Secondary prevention of VTE: who, how long, with what?

Giancarlo Agnelli

Internal & Cardiovascular Medicine - Stroke Unit

University of Perugia, Italy

Treatment of venous thromboembolism

UFH
LMWH
Fondaparinux
Thrombolysis
NOAs

Vitamin K antagonists

INR 2.0-3.0

2.0-3.0 or 1.5-1.9

NOAs

Initial treatment

Long term-treatment

Extended* treatment

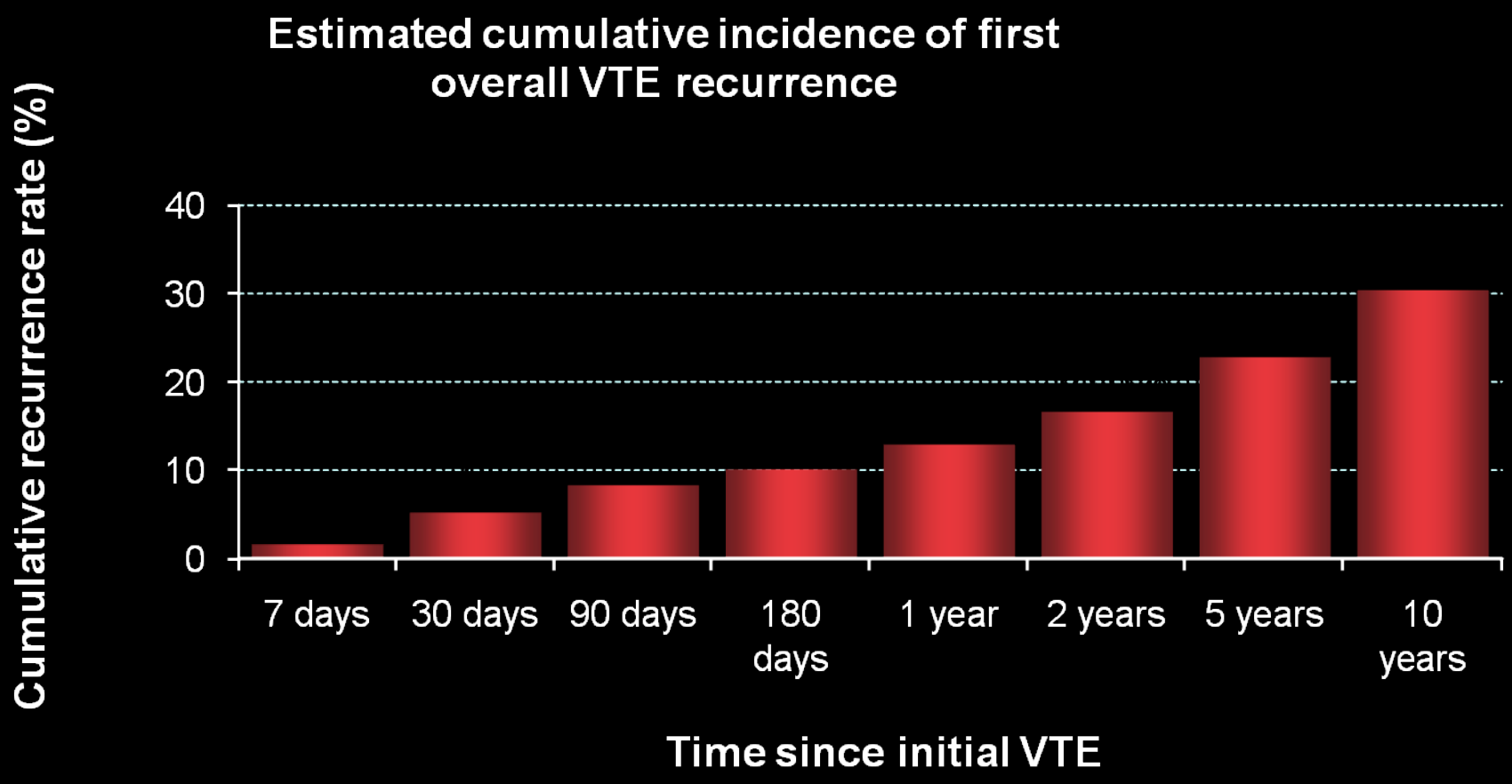
≥5 days

at least 3 months

indefinite*

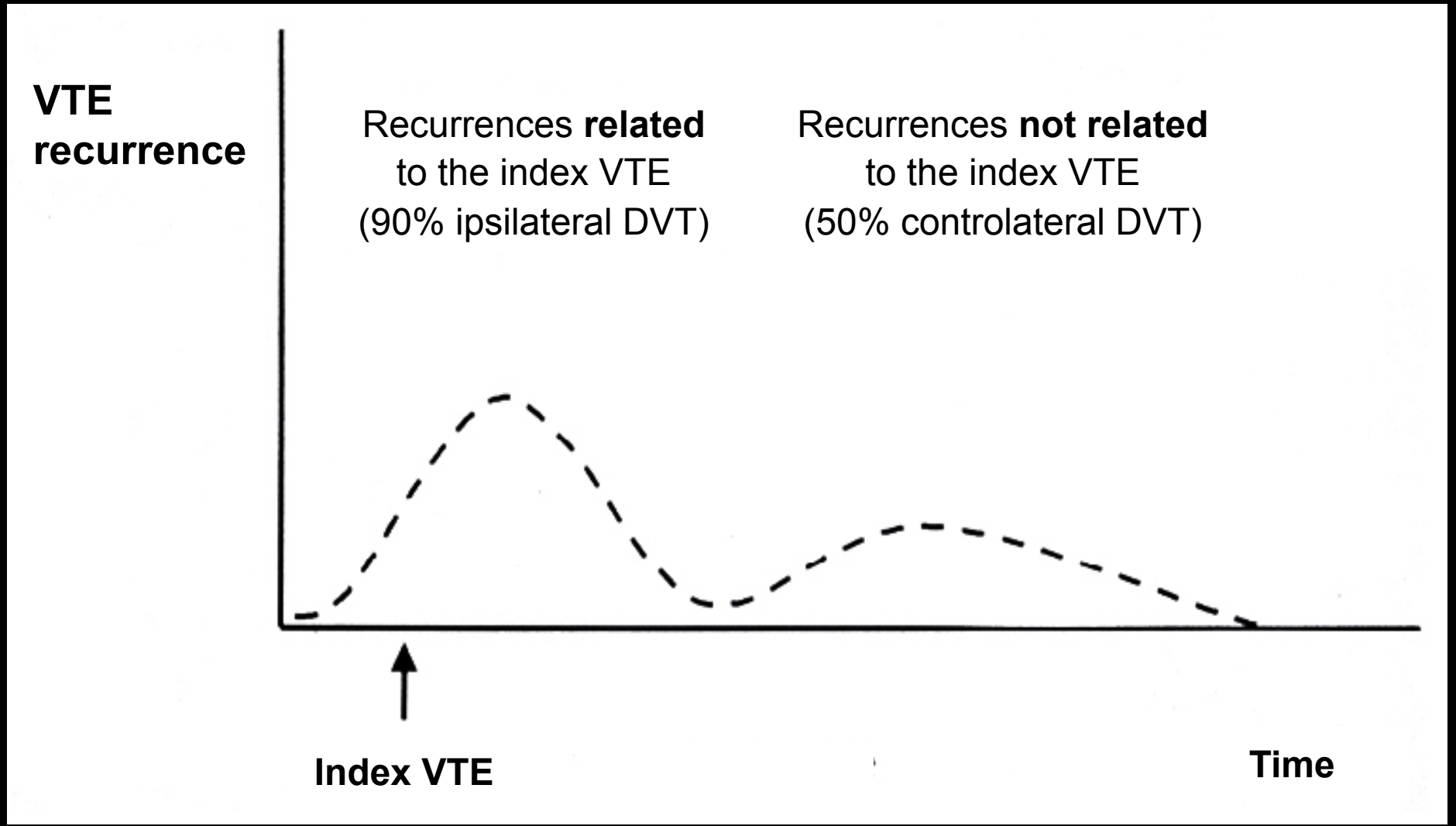
*With re-assessment of the individual risk-benefit at periodic intervals (not necessarily forever)

Cumulative incidence of VTE recurrence

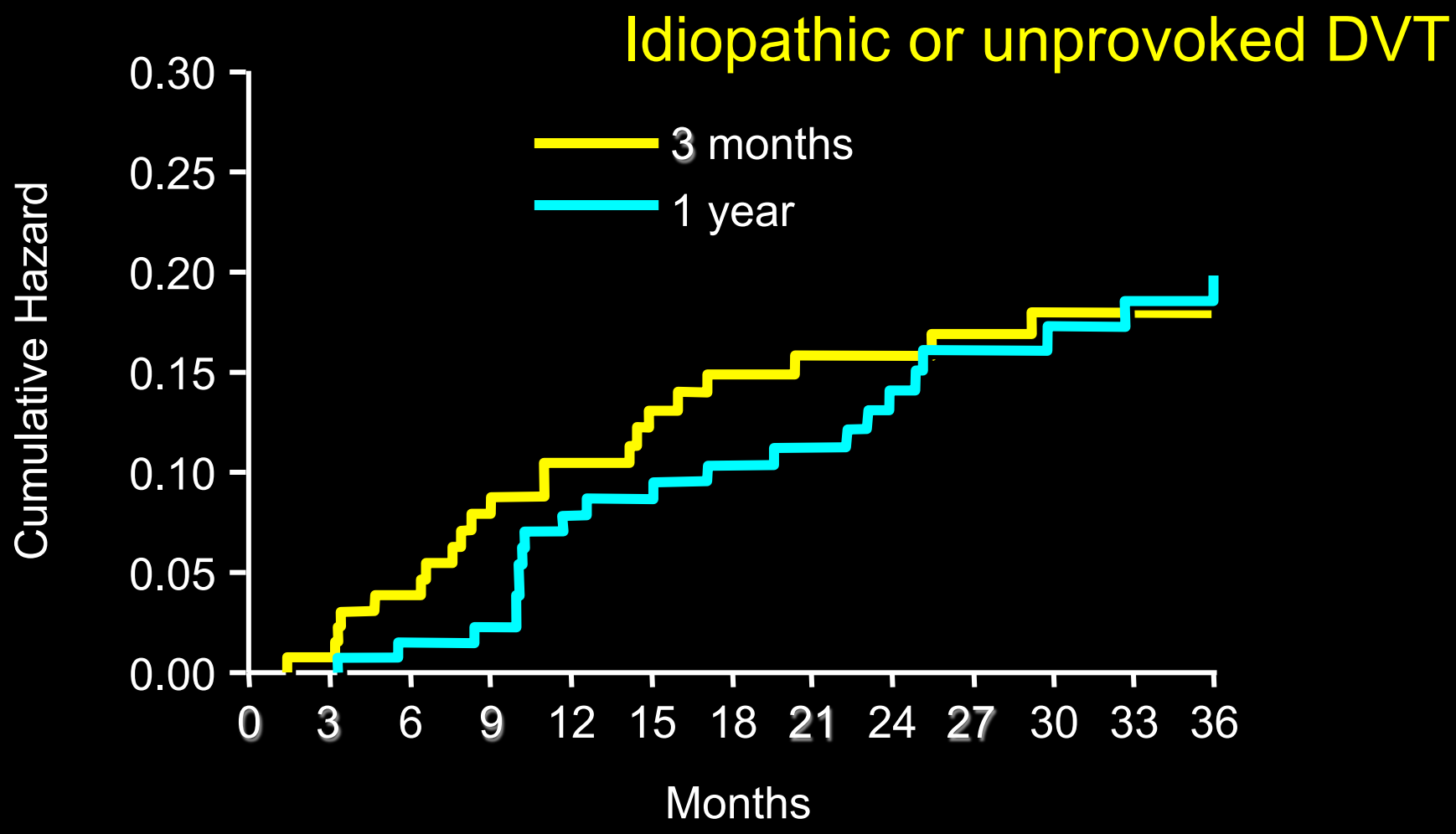


Heit JA, et al. *Arch Intern Med*. 2000;160:761-768.

Time course of VTE recurrence



Warfarin Optimal Duration Italian study



Agnelli G, et al. *N Engl J Med*. 2001;345:165-169.

Duration of anticoagulant treatment for VTE

Determinants for the decision

1. Risk of recurrence after VKA discontinuation
2. Risk of bleeding while on treatment
3. Patient preference (& burden on health care system)

VTE recurrence after anticoagulation withdrawal

	Recurrence risk	
	1st year	5 years
Major reversible risk factor	3%	10%
Minor reversible risk factor	5%	15%
Idiopathic 1st episode	10%	> 30%

Bleeding in patients receiving AVK for VTE

	Annual ICH Rate	Case fatality rate
Entire period	1.15% pts-y	9.4%
Initial 3 months	1.48% pts-y	9.3%
After initial 3 months	0.65 % pts-y	9.1%

Linkins LA, et al. *Ann Intern Med*. 2003;139:893-900.

Fatal recurrences & fatal bleeding

Case fatality rate

Recurrent VTE: 12.1% *
(unprovoked: 5.5%)

Major bleeding: 19.7%

Case fatality rate (beyond 3 months)

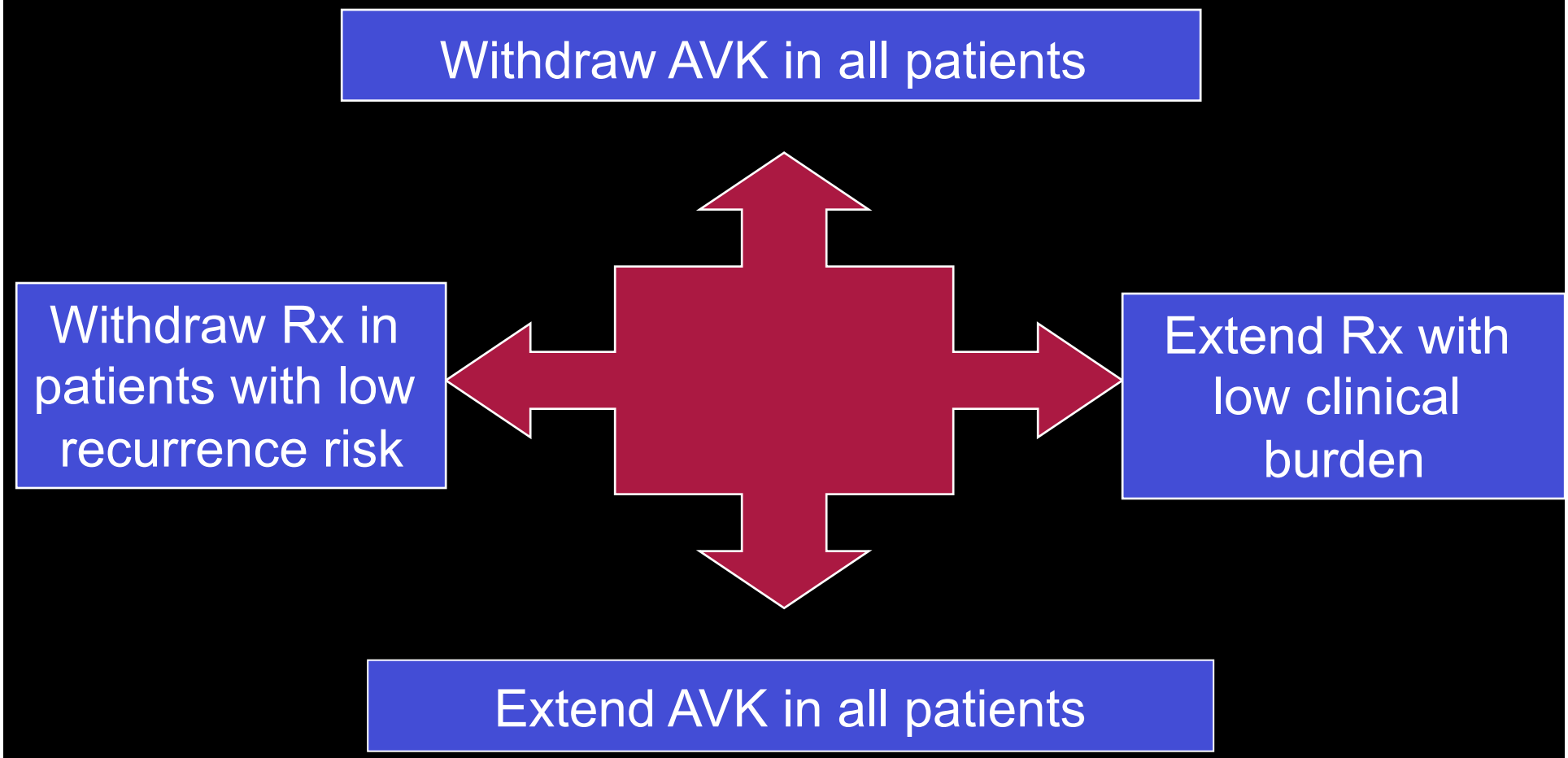
Recurrent VTE: 2.0%

Major bleeding: 18.2%

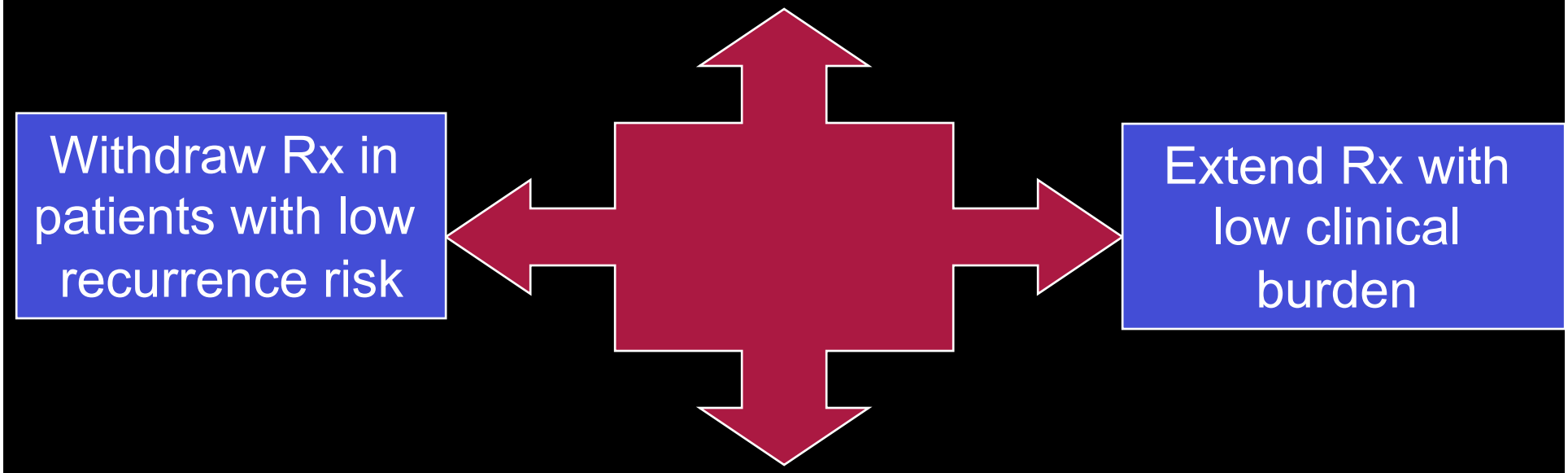
* PE: 18.5%, DVT 6.3%

Lecumberri R, et al. Thromb Haemost. 2013;110:834-843.

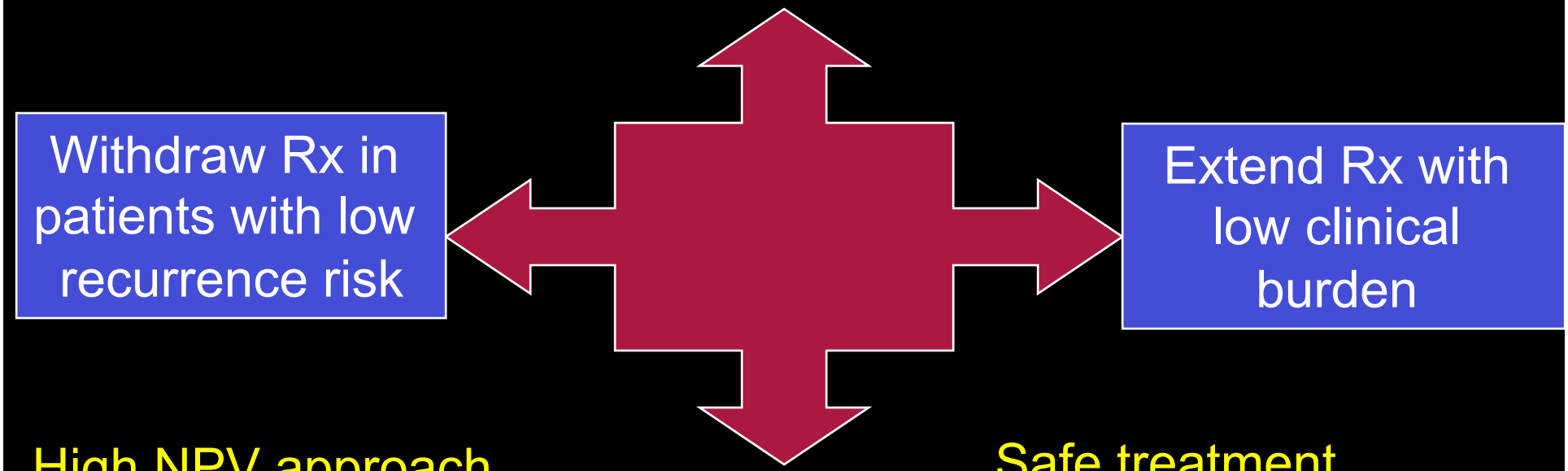
Options after the initial AVK treatment



Options after the initial AVK treatment



Options after the initial AVK treatment



High NPV approach
Acceptable recurrence rate

Safe treatment
Reasonable practicality

1. Withdraw with low risk of recurrence

Options

1. Normal D-dimer after discontinuation of anticoagulant treatment (Palareti 2006)
2. Residual venous occlusion at anticoagulant withdrawal (Prandoni 2008)

Cautions

Reasonable NPV for early and medium-term recurrence

NPV for late recurrence still unclear

2. Extend with low clinical burden

Essential requirements of the intervention

1. Proven safety
2. Reasonable efficacy (40-60% RRR)
3. Low expenditure

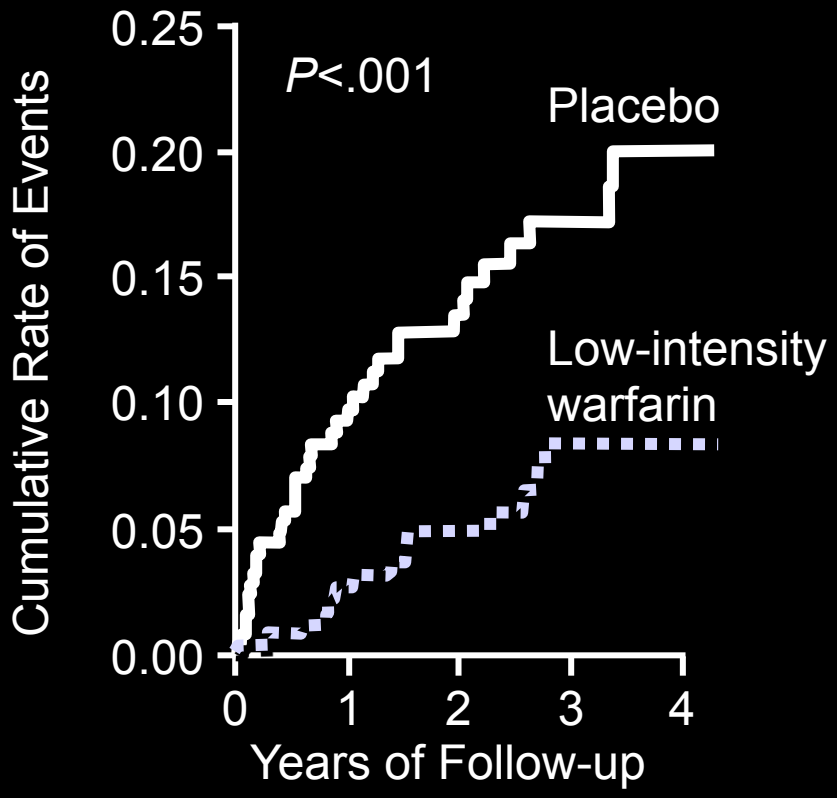
2. Extend with low clinical burden

Options

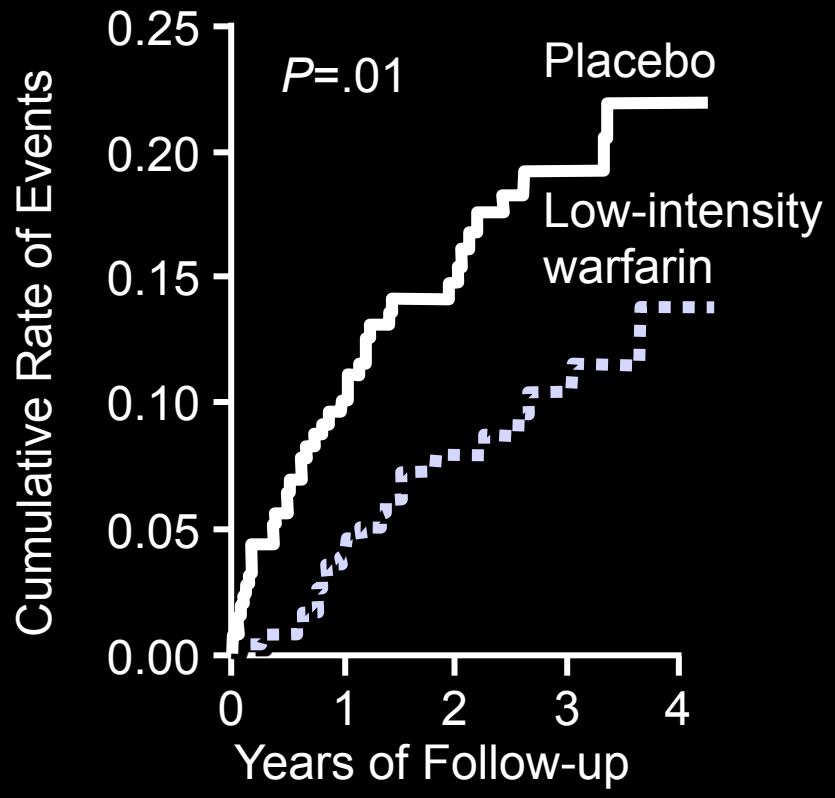
1. Low-intensity warfarin
2. Aspirin
3. New antithrombotic drugs with better profile

Prevent

Recurrent VTE



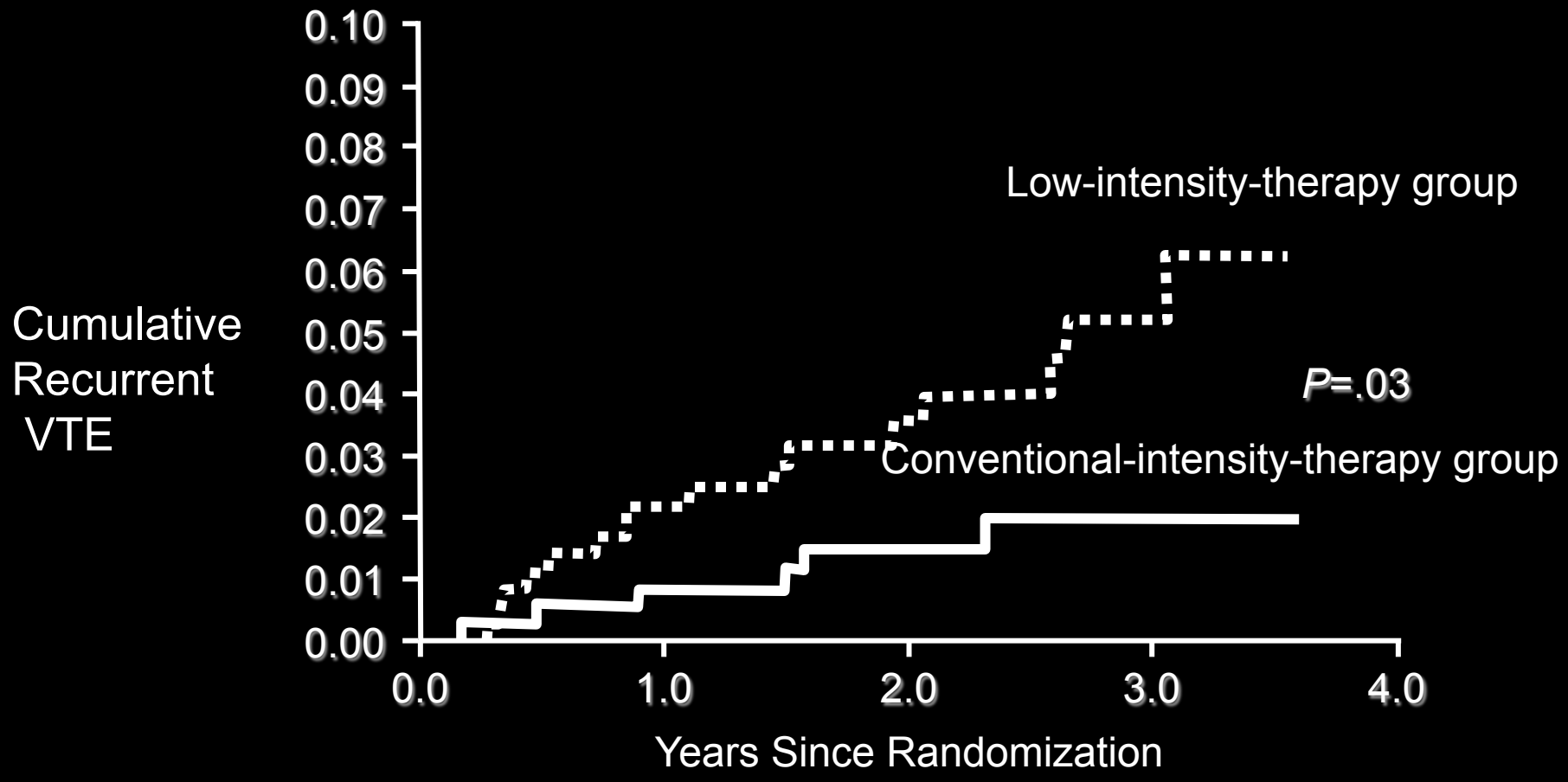
Composite Endpoint*



*Composite study endpoint of recurrent venous thromboembolism, major hemorrhage, or death from any cause (right).

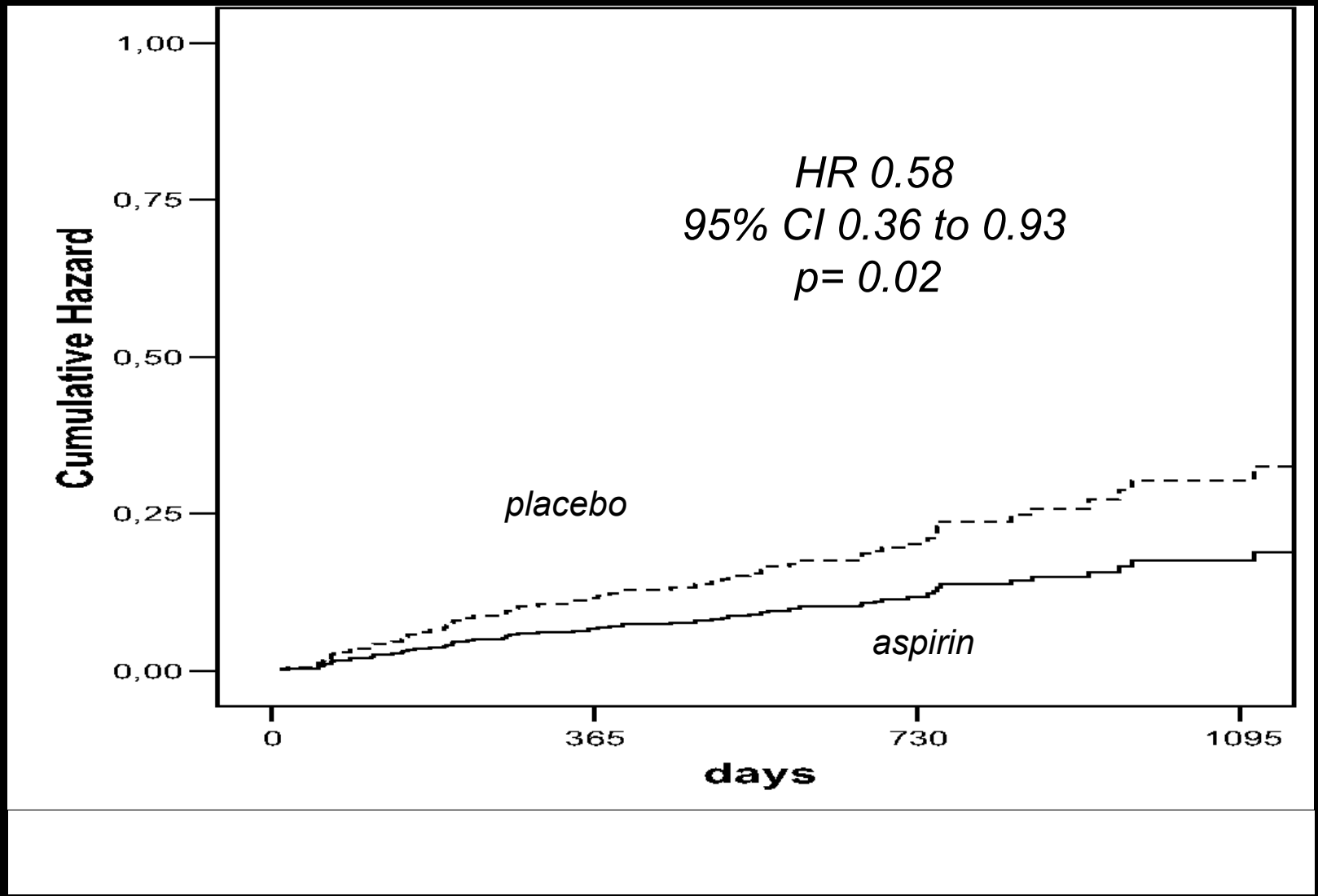
Ridker PM, et al. *N Engl J Med*. 2003;348:1425-1434.

Elate



Kearon C, et al. *N Engl J Med*. 2003;349:631-639.

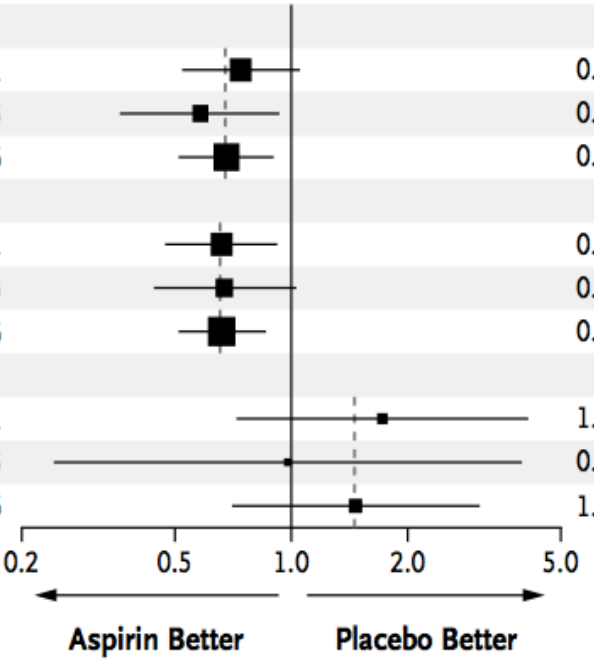
Warfasa: VTE recurrences



Becattini C, et al. *N Engl J Med*. 2012;366:1959-1967.

Warfasa & Aspire: pooled analysis

Outcome and Study	Placebo	Aspirin	Hazard Ratio (95% CI)	P Value	P Value for Heterogeneity
	no. of events/total no. of patients				
Venous thromboembolism					0.42
ASPIRE	73/411	57/411	0.74 (0.52–1.05)	0.09	
WARFASA	43/197	28/205	0.58 (0.36–0.93)	0.02	
Pooled	116/608	85/616	0.68 (0.51–0.90)	0.007	
Major vascular events					0.96
ASPIRE	88/411	62/411	0.66 (0.48–0.92)	0.01	
WARFASA	48/197	36/205	0.67 (0.43–1.03)	0.06	
Pooled	136/608	98/616	0.66 (0.51–0.86)	0.002	
Clinically relevant bleeding					0.50
ASPIRE	8/411	14/411	1.72 (0.72–4.11)	0.22	
WARFASA	4/197	4/205	0.98 (0.24–3.96)	0.97	
Pooled	12/608	18/616	1.47 (0.70–3.08)	0.31	



Brighton et al NEJM 2012

Inspire (Warfasa & Aspire)

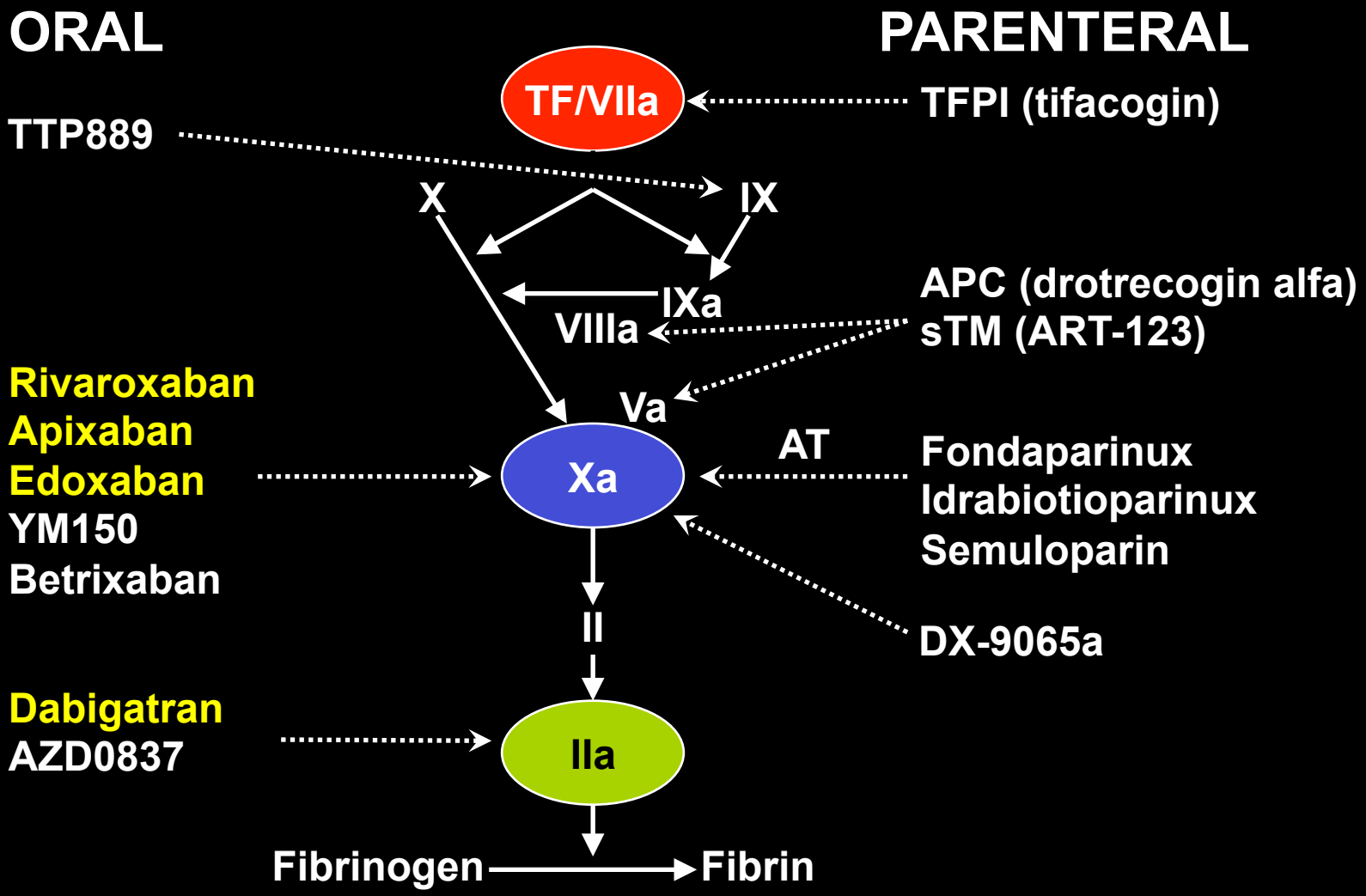
Patient-level analysis

Recurrent VTE: 7.5 vs. 5.1 year, RR 0.68 (0.51-0.90)

Major bleeding: aspirin 0.5% per year
placebo 0.4% per year

Based on 1224 patients, average study period 30.4 months

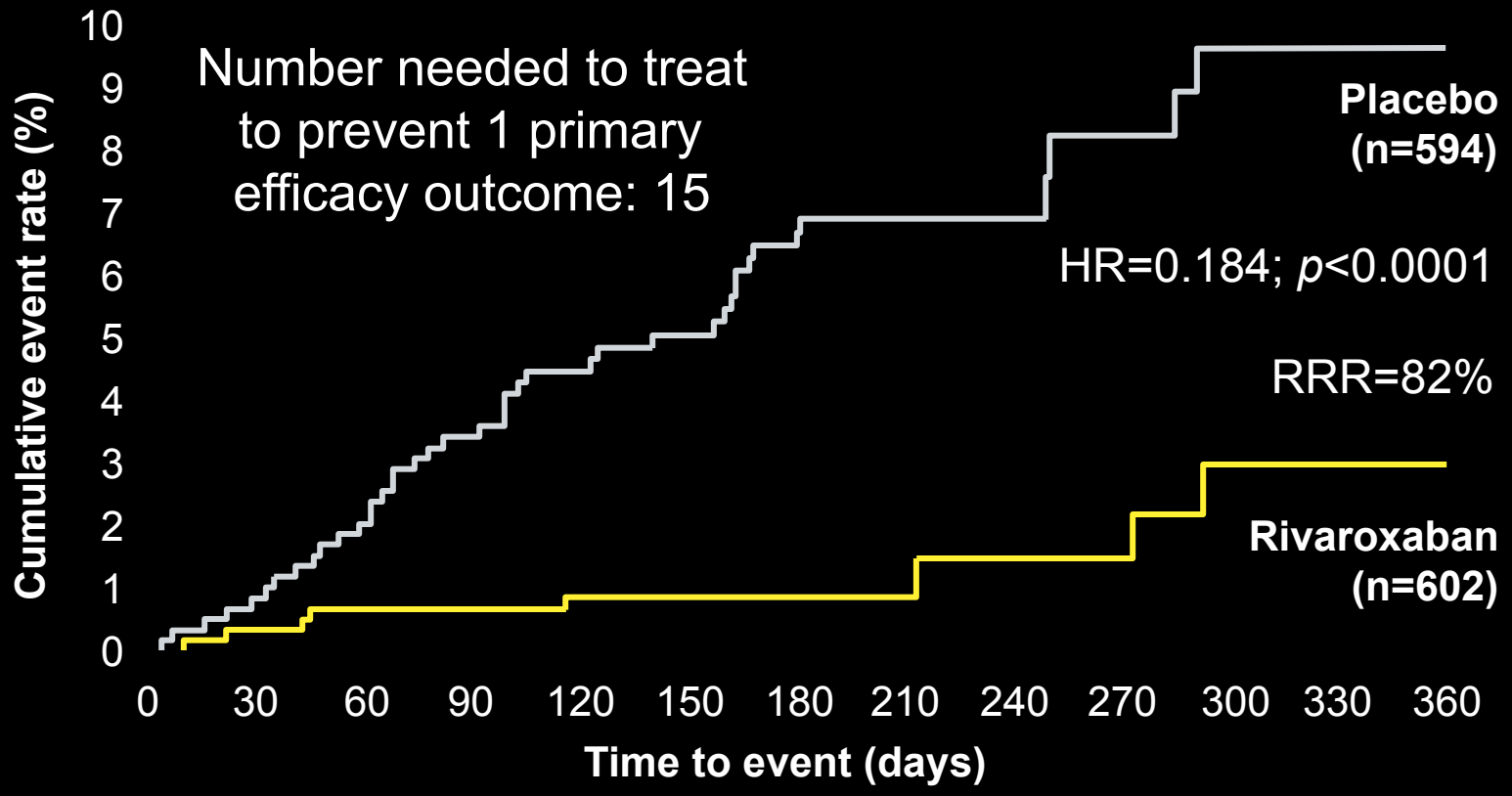
Phase III new oral anticoagulants for VTE treatment



Extended treatment studies with new oral anticoagulants

1. Einstein Extension (Rivaroxaban)
2. Amplify Extension (Apixaban)
3. Remedy & Resonate (Dabigatran)

Einstein Extension: Primary efficacy outcome



Riva	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

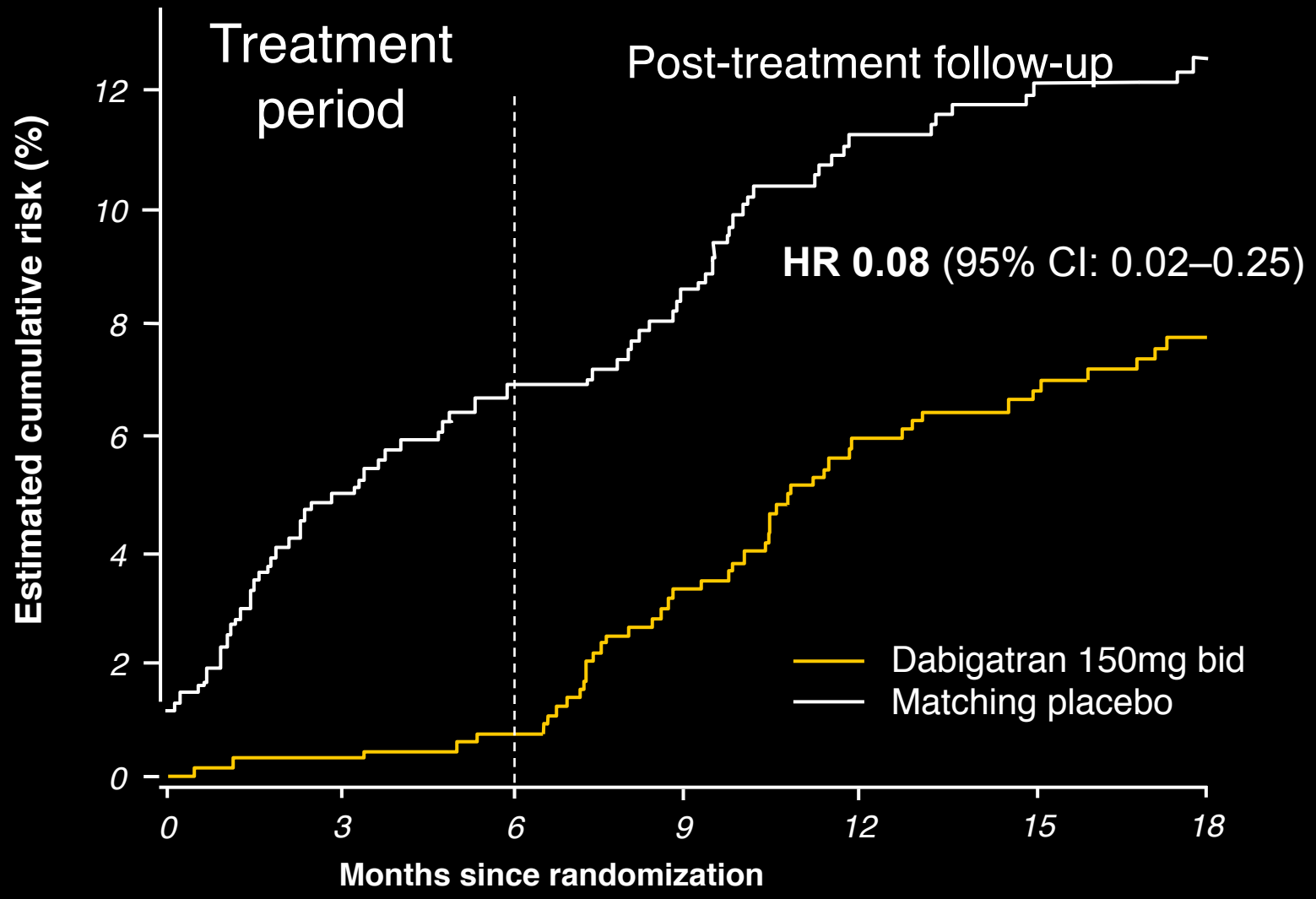
ITT population

Einstein Extension: Major bleeding

	Placebo (n=590)	Riva (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 hemoglobin ≥2 g/dL and/or transfusion		
Gastrointestinal bleeding	0	3 (0.5%)
Menorrhagia	0	1 (0.2%)

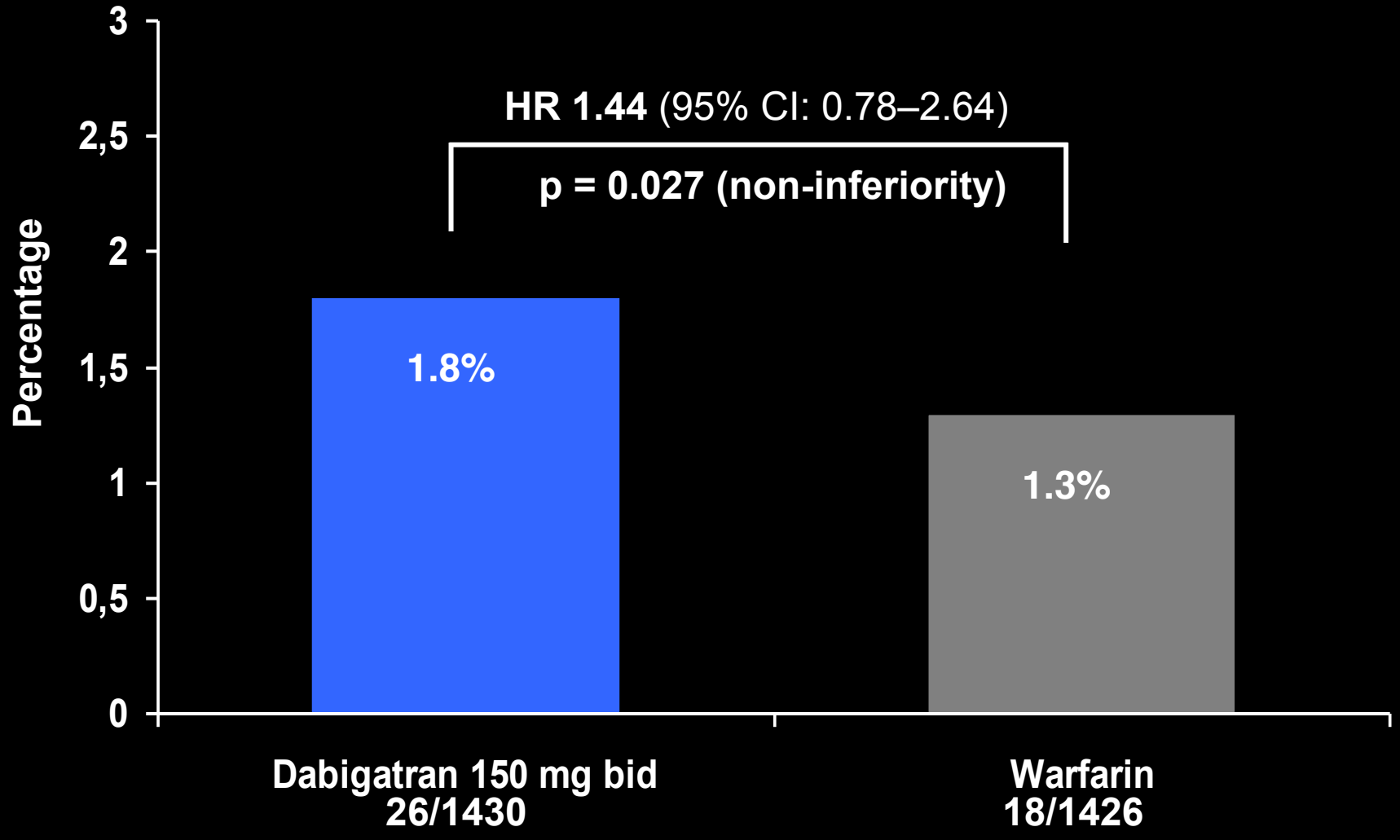
*p=0.11

Resonate



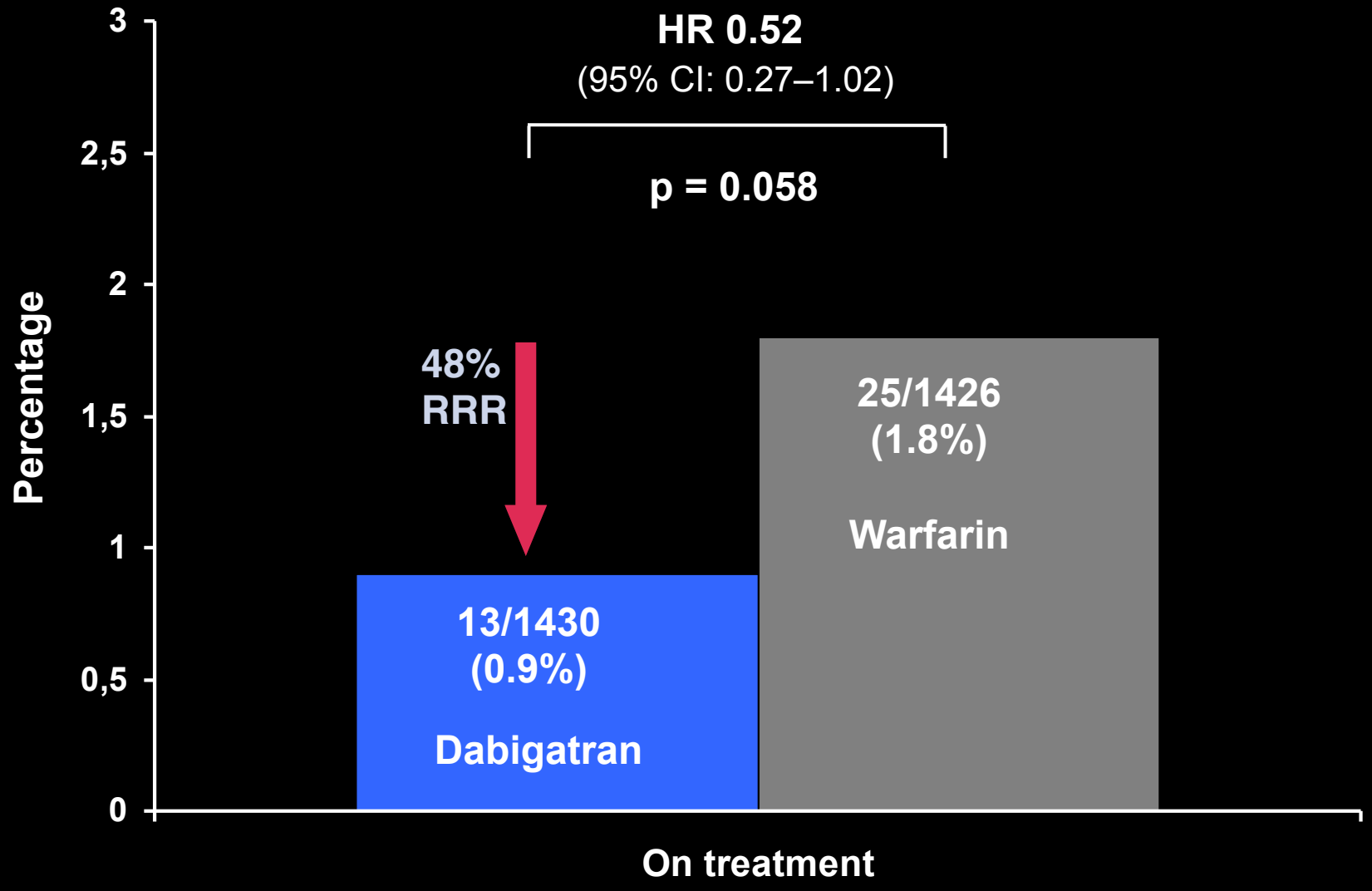
Schulman S, et al. *N Engl J Med*. 2013;368:709-718.

Remedy: Recurrent VTE

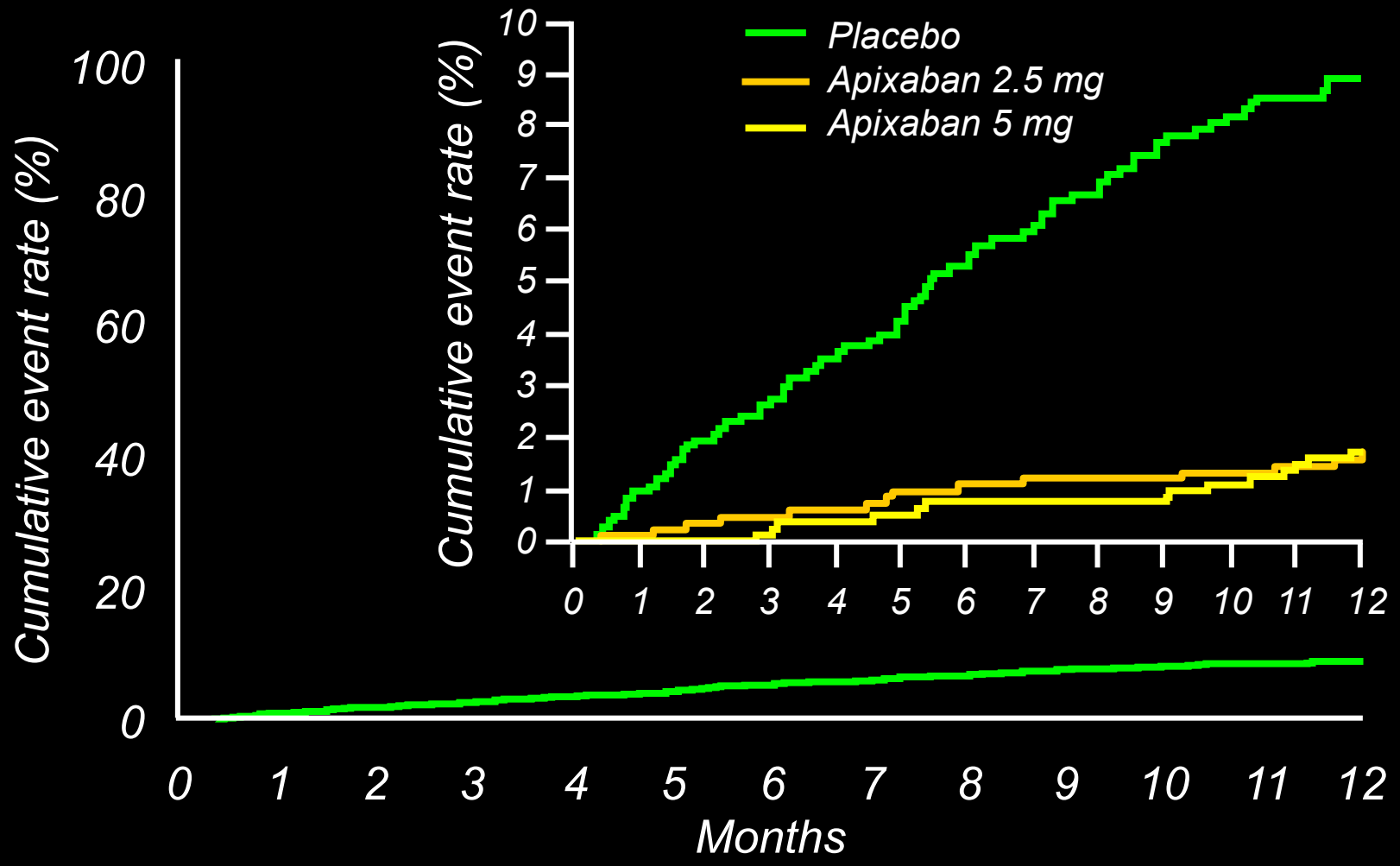


Risk difference 0.38 (95% CI: -0.50–1.25); p < 0.0001 (non-inferiority)

Remedy: Major bleeding



Amplify-Ext: VTE recurrences



Agnelli G, et al. *N Engl J Med*. 2013;368:699-708.

Amplify-Ext: Major & CRNMB

Event	Apixaban 2.5 mg N=840	Apixaban 5 mg N=811	Placebo N=826	Apixaban 2.5 mg vs placebo RR (95% CI)	Apixaban 5 mg vs placebo RR (95% CI)	Apixaban 2.5 mg vs 5 mg RR (95% CI)
Major bleed	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09, 2.64)	0.25 (0.03, 2.24)	1.93 (0.18, 21.25)
Clinically relevant non-major bleed	25 (3.0)	34 (4.2)	19 (2.3)	1.29 (0.72, 2.33)	1.82 (1.05, 3.18)	0.71 (0.43, 1.18)
Major or clinically relevant non-major bleeding	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69, 2.10)	1.62 (0.96, 2.73)	0.74 (0.46, 1.22)

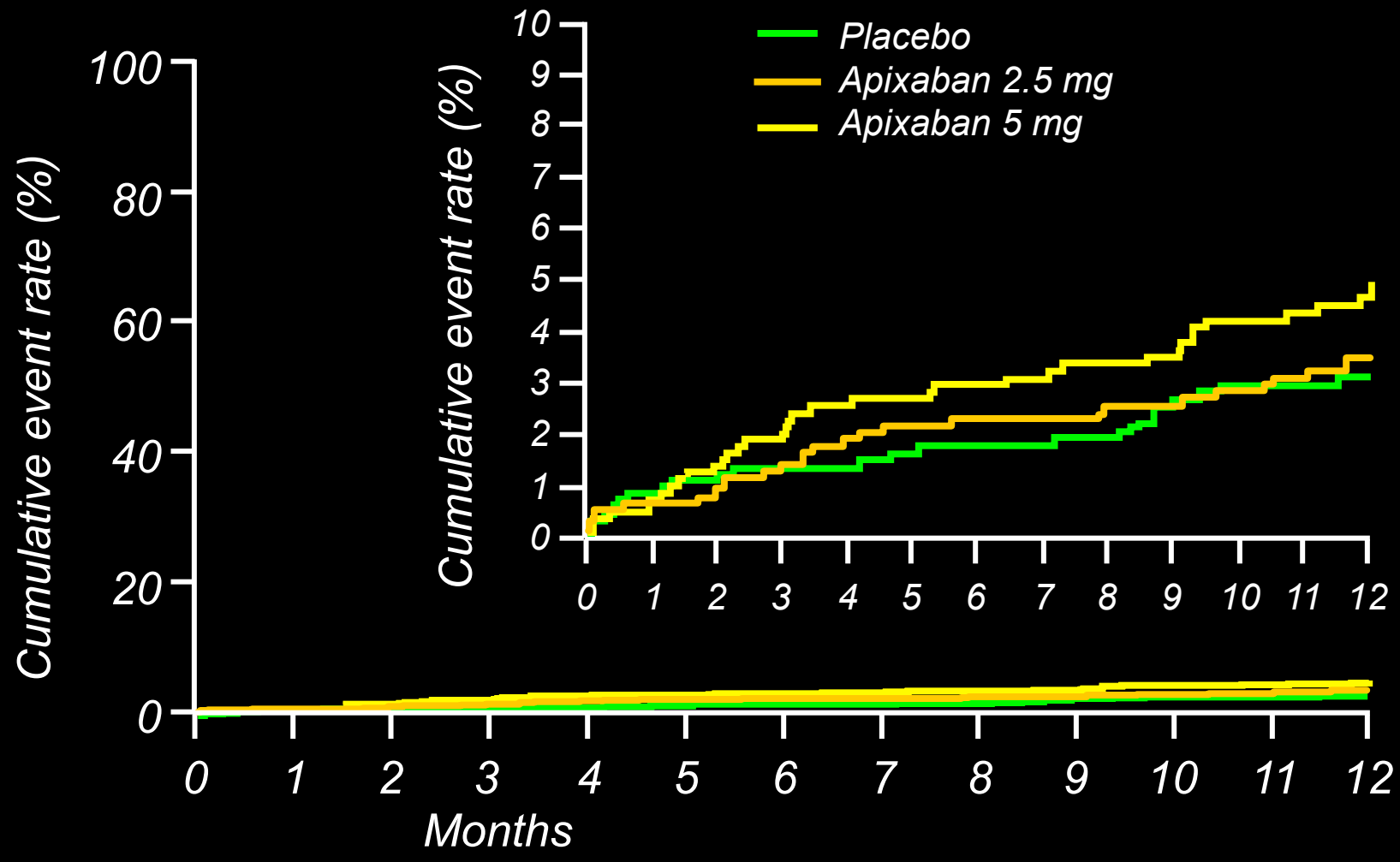
Major Bleeds

- *2.5 mg: 2 events, both Intraocular*
- *5.0 mg: 1 event, Gastrointestinal*
- *Placebo: 4 events, Intraocular, Stroke, Urogenital, Gastrointestinal*

CI, confidence interval; RR, relative risk

Agnelli G, et al. *N Engl J Med*. 2013

Amplify-Ext: Major & CRNMB



Agnelli G, et al. *N Engl J Med.* 2013

Amplify-Ext: Clinical interpretation

	Apixaban 2.5 mg	Apixaban 5 mg
NNT to prevent one recurrent VTE	14	14
NNH - one major or clinically relevant non-major bleed	200	63

NNH, number needed to harm; NNT, number needed to treat; VTE, venous thromboembolism

Agnelli G, et al. *N Engl J Med.* 2013

Conclusions

- All VTE patients should receive secondary prevention
- Extended treatment should be given after a careful individual risk-benefit assessment
- Risk-benefit should be periodically re-assessed
- Aspirin is associated with a 30-40% RR, safe and inexpensive
- NOAs are effective and safe for extended VTE treatment
- Low dose NOAs are to be preferred over other strategies