büller HR et al. N Engl J Med 2010;363:2499-510*

Conclusions

- In patients who had completed 6 or 12 months of anticoagulation, rivaroxaban showed:
  - An 82% relative risk reduction in the recurrence of VTE (HR=0.184; $p<0.0001$)
  - Absolute risk reduction of 5.8% hence, 15 patients need to be treated to prevent one recurrent VTE event
  - Low incidence of major bleeding (0.7%; $p=0.11$; NNH approximately 139)
  - Efficacy and safety results were consistent irrespective of bodyweight and creatinine clearance
  - Modest increase in clinically relevant non-major bleeding (5.4% vs 1.2%: $p<0.01$)
  - No signal for liver toxicity
- Oral rivaroxaban, 20 mg once-daily, provides clinicians and patients with a simple and effective option for continued anticoagulant treatment

Questions to be Answered

1. Efficacy for PE
2. Efficacy in preventing recurrence in patients with
   (a) Cancer
   (b) Thrombophilias
3. Better vein recanalization than warfarin?
4. Efficacy in preventing PTS?
5. Efficacy in preventing pulmonary hypertension?
6. Duration?