
## NAO e TEV:
## INDICAZIONI, VANTAGGI ED EVVENTI AVVERSI

# DURATA DELLA TERAPIA ANTICOAGULANTE DEL TEV

Dott. Raffaella Benedetti
Centro Emostasi e Trombosi
Ospedale Piacenza

# Le recidive del TEV: alcune cifre

- 3-10% /anno dopo il primo episodio
- 40% dopo 10 anni dalla sospensione del trattamento anticoagulante
- 52% nelle forme idiopatiche, 22% nelle forme secondarie

- 30/1000 persone/giorno nei primi 7 giorni
- 10/1000 persone/giorno nei primi 6-12 mesi
- 4/1000 persone/giorno dopo 5 e 10 anni

# Current Recommendations for the Management of Unprovoked VTE

| | | ACCP recommendation | Grade of recommendation |
|---|---|---|---|
| CHEST | Unprovoked DVT or PE | Extended therapy if bleeding risk is low/moderate | 2B |
| | | 3 months if bleeding risk is high | 1B |

In patients with DVT of the leg or PE and no cancer, as long-term anticoagulant therapy (first 3 months), we suggest dabigatran, rivaroxaban, apixaban or edoxaban **over VKA** therapy (all Grade 2B)[1]

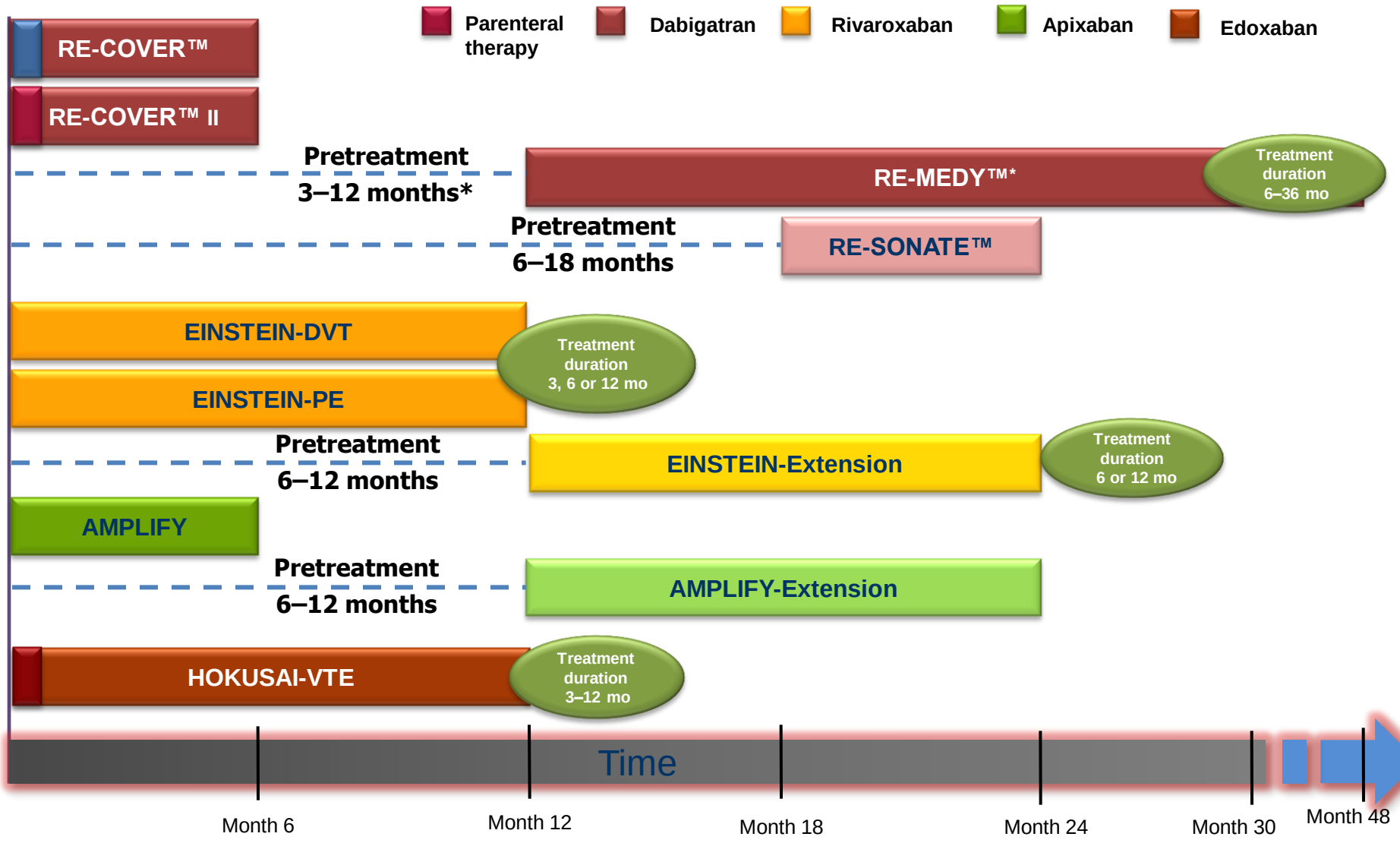
| | Class of recommendation | Level of evidence |
|---|---|---|
| **Unprovoked PE: ≥3 months** | I | A |
| **First episode of unprovoked PE and low bleeding risk: consider extended treatment (>3 months)** | IIa | B |
| **Second episode of unprovoked PE: indefinite duration** | I | B |
| **Risk–benefit of continuing anticoagulation should be reassessed at regular intervals** | I | C |

EUROPEAN SOCIETY OF CARDIOLOGY®

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[2]

1. Kearon C *et al*, *Chest* 2016;149:315–352; 2. Konstantinides SV *et al*, *Eur Heart J* 2014;35:3033–3069

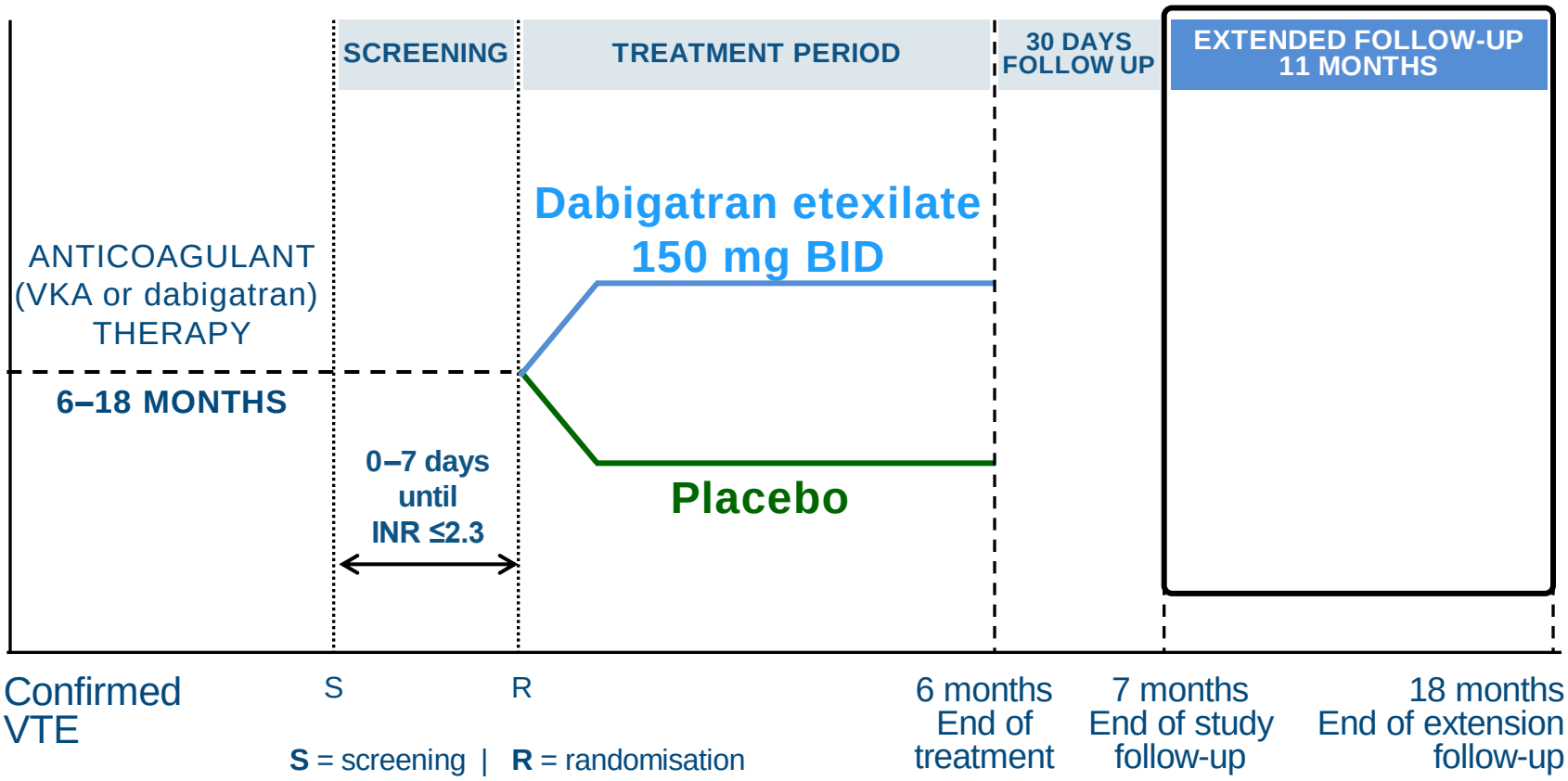
# Overview trials




*RE-MEDY™ original protocol, 3–6 months of pretreatment, then 18 months on study drug; amendment allowed 3–12 months of pretreatment, then **up to 36 months** on study drug

# RE-SONATE: Trial design

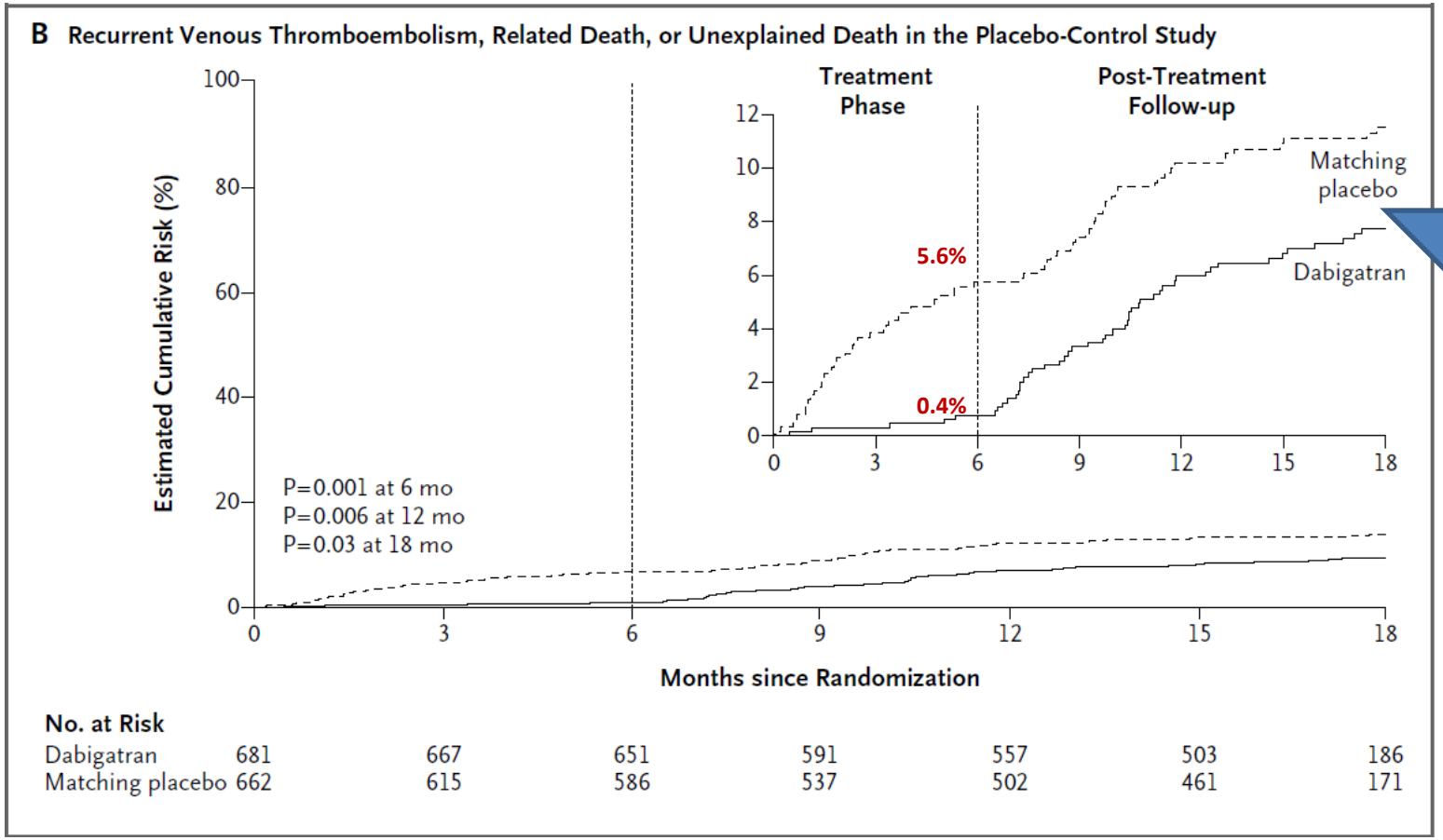
RESONATE™
Study of secondary prevention of venous thromboembolism




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

Schulman S et al. N Engl J Med 2013;368:709–18

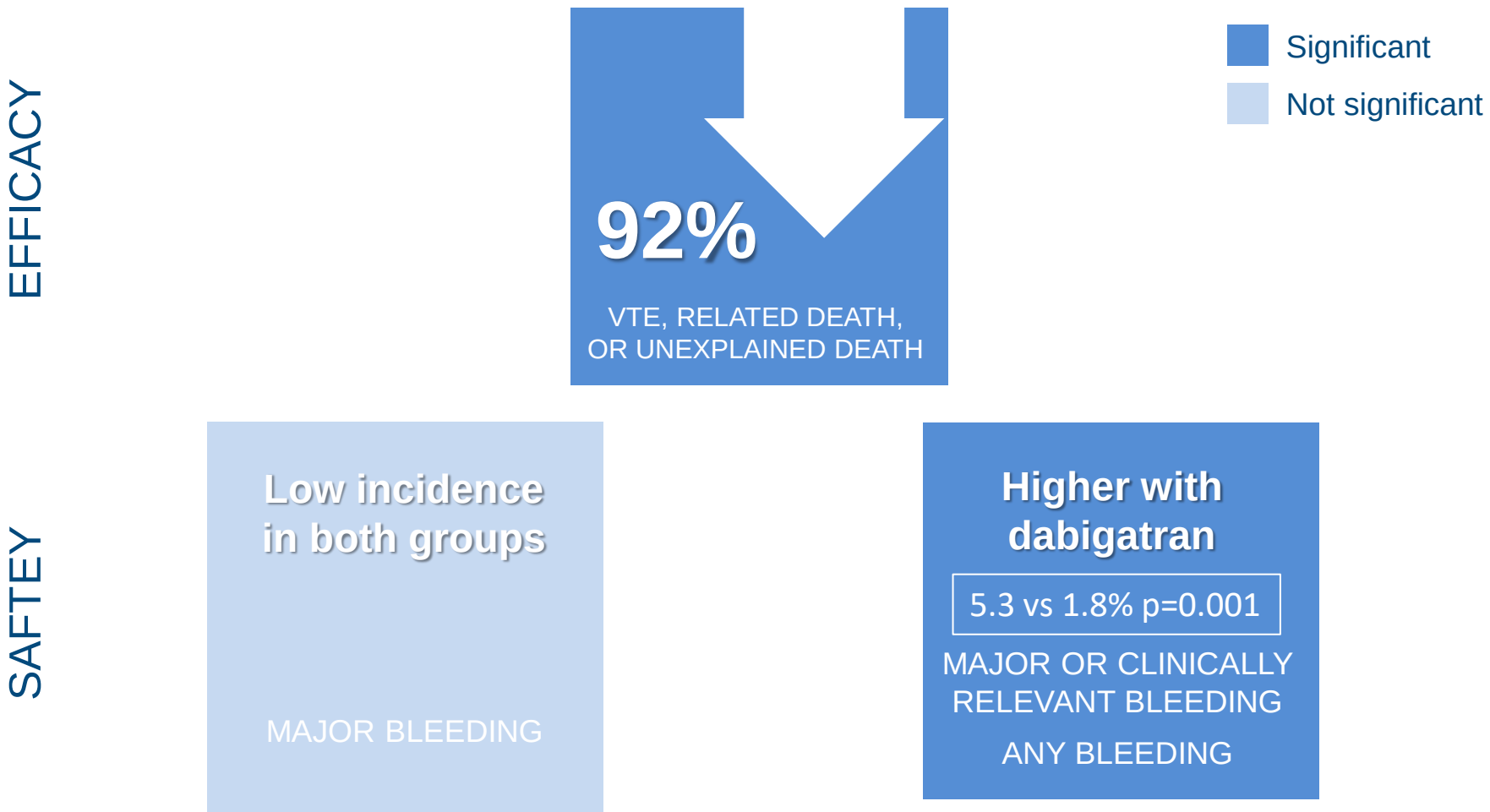
# RE-SONATE: efficacy data




RRR -92%

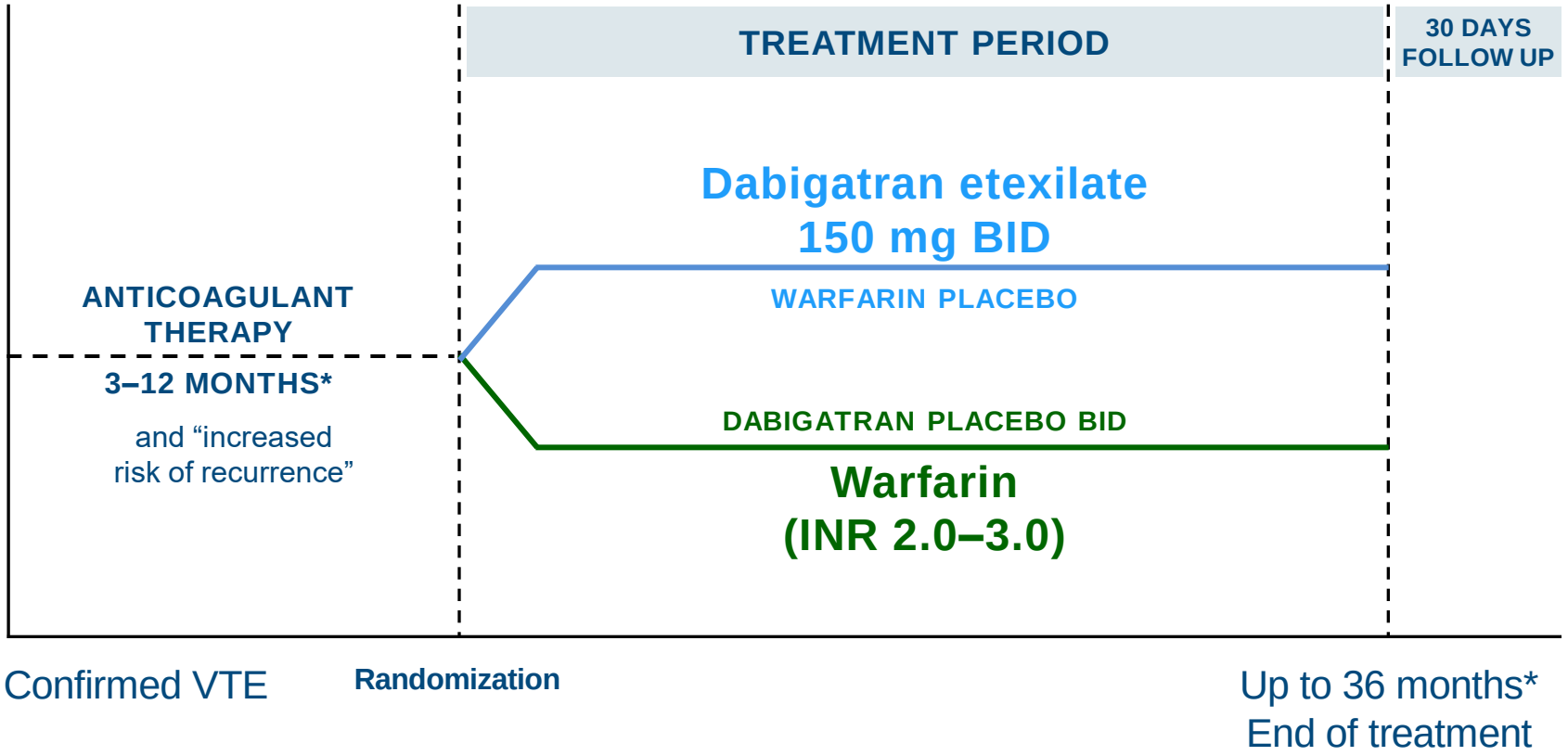
Schulman S et al. N Engl J Med 2013;368:709–18

# RE-SONATE™ assessed dabigatran vs placebo for the prevention of recurrence




Schulman et al. N Engl J Med 2013

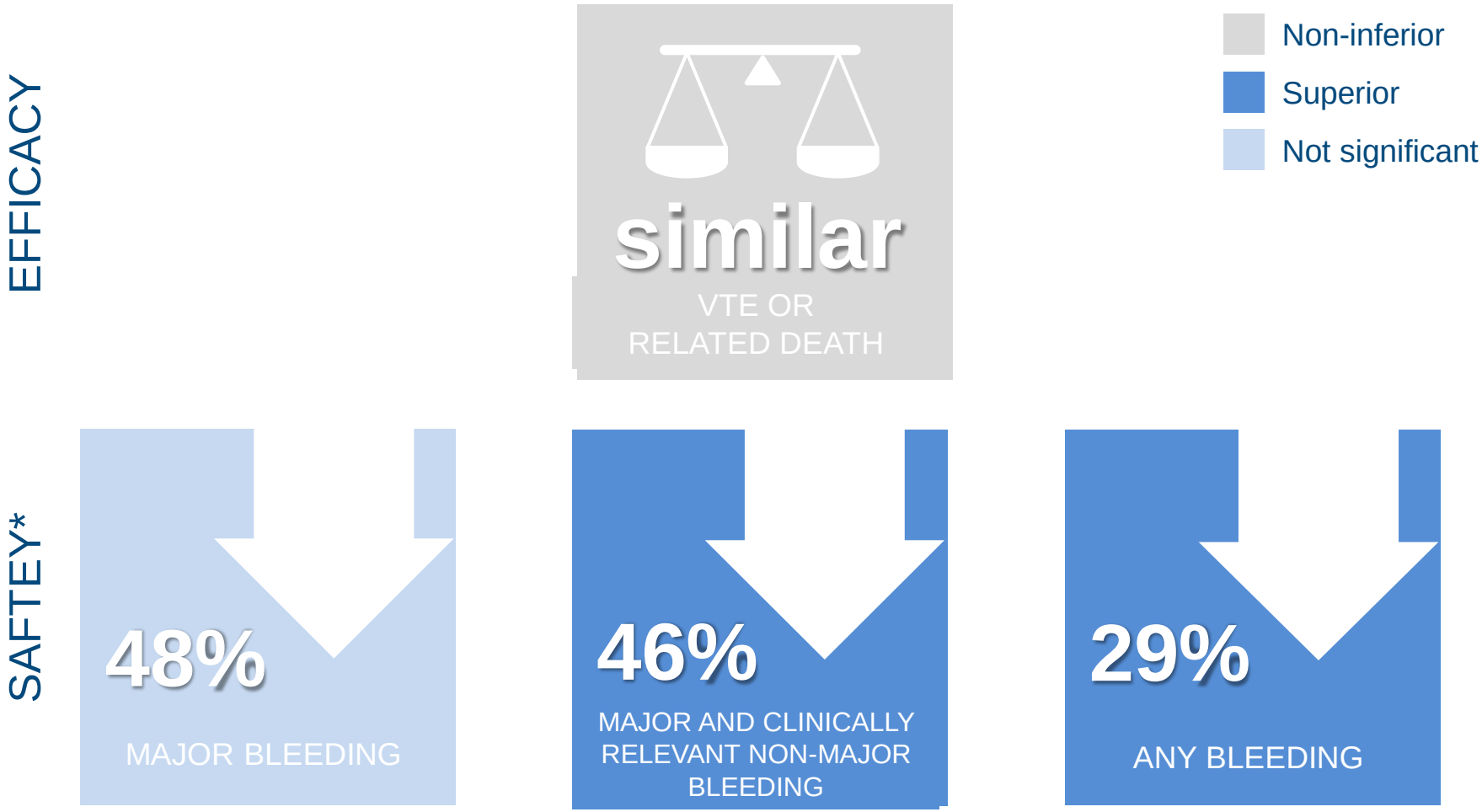
# RE-MEDY: Trial design




*Original protocol, 3–6 months of pretreatment, then 18 months on study drug; amendment allowed 3–12 months of pretreatment, then up to 36 months on study drug

Schulman S et al. N Engl J Med 2013;368:709–18

# RE-MEDY™ assessed dabigatran vs warfarin for the prevention of recurrence

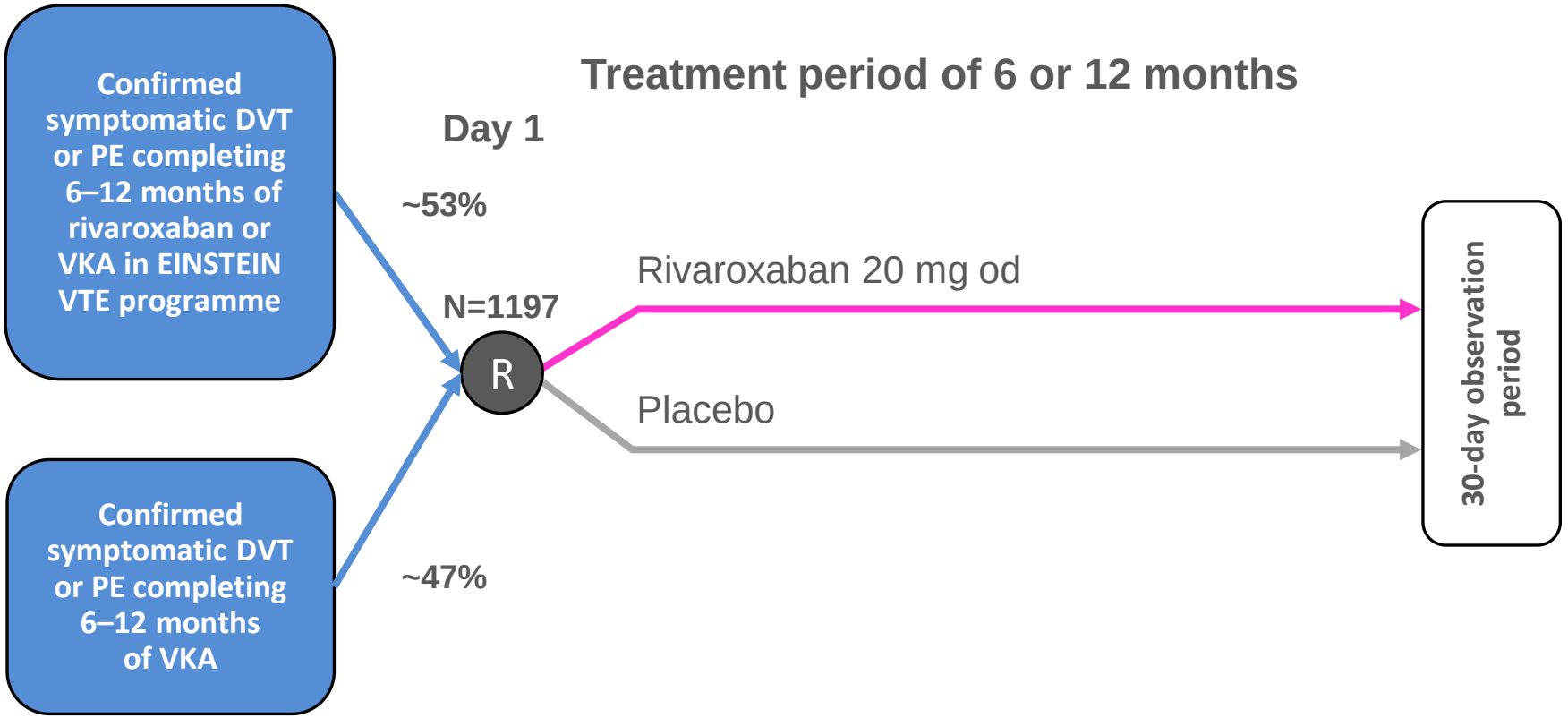



*Major bleeding numerically lower with dabigatran vs warfarin; major and clinically relevant non-major bleeding and any bleeding were significantly lower with dabigatran vs warfarin

Schulman et al. N Engl J Med 2013

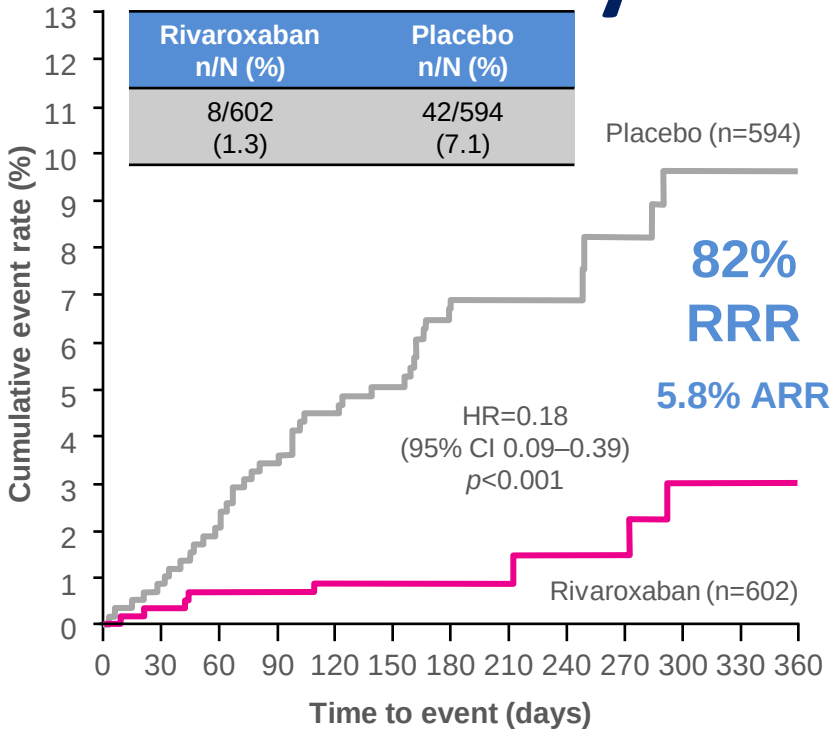
# EINSTEIN EXT: Study Design

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




1. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510

# EINSTEIN EXT: Efficacy and Safety Data




| Number of patients at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Riva | 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 |

| | Rivaroxaban (n=598) | | Placebo (n=590) | |
|---|---|---|---|---|
| | n | % | n | % |
| **Major bleeding** | **4** | **0.7*** | **0** | **0** |
| **Bleeding contributing to death** | **0** | **0** | **0** | **0** |
| Bleeding in a critical site | 0 | 0 | 0 | 0 |
| Associated with fall in haemoglobin ≥2 g/dl and/or transfusion of ≥2 units | 4 | 0.7 | 0 | 0 |
| Gastrointestinal bleeding | 3 | 0.5 | 0 | 0 |
| Menorrhagia | 1 | 0.2 | 0 | 0 |

Safety population; *$p$=0.11

NNT = 17

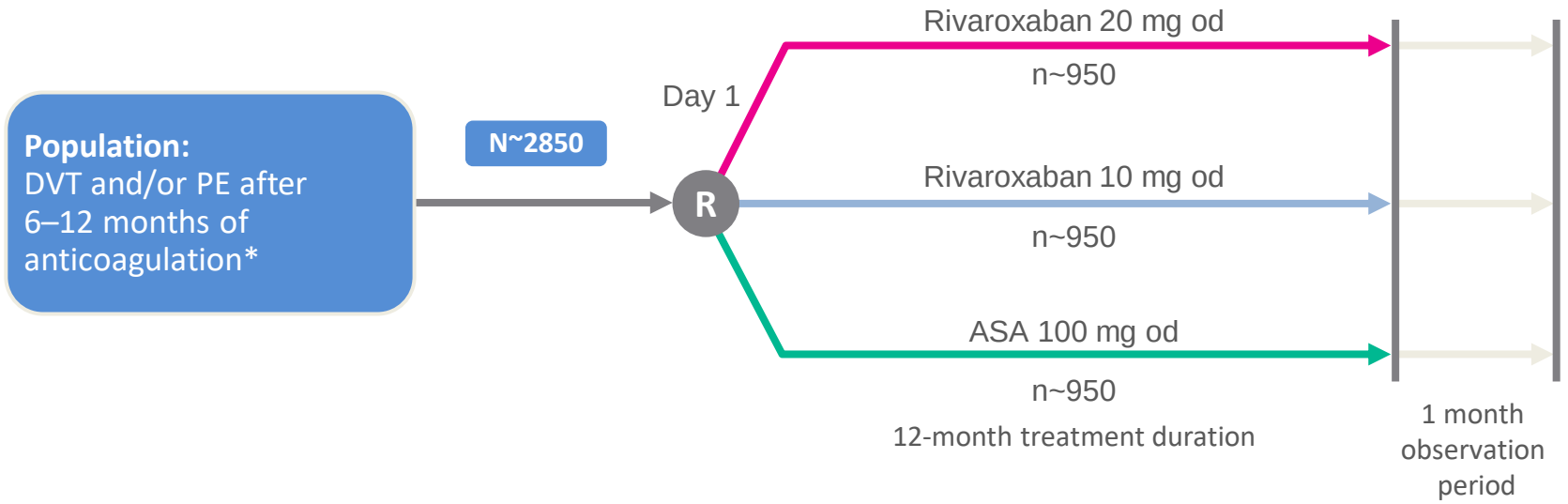
NNH = 143

Recurrent VTE measured in the ITT population; all analyses were based on the first event

The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–2510
Wells PS et al. CHEST 2016 in press

# EINSTEIN CHOICE: Study Design

**Objective:** efficacy and safety of reduced-dosed rivaroxaban, standard-dosed rivaroxaban versus ASA for the long-term secondary prevention of recurrent symptomatic VTE in patients with symptomatic DVT and/or PE

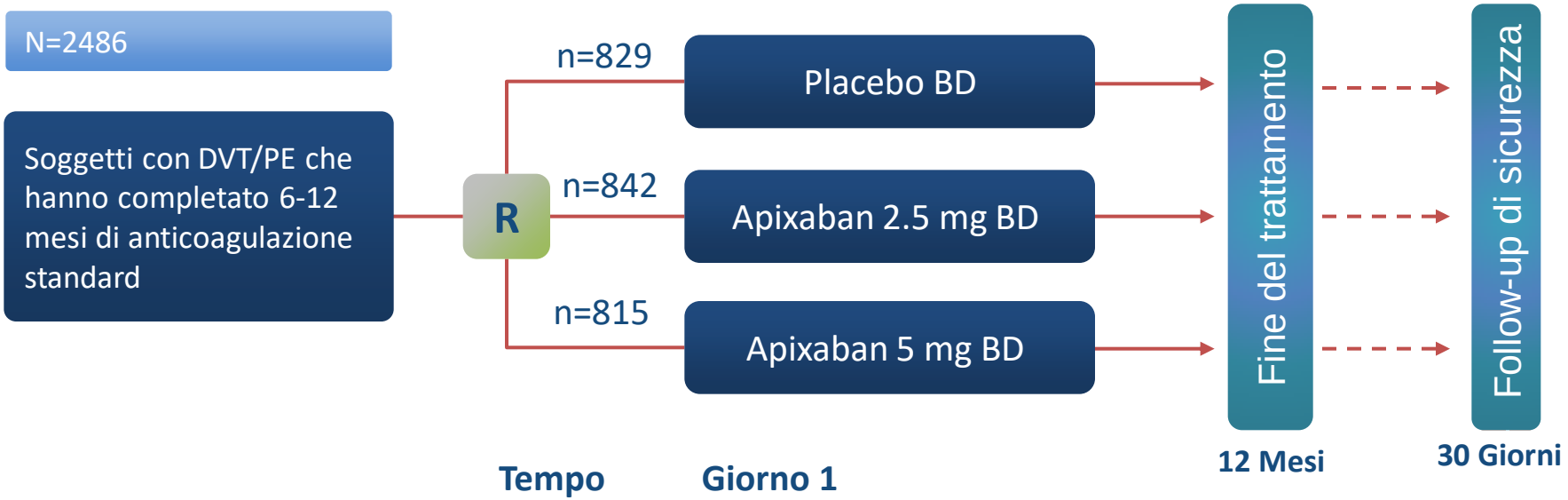



**Short design:** Multicentre, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study

*Completed 6–12 months (±1 month) with interruption of anticoagulation ≤1 week at randomization

www.clinicaltrials.gov/ct2/show/NCT02064439; Weitz JI *et al*, *Thromb Haemost* 2015;114:645–650

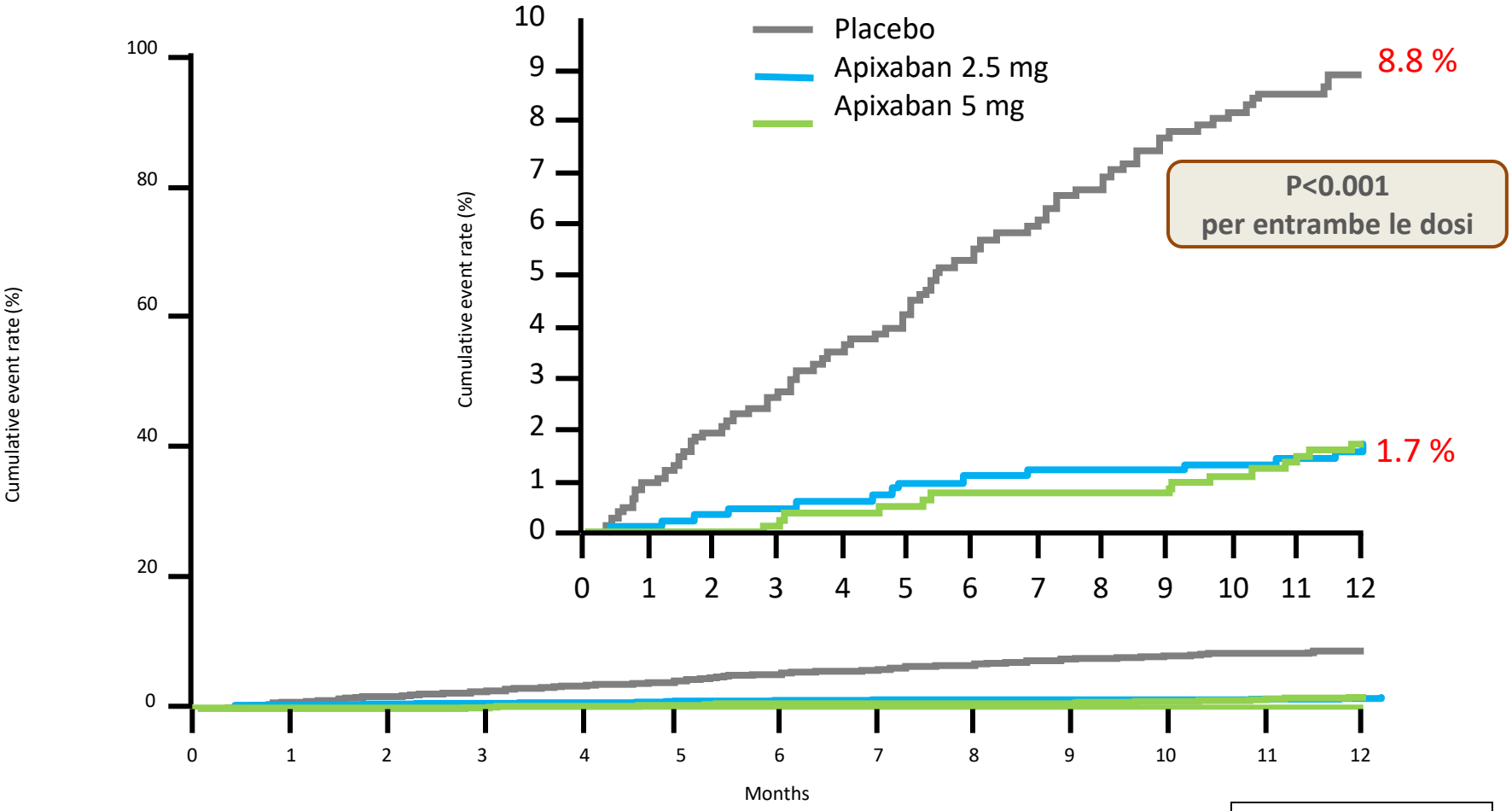
# AMPLIFY EXTENSION: study design




**N stabilito sul potere del 90% di determinare la superiorità di apixaban sul placebo (~60% RRR) utilizzando un two-sided alpha=0.025 per confrontare ciascun braccio di apixaban al placebo**

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

# AMPLIFY EXTENSION: efficacy outcames




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

# AMPLIFY EXTENSION: safety outcames

| Outcame | 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 5mg RR (95% CI) |
|---|---|---|---|---|---|---|
| **Major bleeding** | 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** | 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 bleeding and CRNM 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) |

**Sanguinamenti maggiori**

- **2.5 mg: 2 eventi, entrambi intraoculari**
- **5.0 mg: 1 evento, gastrointestinale**
- **Placebo: 4 eventi, intraoculare, ictus, urogenitale, gastrointestinale**

CI, intervallo di confidenza; RR, rischio relativo
CRNM, non maggiore clinicamente rilevante

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

AMPLIFY-EXT

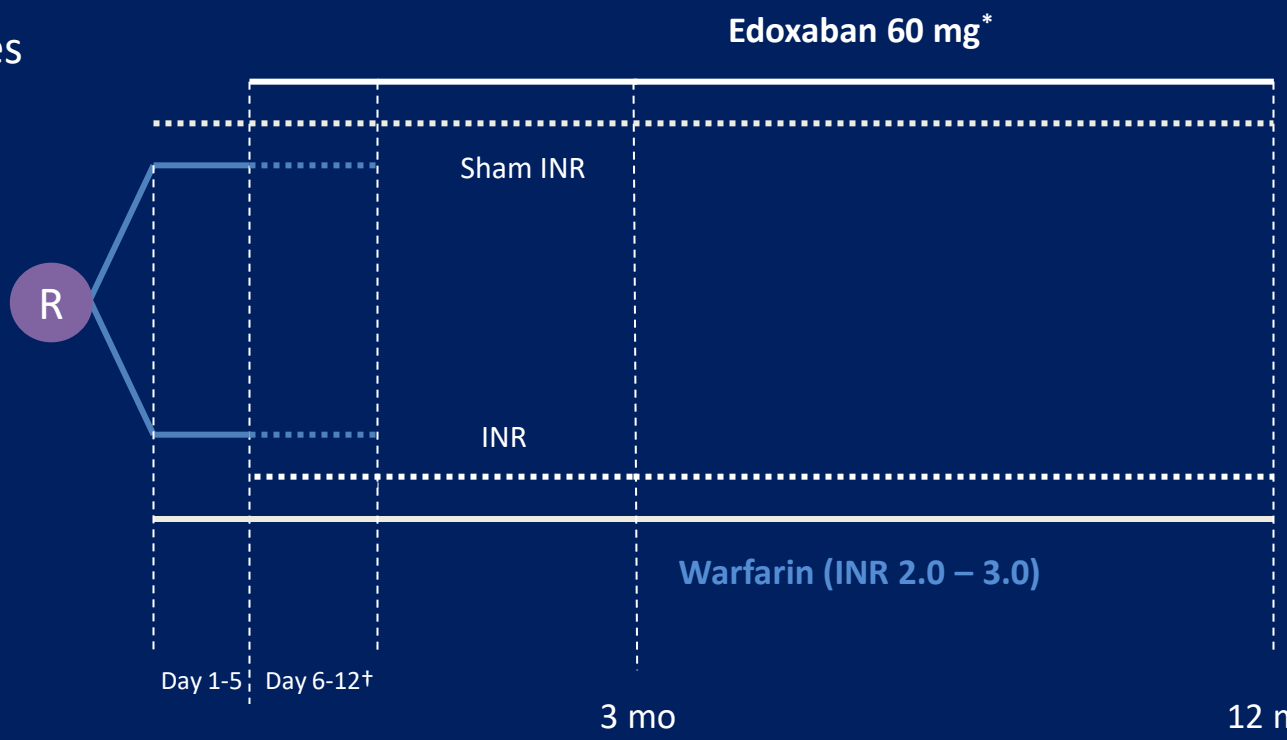
# Hokusai-VTE: Study Design

Randomized, double-blind, event-driven study

N=8,292
439 sites in 37 countries

Objectively confirmed VTE

Stratified randomization:
- DVT / PE
- Dose of edoxaban
- Risk factors




**Patients followed for 12-months or until study closure regardless of treatment duration**

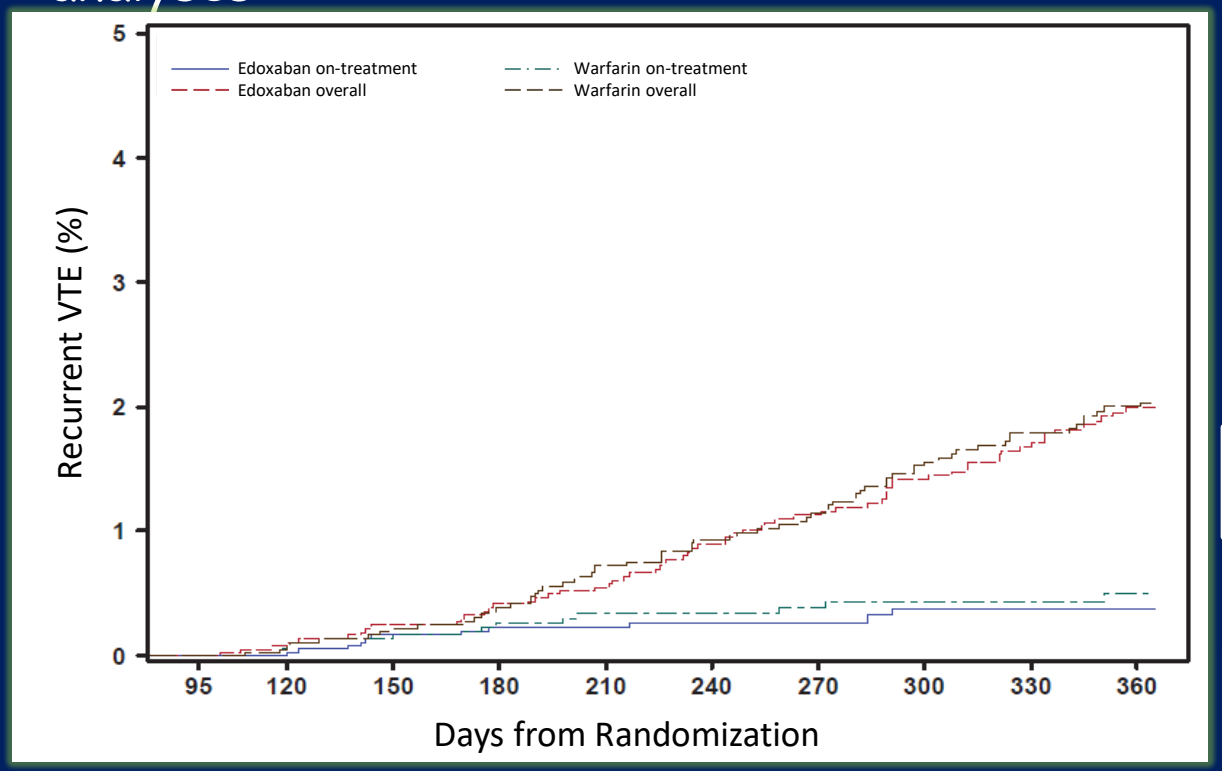
- Edoxaban
- Placebo Edoxaban
- Warfarin
- Placebo Warfarin
- Low-molecular-weight heparin / UFH

*Dose was halved to 30 mg in patients perceived to be at higher risk for bleeding by predefined criteria
†During days 6-12 edoxaban or placebo edoxaban was started once heparin was stopped

Raskob et al. J Thromb Haemost 2013;11:1287–1294
The Hokusai-VTE Investigators. N Engl J Med 2013

# HOKUSAI: Extended Treatment Period (>3 – 12 Months)

- Cumulative incidence of recurrent VTE was similar between edoxaban and warfarin for both on-treatment and overall analyses




**Warfarin overall**
**Edoxaban overall**

**HR 0.97**
**(95% CI 0.7-1.4)**

**Warfarin**
**Edoxaban on-treatment**

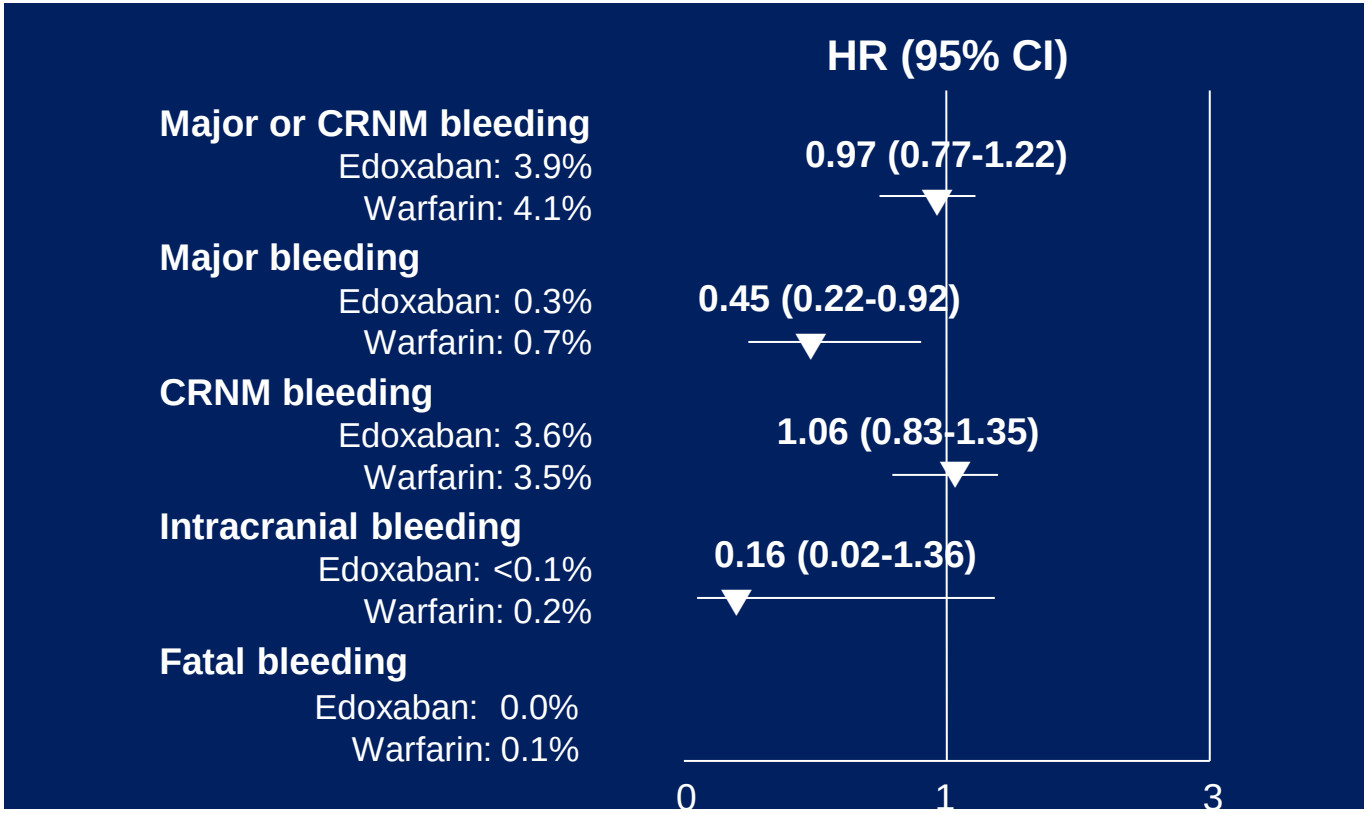
**HR 0.78**
**(95% CI 0.36-1.72)**

VTE = venous thromboembolism; HR = hazard ratio; CI = confidence interval.

Raskob G et al. *Lancet Haematol.* 2016, May;3(5):e228-36.

# HOKUSAI: Extended Treatment Period (>3 – 12 Months)

- Significantly lower incidence of major bleeding was observed with edoxaban vs warfarin during the extended treatment period in the on-treatment analysis

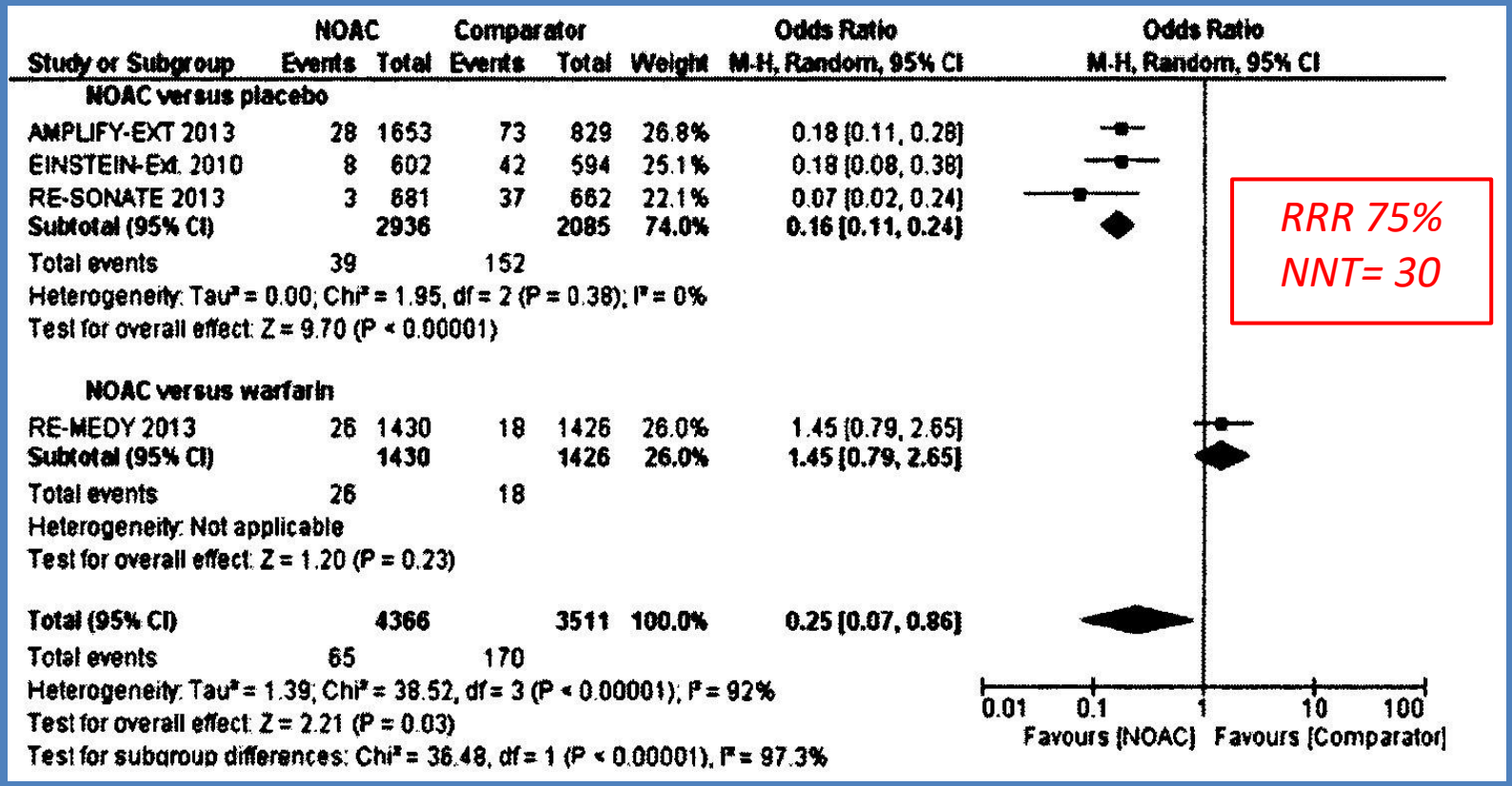



HR = hazard ratio; CI = confidence interval; CRNM = clinically relevant non-major.

Raskob G et al. *Lancet Haematol.* 2016. May;3(5):e228-36.

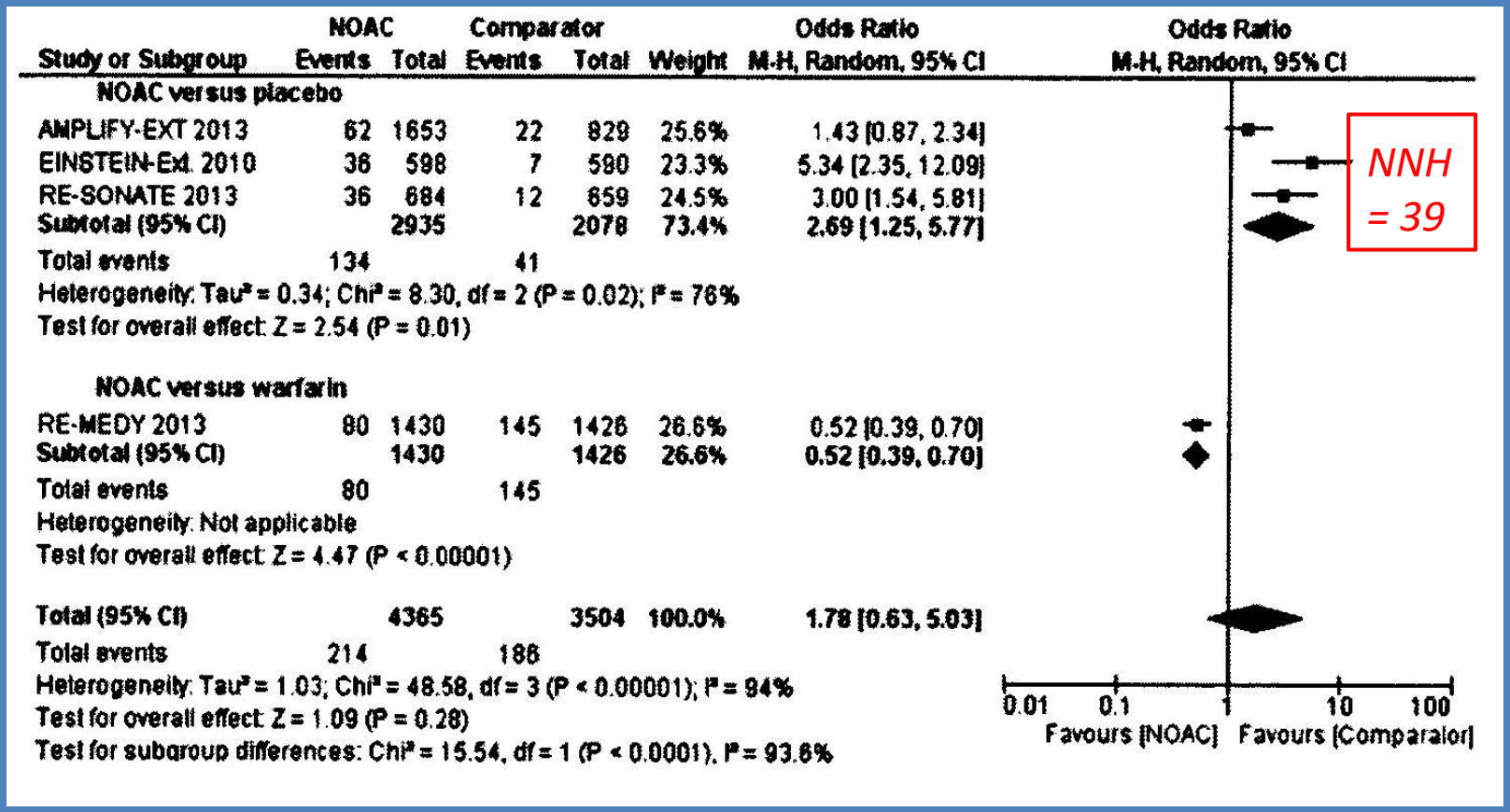
# Systematic review and meta-analyses:

## *Recurrent VTE or VTE-related death*



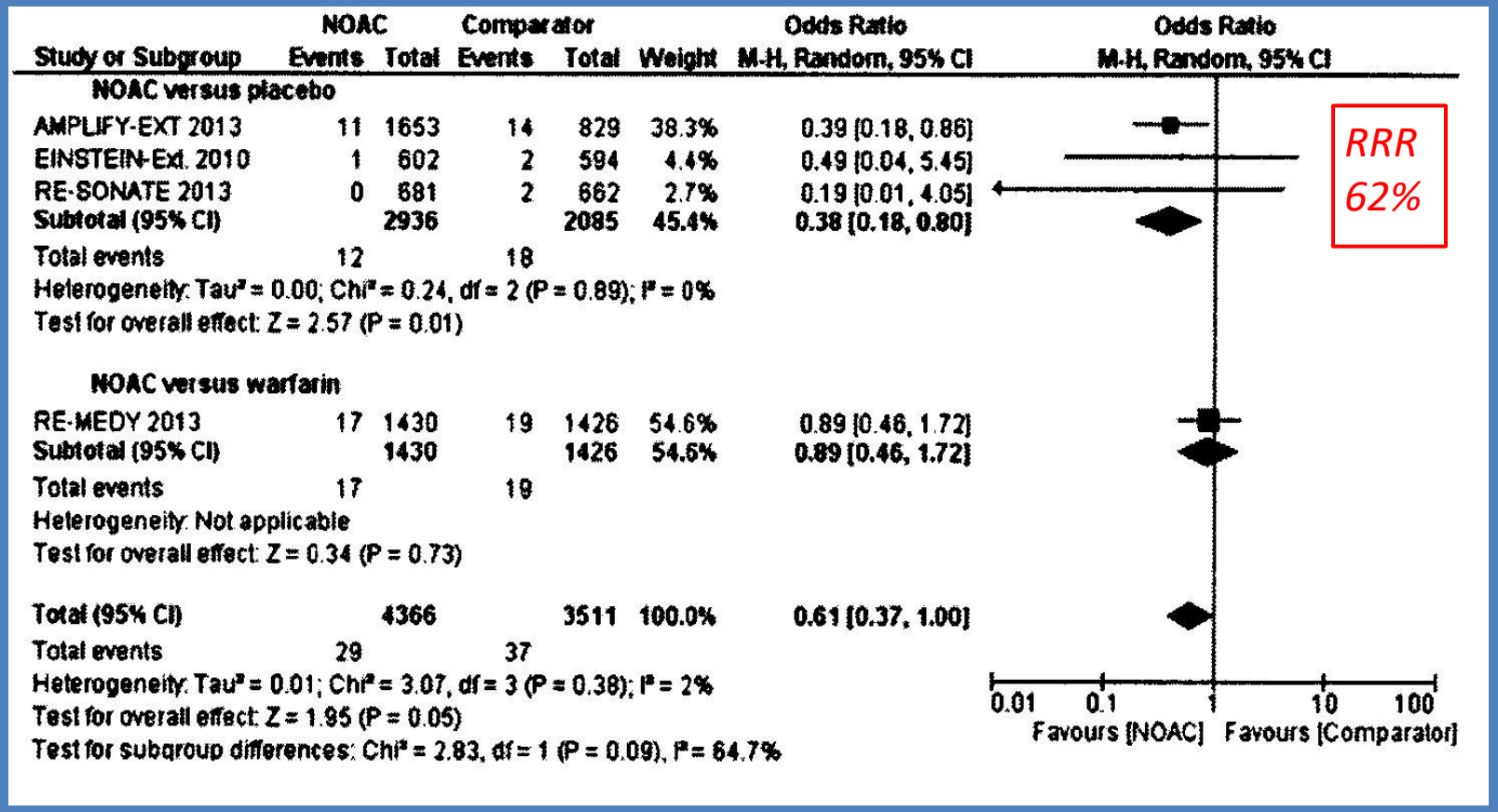

Sardar, Drugs, 2013

# Systematic review and meta-analyses: *Major or* CRNMB




Sardar, Drugs, 2013

# Systematic review and meta-analyses: *All-cause mortality*




Sardar, Drugs, 2013

# Conclusioni

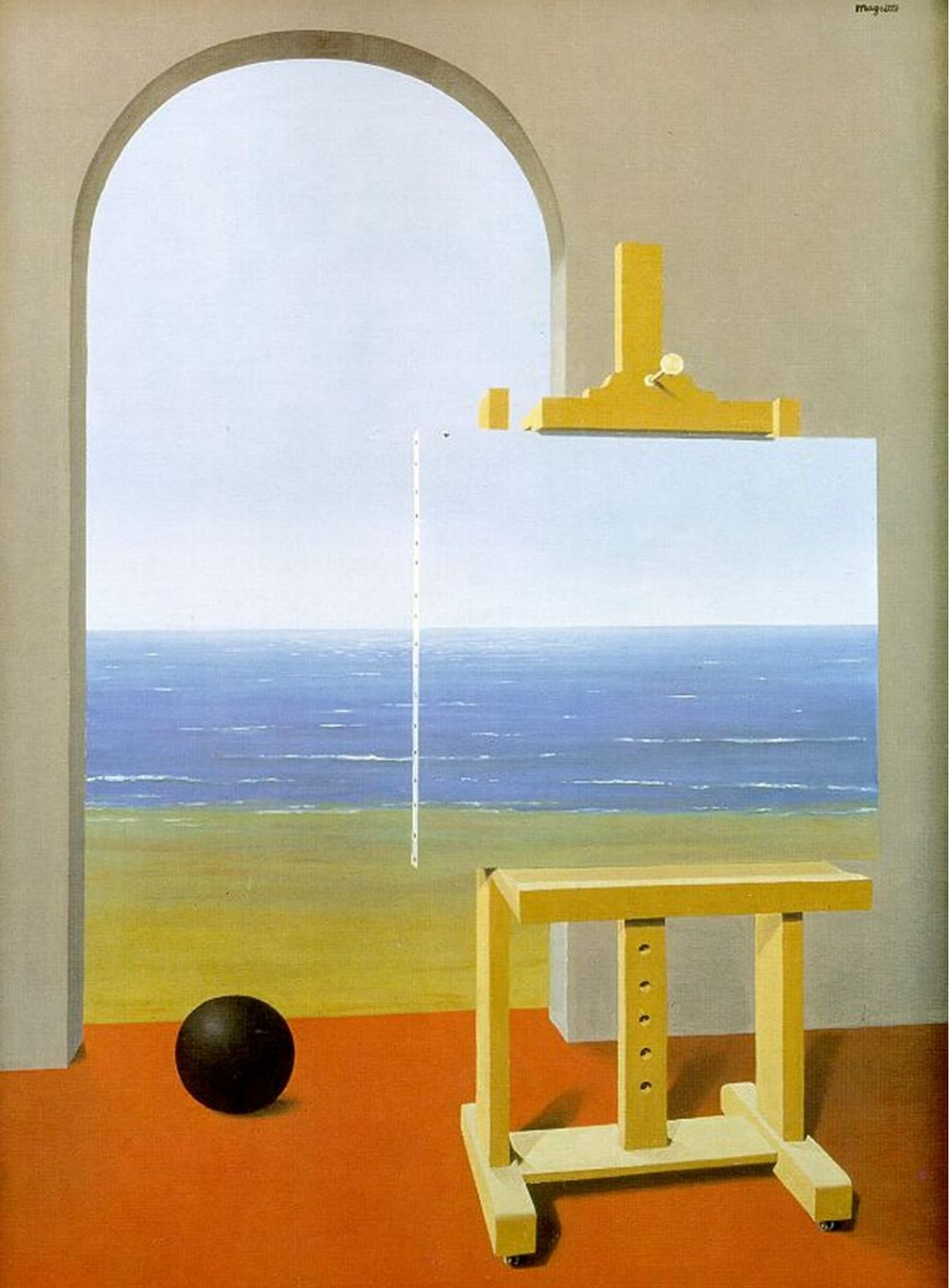
- I pazienti con TEV idiopatico presentano un elevato rischio di recidiva
- In tali pazienti e nei pazienti con recidive di TEV, le linee guida ACCP raccomandano di considerare la possibilità di un trattamento anticoagulante a tempo indeterminato
- I dati di real life indicano che solo il 20 % di questi pazienti è ancora in trattamento a 2 anni dall'evento acuto

# Conclusioni

- I nuovi anticoagulanti orali dimostrano un profilo di elevata efficacia e sicurezza nel trattamento a lungo termine del TEV idiopatico
- I nuovi anticoagulanti orali dimostrano di essere superiori al placebo nella prevenzione del TEV e della mortalità correlata al TEV  senza determinare aumento di emorragie maggiori
- Rispetto al warfarin, dabigatran ed edoxaban dimostrano simile efficacia e maggiore sicurezza in termini di riduzione di eventi emorragici

# Conclusioni

- L’impiego dei nuovi anticoagulanti orali nella pratica clinica potrà semplificare le scelte del clinico, migliorare l’aderenza alle indicazioni delle principali linee guida internazionali ottimizzando il trattamento dei pazienti con TEV



# GRAZIE PER L'ATTENZIONE

Magritte
La condizione umana, 1933