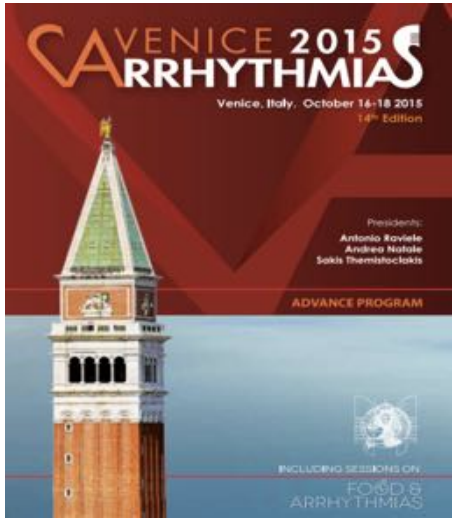


Venice October 16th 2015

The clinical relevance of AMPLIFY programme

Francesco Dentali
Department of Clinical Medicine
Insubria University Varese

Disclosures

Bayer

Bristol-Myers Squibb/Pfizer

Boehringer Ingelheim

Daiichi Sankyo

Sanofi

Alfa Wassermann

- Prof Dentali is being compensated for this talk as a paid consultant for Bristol-Myers Squibb and Pfizer

Significant Morbidity and Mortality of VTE

Morbidity

- Approximately 5%–7% of patients with VTE have a recurrence during the first 3 months while on treatment[1]
- Without extended treatment after unprovoked VTE, a recurrence occurs in[2]
  - 15% of patients by 1 year
  - 41% of patients by 5 years
- VTE is associated with long-term, clinically significant complications, including PTS and CTEPH[1]

Mortality

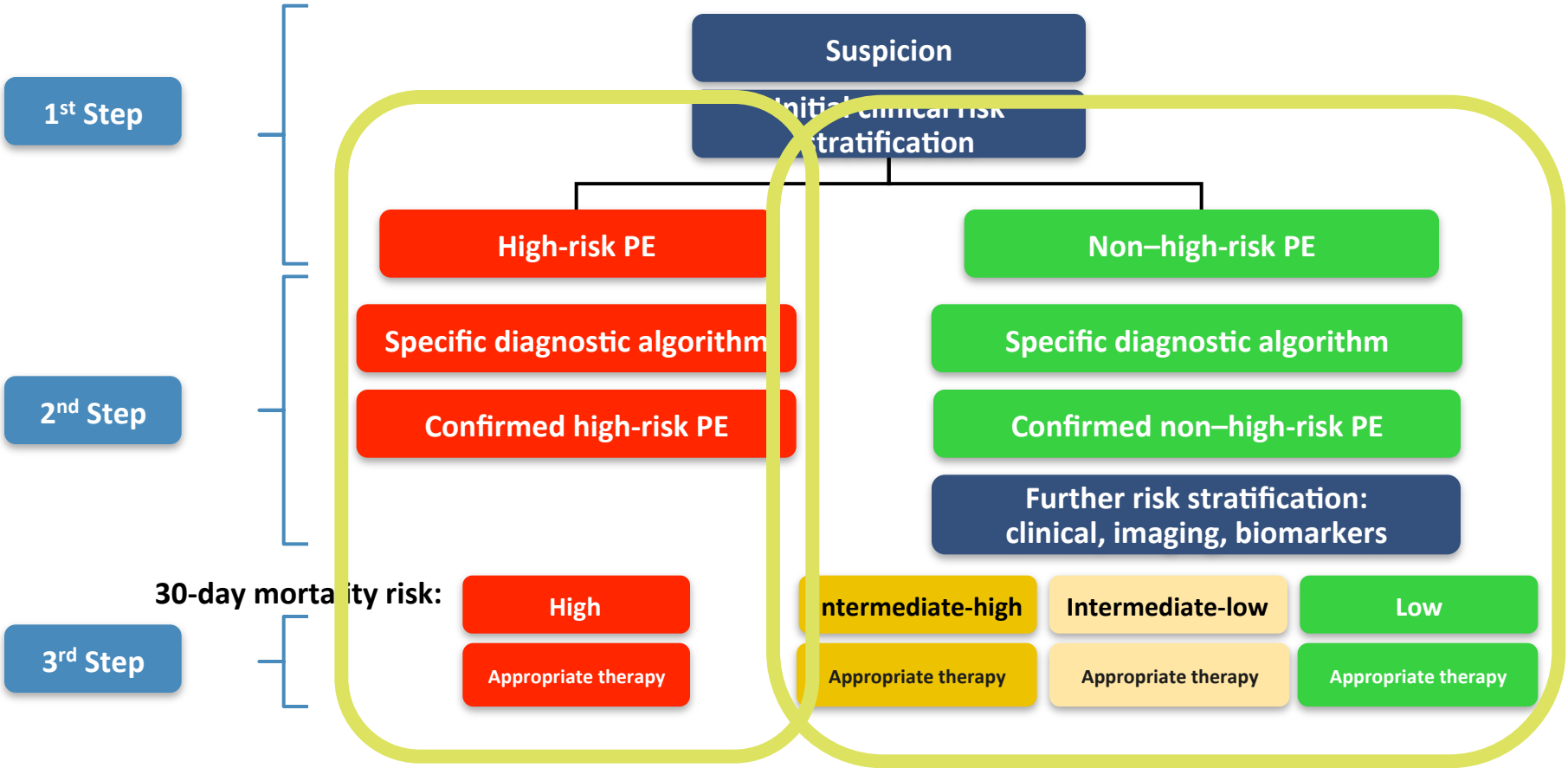
- Nearly 550,000 annual deaths due to VTE across the EU[3]
- Patients with PE after a course of anticoagulation (mean, 6 months) may have up to a 12.3% case-fatality rate from recurrent PE (mean follow-up, 54 months)[4]
- PE may be responsible for 1 in ~10 hospital deaths[5]

PTS=post-thrombotic syndrome; CTEPH=chronic thromboembolic pulmonary hypertension.

1. Palareti G. *Scientifica*. 2012;2012:1-17.
2. Prandoni P et al. *Haematologica*. 2007;92:199-205.
3. Cohen AT et al. *Thromb Haemost*. 2007;98:756-764.
4. Douketis J et al. *Ann Intern Med*. 2007;147:766-774.
5. Geerts WH et al. *Chest*. 2004;126(suppl 3):338S-400S.

Management of Acute Pulmonary Embolism: A Three-Step Approach Upon Suspicion of PE[1,2]

1. Immediately identify whether patient is high-risk
2. Confirm PE and further stratify the non-high-risk patients
3. Treat with therapy appropriate for the patient's risk level



1. Konstantinides S. Presented at: European Society of Cardiology Congress 2014; August 30-September 3, 2014; Barcelona, Spain. FP1116.
2. Konstantinides S et al. *Eur Heart J*. 2014;35:3033-3069, 3069a-3069k.

Classification of Patients Based on Risk Scores, RV Dysfunction, and Biomarkers

- PESI Class III to V indicates moderate to very high 30-day mortality risk; simplified PESI (sPESI) ≥1 point indicates high 30-day mortality risk

Early Mortality Risk		Risk Parameters and Score			
		Shock or Hypotension	PESI Class III-V or sPESI ≥1	Signs of RV Dysfunction on an Imaging Test*	Cardiac Laboratory Biomarkers†
High		+	(+)‡	+	(+)‡
Intermediate	Intermediate-high	-	+	Both positive	
	Intermediate-low	-	+	Either one (or none) positive§	
Low		-	-	Assessment optional; if assessed, both negative§	

* Echocardiographic criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV/LV diameter ratio; hypokinesia of the free RV wall; increased velocity of the tricuspid regurgitation jet; or combinations of the above.

† Markers of myocardial injury (eg, elevated cardiac troponin I or -T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma).

‡ Neither calculation of PESI (or sPESI) nor laboratory testing is considered necessary in patients with hypotension or shock.

§ Patients in the PESI Class I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction in imaging tests, are also to be classified into the intermediate-low-risk category.

LV=left ventricular; PESI=Pulmonary Embolism Severity Index; RV=right ventricular.

Konstantinides S et al. *Eur Heart J*. 2014;35:3033-3069, 3069a-3069k.

Antithrombotic Therapy for VTE Disease

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

Clive Kearon, Elie A. Akl, Anthony J. Comerota, Paolo Prandoni, Henri Bounameaux, Samuel Z. Goldhaber, Michael E. Nelson, Philip S. Wells, Michael K. Gould, Francesco Dentali, Mark Crowther and Susan R. Kahn

- **UHF**
- **LMWH**
- **Fondaparinux**

Vitamin K antagonists

Initial treatment	INR 2.0-3.0	2.0-3.0 or 1.5-1.9
Long term-treatment		
Extended* treatment		
≥ 5 days	**at least 3 months**	**indefinite***

* With re-assessment of the individual risk-benefit at periodic interval

Kearon C et al. Chest 2012; 141: 419-494

Antithrombotic Therapy for VTE Disease

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- UHF
- LMWH
- Fondaparinux

1

Initial treatment

Vitamin K antagonists

INR 2.0-3.0 2.0-3.0 or 1.5-1.9

Long term-treatment

2

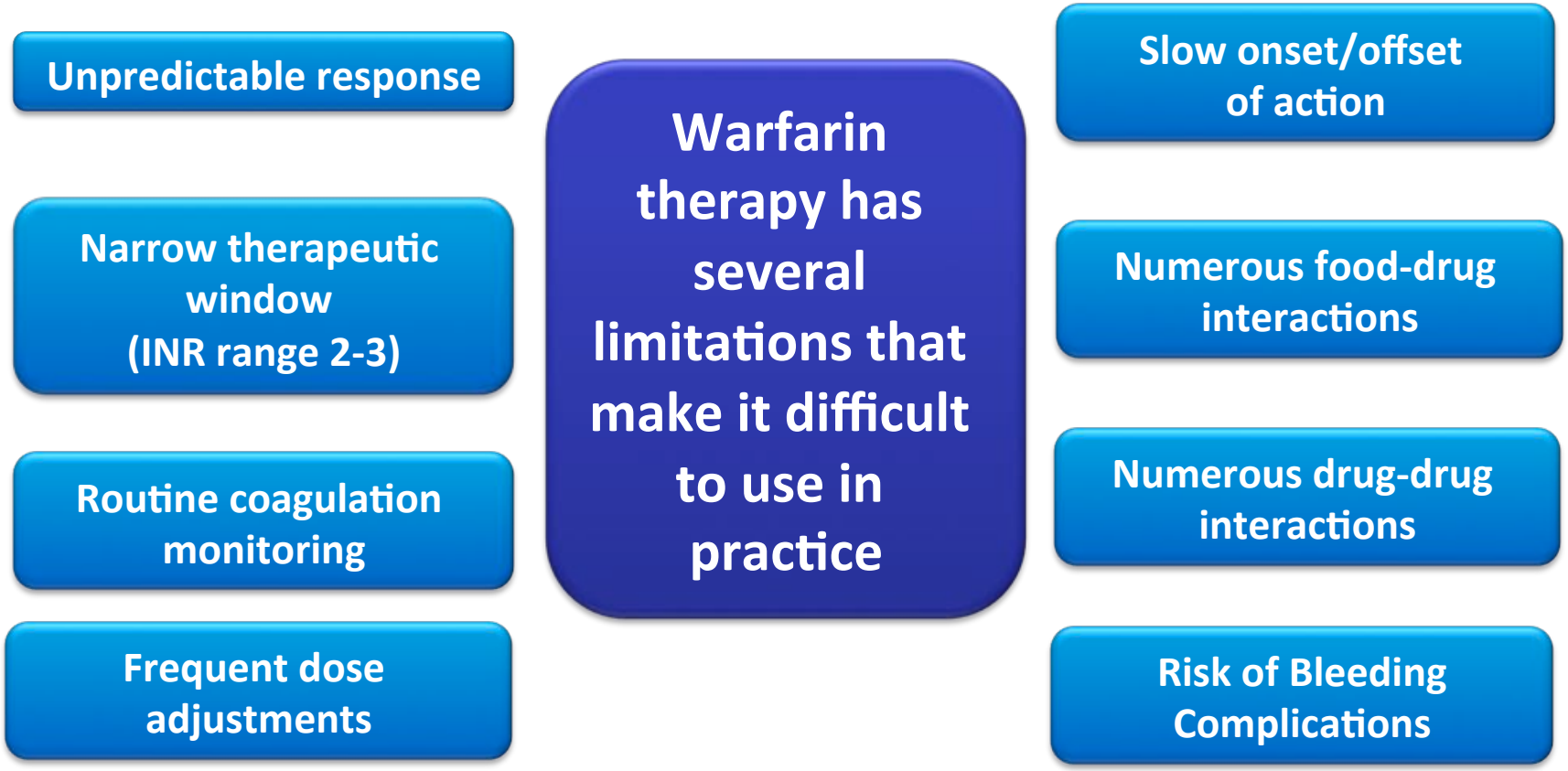
Extended* treatment

≥ 5 days at least 3 months indefinite*

3

* With re-assessment of the individual risk-benefit at periodic intervals

Kearon C et al. Chest 2012; 141: 419-494



- Warfarin was #1 in 2003 and 2004 in the number of mentions of "deaths for drugs causing adverse effects in therapeutic use"
- Warfarin caused 6% of the 702,000 ADEs treated in the ED/year; 17% required hospitalization

J Thromb Thrombolysis 2008

VTE Treatment Trials With NOACs

- According to the ACCP 2012 guidelines, the framework of anticoagulation for VTE treatment includes initial (0 to ~7 days), long-term (~7 days to ~3 months) and extended treatment (~3 months to indefinite)[1]

Initial 5 Days of Parenteral Required?	Study Drug	Initial/Long-term Treatment	Extended Treatment
		Trial Name	Trial Name
No (Single-agent approach)	Apixaban	AMPLIFY[2]	AMPLIFY-EXT[8]
	Rivaroxaban	EINSTEIN-DVT[3]	EINSTEIN-EXT[3]
		EINSTEIN-PE[4]	
Yes	Dabigatran	RE-COVER[5]	RE-MEDY[9]
		RE-COVER II[6]	RE-SONATE[9]
	Edoxaban	Hokusai-VTE[7]	—

ACCP=American College of Chest Physicians.

1. Kearon et al. *Chest*. 2012;141(2):e419S-e494S.
2. Agnelli G et al. *N Engl J Med.* 2013;369:799-808.
3. Bauersachs R et al. *N Engl J Med*. 2010;363:2499-2510.
4. Büller HR et al. *N Engl J Med*. 2012;366:1287-1297.
5. Schulman S et al. *N Engl J Med*. 2009;361:2342-2352.
6. Schulman S et al. *Circulation*. 2014;129:764-772.
7. Büller HR et al. *N Engl J Med*. 2013;369:1406-1415.
8. Agnelli G et al. *N Engl J Med*. 2013;368:699-708.
9. Schulman S et al. *N Engl J Med*. 2013;368:709-718.

Initial VTE Treatment NOAC Trial Designs

NOAC	Trial	Number of Patients*	Design	Parenteral Required Before NOAC?	NOAC Dosing	Comparator	Treatment Length (mo)
Apixaban	AMPLIFY™[1]	5395 DVT: 3532 PE: 1836	Double blind	No	Apixaban 10 mg BID for 7d, then 5 mg BID	Enoxaparin bridge to warfarin	6
Rivaroxaban	EINSTEIN-DVT[2]	DVT: 3449	Open label	No	Rivaroxaban 15 mg BID for 21d, then 20 mg OD	Enoxaparin bridge to VKA	3, 6, or 12‡
	EINSTEIN-PE[3]	PE: 4832					
Dabigatran	RE-COVER™[4]	2539 DVT:1749 PE: 786	Double blind	LMWH, UFH, or fondaparinux ≥5 days	Dabigatran 150 mg BID	Warfarin	6
	RE-COVER™ II[5]	2568 DVT: 1750 PE: 816					
Edoxaban	Hokusai-VTE[6]	8240 DVT: 4921 PE: 3319	Double blind	Enoxaparin or UFH ≥5 days	Edoxaban 60 mg OD†	Warfarin	3–12

* DVT indicates DVT only; PE indicates a diagnosis of PE with or without DVT.

† 60 mg OD for most patients; 30 mg OD for select criteria (eg, ≤60 kg, creatinine clearance=30–50 mL/min).

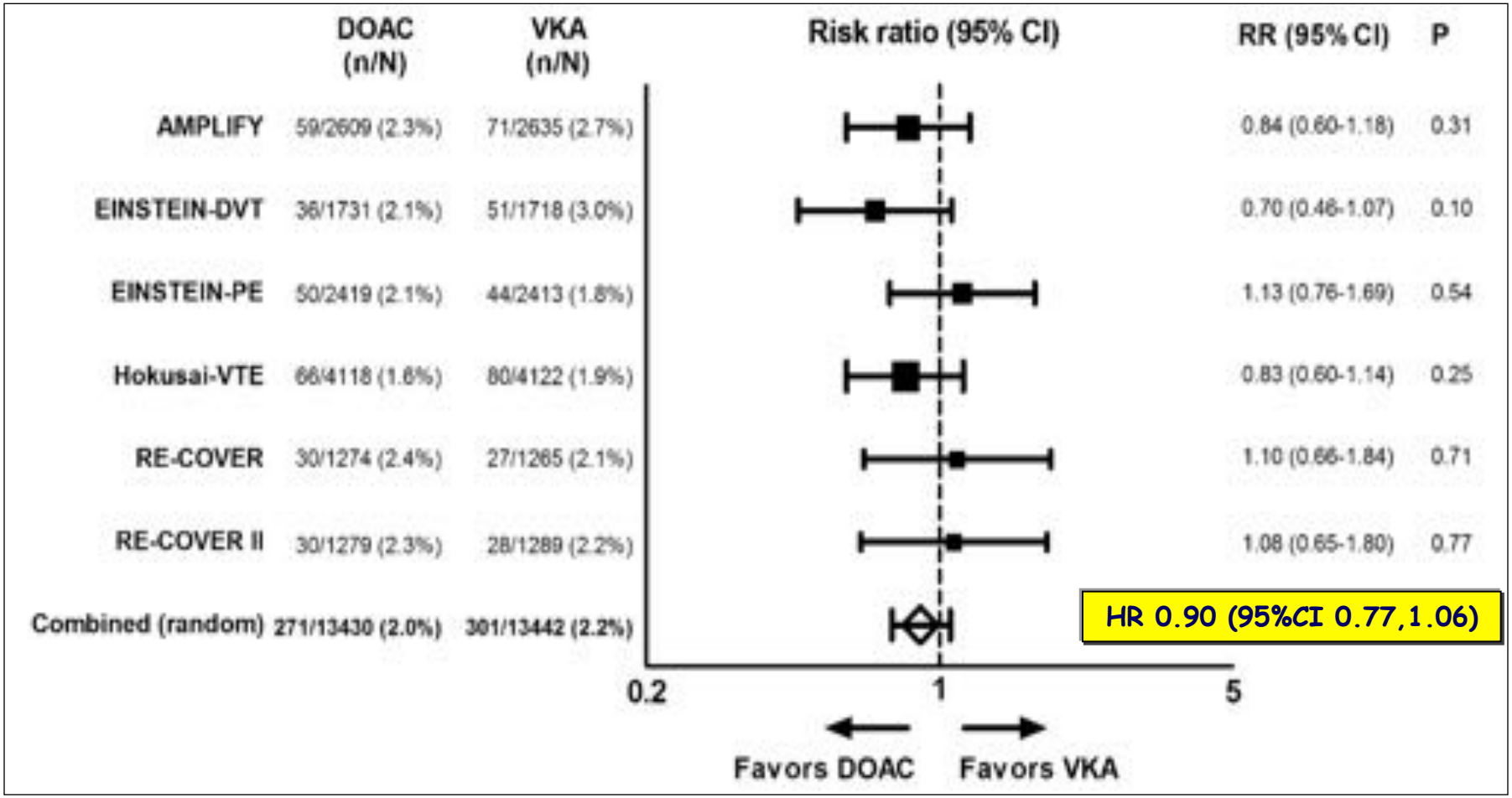
‡ Duration of treatment was determined by the treating physician before randomization. Most patients received 6 or 12 months of therapy.

LMWH=low molecular weight heparin; UFH=unfractionated heparin.

1. Agnelli G et al. *N Engl J Med.* 2013;369:799-808.
2. Bauersachs R et al. *N Engl J Med*. 2010;363:2499-2510
3. Büller HR et al. *N Engl J Med*. 2012;366:1287-1297.

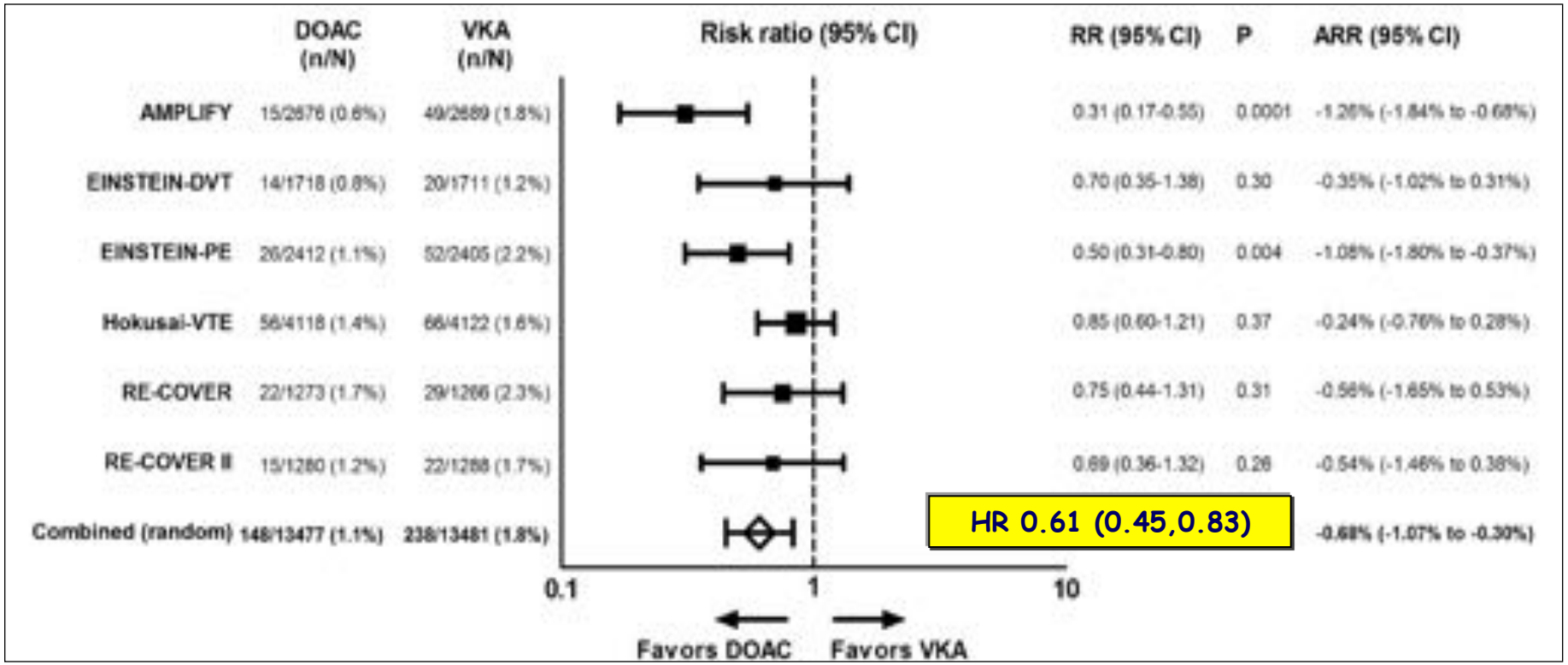
VTE recurrence

DOACs vs VKAs



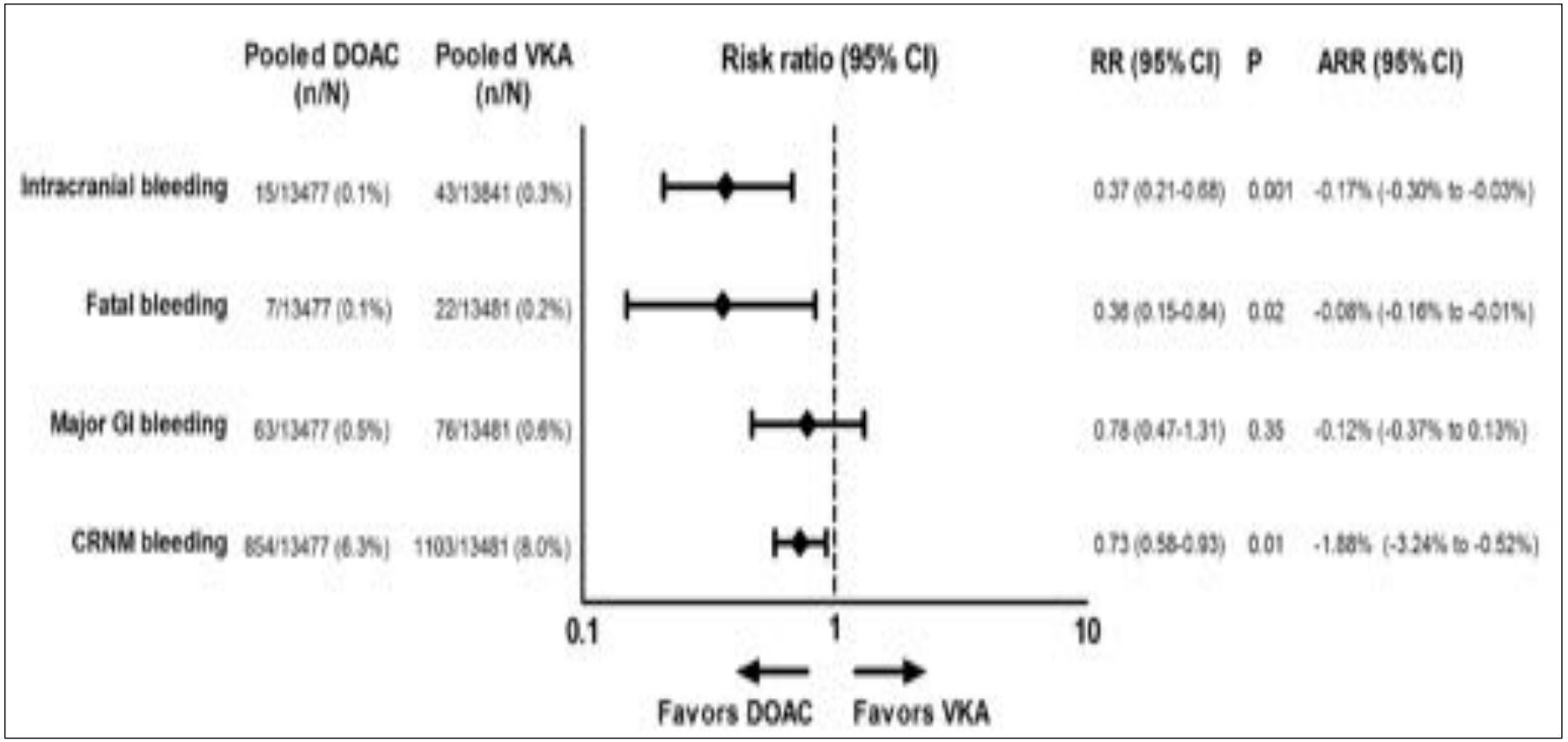
Van Es et al. Blood 2014

Major Bleeding



Van Es et al. Blood 2014

Other End Points



Van Es et al. Blood 2014

Dabigatran

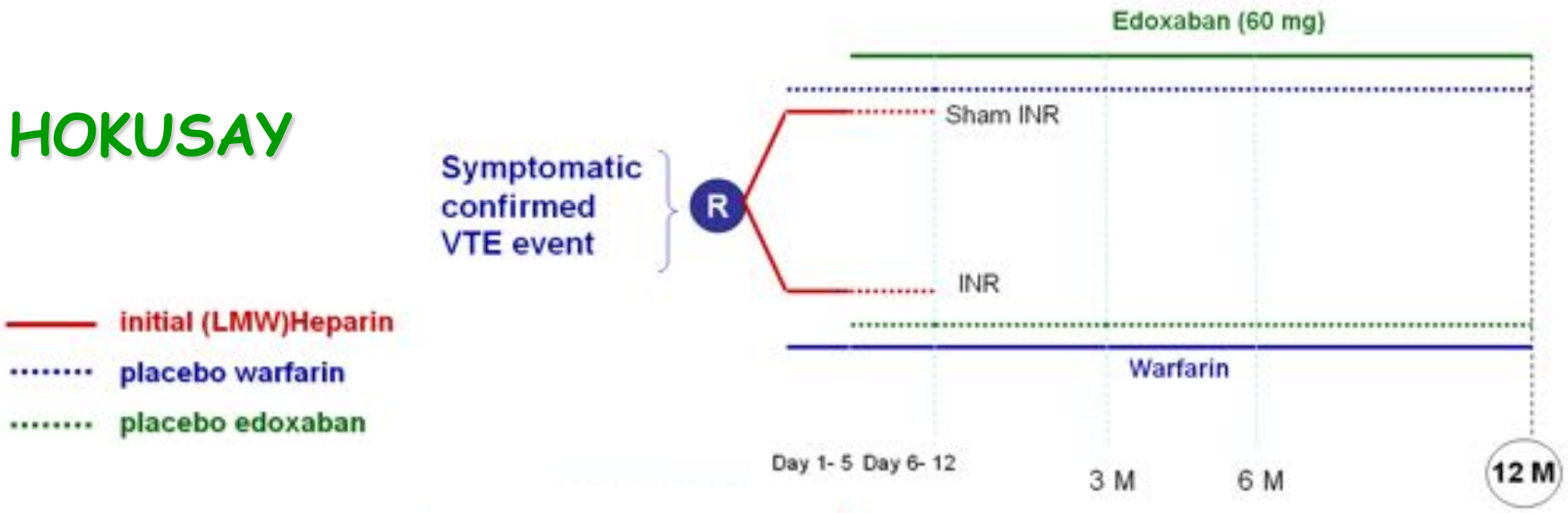
Apixaban

Edoxaban

Rivaroxaban

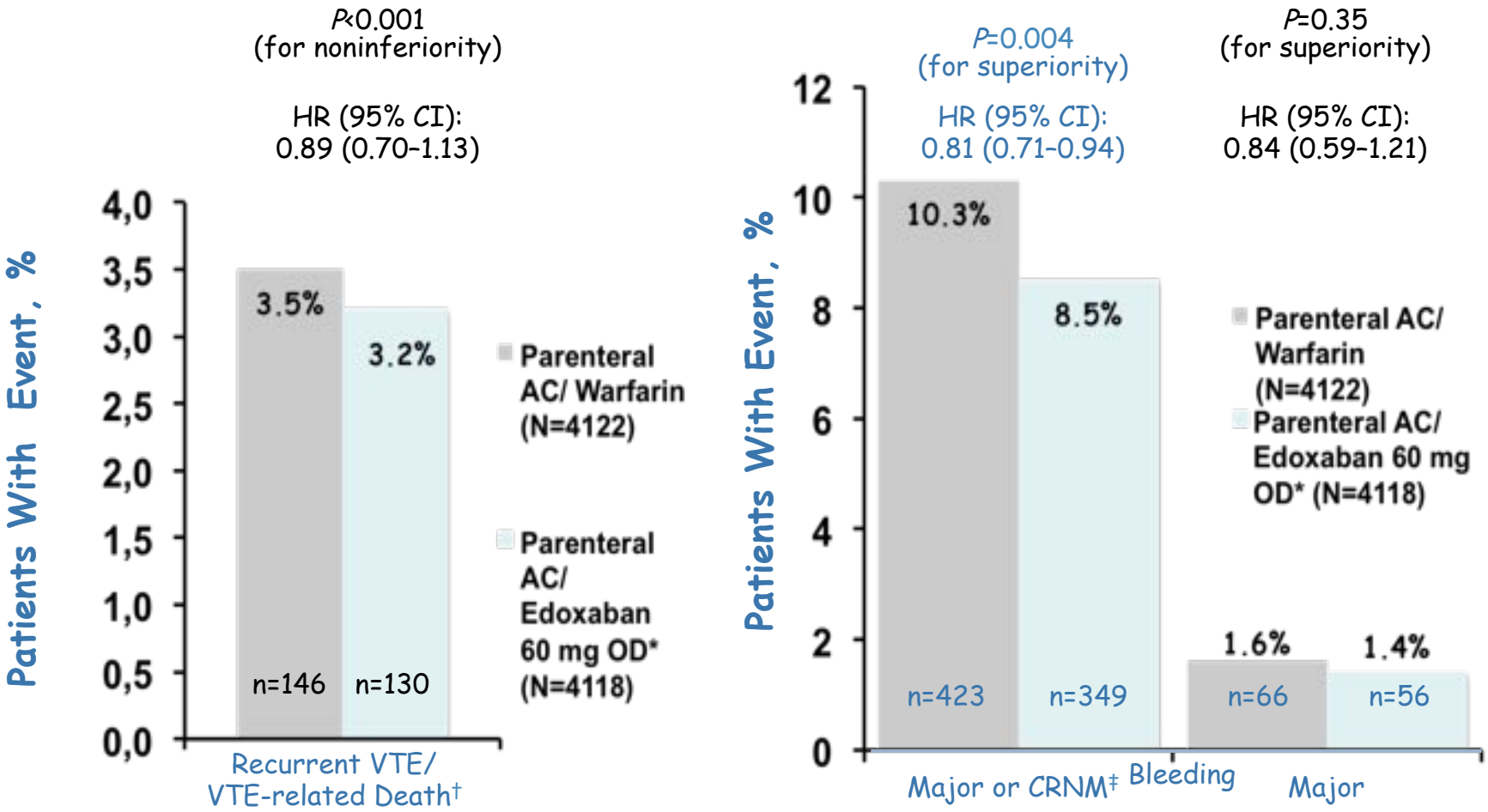
Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

HOKUSAY



NEJM 2013; 369: 1406-15

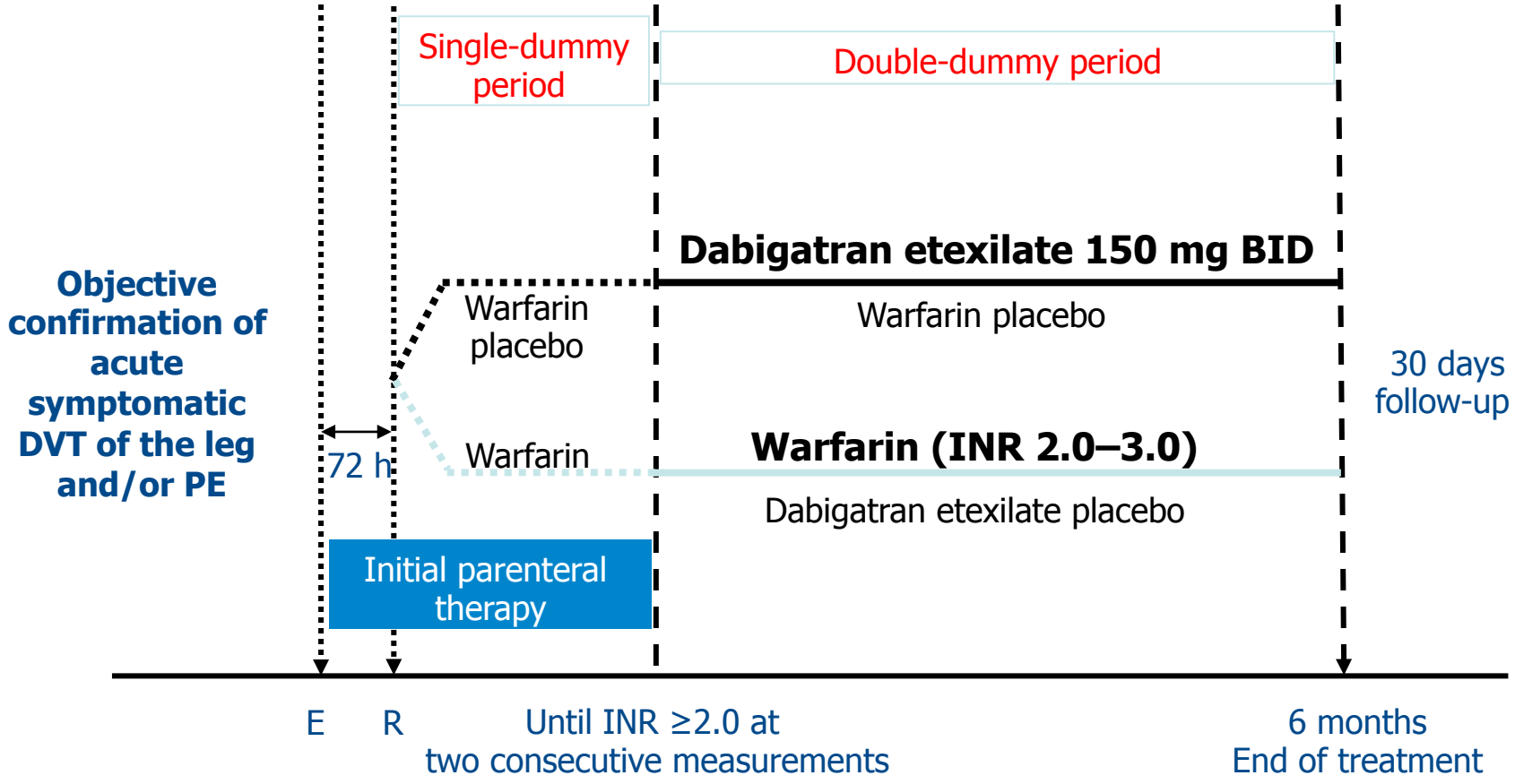
Hokusai-VTE Efficacy and Safety Outcomes



Büller et al. *N Engl J Med.* 2013.

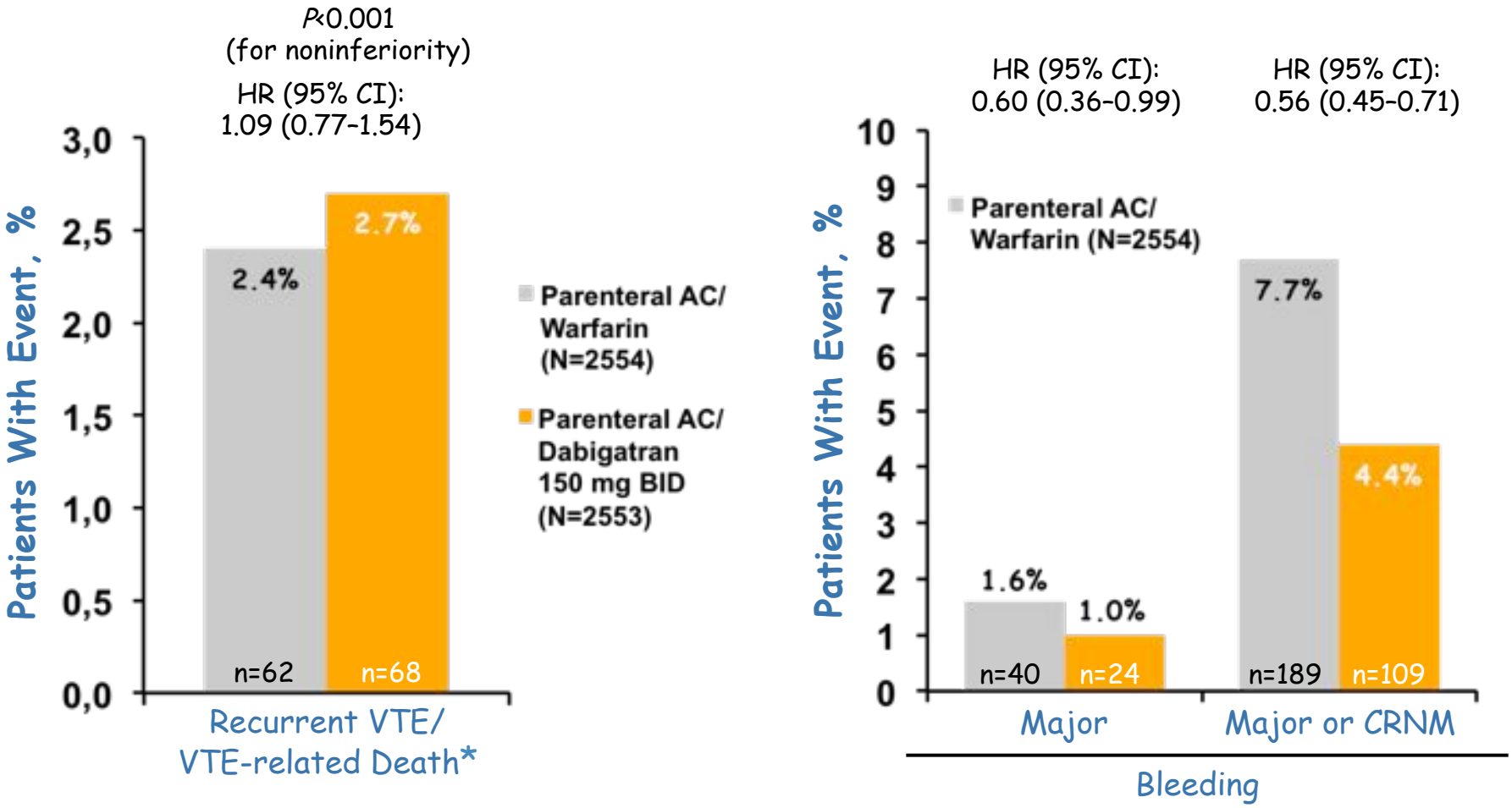
Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

RECOVER I and II



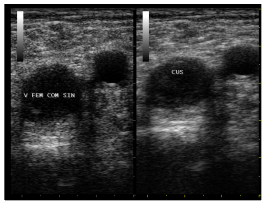
NEJM 2013
Circulation 2014

Pooled RE-COVER and RE-COVER II Efficacy and Safety Outcomes



Schulman S et al. *Circulation*. 2014.

Oral Rivaroxaban for Symptomatic Venous Thromboembolism



DVT without symptomatic PE

N° 3449

PE with or without DVT

N° 4832

R

RIVAROXABAN 15 mg bid

21 days

RIVAROXABAN 20 mg od

Duration of treatment (3-6-12 months)

Enoxaparin 1 mg/Kg bid ≥ 5 days

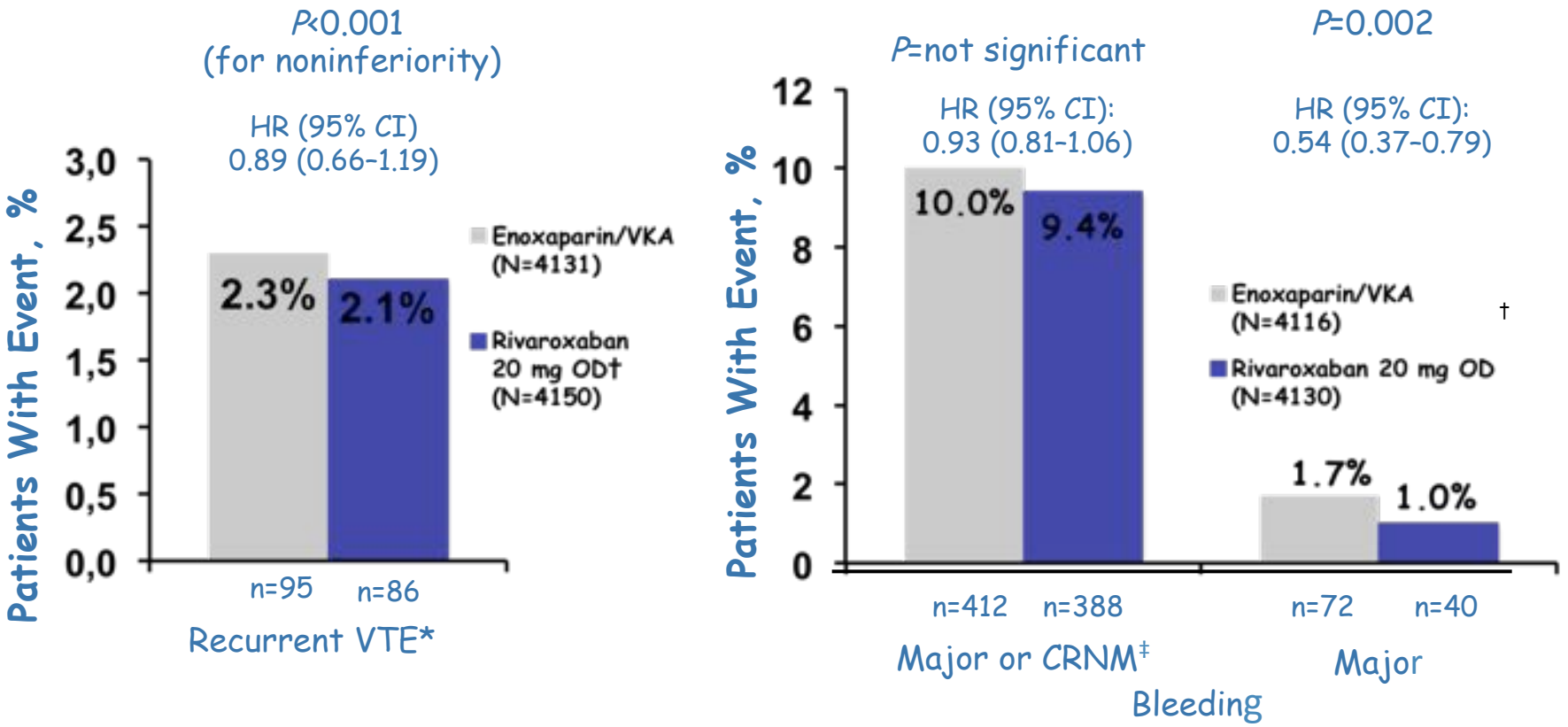
+

VKA (INR 2-3)

Period of Observation 30 days

EINSTEIN investigators NEJM 2010

Pooled EINSTEIN-DVT and -PE Efficacy and Safety Outcomes



Day 21 analysis:

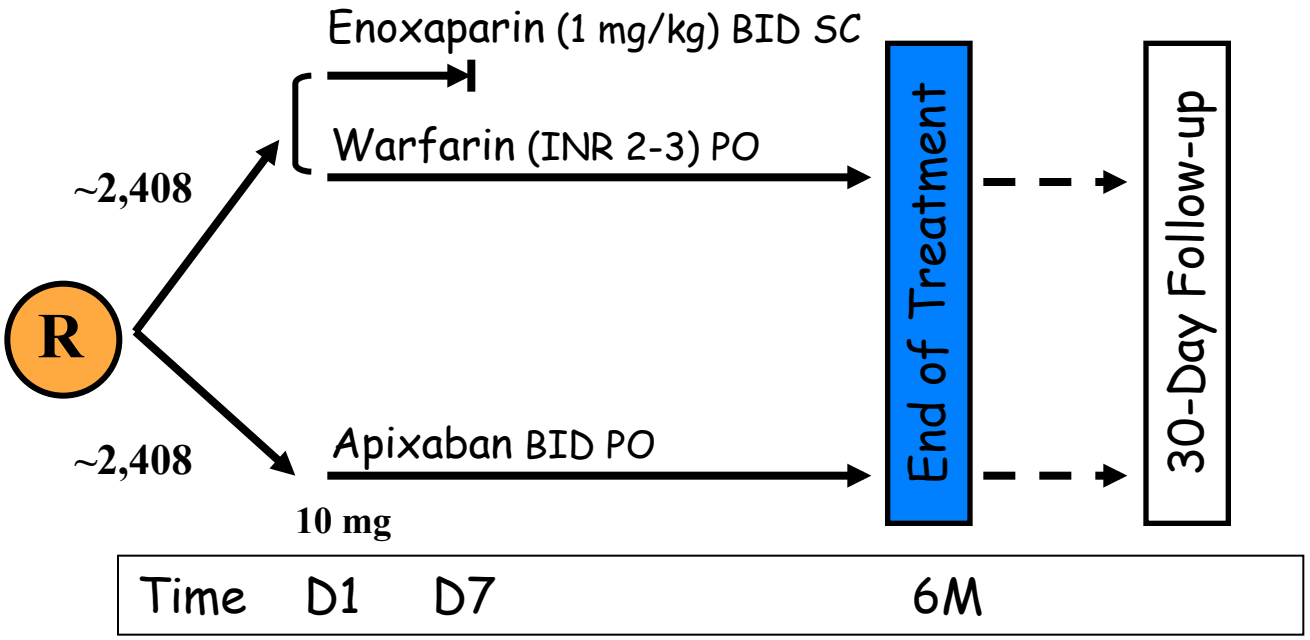
Recurrent VTE
Enoxaparin/VKA 1.2% vs rivaroxaban 0.9%

Major bleeding
Enoxaparin/VKA 0.8% vs rivaroxaban 0.4%

1. Prins MH et al. *Thrombosis J.* 2013;11:21.
2. Bauersachs R et al. *N Engl J Med.* 2010;363:2499-2510.

Apixaban for the treatment of VTE AMPLIFY study design

Subjects with confirmed symptomatic DVT/PE requiring treatment for ≥6 months



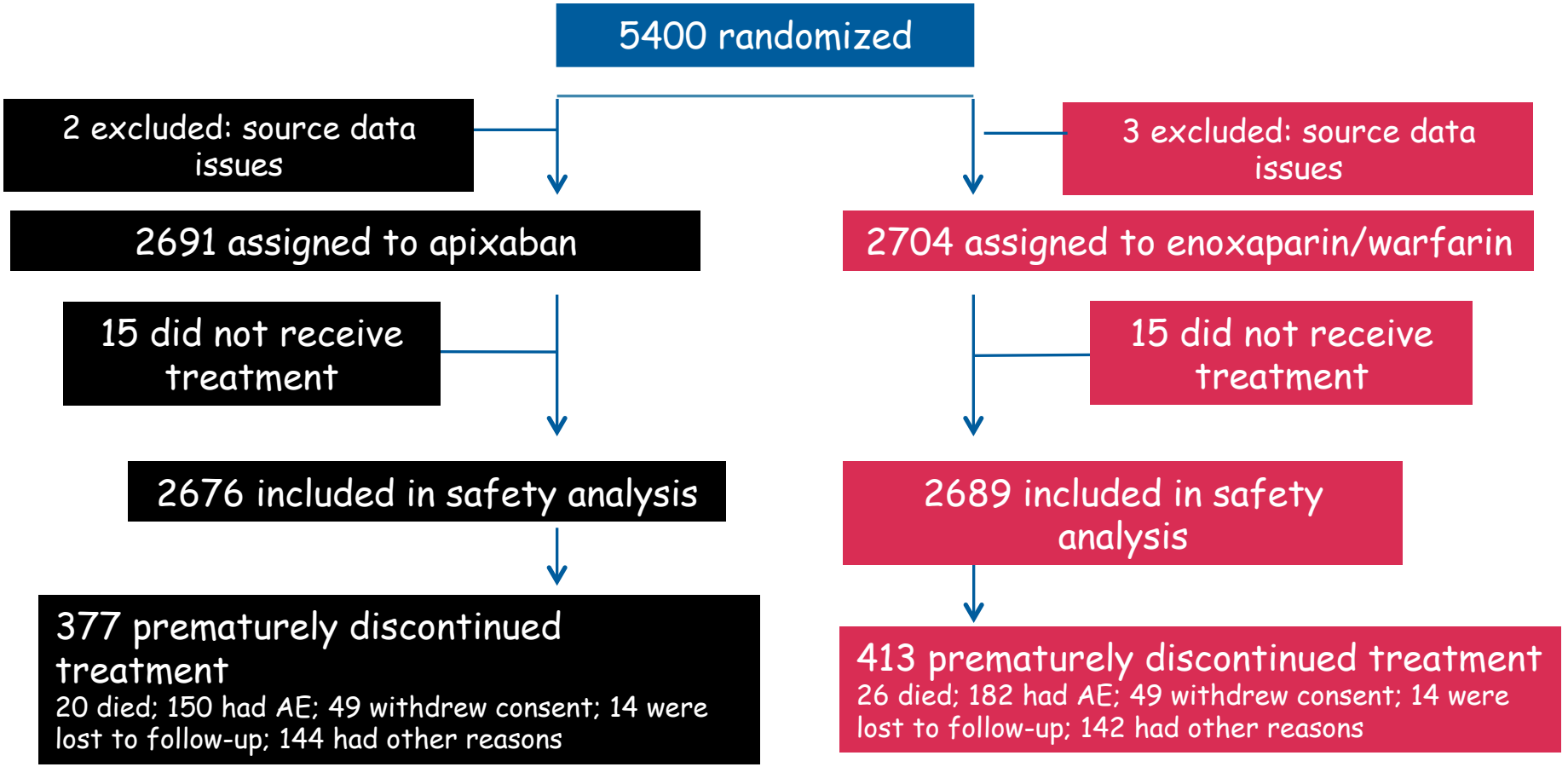
Agnelli et al N Engl J Med 2013

AMPLIFY: study outcomes

- Primary efficacy outcome
  - Incidence of the adjudicated composite of recurrent symptomatic VTE or death related to VTE
- Primary safety outcome
  - Adjudicated major bleeding
- Secondary outcomes included:
  - Each component of the primary efficacy outcome
  - Death from CV causes; death from any cause
  - Composite measure:
    - Symptomatic recurrent VTE, death from CV causes, with death from any cause, or with death related to VTE plus major bleeding
  - Major bleeding and clinically relevant non-major bleeding

Agnelli G et al. N Engl J Med 2013

AMPLIFY: patient flow



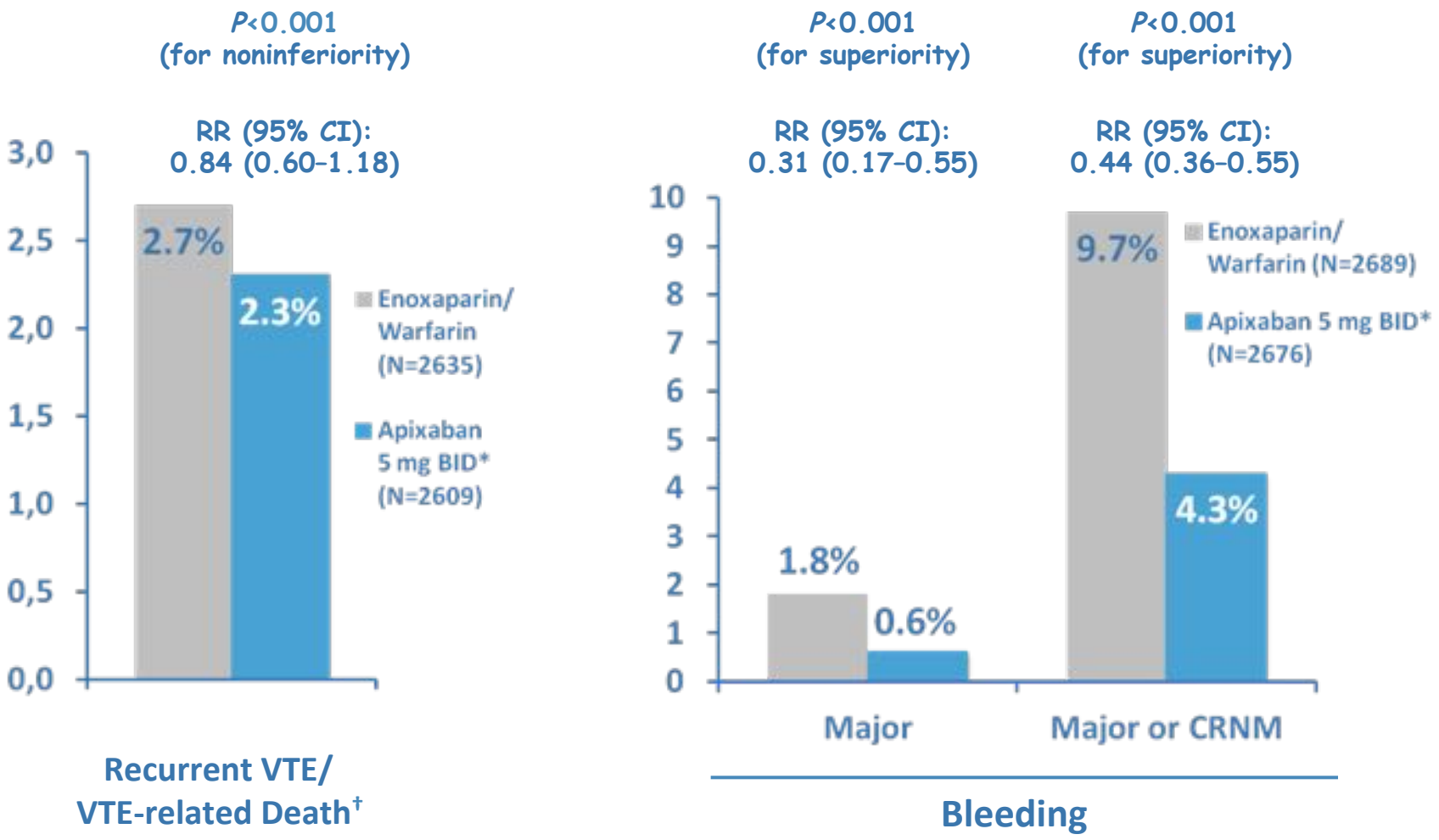
Agnelli G et al. NEJM 2013

AMPLIFY: baseline characteristics

	Apixaban n=2691	Enoxaparin/warfarin n=2704
Mean age, yrs (SD)	57.2 (16.0)	56.7 (16.0)
Male sex, n (%)	1569 (58.3)	1598 (59.1)
Mean weight, kg (SD)	84.6 (19.8)	84.6 (19.8)
Distribution, n (%)		
≤60 kg	231 (8.6)	245 (9.1)
>60 to <100 kg	1932 (71.8)	1936 (71.6)
≥100 kg	522 (19.4)	518 (19.2)
Creatinine clearance, n (%)		
≤30 mL/min	14 (0.5)	15 (0.6)
>30 to ≤50 mL/min	161 (6.0)	148 (5.5)
>50 to ≤80 mL/min	549 (20.4)	544 (20.1)
>80 mL/min	1721 (64.0)	1757 (65.0)
Qualifying diagnosis, n (%)		
DVT	1749 (65.0)	1783 (65.9)
PE	678 (25.2)	681 (25.2)
PE with DVT	252 (9.4)	225 (8.3)

Agnelli G et al. NEJM 2013

AMPLIFY™ Efficacy and Safety Outcomes



* Patients in the apixaban arm received 10 mg BID for the first 7 days, followed by 5 mg BID.

† PE was considered to be the cause of death if death could not be attributed to a documented cause and PE could not be ruled out.

‡ Primary safety outcome.

CI=confidence interval; CRNM=clinically relevant nonmajor; RR=relative risk.

Agnelli G et al. *N Engl J Med.* 2013;369:799-808.

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

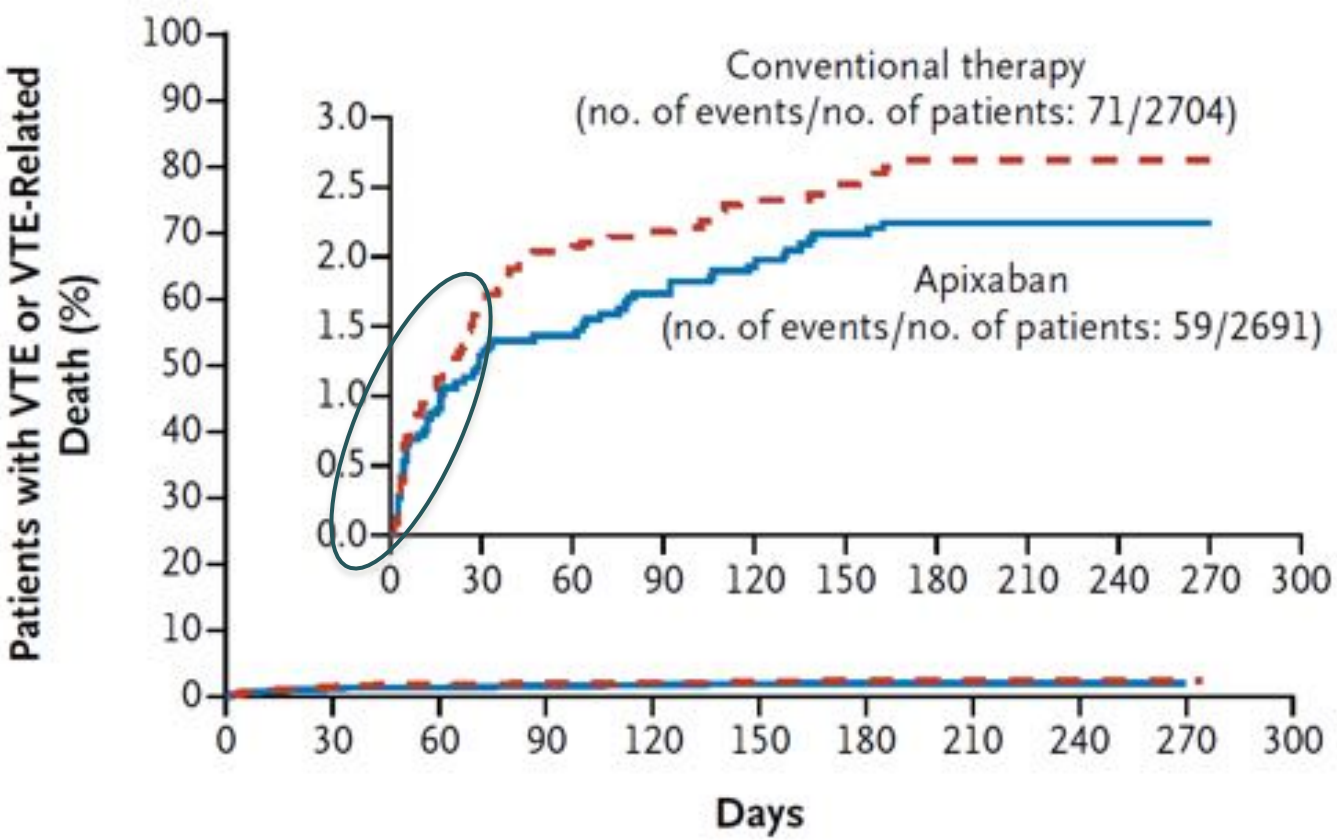
AMPLIFY

Event rate	
APIXABAN	2.3 %
Enox- WARFARIN	2.7 %

Efficacy outcome

Recurrent venous thromboembolism

HR= 0.84 (95% CI= 0.60-1.18)



Agnelli G et al. NEJM 2013

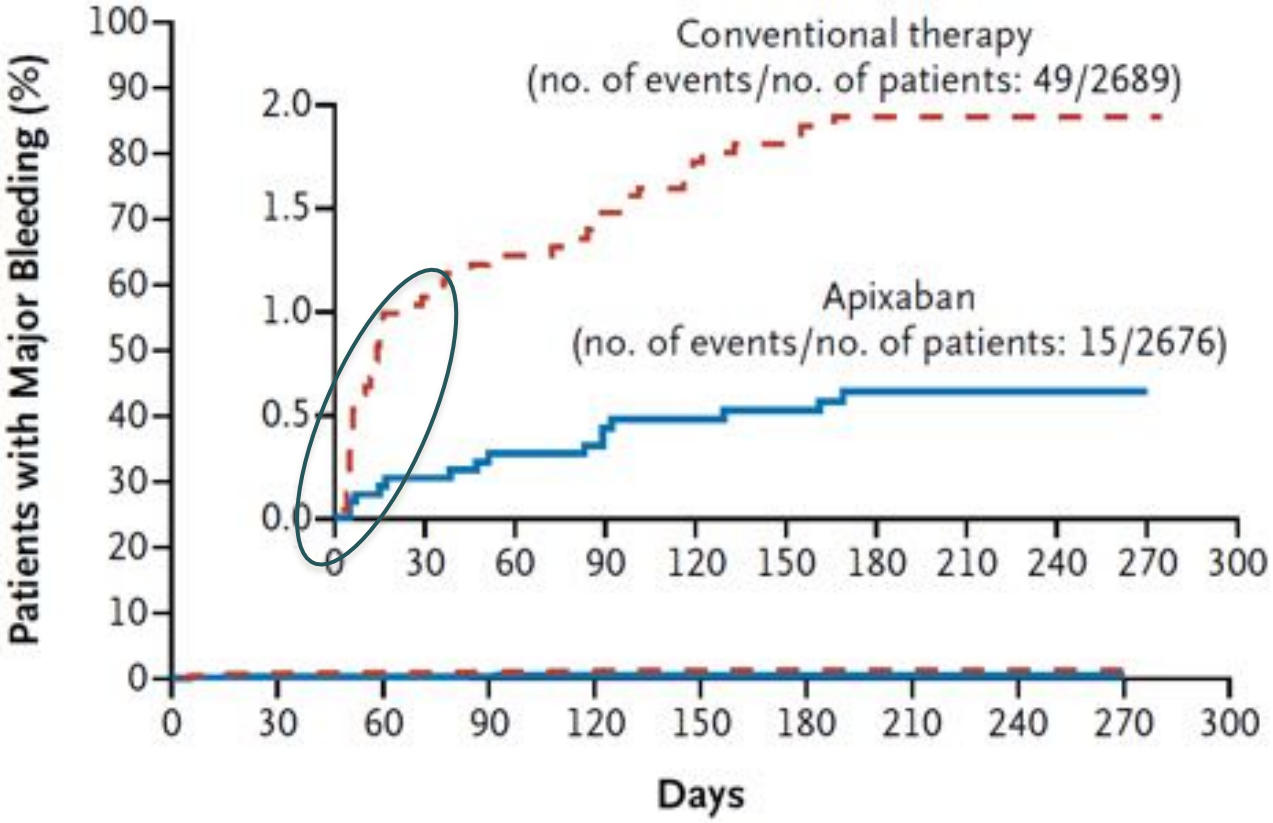
Oral Apixaban for the Treatment of Acute Venous Thromboembolism

AMPLIFY

Major Bleeding

HR= 0.31 (95% CI= 0.17-0.55)

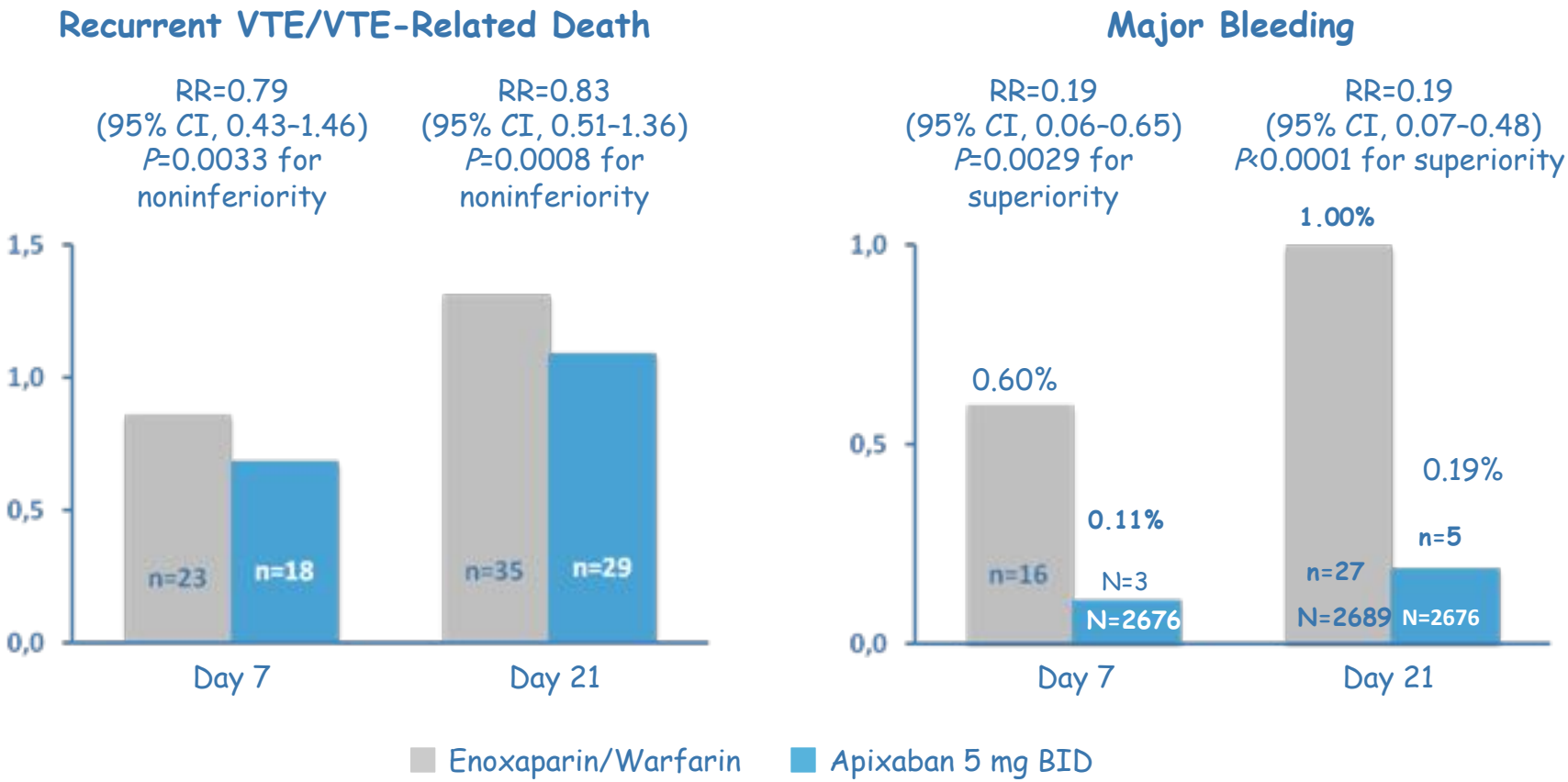
Event rate	
APIXABAN	0.6 %
Enox- WARFARIN	1.8 %



Agnelli G et al. NEJM 2013

AMPLIFY Efficacy and Safety Outcomes in First 7 and 21 Days of Treatment

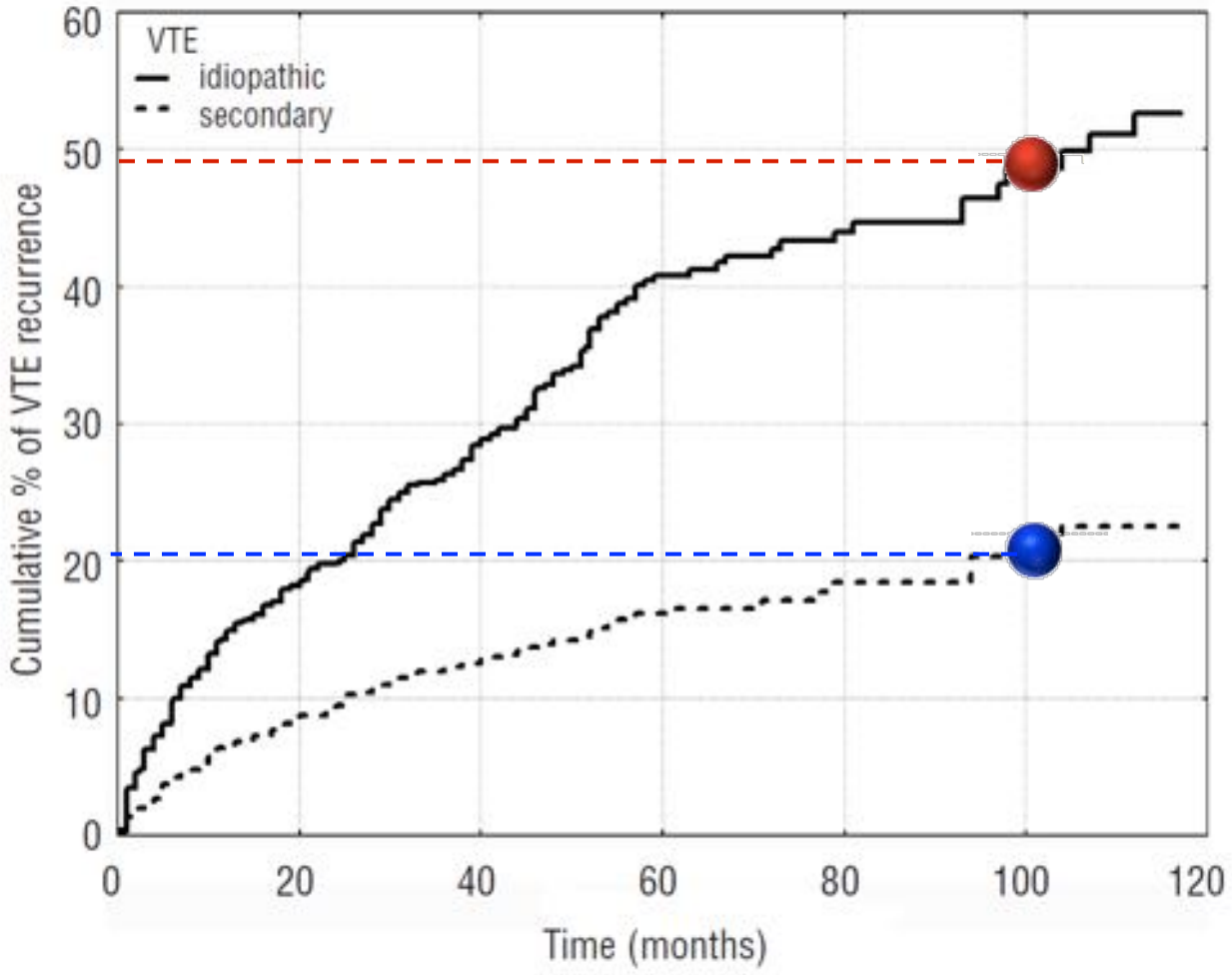
- Compared with enoxaparin/warfarin, apixaban was noninferior for recurrent VTE/VTE-related death at 7 and 21 days, and was associated with significantly fewer major bleeding events



Raskob GE et al. Presented at: 60th Annual Meeting of the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee; June 23-26, 2014; Milwaukee, WI. Poster COA28.

The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients

Figure 3. Cumulative incidence of recurrent thromboembolism separately in patients with idiopathic (unprovoked) and secondary VTE.



Prandoni P et al. Haematologica 2007

VTE Treatment Trials With NOACs

- According to the ACCP 2012 guidelines, the framework of anticoagulation for VTE treatment includes initial (0 to ~7 days), long-term (~7 days to ~3 months) and extended treatment (~3 months to indefinite)[1]

Initial 5 Days of Parenteral Required?	Study Drug	Initial/Long-term Treatment	Extended Treatment
		Trial Name	Trial Name
No (Single-agent approach)	Apixaban	AMPLIFY[2]	AMPLIFY-EXT[8]
	Rivaroxaban	EINSTEIN-DVT[3]	EINSTEIN-EXT[3]
		EINSTEIN-PE[4]	
Yes	Dabigatran	RE-COVER[5]	RE-MEDY[9]
		RE-COVER II[6]	RE-SONATE[9]
	Edoxaban	Hokusai-VTE[7]	—

ACCP=American College of Chest Physicians.

1. Kearon et al. *Chest*. 2012;141(2):e419S-e494S.
2. Agnelli G et al. *N Engl J Med.* 2013;369:799-808.
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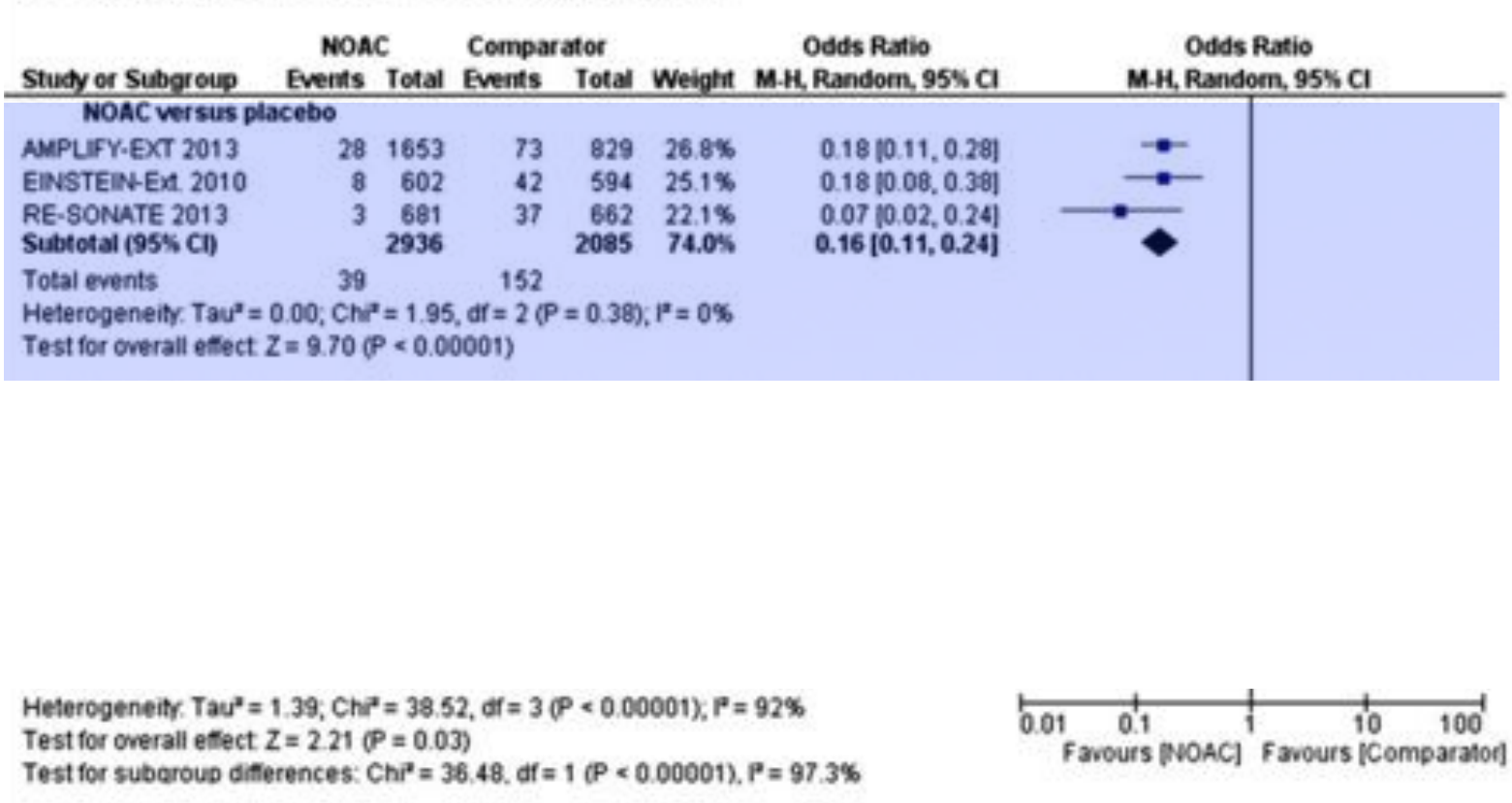
8. Agnelli G et al. *N Engl J Med*. 2013;368:699-708.
9. Schulman S et al. *N Engl J Med*. 2013;368:709-718.

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

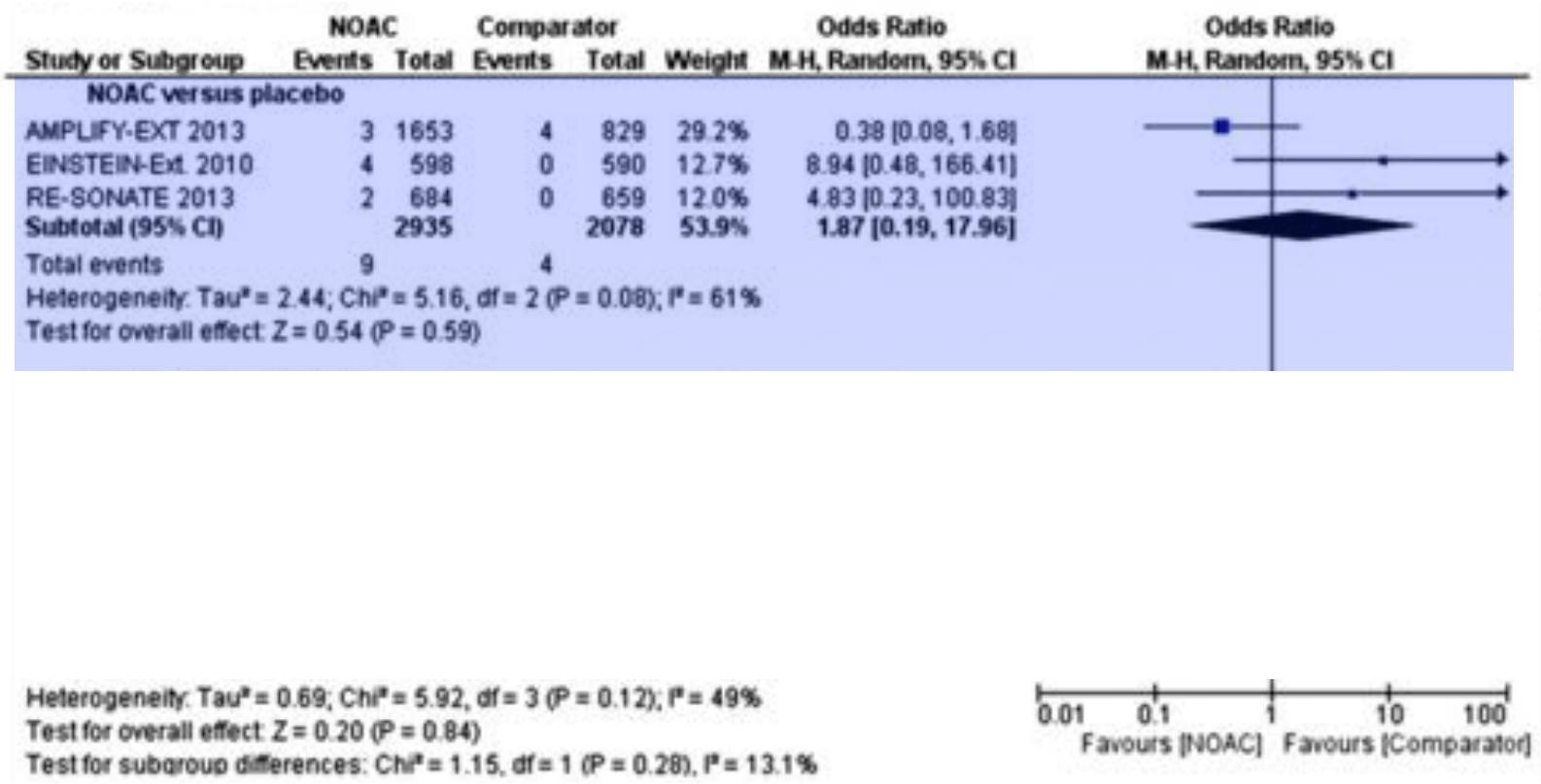
Recurrent symptomatic VTE and VTE-related deaths



Sardar P et al. Drugs 2013

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

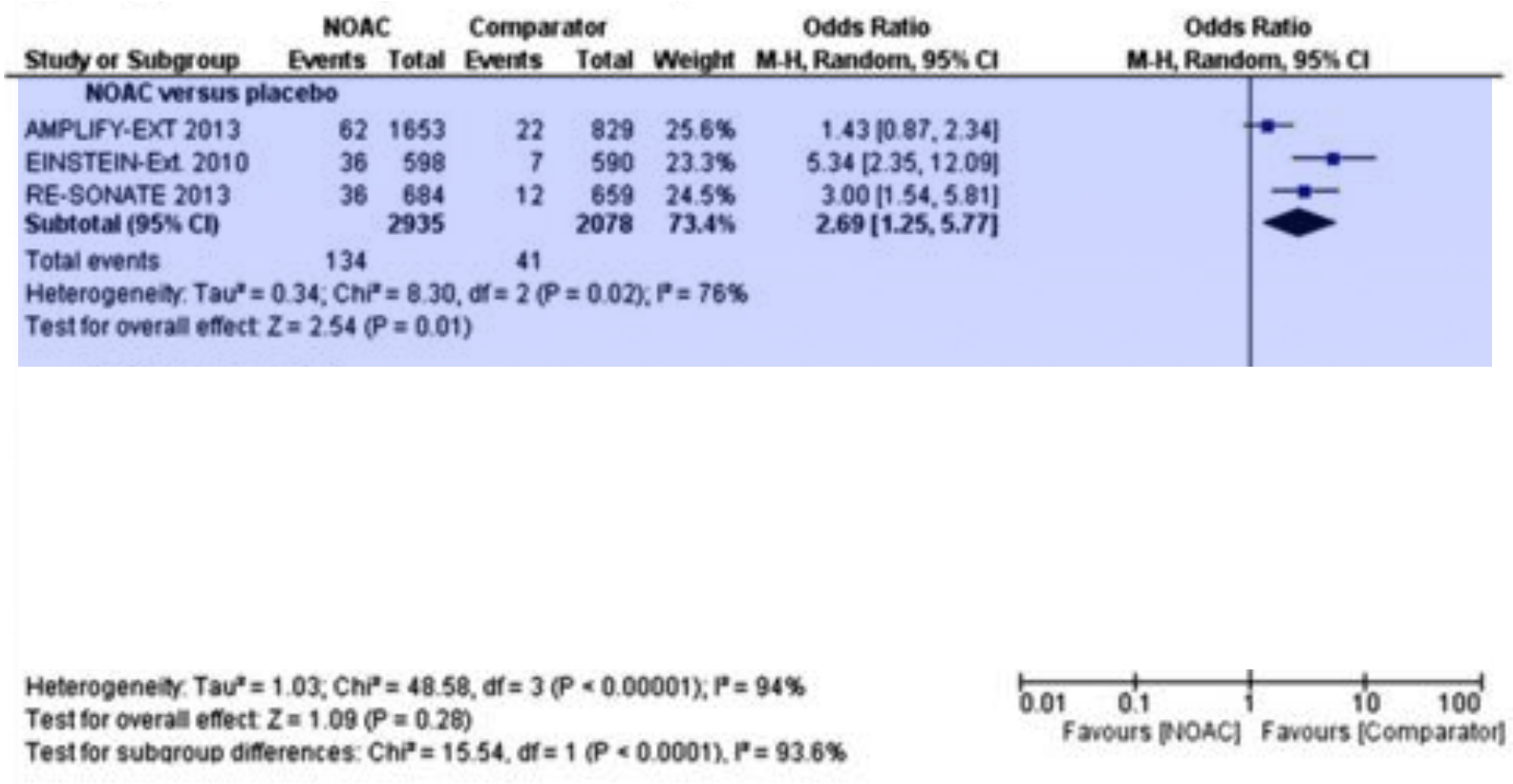
Major bleeding



Sardar P et al. Drugs 2013

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

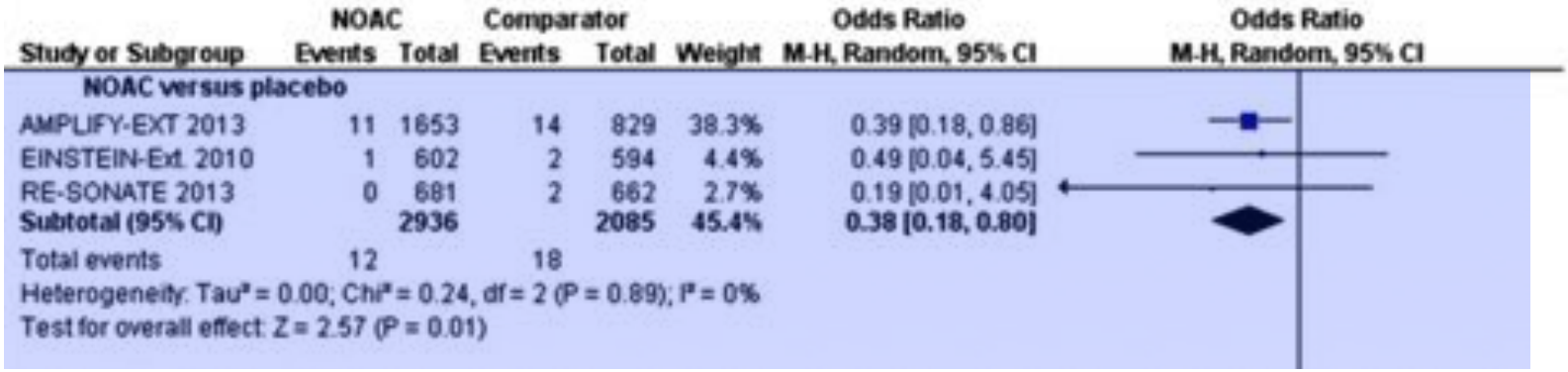
Major or Clinically Relevant Nonmajor Bleeding



Sardar P et al. Drugs 2013

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

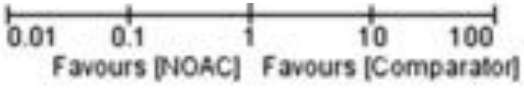
All-cause mortality



Study or Subgroup	NOAC Events	NOAC Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Random, 95% CI
NOAC versus placebo						
AMPLIFY-EXT 2013	11	1653	14	829	38.3%	0.39 [0.18, 0.86]
EINSTEIN-Ext. 2010	1	602	2	594	4.4%	0.49 [0.04, 5.45]
RE-SONATE 2013	0	681	2	662	2.7%	0.19 [0.01, 4.05]
Subtotal (95% CI)		**2936**		**2085**	**45.4%**	**0.38 [0.18, 0.80]**
Total events	12		18			

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)

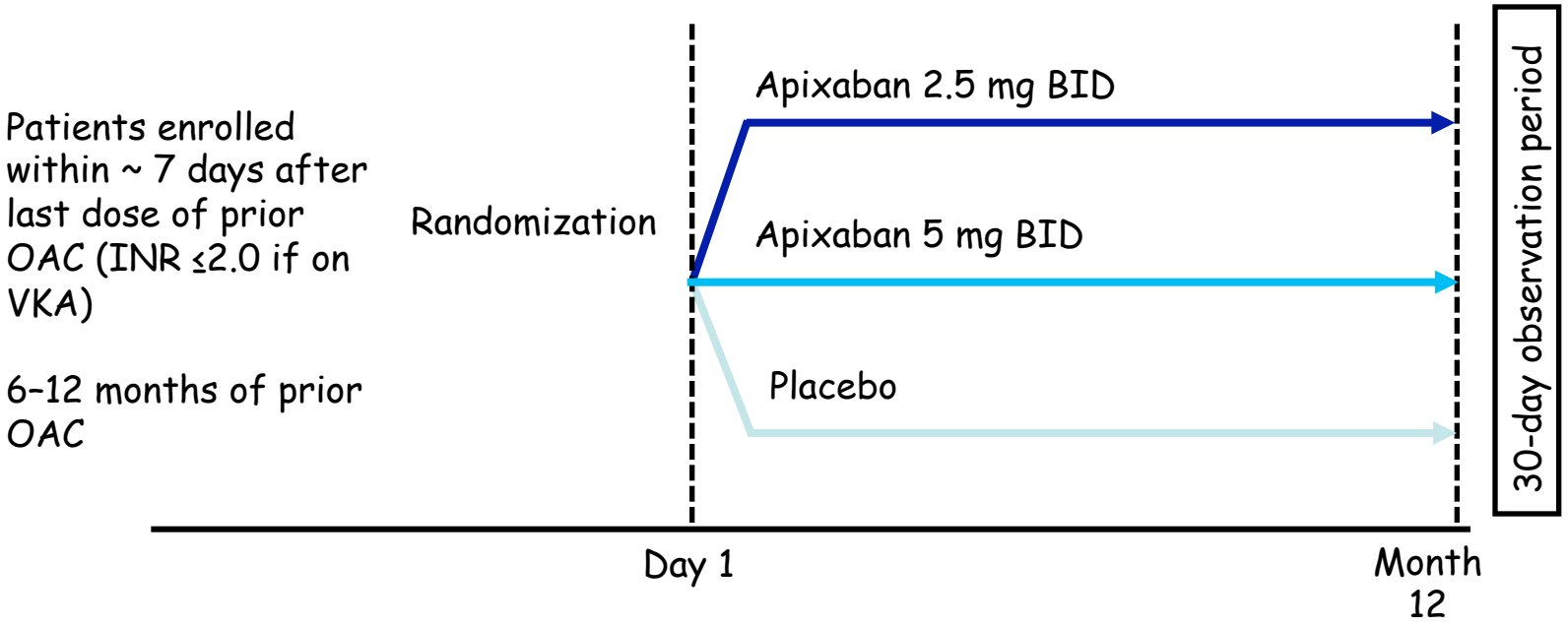
Odds Ratio M-H, Random, 95% CI



Heterogeneity: Tau² = 0.01; Chi² = 3.07, df = 3 (P = 0.38); I² = 2%
Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Chi² = 2.83, df = 1 (P = 0.09), I² = 64.7%

Sardar P et al. Drugs 2013

Amplify-EXT: study design



Agnelli et al. N Engl J Med 2013

Amplify-EXT: eligibility criteria

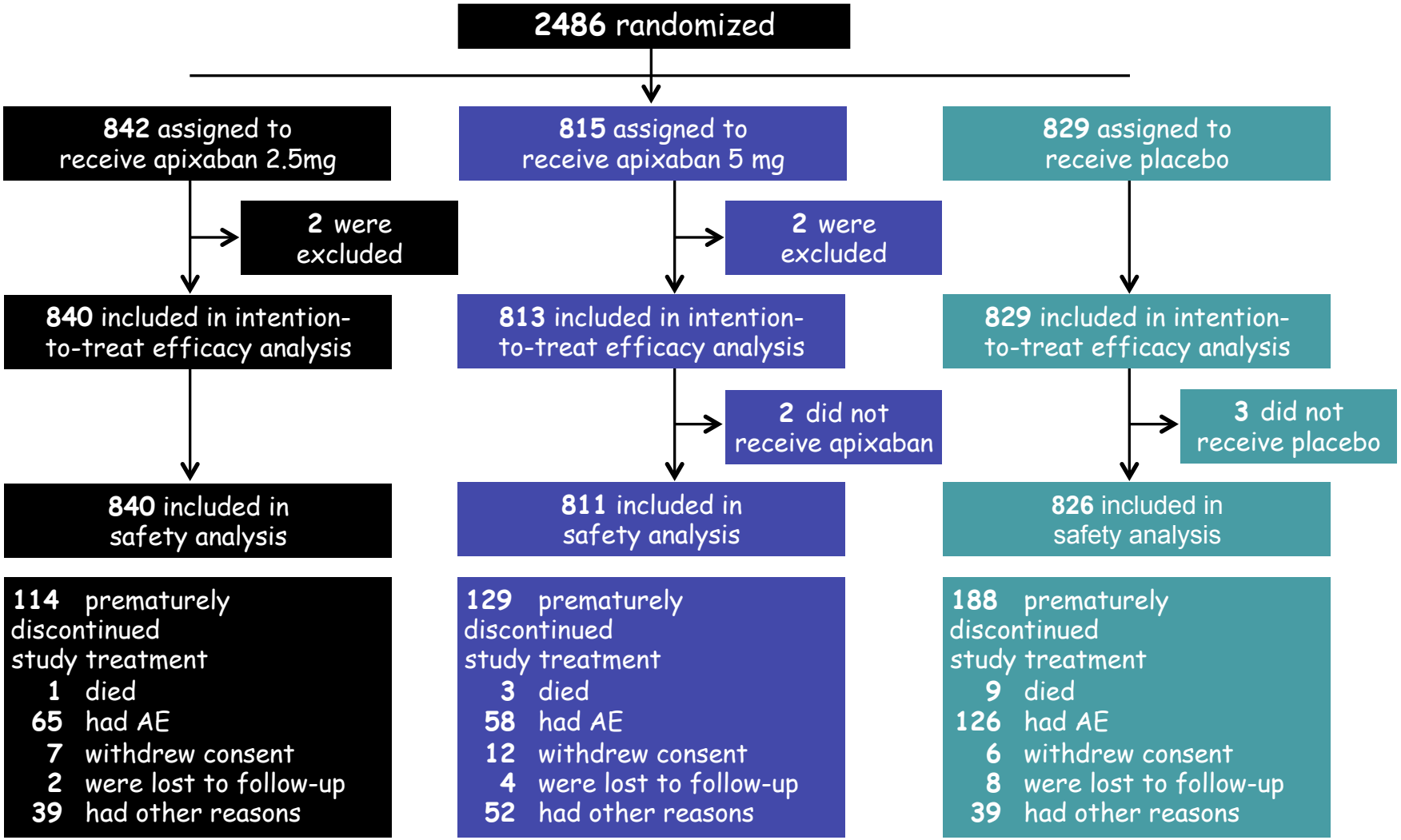
- **Key inclusion**
  - ≥18 years of age
  - Objectively confirmed, symptomatic DVT or PE (with/without DVT)
  - Treated for 6–12 months with standard anticoagulant or completed treatment with apixaban or enoxaparin/warfarin in AMPLIFY
  - No symptomatic recurrence during prior anticoagulant therapy
  - Clinical equipoise about the continuation or cessation of anticoagulant

  Key exclusion
  - Contraindication to continued anticoagulant therapy
  - Requirement for ongoing anticoagulant therapy, DAPT, or ASA >165 mg daily
  - Haemoglobin level of <9 mg/dL, a platelet count <100 000/mm^3, serum creatinine >2.5 mg/dL or a calculated CrCl <25 mL/min, ALT or AST level >2×ULN, or a total bilirubin level >1.5×ULN

Amplify-EXT: study outcome

- Primary efficacy outcome:
  - Composite of symptomatic recurrent VTE or death from any cause
- Primary safety outcome:
  - Major bleeding
- Secondary outcomes included:
  - Symptomatic recurrent VTE or death related to VTE
  - Composite of symptomatic recurrent VTE, death related to VTE, MI, stroke, or death related to CV disease
  - Composite of major or CRNM bleeding

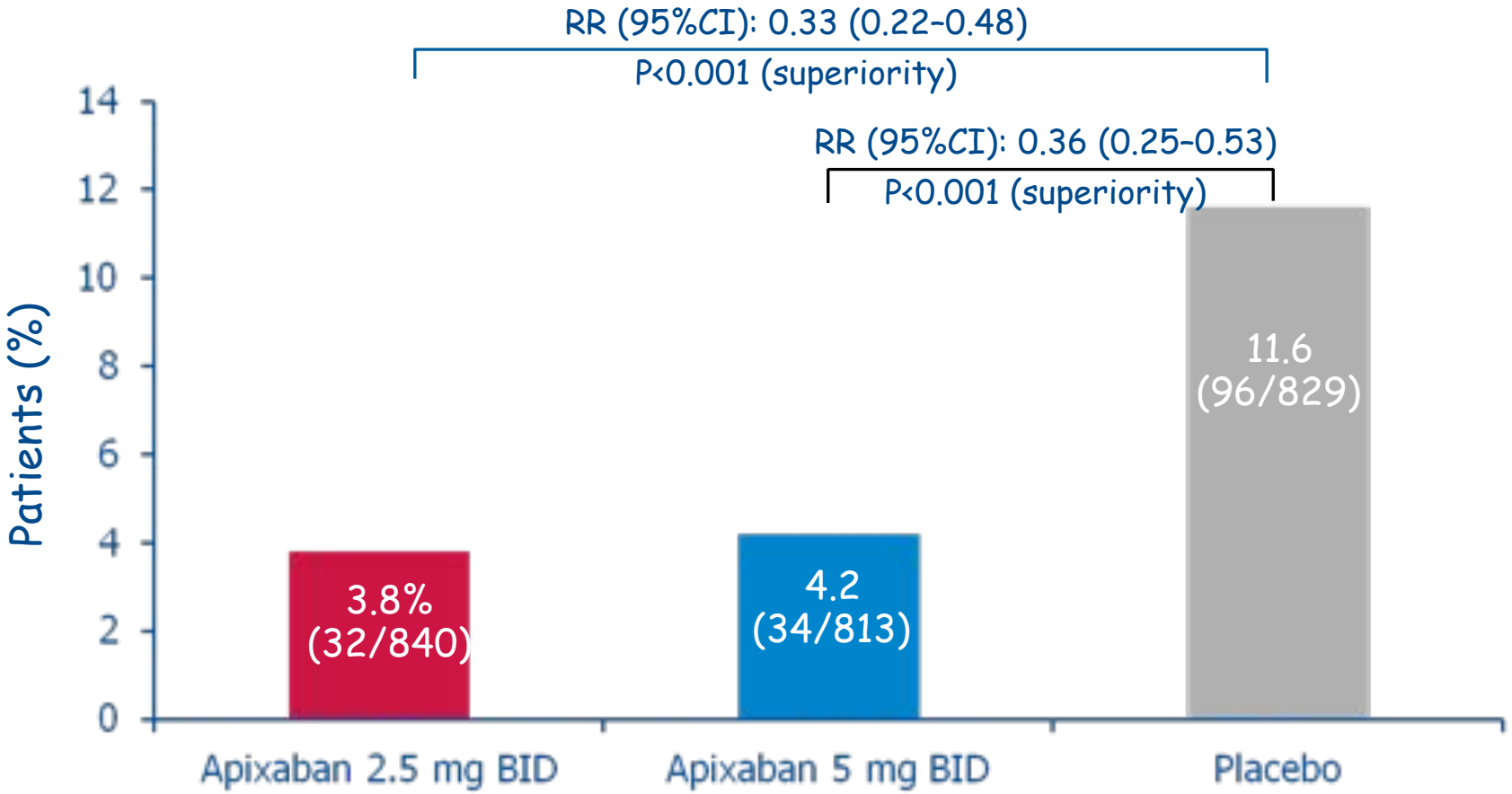
Amplify-EXT: patient flow



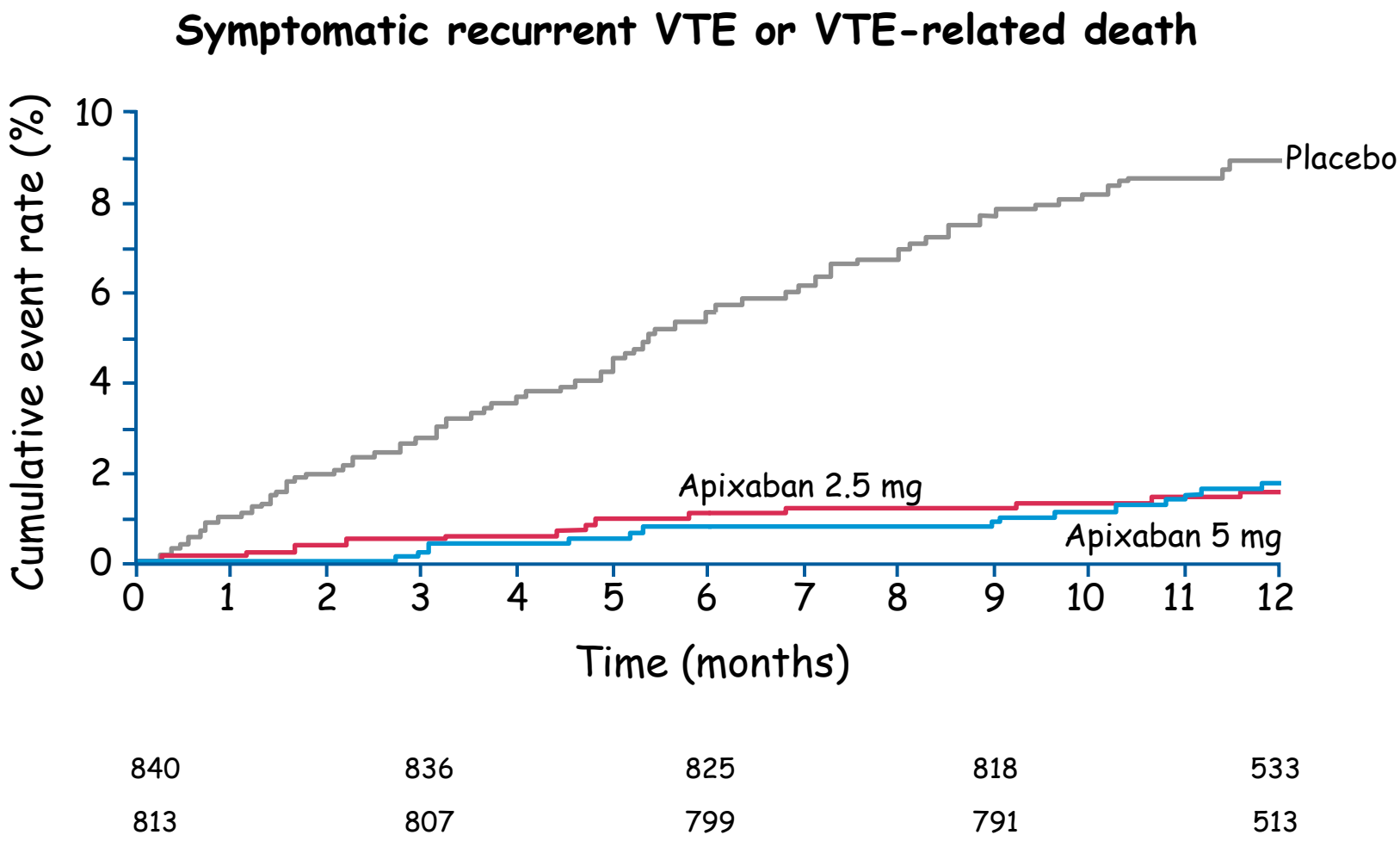
Amplify-EXT: baseline characteristics

	Apixaban 2.5 mg (n=840)	Apixaban 5 mg (n=813)	Placebo (n=829)
Mean age, yrs (SD)	56.6 (15.3)	56.4 (15.6)	57.1 (15.2)
Male sex, n (%)	487 (58.0)	469 (57.7)	468 (56.5)
Mean weight, kg (SD)	85.7 (19.8)	85.7 (19.1)	84.7 (18.6)
≤60 kg	58 (6.9)	59 (7.3)	48 (5.8)
>60 kg	780 (92.9)	751 (92.4)	778 (93.8)
Creatinine clearance, n (%)			
≤30 mL/min	1 (0.1)	3 (0.4)	2 (0.2)
>30 to ≤50 mL/min	47 (5.6)	41 (5.0)	44 (5.3)
>50 to ≤80 mL/min	174 (20.7)	168 (20.7)	194 (23.4)
>80 mL/min	595 (70.8)	580 (71.3)	564 (68.0)
Initial diagnosis, n (%)			
DVT	544 (64.8)	527 (64.8)	551 (66.5)
PE	296 (35.2)	286 (35.2)	278 (33.5)

Amplify-EXT: VTE recurrence or death from any cause



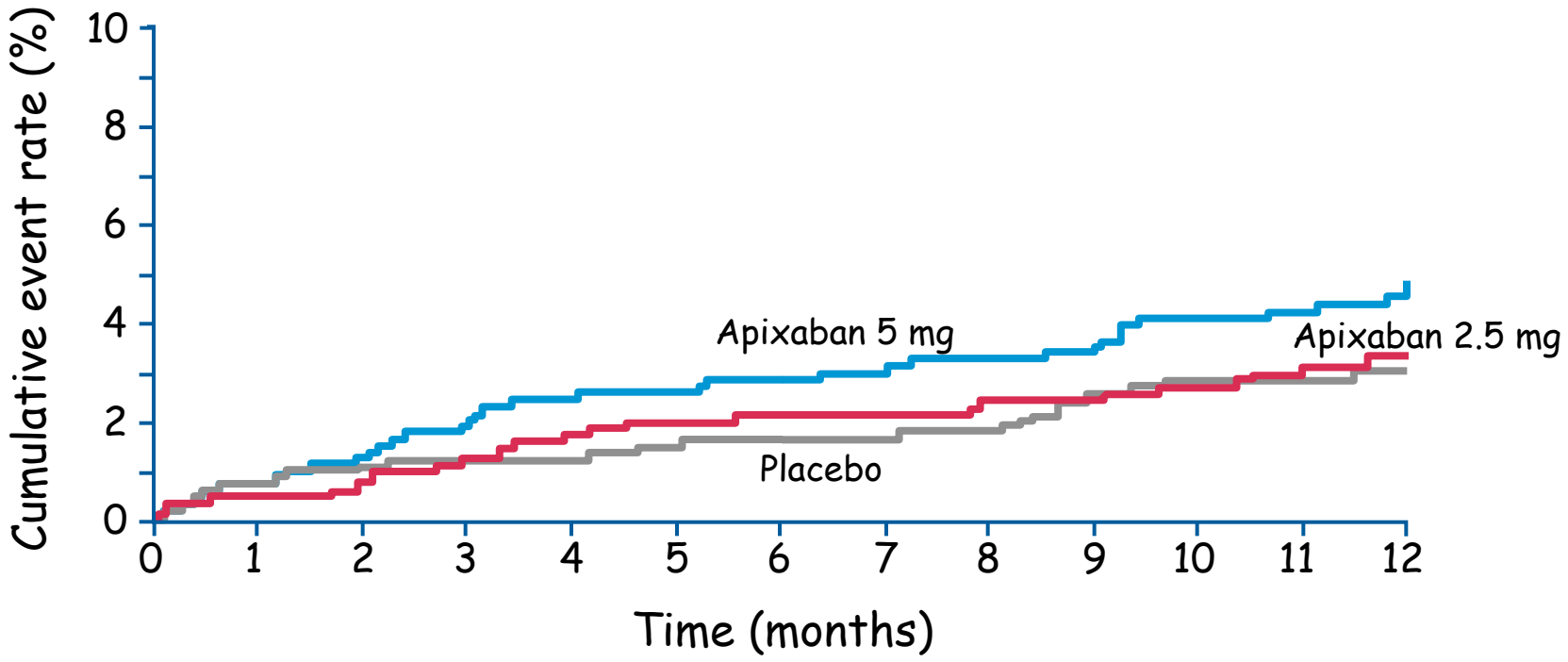
Amplify-EXT: time to event



Amplify-EXT: efficacy outcomes

	Apixaban 2.5 mg (n=840)	Apixaban 5 mg (n=813)	Placebo (n=829)	2.5 mg vs placebo RR (95% CI)	5 mg vs placebo RR (95% CI)	2.5 mg vs 5 mg RR (95% CI)
Recurrent VTE or death from any cause, n (%)	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22-0.48)	0.36 (0.25-0.53)	
Recurrent VTE/ VTE-related death, n (%)	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11–0.33)	0.20 (0.11–0.34	0.97 (0.46–2.02)
Non-VTE-related CV death, MI, or stroke	4 (0.5)	5 (0.6)	11 (1.3)	0.36 (0.11–1.12)	0.47 (0.16–1.33)	0.77 (0.21–2.88)
Recurrent VTE, VTE-related death, MI, stroke, or CV disease-related death	18 (2.1)	19 (2.3)	83 (10.0)	0.21 (0.13–0.35)	0.23 (0.14–0.38)	0.92 (0.48–1.74)

Major or clinically relevant non-major bleeding



840	786	759	737	354
811	751	716	689	331
823	749	687	651	298

Amplify-EXT: safety outcomes

	Apixaban 2.5 mg (n=840)	Apixaban 5 mg (n=813)	Placebo (n=829)	2.5 mg vs placebo RR (95% CI)	5 mg vs placebo RR (95% CI)	2.5 mg vs 5 mg RR (95% CI)
Major bleeding, n %	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)
CRNM bleeding, n (%)	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 CRNM bleeding, n (%)	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)
VTE, VTE-related death, MI, stroke, CV disease-related death, or major bleeding, n (%)*	20 (2.4)	20 (2.5)	86 (10.4)	0.23 (0.14-0.37)	0.24 (0.15-0.38)	0.97 (0.52-1.79)

Acute phase treatement

Patients without shock

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

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Acute phase treatement

Patients without shock

Recommendations	Class[a]	Level[b]	Ref[c]
PE without shock or hypotension (intermediate-or low-risk)[d]			
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*	293, 294
As an alternative to VKA treatment, administration of edoxaban* is recommended following acute-phase parenteral anticoagulation.	I	B	298

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Long Term treatement

Patients without shock

Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily, or 110 mg twice daily for patients ≥80 years of age or those under concomitant verapamil treatment) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary.[d]	IIa	B[e]	295, 370, 371

Kostantinides, Agnelli et al: EHJ 2014

Take home message

- VTE is a common disease with associated with significant morbidity and mortality
- NOACs are now approved by the EMA for VTE treatment
  - Included in the recommendations in the 2014 PE ESC guidelines
  - In AMPLIFY, compared with enoxaparin/warfarin, apixaban was noninferior in recurrent VTE or VTE-related death, with a significant reduction in MB
  - In AMPLIFY ext, apixaban2.5 mg x 2/die reduced VTE recurrence without increasing MB or CRNMB