ADVANCES IN CARDIAC ARRHYTHMIAS *and* GREAT INNOVATIONS IN CARDIOLOGY

XXVII GIORNATE CARDIOLOGICHE TORINESI

Navigating through the current scientific evidence of NOACs

Selecting the right balance in VTE

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Navigating through the current scientific evidence of NOACs
Selecting the right balance in VTE

- Evidence of NOACs in VTE: an overview
- The issue of initial parenteral anticoagulation
- NOACS in perspective: an ultimate balance

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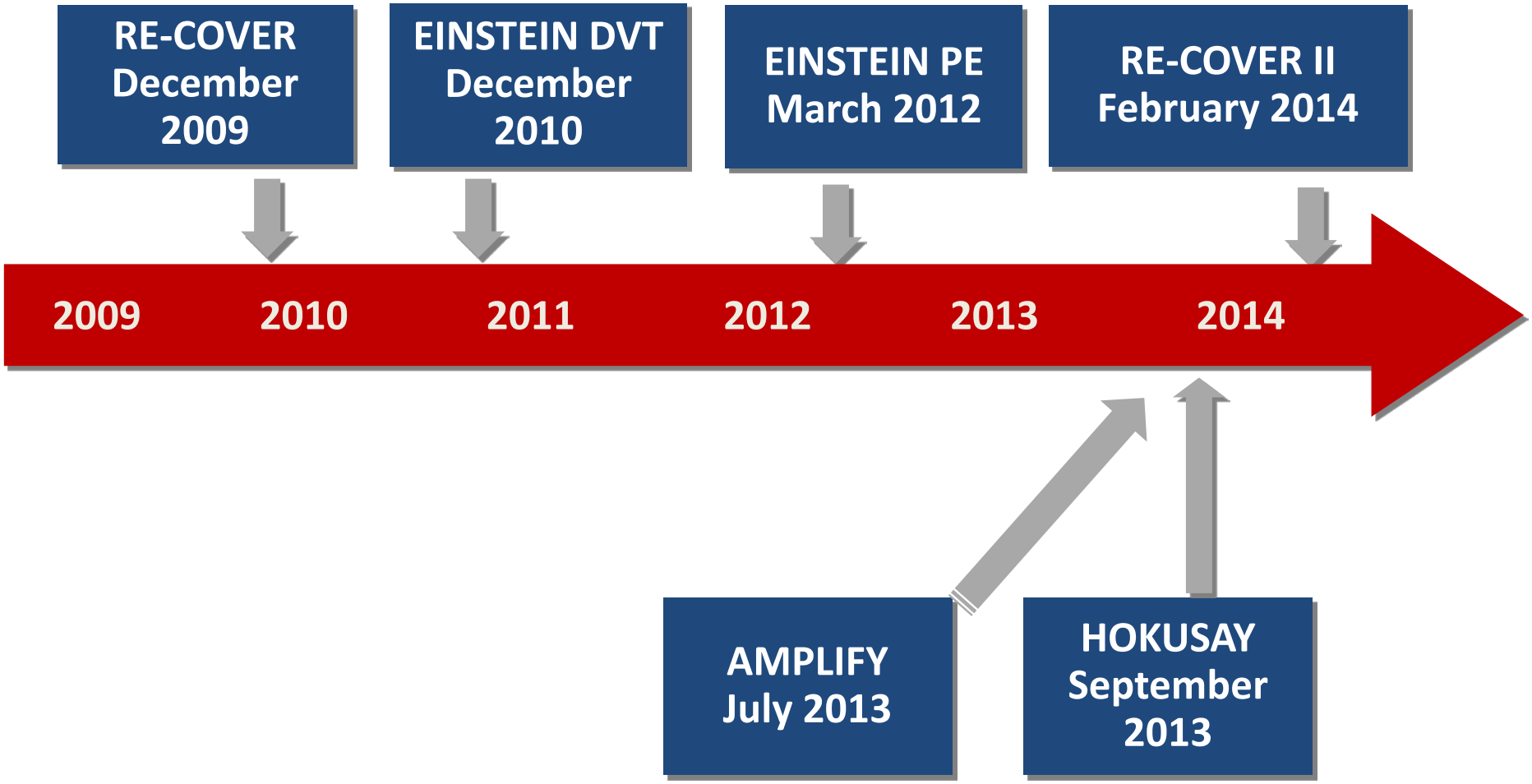
Acute VTE: NOACs clinical trial plot in last years



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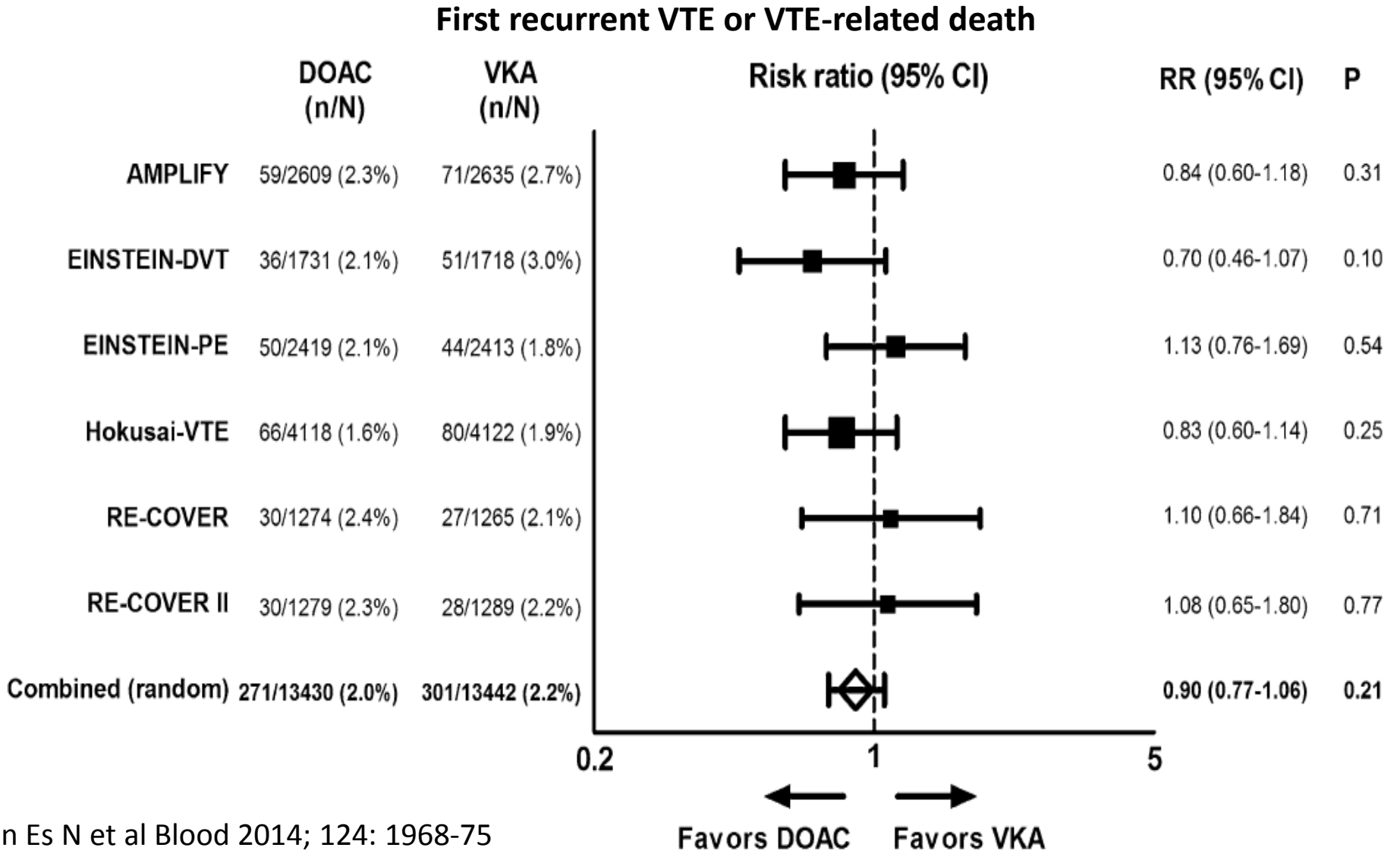
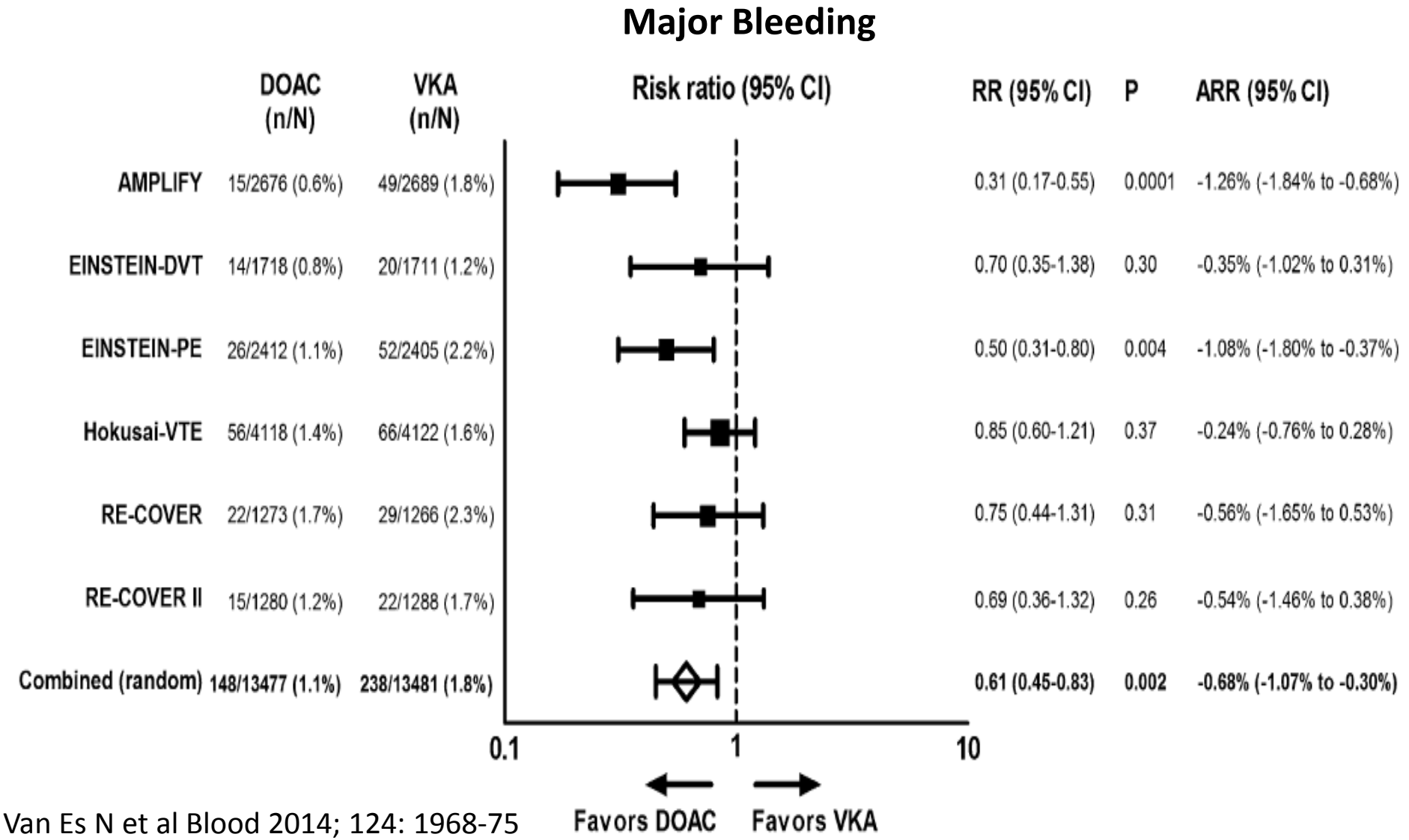
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Study	RE-COVER & RE-COVER II	EISTEIN-PE EINSTEIN-DVT	AMPLIFY	HOKUSAI
Design	Double blind	**PROBE**	Double blind	Double blind
N° Pts	5.107	8.281	5.395	8.240
Treatment approach	Switching approach	**Single-drug approach**	**Single-drug approach**	Switching approach
Dosing schedule	5-10 days of LMWH and then Dabi 150 mg BID	15 mg BID for three weeks then 20 mg QD	10 mg BID for 1 week then 5 mg BID	5 days of LMWH and then Edoxaban 60 mg QD
Treatment period	6 months	3-6-12 months	6 months	3-12 months
Primary Efficacy Endpoint	Recurrent symptomatic VTE (DVT, fatal or non-fatal PE)	Recurrent symptomatic VTE (DVT, fatal or non-fatal PE)	Recurrent symptomatic VTE (DVT, fatal or non-fatal PE)	Recurrent symptomatic VTE (DVT, fatal or non-fatal PE)
Primary Safety Endpoint	Major and non-major clinically relevant bleeding	Major and non-major clinically relevant bleeding	**Major and the composite of MB and NMCRB**	Major and non-major clinically relevant bleeding

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials



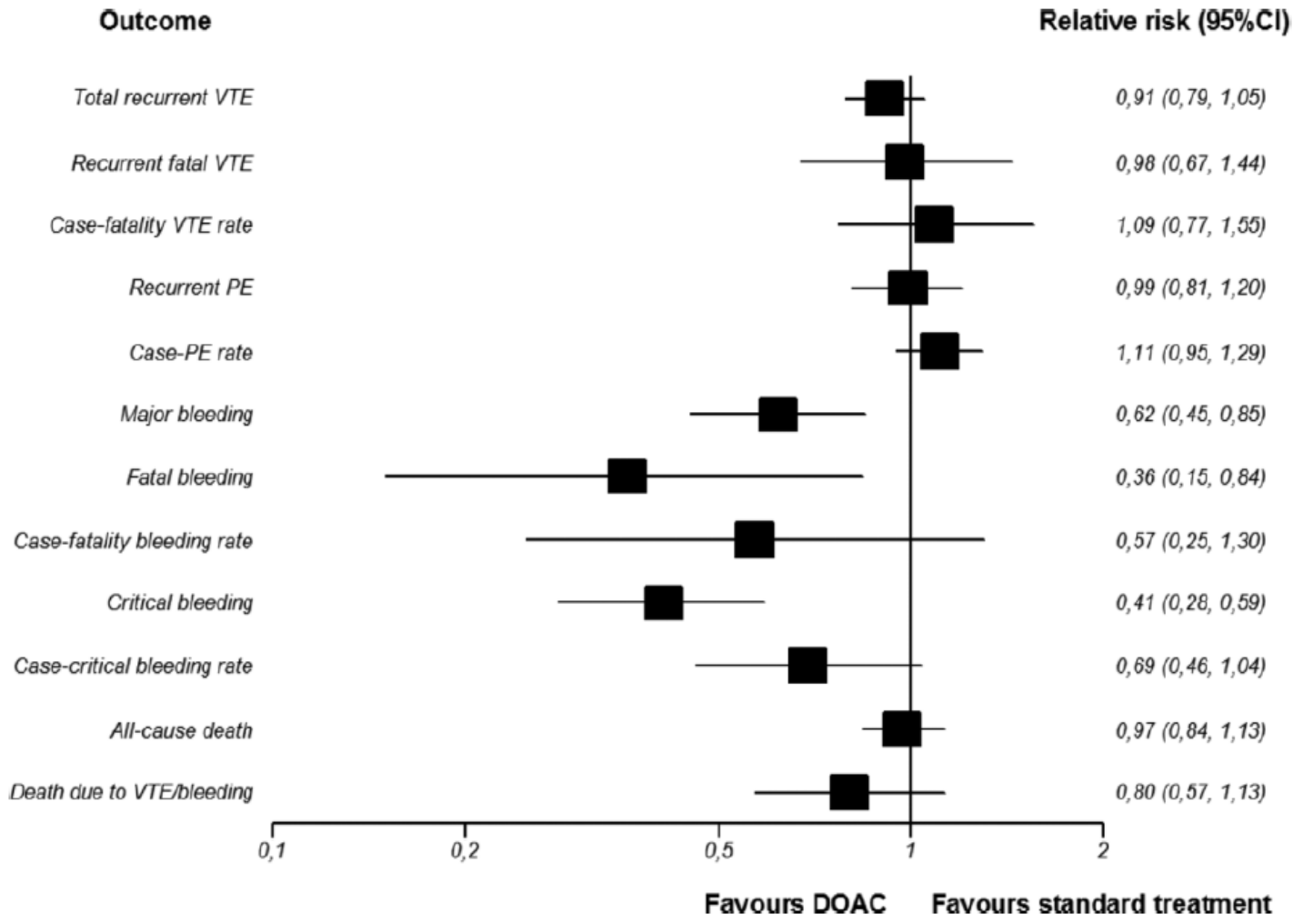
Van Es N et al Blood 2014; 124: 1968-75

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials



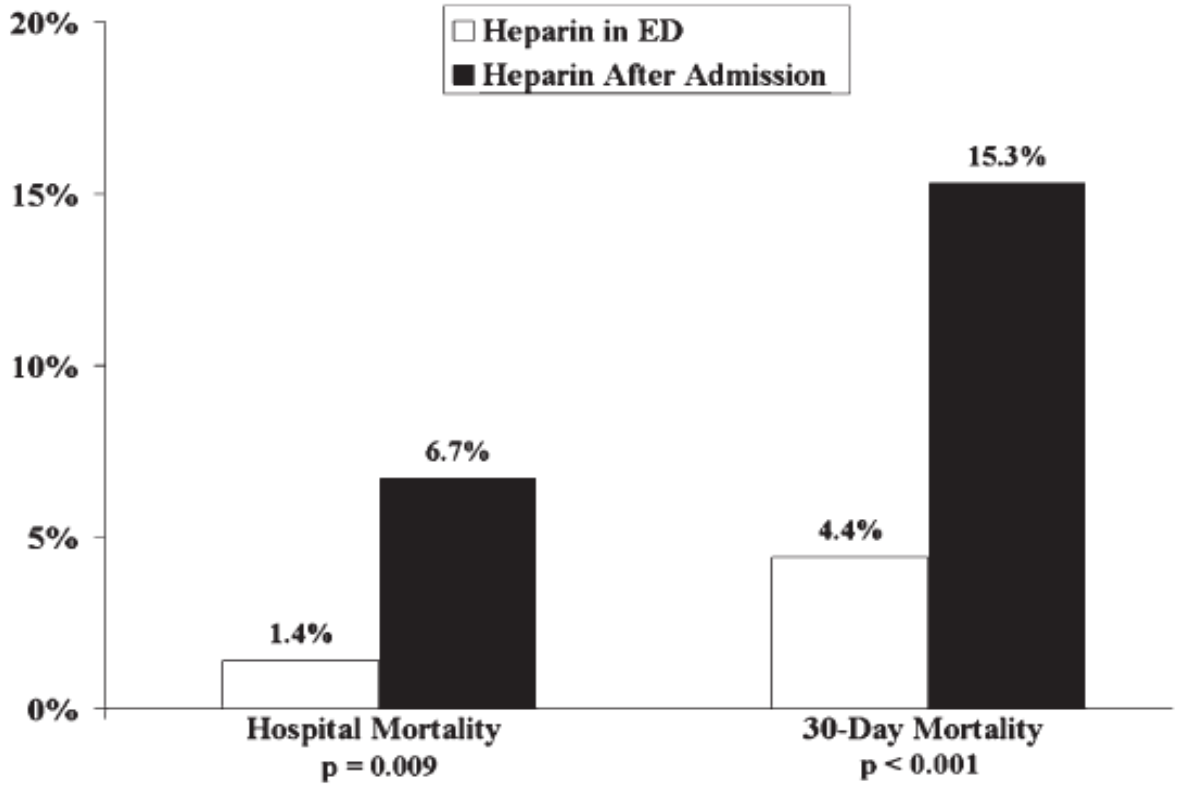
Van Es N et al Blood 2014; 124: 1968-75

Outcomes during initial treatment (DOAC vs standard treatment)



Gomez Outes A et al J Cardiovasc Pharmacol Ther 2015; 20: 490 -500

Early anticoagulation is associated with reduced mortality for acute pulmonary embolism



Smith SB et al CHEST 2010;137:1382-90

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Antithrombotic Therapy for VTE Disease

- 2.2.1. In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).

- 2.2.2. In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).

- 2.2.3. In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results.

Kearon C et al CHEST 2012; 141(2)(Suppl):e419S–e494S

Therapeutic schemes in VTE studies with NOACs

Study and Drug	
RECOVER & RECOVER 2 dabigatran	Parenteral anticoagulation for 6 (5-8) days followed by Dabigatran 150 mg bid
EINSTEIN DVT rivaroxaban	Rivaroxaban 15 mg bid for three weeks then 20 mg q.i.d.
EINSTEIN PE rivaroxaban	Rivaroxaban 15 mg bid for three weeks then 20 mg q.i.d.
AMPLIFY apixaban	Apixaban 10 mg bid for 7 days then 5 mgb.i.d.
HOKUSAI edoxaban	Enoxaparin or UFH for 6 (5-8) days followed by Edoxaban 30/60 mg qid

Schulman S et al Circulation 2014;129:764-72.
Einstein Investigators NEJM 2010;363:2499-510
Einstein PE Investigators NEJM 2012;366:1287-97
Agnelli GC et al NEJM 2013;369:799-808
Buller HR et al.N Engl J Med 2013;369:1406-15.

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	Events, % (n/N)		HR (95% CI)
	Dabigatran	Warfarin	
Major bleeding events	1.4 (37/2.553)	2.0(51/2554)	**0.73 (0.48–1.11)**
Major or clinically relevant non-major bleeding events	5.3 (136/2.553)	8.5 (217/2.554)	**0.62 (0.50–0.76)**
Any bleeding events	16.1 (411/2.553)	22.2 (567/2.554)	**0.70 (0.61–0.79)**

The safety profile is similar regardless to index event (DVT or PE)

Schulman S et al. N Engl J Med 2009; Schulman S et al. Circulation 2014

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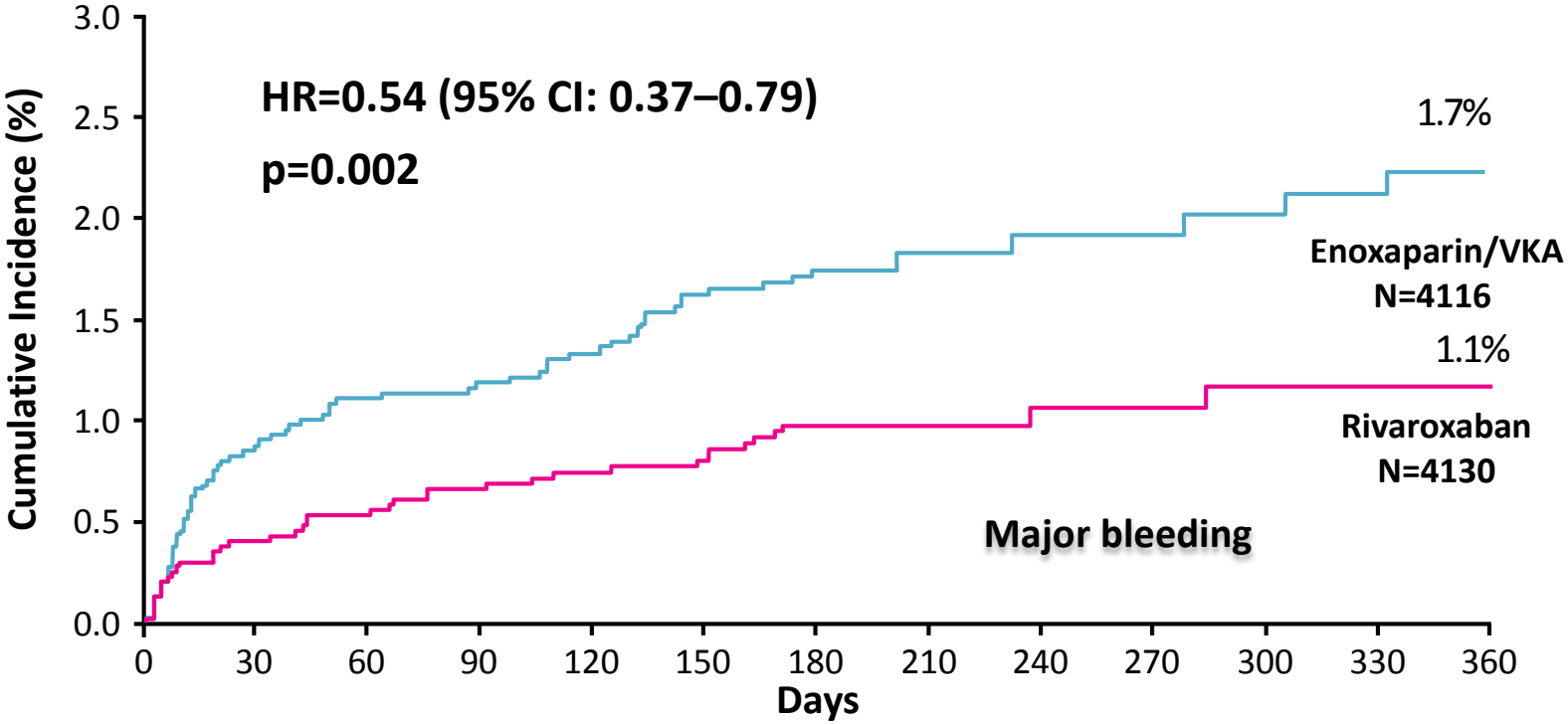

The EINSTEIN Investigators. N Engl J Med 2010; The EINSTEIN Investigators. N Engl J Med 2012

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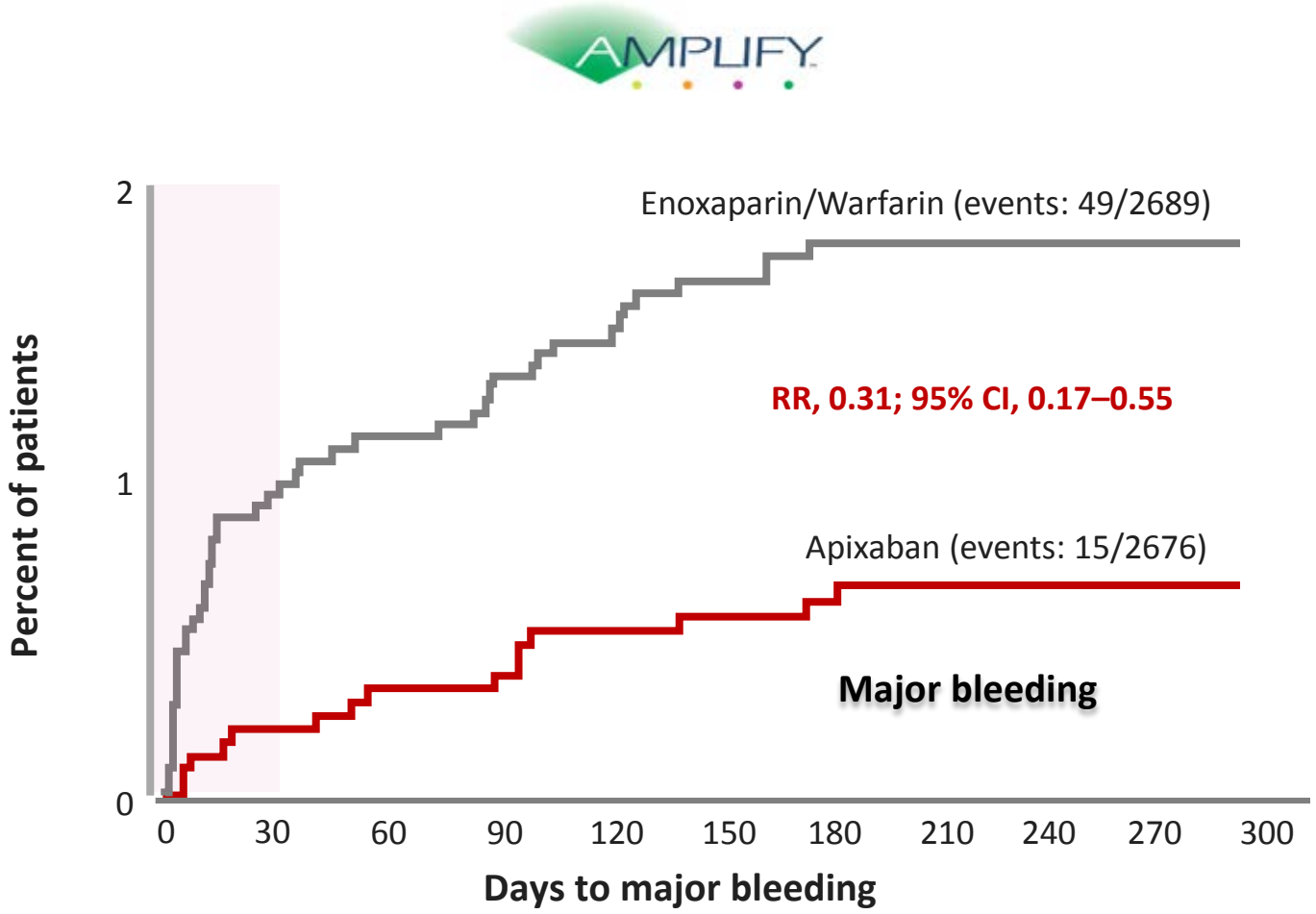

Agnelli G et al. N Engl J Med 2013

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Events	Apixaban n=2676	Enoxaparin/ Warfarin n=2689	Relative Risk (95% CI)	RRR	P Value
Major Bleeding, n (%)	15 (0,6)	49 (1,8)	**0,31 (0,17–0,55)**	**69%**	<0,001 superiority
CRNM Bleeding, n (%)	103 (3,8)	215 (8,0)	**0,48 (0.38–0.60)**	**52%**	
Major Bleeding or CRNM, n (%)	115 (4,3)	261 (9,7)	**0.44 (0.36–0.55)**	**56%**	<0,001

Agnelli G et al. N Engl J Med 2013

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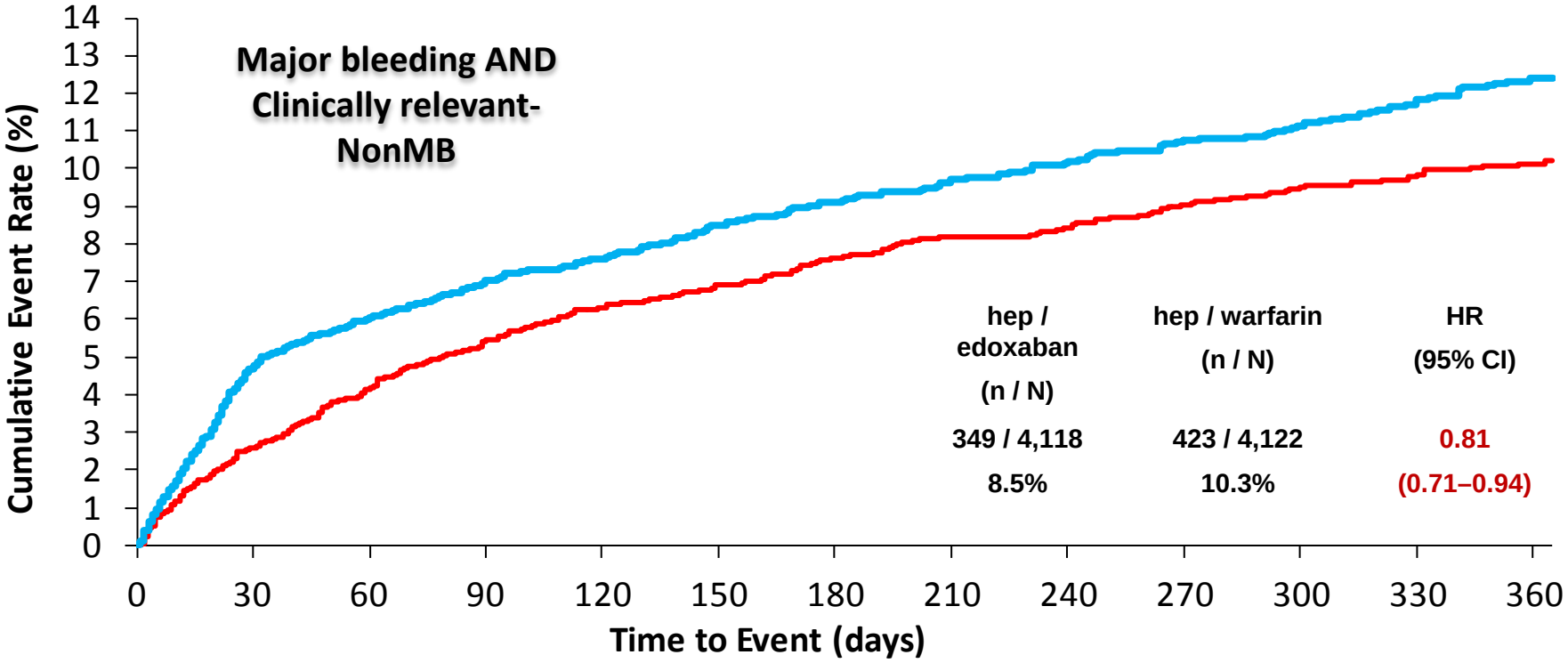


Büller H et al. N Engl J Med 2013

Pre-study Heparin in EINSTEIN studies

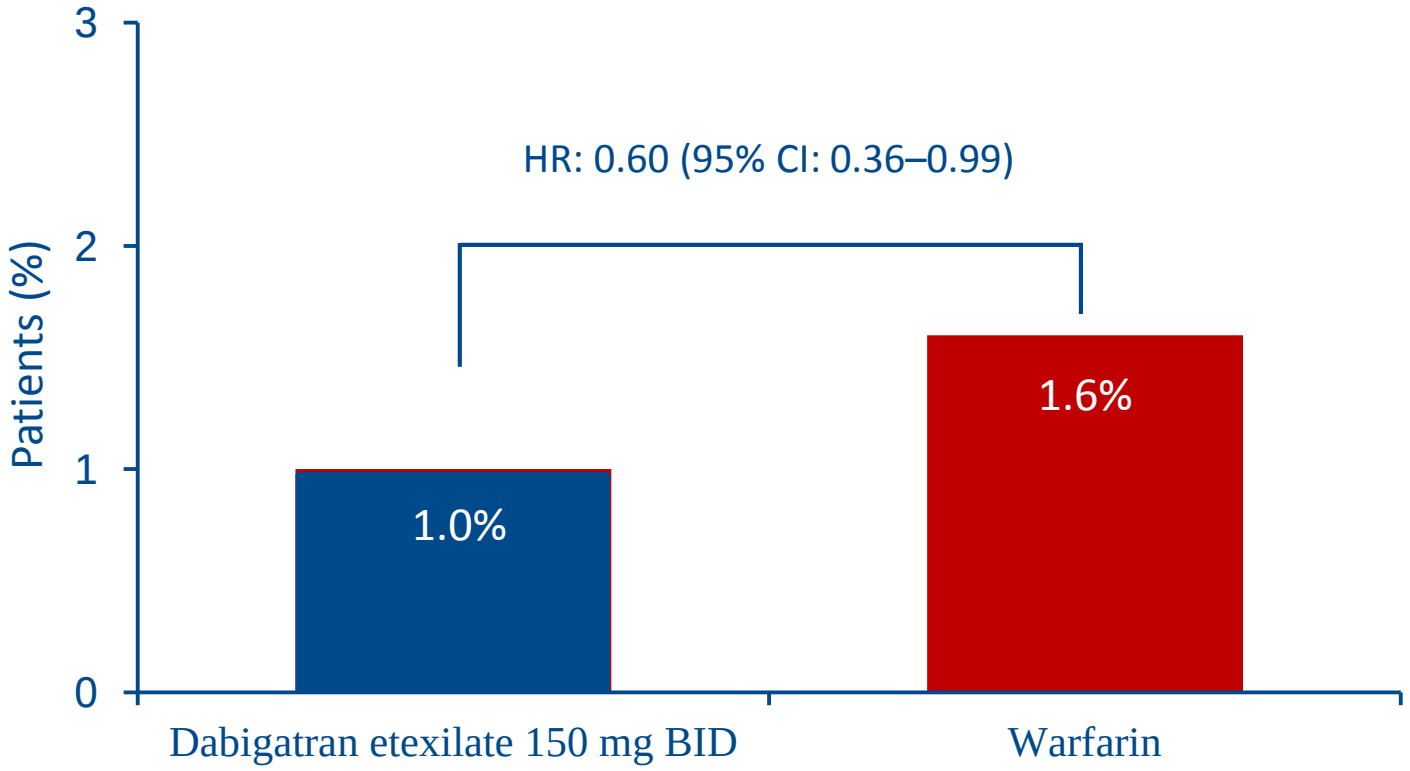
Variable	Rivaroxaban (*n* = 4,150)	Enoxaparin/VKA (*n* = 4,131)
No prestudy heparin use, *n* (%)	649 (15.6)	695 (16.8)
Prestudy heparin use (days), *n* (%)		
≤0.5	337 (8.1)	378 (9.2)
1	2,103 (50.7)	2,022 (48.9)
>1–2	1,006 (24.2)	980 (23.7)
>2	55 (1.3)	56 (1.4)
Mean (±SD)*	1.04 (±0.74)	1.03 (±0.42)
Median (IQR)*	1.00 (0.79 to 1.11)	1.00 (0.78 to 1.10)

*Patients who received prestudy heparin only.
IQR = interquartile range; VKA = vitamin K antagonist

Prandoni P et al Acad Emerg Med 2015

RE-COVER/RE-COVER II: major bleeding

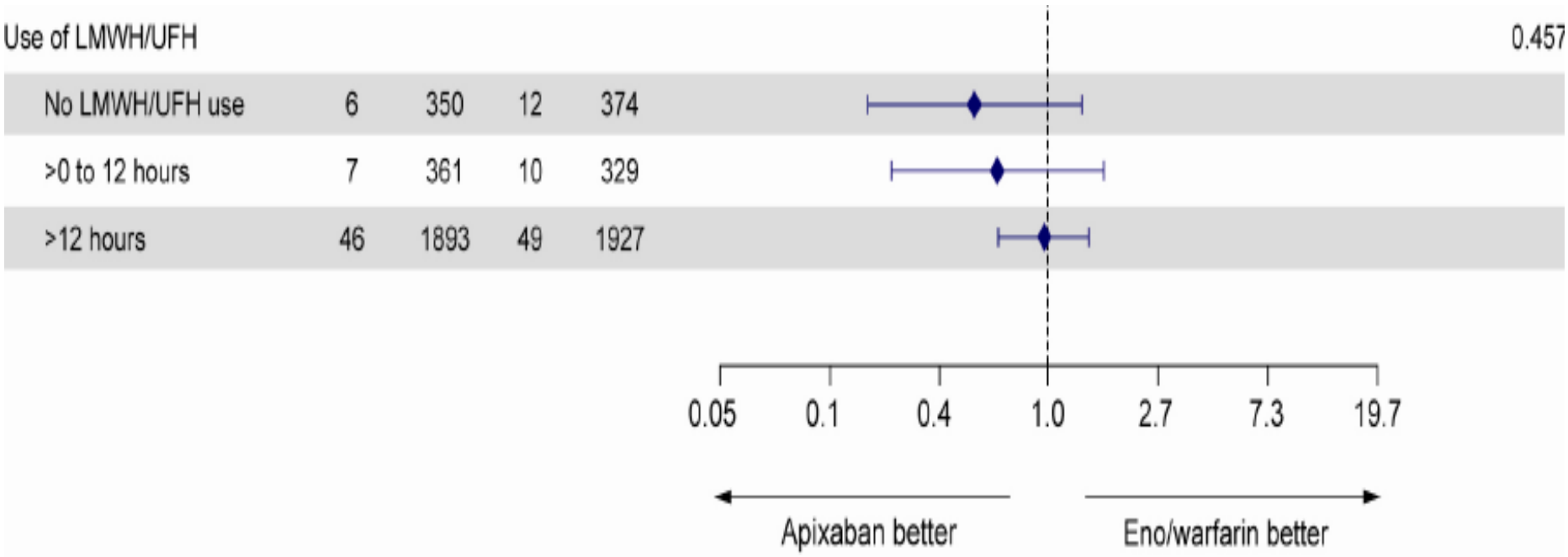
Incidence of major bleeding significantly lower with dabigatran vs warfarin during period where only oral anticoagulant was received (pooled data)



Significance based on upper limit of 95% CI not crossing 1.0

Schulman S et al. Circulation 2013; DOI: 10.1161/CIRCULATIONAHA.113.004450

AMPLIFY: Relative Risk of the Primary Safety Outcomes According to Use of Initial Parenteral Anticoagulation

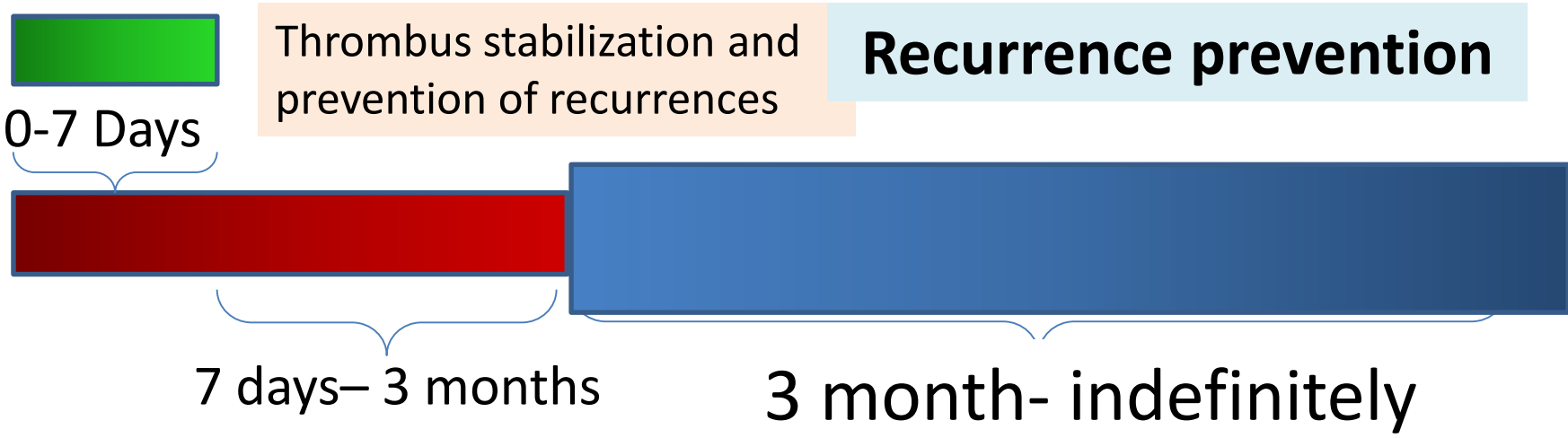


Agnelli G et al. N Engl J Med 2013

9th ACCP Guidelines

VTE and phases of anticoagulation

Initial treatment with parenteral anticoagulation
LMWH (2B), Fondaparinux, UFH (2C)



Long-term treatment with VKAs,LMWH, rivaroxaban, dabigatran

Kearon C et al CHEST 2012; 141(2)(Suppl):e419S–e494S

Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting

Kearon C, Iorio A, Palareti G, on behalf of the Subcommittee on Control of Anticoagulation of the SSC of the ISTH. J Thromb Haemost 2010; 8: 2313–5.

"we suggest that a risk of recurrence appreciably higher than 5% at 1 year and 15% at 5 years would not be acceptable to many physicians and patients, and would usually discourage stopping anticoagulant therapy."

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Recurrent VTE Event Rates During Anticoagulant Therapy

13 prospective cohort studies and 56 randomized, controlled trials

Outcome	Event Rate, by Therapy Duration	
	Any VTE†	
	3 mo	6 mo
Patients, *n*	19 027	11 032
Case-fatality rate (95% CI), %	11.3 (8.0–15.2)	13.7 (9.0–19.2)
Recurrent fatal VTE (95% CI), %	0.4 (0.3–0.6)	0.5 (0.3–0.7)

Outcome	Event Rate, after Therapy
	Any VTE†
Patients, *n*	47663
Case-fatality rate (95% CI), %	3.6 (1.9-5.7)
Recurrent fatal VTE (95% CI), %	0.3(0.1-0.4)

Carrier M et al. Ann Intern Med 2010 4;152:578-89

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Bleeding Event Rates During Anticoagulant Therapy

13 prospective cohort studies and 56 randomized, controlled trials

Outcome	Event Rate, by Therapy Duration	
	Any VTE†	
	3 mo	6 mo
Patients, *n*	19 027	11 032
Case-fatality rate (95% CI), *%*	11.3 (7.5–15.9)	11.0 (4.8–13.2)
Recurrent fatal VTE (95% CI), *%*	0.2 (0.1–0.3)	0.2 (0.1–0.3)

Carrier M et al. Ann Intern Med 2010 4;152:578-89

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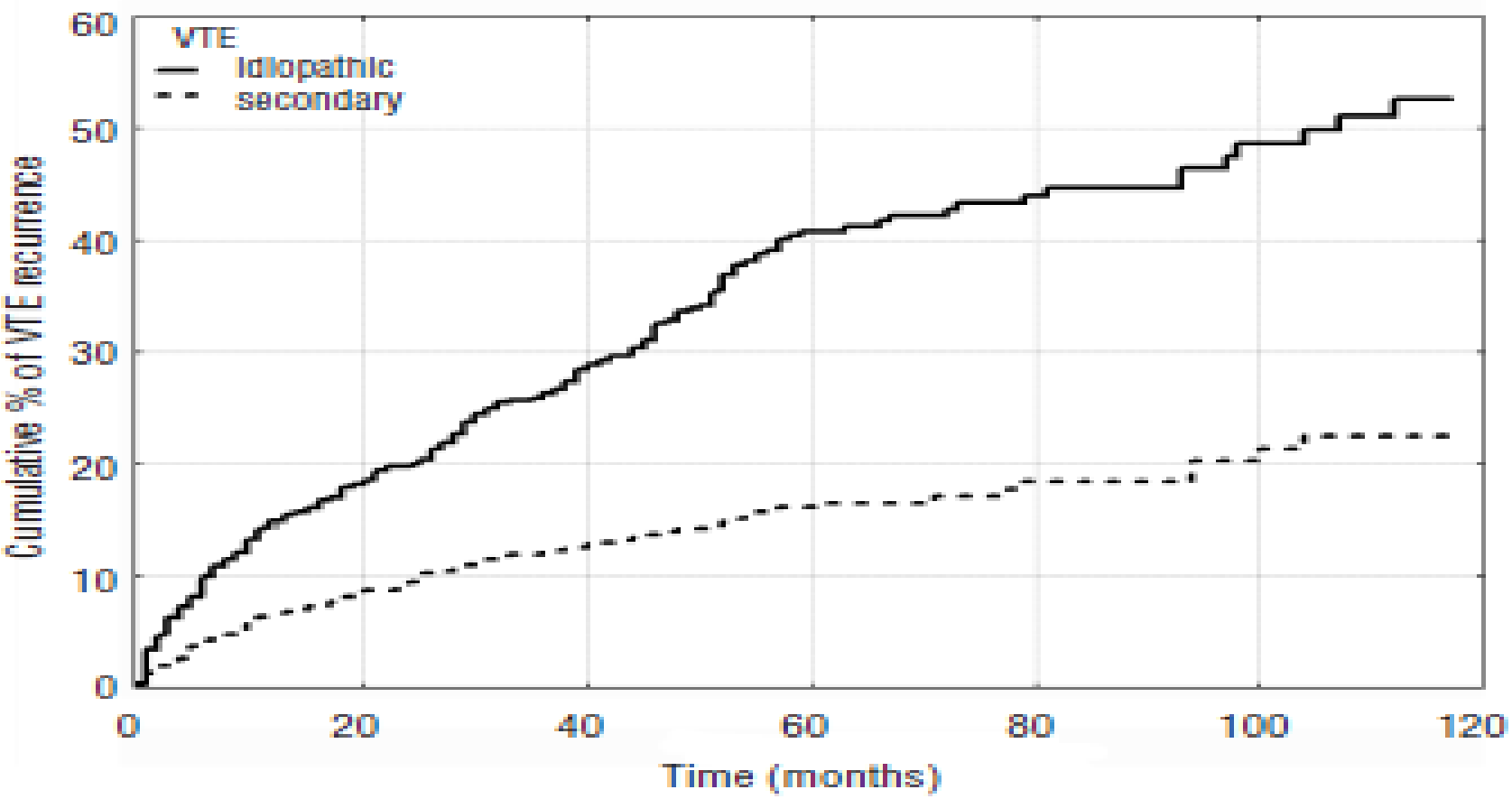

Prandoni P, et al. Haematologica 2007

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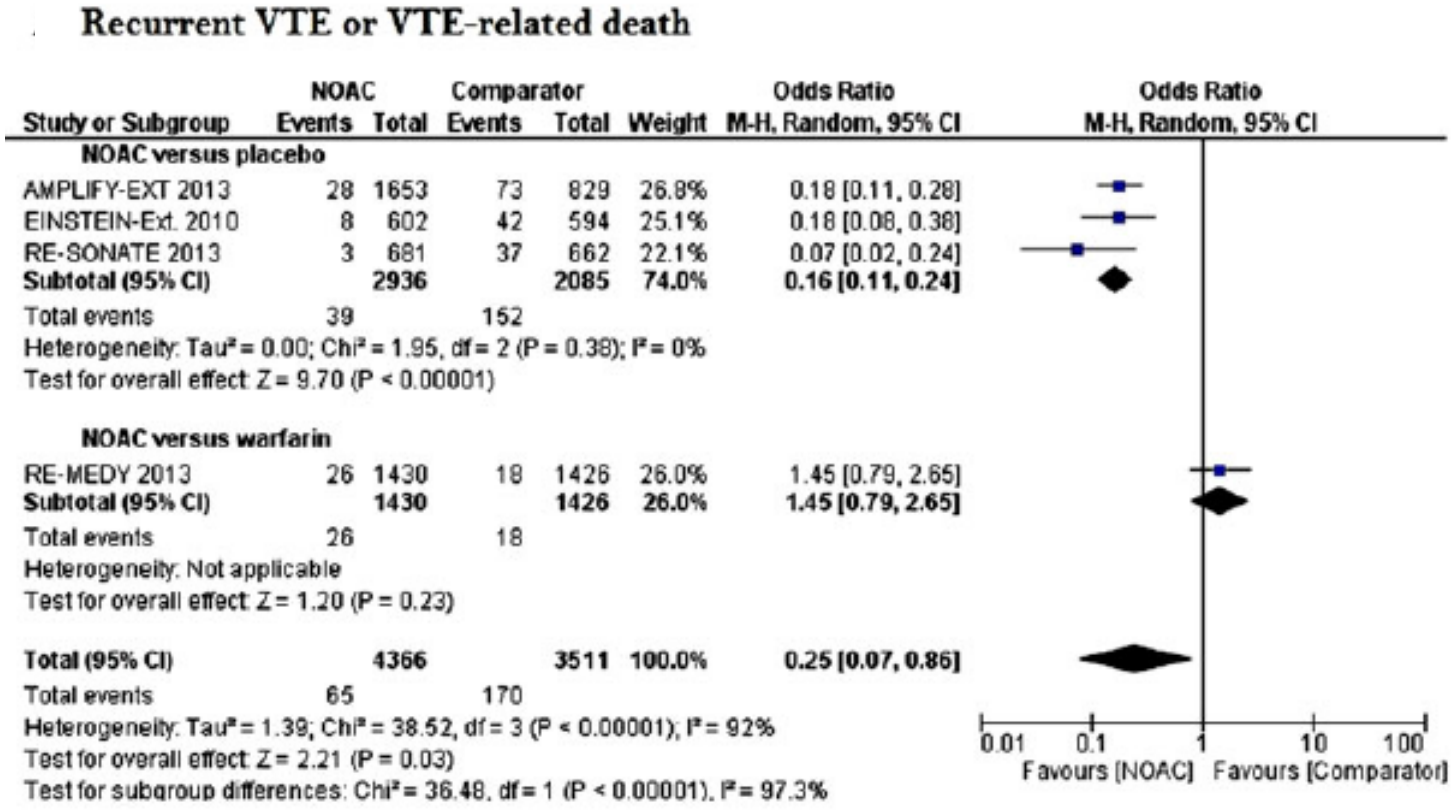
Efficacy and Safety of New Oral Anticoagulants for Extended Treatment of Venous Thromboembolism: Systematic Review and Meta-Analyses of Randomized Controlled Trials



Sardar P et al Drugs 2013

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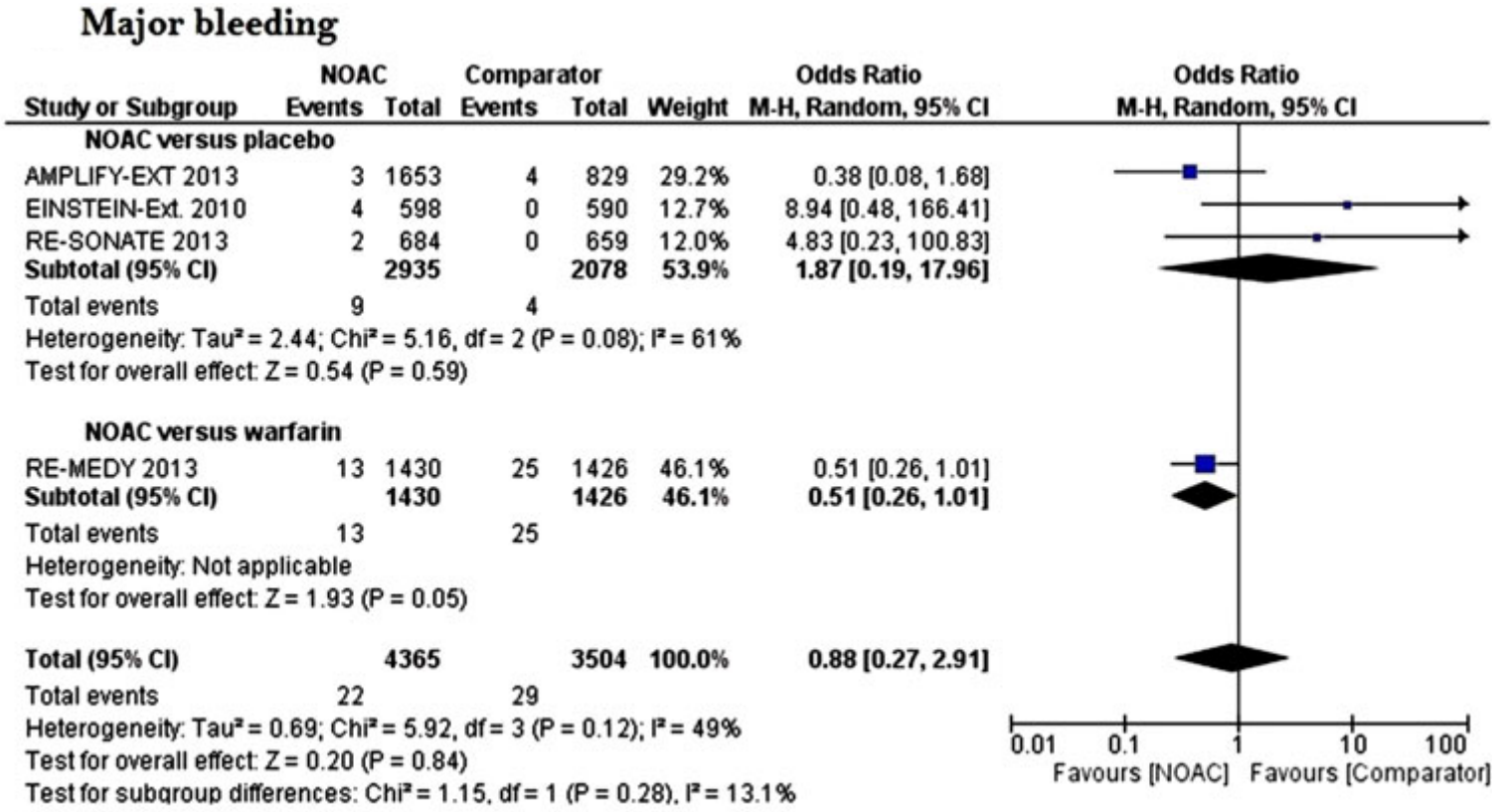

Sardar P et al Drugs 2013

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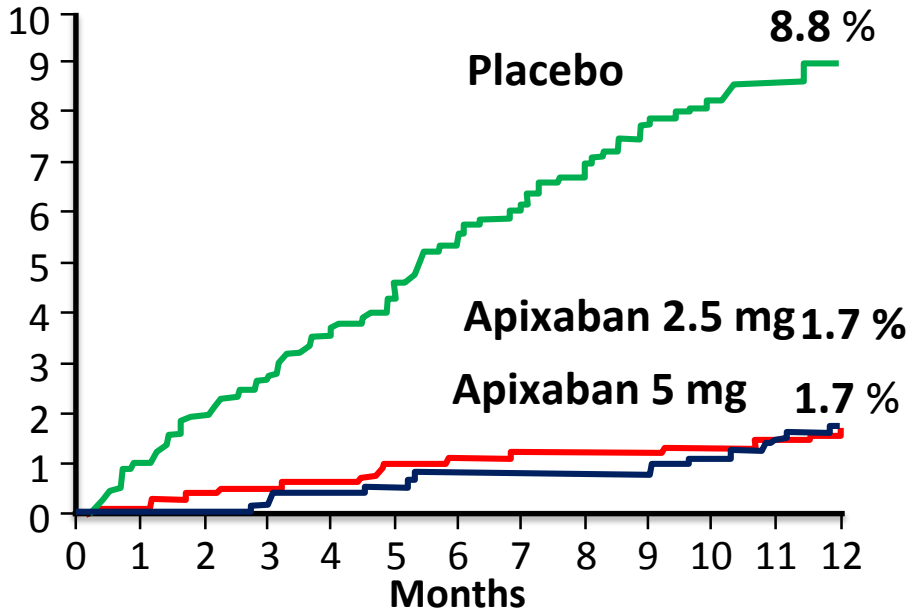
Extended phase/secondary prevention of VTE
AMPLIFY-EXT study

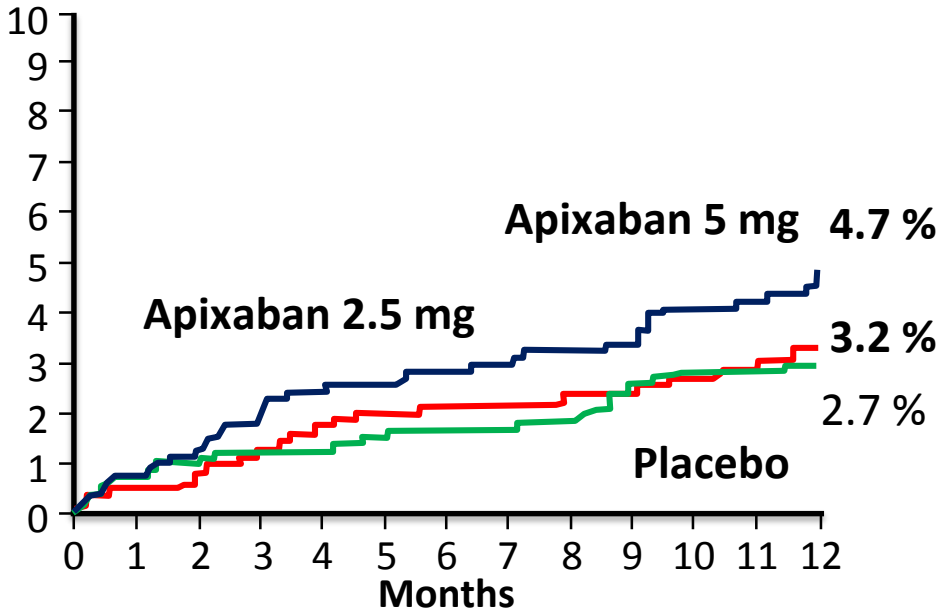
VTE recurrence

n=2 482



Apixaban 2.5 mg/placebo: HR = 0.19 (0.11–0.33)
Apixaban 5 mg/placebo: HR = 0.20 (0.11–0.34)

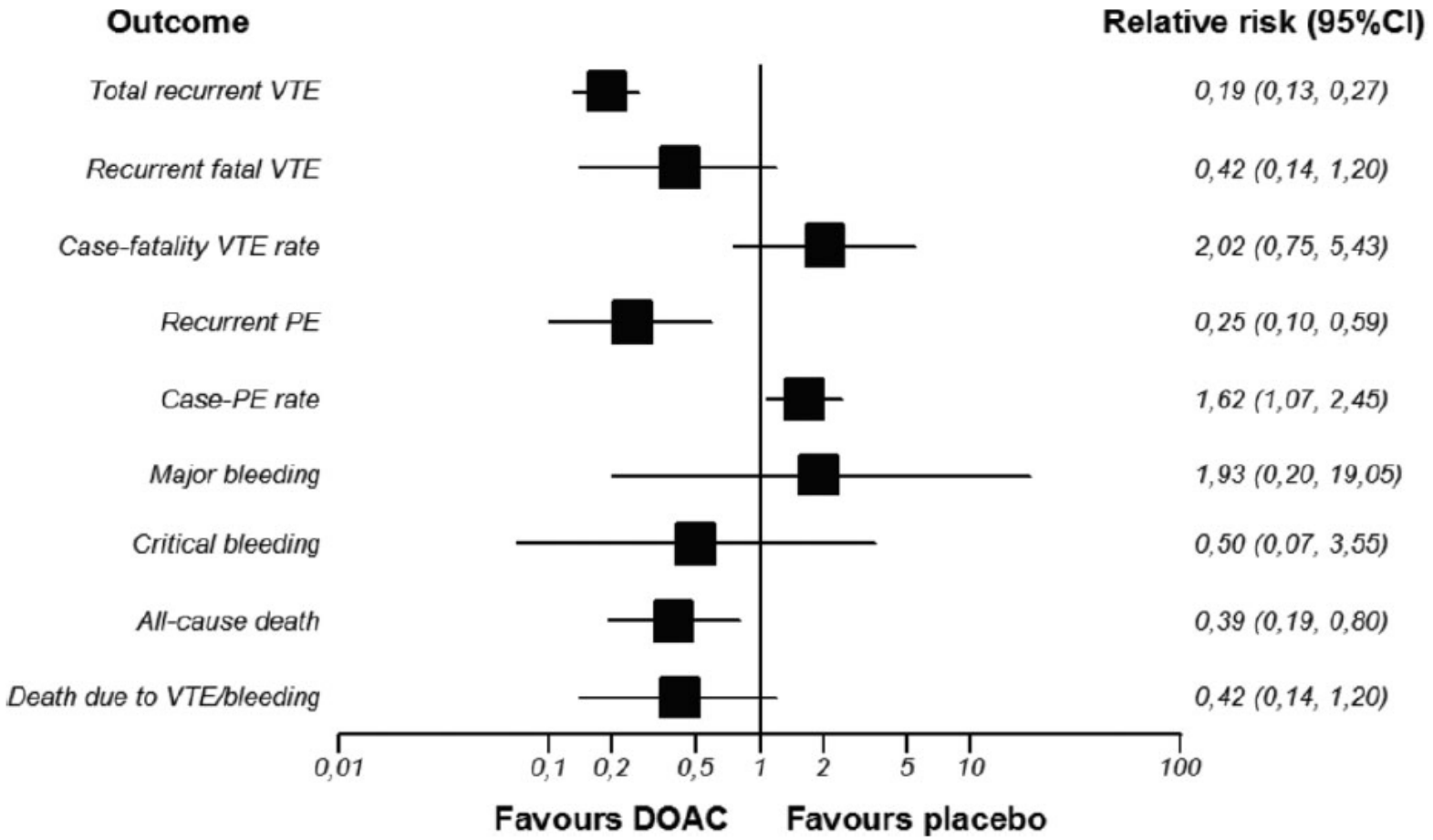
Major or CRNM bleeding



Apixaban 2.5 mg/placebo: HR = 1.20 (0.69–2.10)
Apixaban 5 mg/placebo: HR = 1.62 (0.96–2.73)

Agnelli G et al. N Engl J Med 2013

Outcomes during extended treatment (DOAC vs standard treatment)



Gomez Outes A et al J Cardiovasc Pharmacol Ther 2015; 20: 490 -500

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CONCLUSIONS

In the context of the initial treatment of VTE NOACS are equally effective compared to warfarin and safer as regards the major bleeding

The observed lower fatal bleeding together with reduced case-fatality rate due to bleeding episodes in NOACs-treated patients strengthens their better safety profile

The initial parenteral anticoagulation appears to play a role in determining the risk of bleeding

The benefits of extended treatment with NOACs in terms of VTE reduction are also allowed by their low risk of bleeding