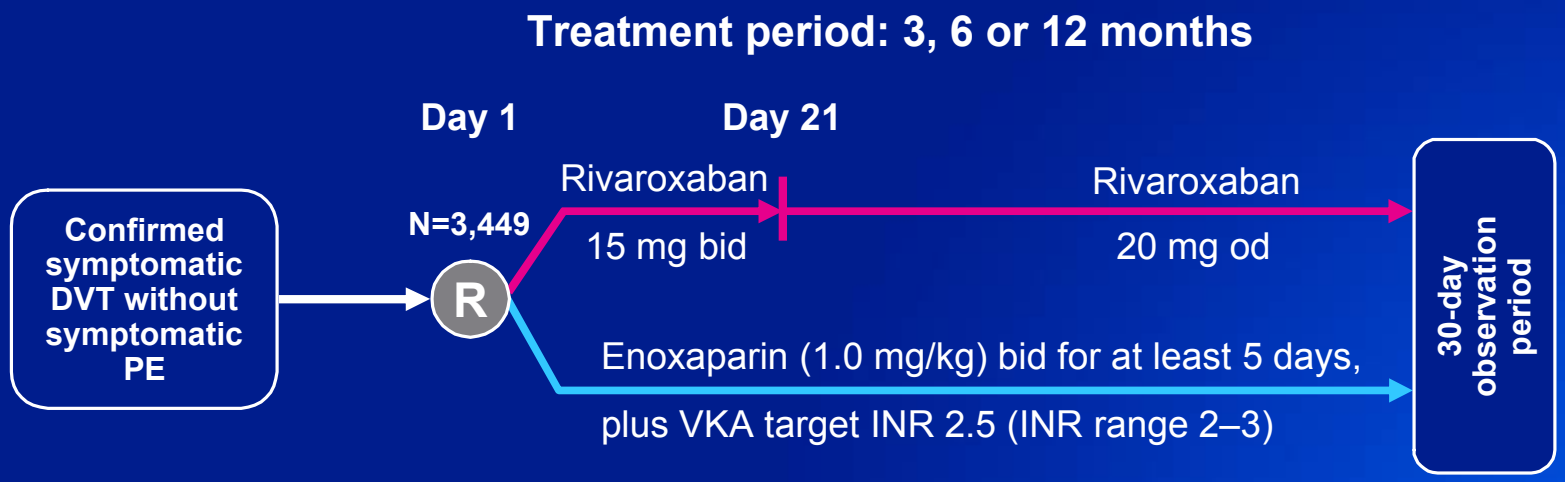
EINSTEIN DVT: study design

Randomized, open-label, event-driven, non-inferiority study

- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry
- 88 primary efficacy outcomes needed



EINSTEIN DVT/PE: study outcomes

Primary efficacy outcome*

- Symptomatic recurrent VTE:
  composite of recurrent DVT, non-fatal PE or fatal PE

Principal safety outcome*

- Combination of major and non-major clinically relevant bleeding

***Adjudicated by the central independent and blinded adjudication committee**

**1. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510;
2. EINSTEIN DVT, PE Evaluation Study Information. Available at http://clinicaltrials.gov. Accessed 10 June 2011; 3. EINSTEIN Integrated Protocol/Study number 11702/ Version no 2.0/08Jun2009, incl. Amend 2, 3, 4**

EINSTEIN DVT: conclusions

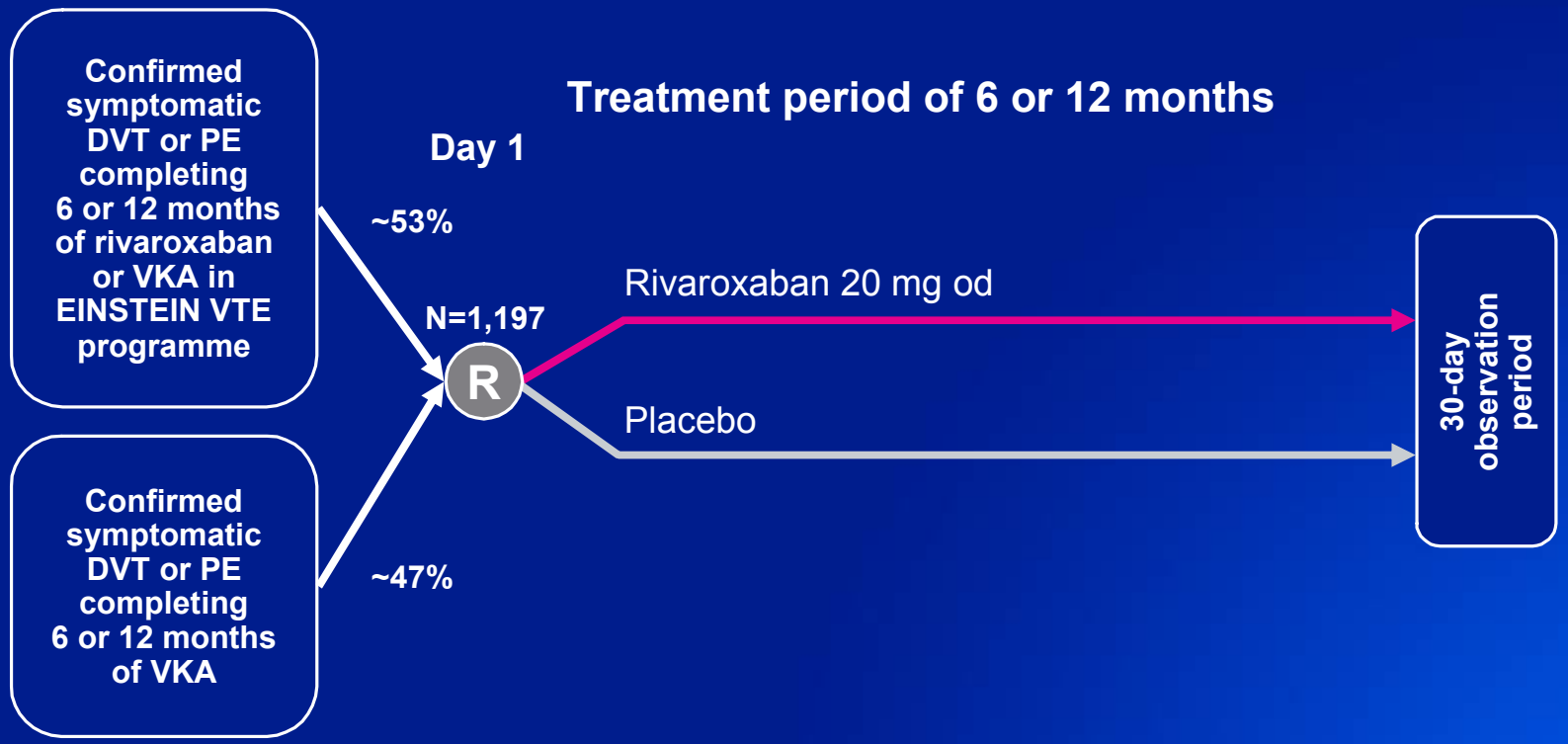
- In patients who had acute symptomatic proximal DVT, without symptomatic PE, rivaroxaban showed:
  - Non-inferiority to LMWH/VKA for efficacy: HR=0.68 (95% CI 0.44–1.04); *p*<0.001 for non-inferiority
  - Similar findings for principal safety outcome: HR=0.97 (95% CI 0.76–1.22); *p*=0.77
  - Consistent efficacy and safety results irrespective of age, body weight, gender, creatinine clearance and cancer
  - No evidence for liver toxicity

In conclusion, oral rivaroxaban, at a dose of 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily thereafter, without the need for laboratory monitoring, may provide an effective, safe, single-drug approach to the initial and continued treatment of venous thrombosis.

1. EINSTEIN Investigators. *N Engl J Med* 2010 (TBC)

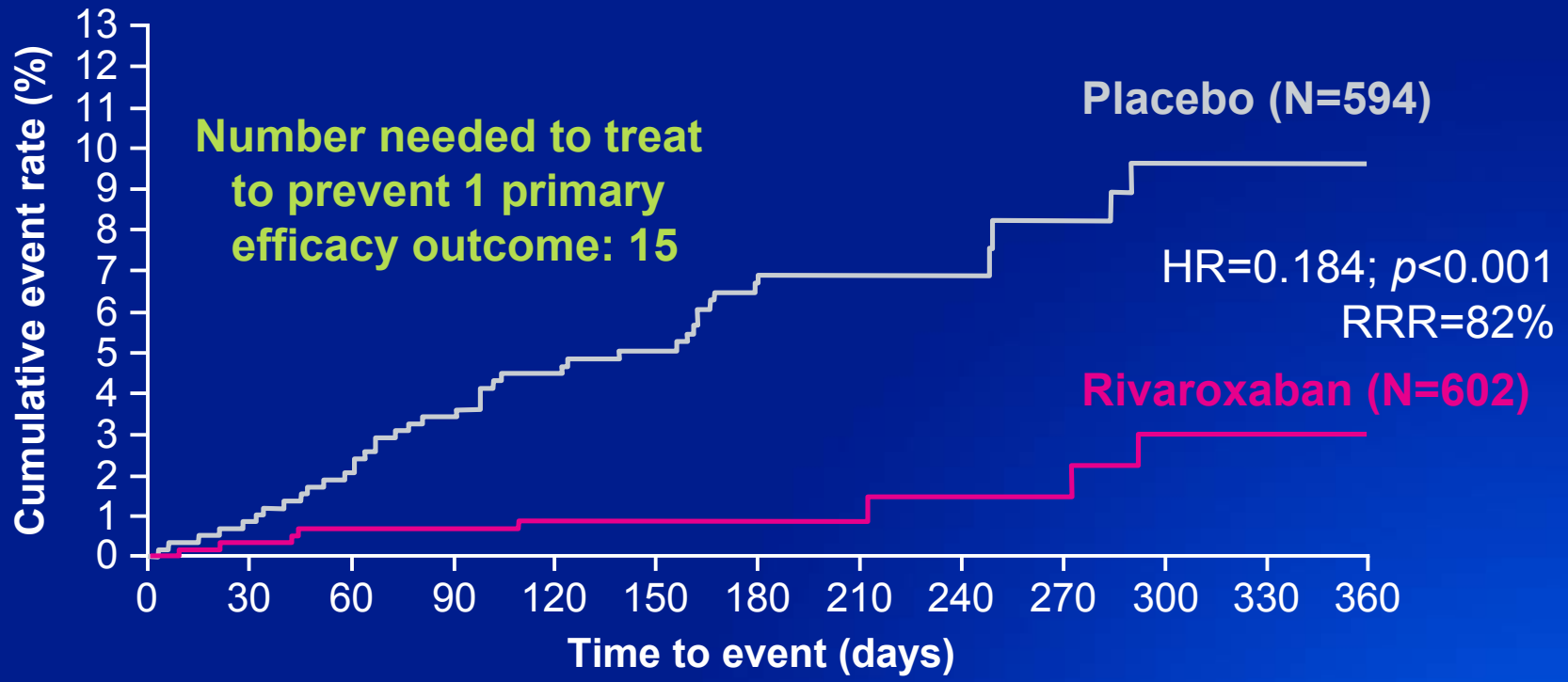
Einstein Extension: study design

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



1. EINSTEIN Investigators. *N Engl J Med* 2010 (TBC)

Primary efficacy outcome analysis: time to first event

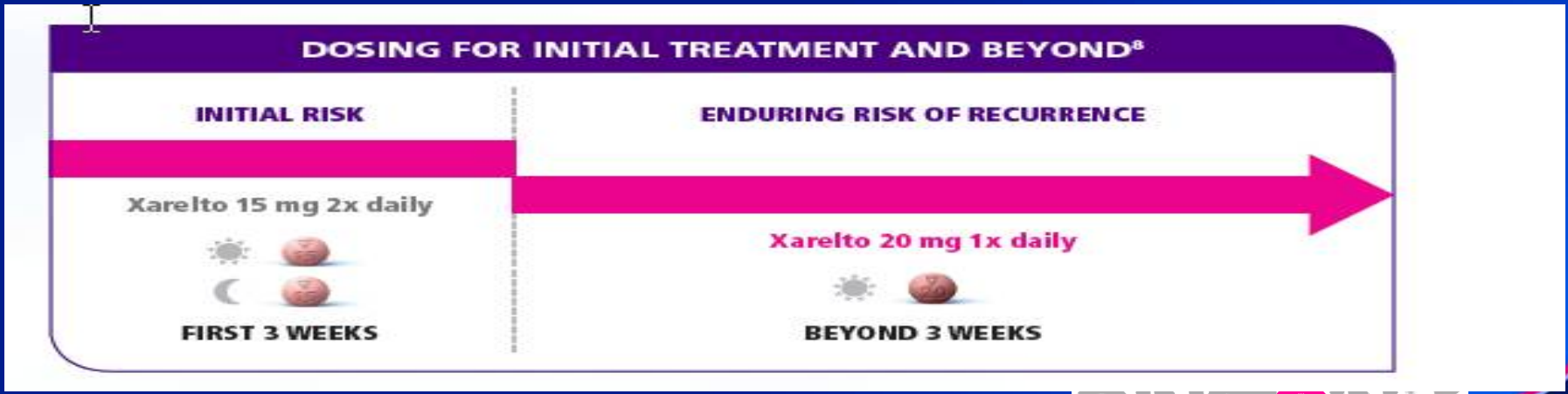


Number of subjects at risk													
Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	555	522	468	444	164	138	133	110	93	85

1. EINSTEIN Investigators. *N Engl J Med* 2010 (TBC)

EINSTEIN EXT: 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*<0.001)
  - Absolute risk reduction 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 od, could provide clinicians and patients with a simple and effective option for continued anticoagulant treatment

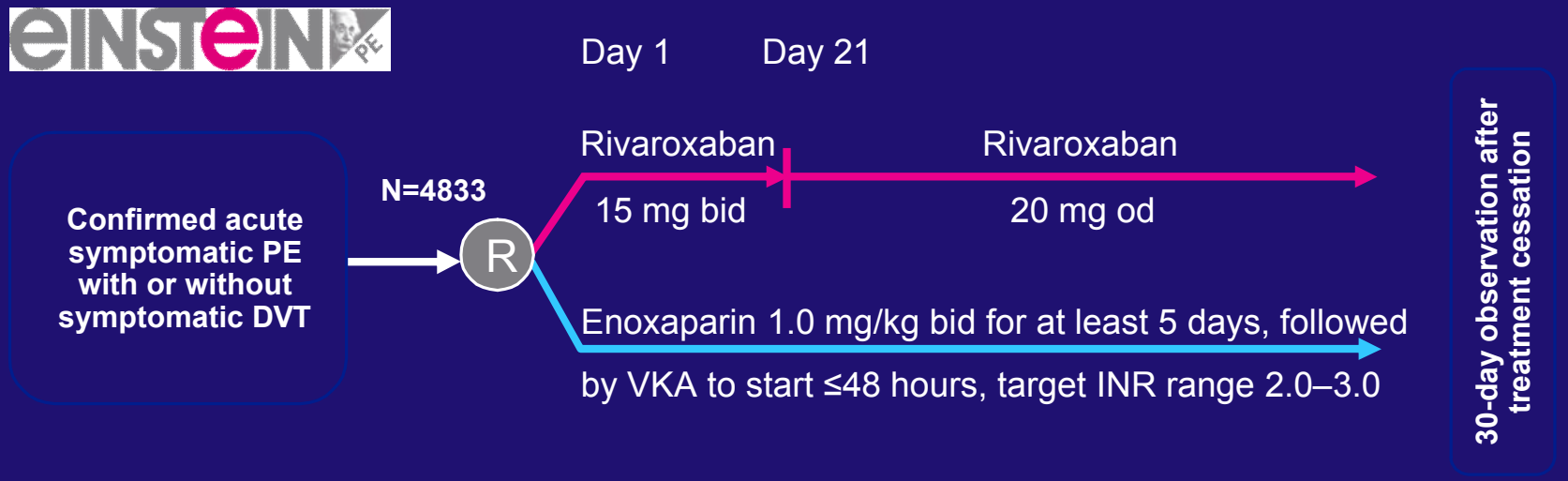


1. EINSTEIN Investigators. *N Engl J Med* 2010 (TBC)

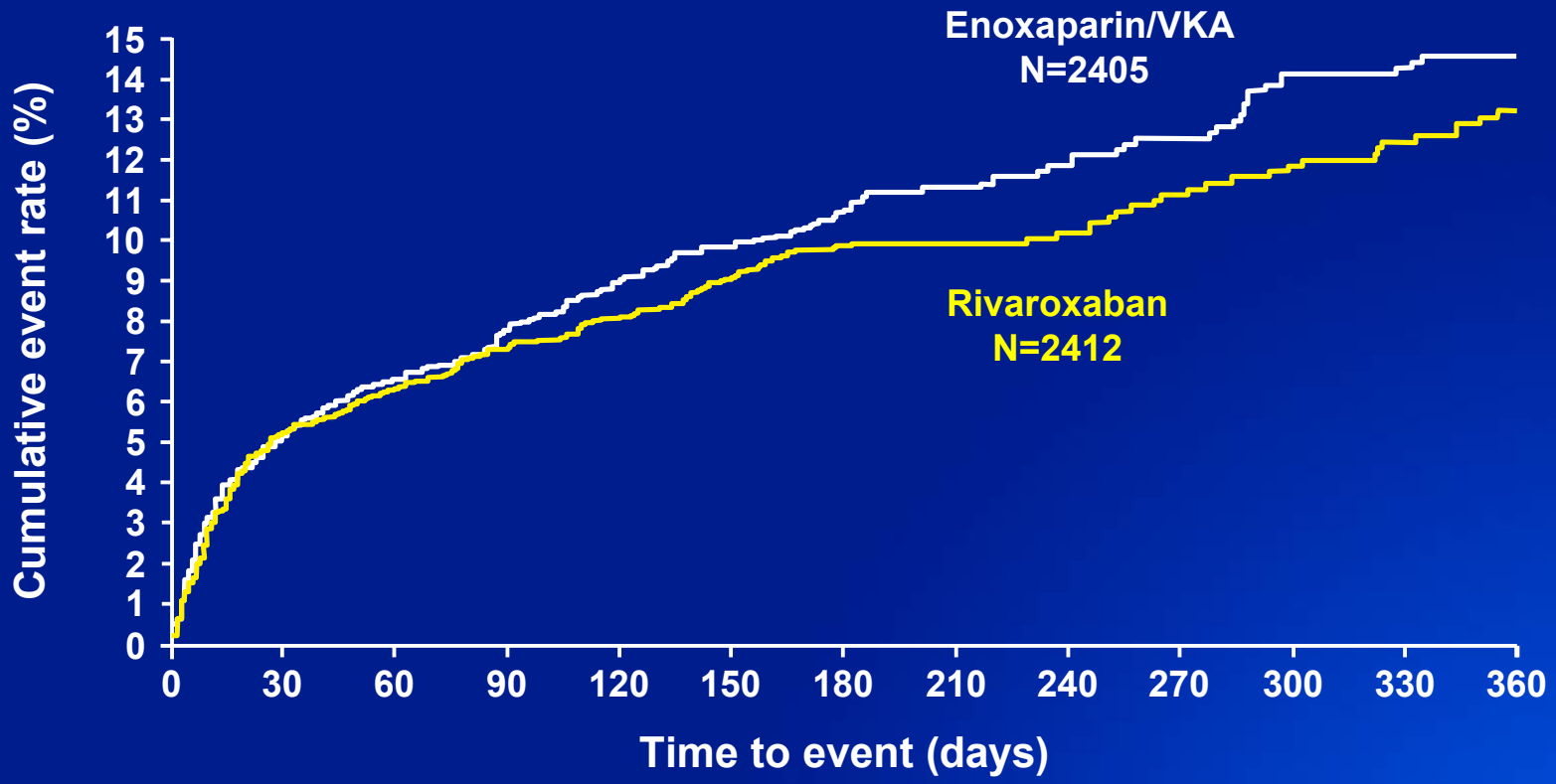
EINSTEIN PE: study design

Randomized, open-label, event-driven, non-inferiority study

- Up to 48 hours' heparins/fondaparinux treatment permitted before study entry



Principal safety outcome:
major or non-major clinically relevant bleeding

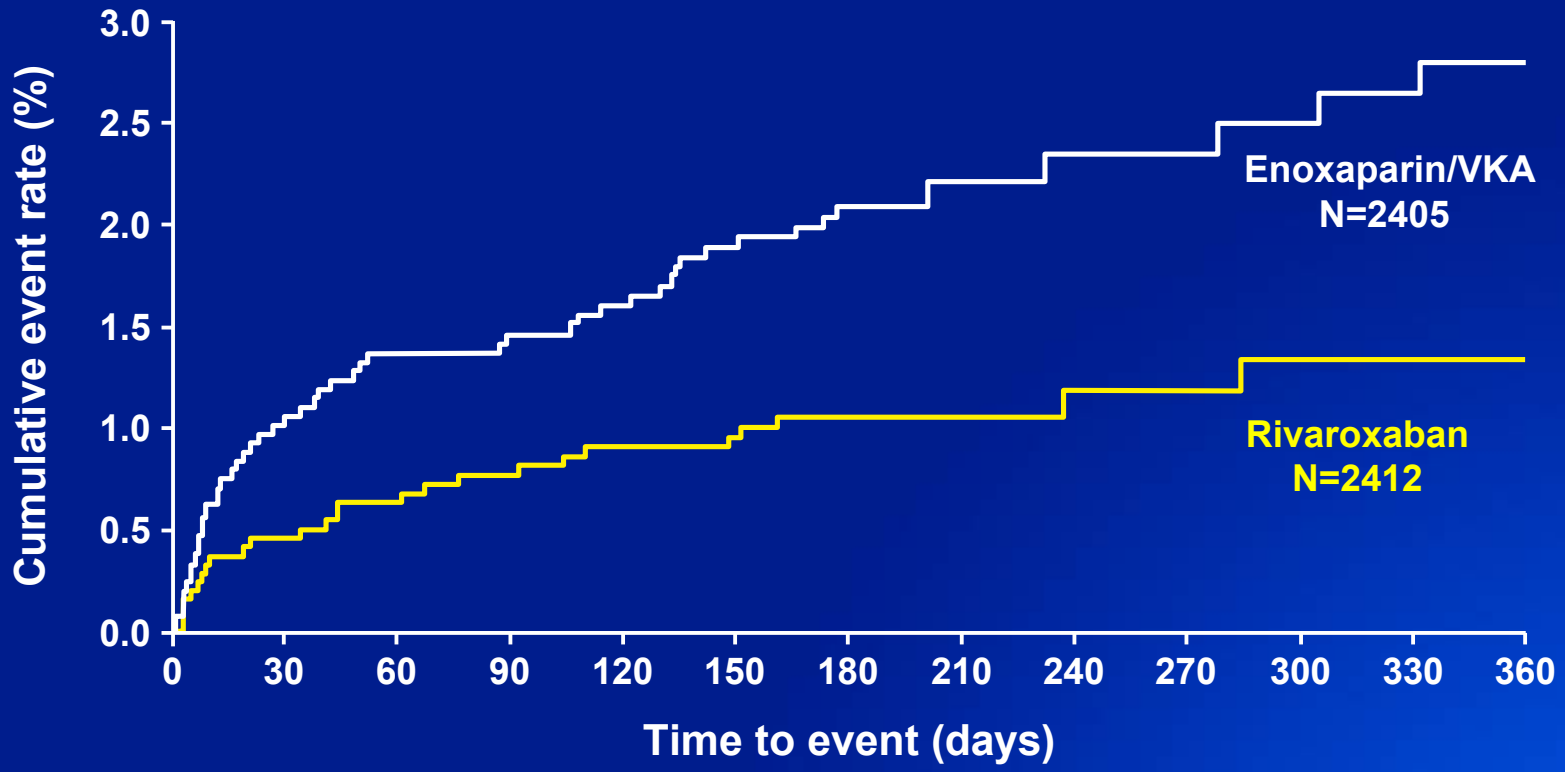


Number of patients at risk													
Rivaroxaban	2412	2183	2133	2024	1953	1913	1211	696	671	632	600	588	313
Enoxaparin/VKA	2405	2184	2115	1990	1923	1887	1092	687	660	620	589	574	251

Safety population

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; 366:1287-1297

Major bleeding



Number of patients at risk													
Rivaroxaban	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Enoxaparin/VKA	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

Safety population

The EINSTEIN–PE Investigators. *N Engl J Med* 2012; 366:1287-1297

Conclusions

In patients with acute symptomatic PE with or without DVT, rivaroxaban showed:

- Non inferiority to LMWH/VKA for efficacy: HR=1.12 (0.75-1.69); p=0.0026 for non inferiority
- Similar findings for principal safety outcome: HR=0.90 (0.76-1.07); p=0.23
- Superiority for major bleeding: HR=0.49 (0.31-0.79) p=0.0032
- Consistent efficacy and safety results irrespective of age, body weight, gender, kidney function and cancer
- No evidence for liver toxicity

RECOVER™

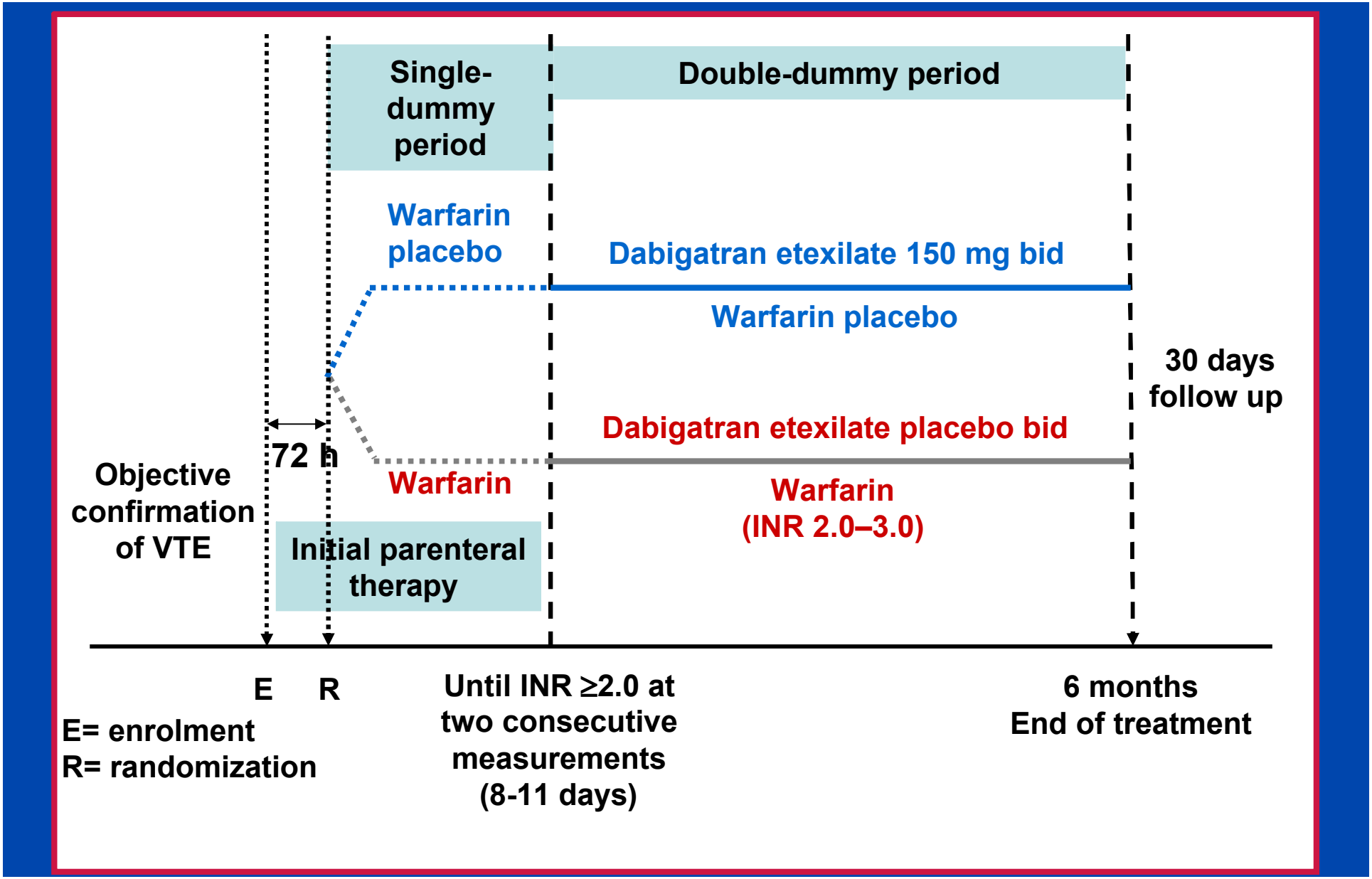
Study of treatment of
venous thromboembolism

A phase III, randomised, double blind, parallel-group study of the efficacy and safety of oral dabigatran etexilate (150 mg bid) compared to warfarin (INR 2.0–3.0) for 6 month treatment of acute symptomatic venous thromboembolism, following initial treatment (5–10 days) with a parenteral anticoagulant approved for this indication.

Dabigatran etexilate is in clinical development and
not licensed for clinical use for acute treatment of VTE

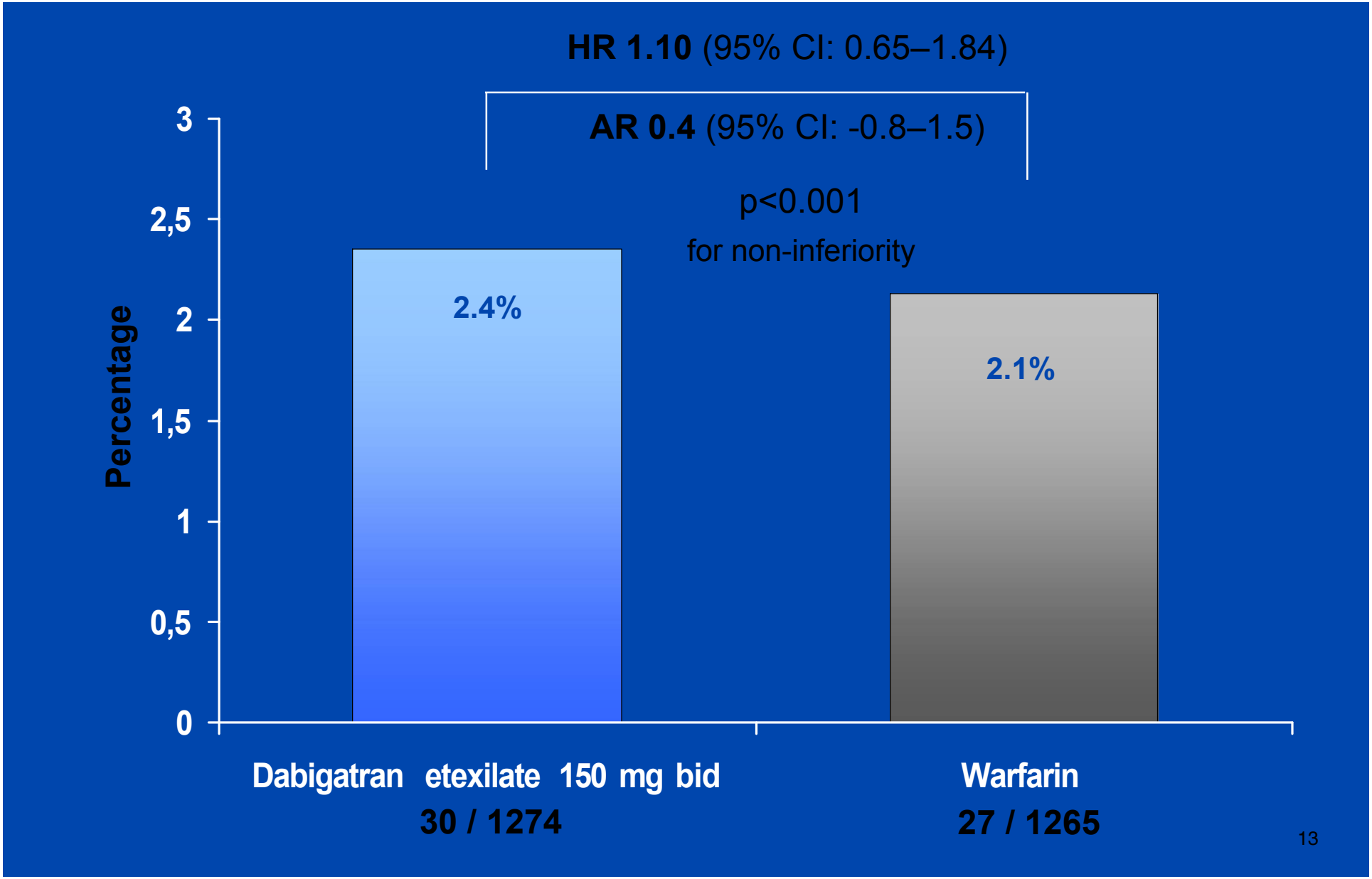
RE-COVER™ Trial Design

RECOVER™
Study of treatment of venous thromboembolism



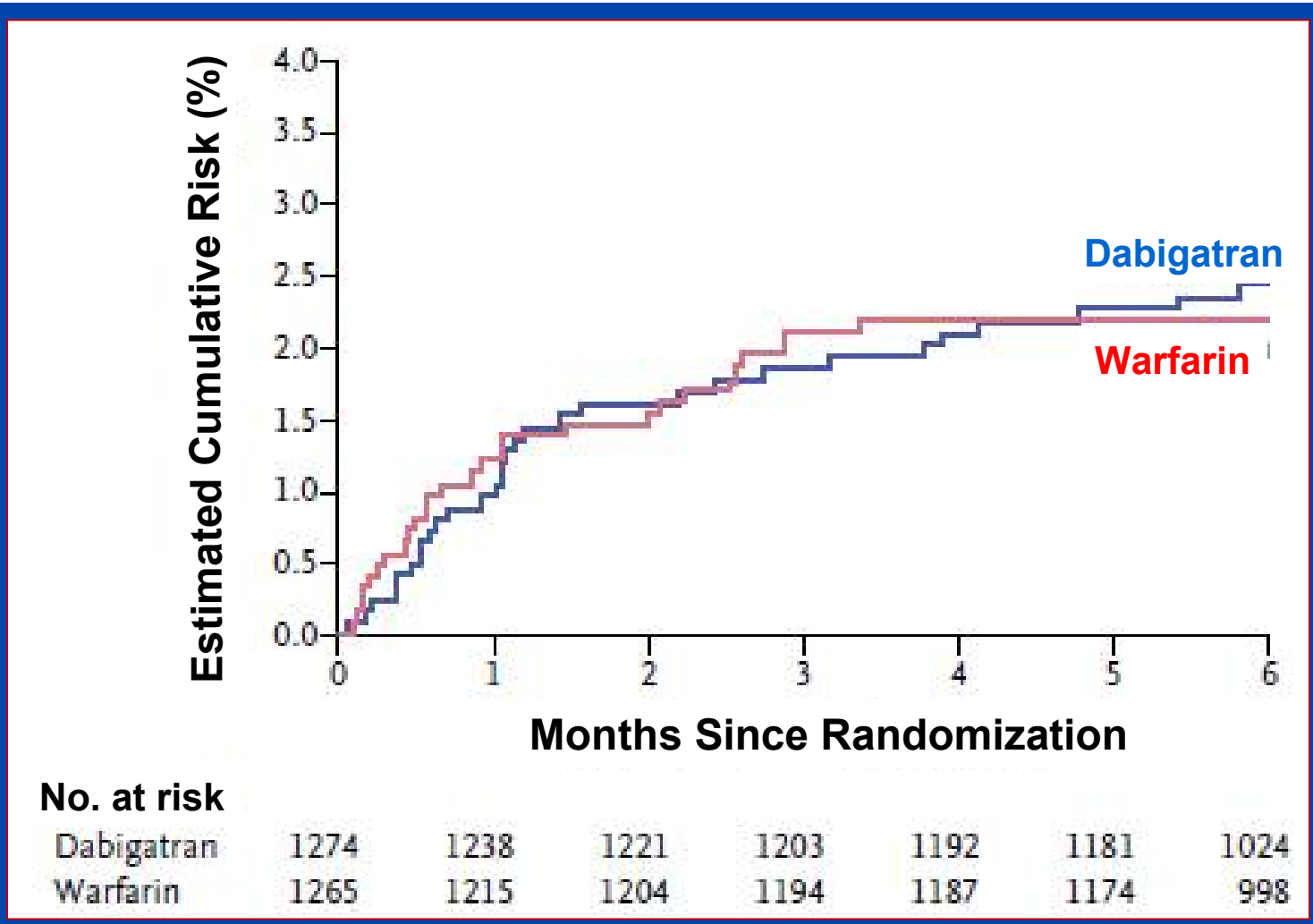
Non-inferior in VTE or related death

RECOVER™
Study of treatment of venous thromboembolism



Cumulative risk of recurrent VTE and related death

RECOVER™
Study of treatment of venous thromboembolism

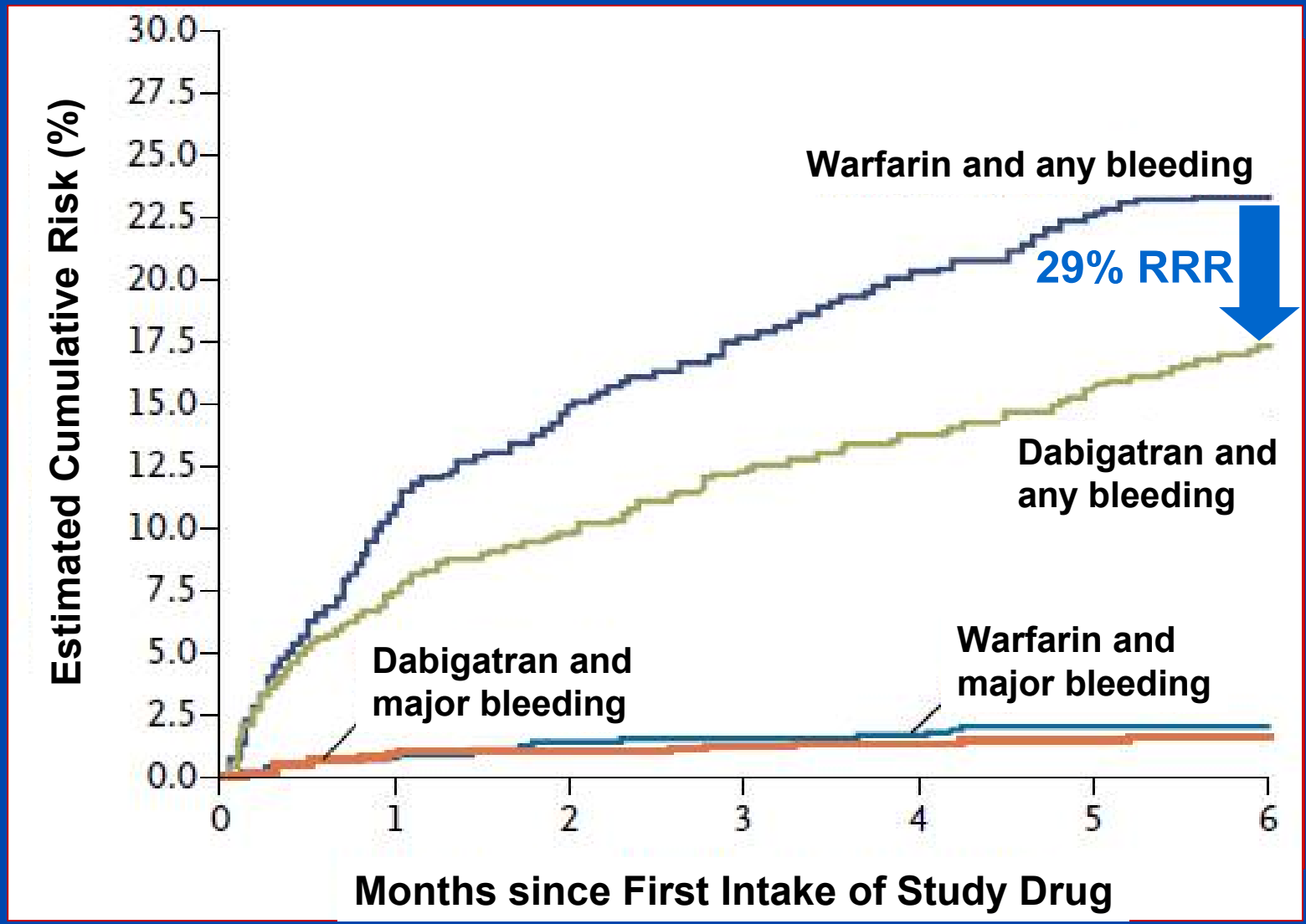


No. at risk							
Dabigatran	1274	1238	1221	1203	1192	1181	1024
Warfarin	1265	1215	1204	1194	1187	1174	998

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

Cumulative risk of first event of major bleeding and of any bleeding

RECOVER™
Study of treatment of venous thromboembolism



The hazard ratio for any bleeding at 6 months is 0.71 (95% CI, 0.59–0.85) in favor of dabigatran (P=0.0002).

Conclusions

RECOVER™
Study of treatment of
venous thromboembolism

- Dabigatran etexilate has comparable efficacy to warfarin
- Dabigatran etexilate has comparable or lower bleeding rates to warfarin
  - Comparable rates of major bleeds
  - Significant reduction in major or clinically relevant bleeds
  - Significant reduction in any bleeds
- For acute VTE, dabigatran etexilate provides a convenient, oral, fixed-dose treatment with the potential to replace warfarin

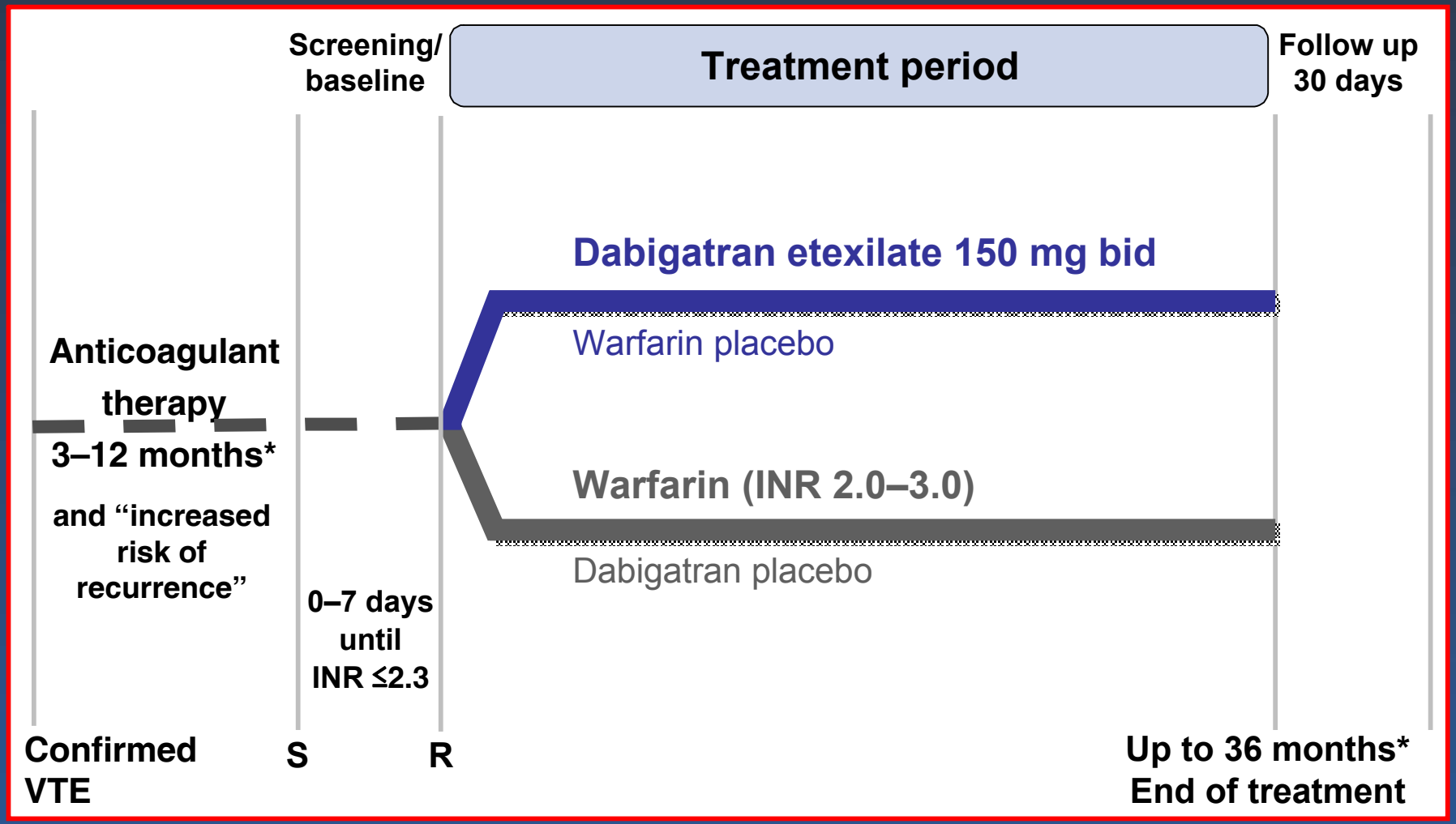
S Schulman,
H Eriksson,
S Goldhaber,
A Kakkar, C Kearon,
A-M Kvamme,
P Mismetti, S Schellong
and J Schnee;
for the RE-MEDY™
Study Group

Dabigatran versus warfarin in the extended treatment of VTE

Disclaimer

- Please note that dabigatran is not approved for the indication described in this study

RE-MEDY™ study design



*Original protocol, 3–6 months of pre-treatment, then 18 months on study drug; amendment allowed 3–12 months of pre-treatment, then up to 36 months on study drug.
S, screening; R, randomization.

Confirmed cardiovascular events

	Dabigatran n (%)	Warfarin n (%)
Treated set	1430 (100)	1426 (100)
Patients with definite acute coronary syndrome (ACS) events, as randomized, on treatment	12 (0.8)	2 (0.1)
Events of definite ACS events, as randomized, on treatment	12	2
Definite myocardial infarction	9	1
Definite ischemia	3	1
Cardiac death	0	0
Definite and likely ACS events in patients, including post-treatment period (6 days)	13 (0.9)*	3 (0.2)

*p = 0.02 versus warfarin.

Conclusions

- Dabigatran etexilate was non-inferior to well-controlled warfarin for the long-term treatment and secondary prevention of symptomatic VTE following initial anticoagulant treatment for 3–12 months after an index venous thrombotic event
- No significant between-treatment differences were found for any of the primary or secondary efficacy endpoints
- There were numerically fewer MBEs and statistically significantly fewer total BEs with dabigatran etexilate than with warfarin
- More acute coronary syndrome events were noted with dabigatran etexilate than with warfarin

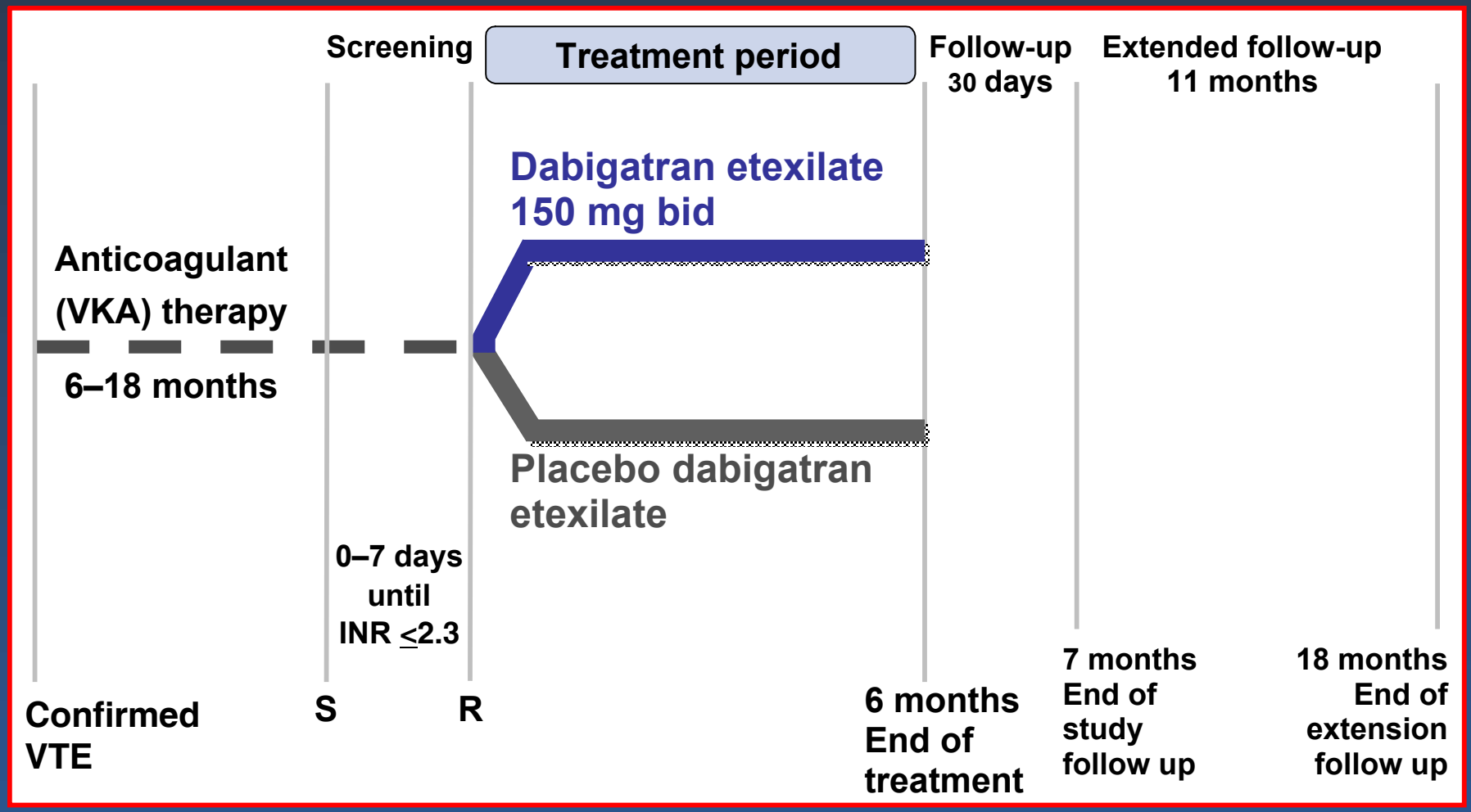
S Schulman,
D Baanstra, H Eriksson,
S Goldhaber, A Kakkar,
C Kearon, P Mismetti,
S Schellong and
J Schnee;
for the RE-SONATE™
Study Group

Dabigatran versus placebo in the extended treatment of VTE

Disclaimer

- Please note that dabigatran is not approved for the indication described in this study

RE-SONATE™ study design



After 36 events, the next (3-month) visit was the final on-treatment visit

S, screening; R, randomization.

Confirmed cardiovascular events

	Dabigatran n (%)	Placebo n (%)
Full analysis set	684 (100)	659 (100)
Any cardiovascular event	3 (0.4)	2 (0.3)
NSTEMI	0	1 (0.2)
STEMI	1 (0.1)	0
Unstable angina	0	0
Transient ischaemic attack	2 (0.3)	0
Ischaemic stroke	0	1 (0.2)
Non-CNS systemic embolism	0	0

No difference in acute coronary syndrome events

CNS, central nervous system; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction.

Conclusions

- Dabigatran etexilate is a highly effective agent for reducing recurrent VTE and unexplained death, with a 92% reduction in risk compared with placebo
- The frequency of major bleeding events is low
- The frequency of any centrally confirmed bleeding events is low, and about two times greater than with placebo
- The frequency of cardiovascular events was low with no difference between treatment groups

Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials

Benjamin D Fox *visiting professor*1, Susan R Kahn *professor of medicine*2, David Langleben *professor of medicine* 1, Mark J Eisenberg *professor of medicine* 1 2, Avi Shimony *visiting scientist* 1

- **Objective** To critically review the effectiveness of the novel oral anticoagulants (rivaroxaban, dabigatran, ximelagatran, and apixaban) in the treatment of acute venous thromboembolism.
- **Design** Systematic review and random effects meta-analysis. Data were extracted independently by two investigators. An adjusted indirect comparison was performed to compare between novel oral anticoagulants.
- **Data sources** Medline, Embase, and Cochrane Library (from inception to April 2012). Hand searching of relevant scientific works and contact with experts.
- **Conclusions** Compared with vitamin K antagonists, the novel oral anticoagulants had a similar risk of recurrence of acute venous thromboembolism and all cause mortality, though rivaroxaban was associated with a reduced risk of bleeding.

BMJ 2012;345:e7498 doi: 10.1136/bmj.e7498 (Published 13 November 2012)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

- Studio randomizzato, in doppio cieco, intention-to-treat
- 2482 Pazienti con TVP
- efficacia e sicurezza di due diversi regimi terapeutici di Apixaban (2,5 mg e 5 mg, due volte al giorno) versus placebo
- somministrazione nei 12 mesi successivi al termine di un periodo di terapia anticoagulante “classica” di 6 o 12 mesi

Ricorrenza del tromboembolismo o la morte ad essa correlata

8,8 % (73) degli 829 Pazienti trattati con Placebo
1,7 % (14) degli 840 Pazienti trattati con Apixaban 2,5 mg BID
(con una differenza percentuale di 7,2 ; 95% CI, 5,0-9,3)
1,7 % (14) degli 813 Pazienti trattati con Apixaban 5 mg BID
(con una differenza percentuale di 7,0 ; 95% CI, 4,9-9,1)
con una P <0,001 per entrambi i confronti

Tassi di sanguinamento maggiore

0.5% nel gruppo Placebo,
0,2% nel gruppo dei Pazienti trattati con Apixaban 2,5 mg BID e
0,1% nel gruppo dei Pazienti trattati con Apixaban 5,0 mg BID

Tassi di sanguinamento clinicamente rilevanti

2,3% nel gruppo placebo,
3.0% nel gruppo dei Pazienti trattati con Apixaban 2,5 mg BID e
4,2% nel gruppo dei Pazienti trattati con Apixaban 5,0 mg BID

Tasso di mortalità per qualsiasi causa

1,7% nel gruppo placebo rispetto allo 0,8% nel gruppo Apixaban 2,5 mg BID
ed allo 0,5% nel gruppo Apixaban 5,0 mg BID