# Νέα αντιπηκτικά φάρμακα και στρατηγικές στη θεραπεία της φλεβικής θρόμβωσης και πνευμονικής εμβολής

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# Diagnosis and Management of Acute Pulmonary Embolism

## The Task Force on Acute Pulmonary Embolism of the European Society of Cardiology

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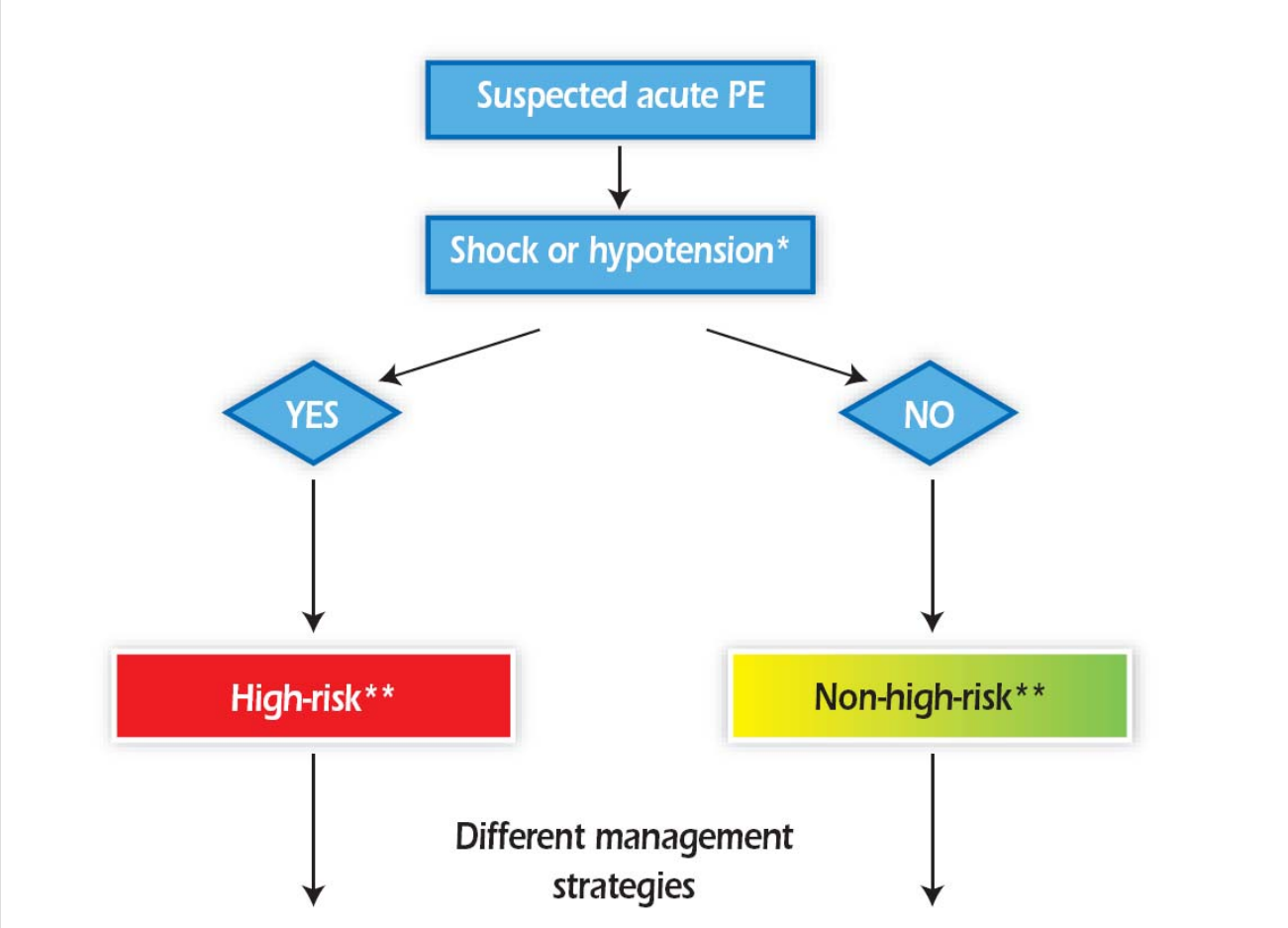
# Management of venous thromboembolism



# Management in the acute phase

High-risk PE

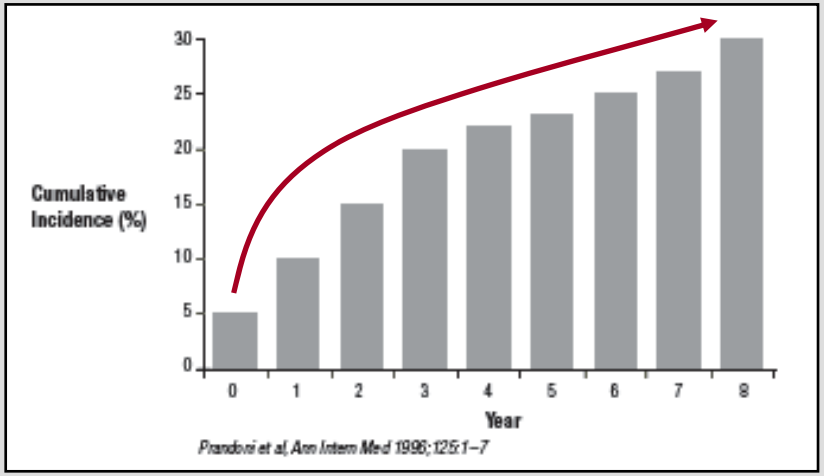
| Recommendation | Class | Level |
|---|---|---|
| Thrombolytic therapy should be used in patients with high-risk PE presenting with cardiogenic shock and/or persistent arterial hypotension | I | A |
| Surgical pulmonary embolectomy is a therapeutic alternative if thrombolysis is absolutely contraindicated or has failed | I | C |
| Catheter embolectomy or fragmentation of proximal pulmonary arterial clots may be an alternative to surgical treatment when thrombolysis is absolutely contraindicated or has failed | IIb | C |

## Non-high-risk PE

| Recommendations | Class [a] | Level [b] |
|---|---|---|
| ▪ Anticoagulation should be initiated without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is still ongoing | I | C |
| ▪ Use of LMWH or fondaparinux is the recommended form of initial treatment for most patients with non-high-risk PE | I | A |
| ▪ In patients at high bleeding risk and in those with severe renal dysfunction UFH with an aPTT target range of 1.5 – 2.5 times normal is a recommended form of initial treatment | I | C |
| ▪ Initial treatment with UFH, LMWH or fondaparinux should be continued for at least 5 days and<br>may be replaced by Vit K antagonists only after achieving target INR levels for at least 2 consecutive days | I<br>I | A<br>C |

# Rationale for long-term secondary prophylaxis

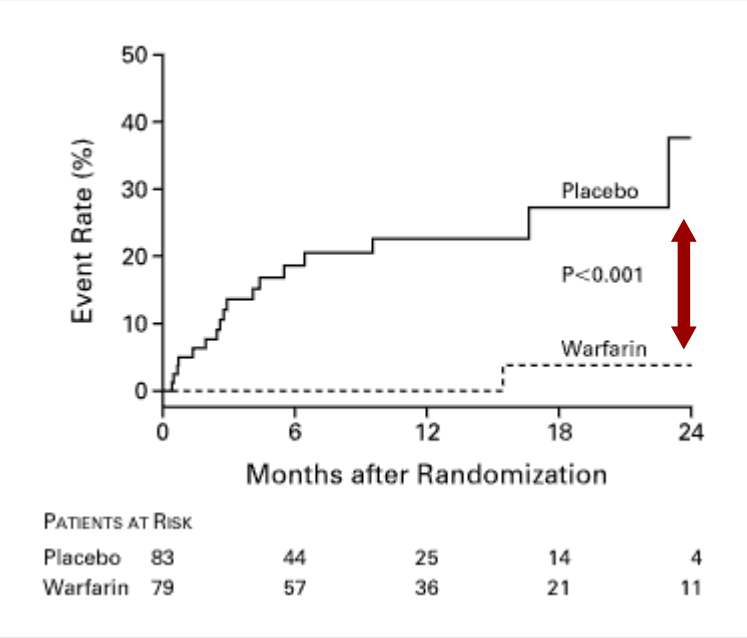
| | Cumulative Incidence | | Survival rate |
|---|---|---|---|
| | Recurrent DVT | Post thrombotic syndrome | |
| **2 years** | 17% | 25% | 80% |
| **5 years** | 24% | 30% | 74% |
| **8 years** | 30% | 30% | 69% |




Prandoni P, et al. Ann Intern Med 1996;125:1-7
Prandoni P, et al. Haematologica 1997; 82: 423-428

# Long-term secondary prophylaxis

Highly effective, BUT…




**Recurrence reduced by 90%**

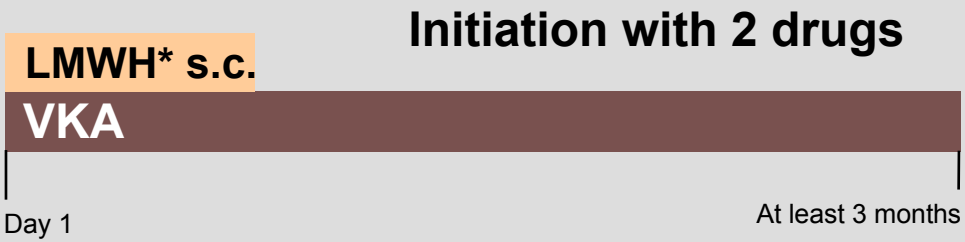
**_Major bleeding_: 3,8% / year**

Study discontinued after 2 years

C Kearon. N Engl J Med 1999;340:910-907

# Current approach to VTE treatment

**Current SOC VTE treatment regimens: 2 anticoagulants**




*Or UFH or fondaparinux

# Long-term secondary prophylaxis: for whom?

| Recommendations | Class [a] | Level [b] |
|---|---|---|
| ▪ For patients with PE secondary to a transient (reversible) risk factor, treatment with a VKA is recommended for 3 months | I | A |
| ▪ For patients with unprovoked PE, treatment with a VKA is recommended for at least 3 months | I | A |
| ▪ Patients with a first episode of unprovoked PE and low bleeding risk, and in whom stable anticoagulation can be achieved, may be considered for long-term oral anticoagulation | IIb | B |
| ▪ For patients with a second episode of unprovoked PE, long-term treatment is recommended | I | A |

# Factors predisposing to PE recurrence

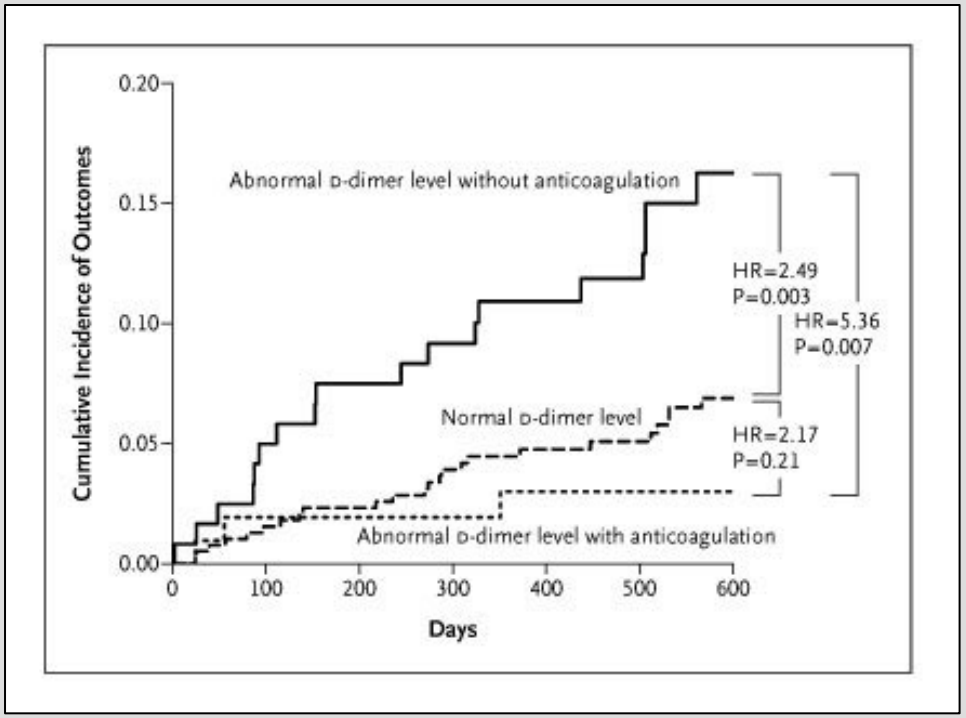
| Pedisposing factor | Relative Risk (HR) |
|---|---|
| ◆ Provoked (surgery, trauma, pregnancy, postpartum, contraception) vs. **unprovoked** PE | ≥ 2,3-2,5 |
| ◆ **Tumor** | 2,0-4,0 |
| ◆ **Antiphospholipid syndrome** | 2,3-8,5 |
| ◆ **Male sex** | ≥1,5 |
| ◆ DVT of **lower** vs. upper extremities | 3,0-4,0 |
| ◆ **Obesity** | 1,3-2,0 |
| ◆ **Index event PE vs. DVT** | Recurrence 2.0-4.0 times more frequent as PE |
| ◆ **Thrombophilia** | 1.4-1.7 (?) |

T Zhu et al. Arterioscler Thromb Vasc Biol 2009;29:298-310

# Possible value of D-Dimer testing

1 month after termination of oral anticoagulation (VKA)

n=608 pts



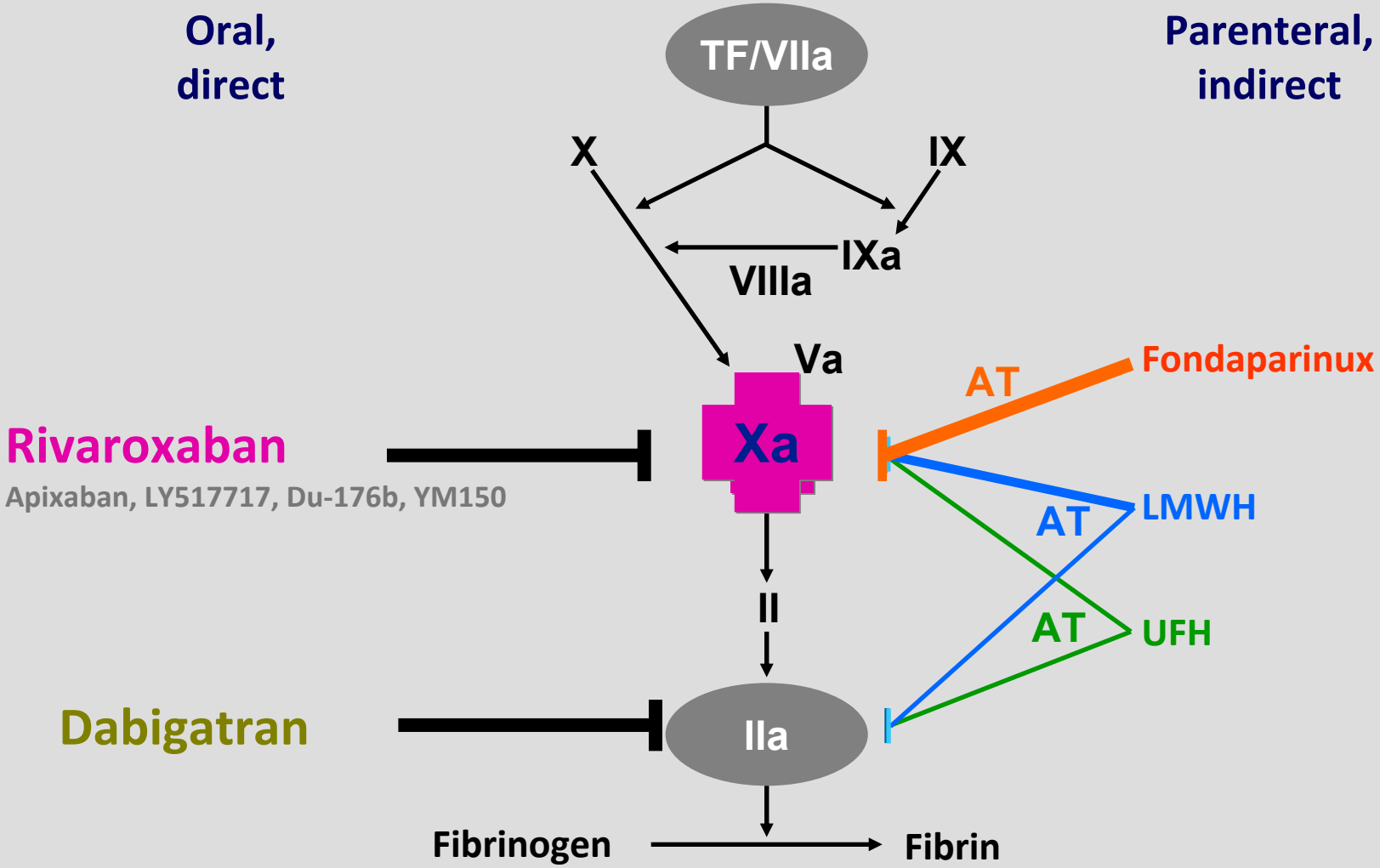

D-Dimer ▲
in 37%

End point: PE recurrence or bleeding; Follow-Up: 1.4 years

G Palareti. N Engl J Med 2006;355:1780-1789

**Meta analysis (7 studies, 1888 pts): recurrence/year 8.9% vs. 3.5%. M Verhovsek. Ann Intern Med 2008;149:481-490**

# Established and new anticoagulants

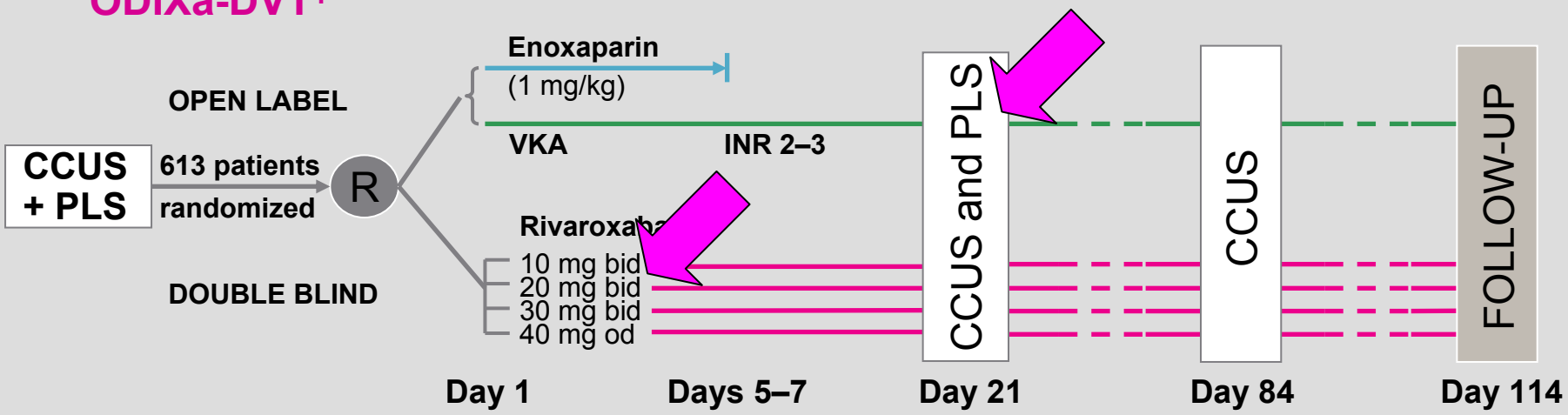


# New anticoagulants in VTE treatment

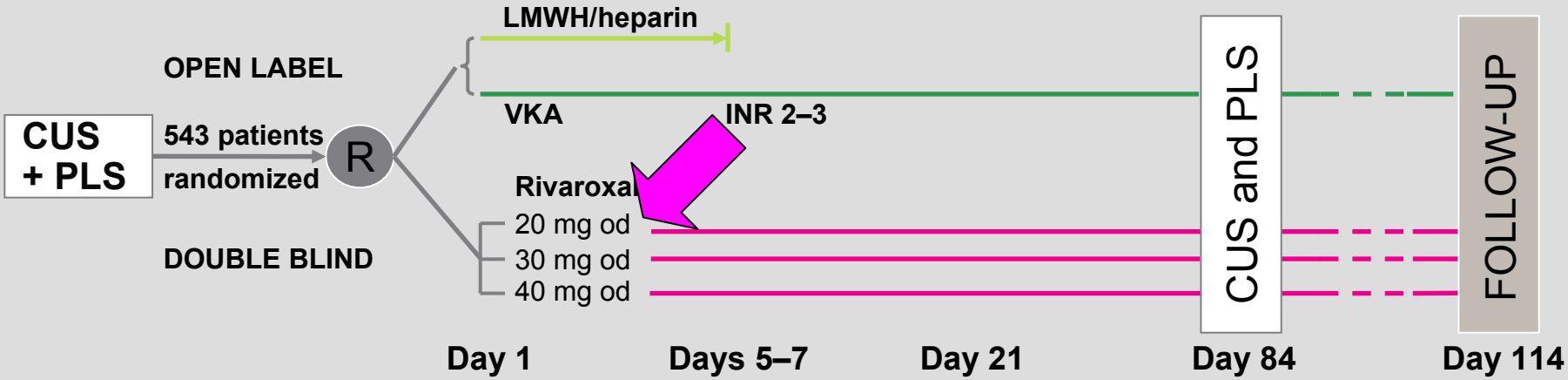
| | Phase II | Phase III |
|---|---|---|
| **Rivaroxaban**<br>Oral, direct Factor Xa inhibitor | **EINSTEIN DVT**<br>Rivaroxaban vs LMWH/UFH followed by VKA[2]<br>**ODIXa-DVT**<br>Rivaroxaban vs enoxaparin followed by VKA[3] | **EINSTEIN DVT/PE**<br>Rivaroxaban for 3, 6 or 12 months vs enoxaparin for ≥5 days followed by VKA for 3, 6, or 12 months<br>**EINSTEIN EXT**<br>Rivaroxaban or placebo for 6 or 12 months after pre-treatment with rivaroxaban or VKA for 6 or 12 months |
| **Dabigatran**<br>Oral, direct thrombin inhibitor | | **RE-COVER & RE-COVER II**<br>5–10 days pre-treatment with LMWH bridging to dabigatran or VKA for 6 months<br>**RE-MEDY**<br>3–6 months treatment with approved anticoagulant; switch to dabigatran or VKA<br>**RE-SONATE**<br>6–18 months VKA followed by 6 months dabigatran or placebo |
| **Apixaban**<br>Oral, direct Factor Xa inhibitor | **Botticelli-DVT**<br>Apixaban vs LMWH or fondaparinux followed by VKA[4] | **AMPLIFY**<br>Apixaban 10 mg bid followed by 5 mg bid for 6 months vs enoxaparin followed by VKA<br>**AMPLIFY-EXT**<br>Apixaban 2.5 mg bid or 5 mg bid for extended 12 months vs placebo |

# Phase II study designs: ODIXa-DVT and EINSTEIN DVT

## ODIXa-DVT[1]




## EINSTEIN DVT[2]




1. Agnelli G, et al. Circulation 2007;116:180–187; 2. Büller HR, et al. Blood 2008;112:2242–2247

# Rivaroxaban outcome measures in phase II

## ODIXa-DVT[1]

**Primary efficacy outcome (at 3 weeks)**

- Improvement in thrombotic burden without recurrent symptomatic VTE, PE or VTE-related death

**Primary safety outcome (at 12 weeks)**

- Incidence of major bleeding up to 2 days after the last dose of study drug

## EINSTEIN DVT[2]

**Primary efficacy outcome (at 12 weeks)**

- Composite of symptomatic recurrent DVT, symptomatic fatal or non-fatal PE and asymptomatic deterioration in thrombotic burden

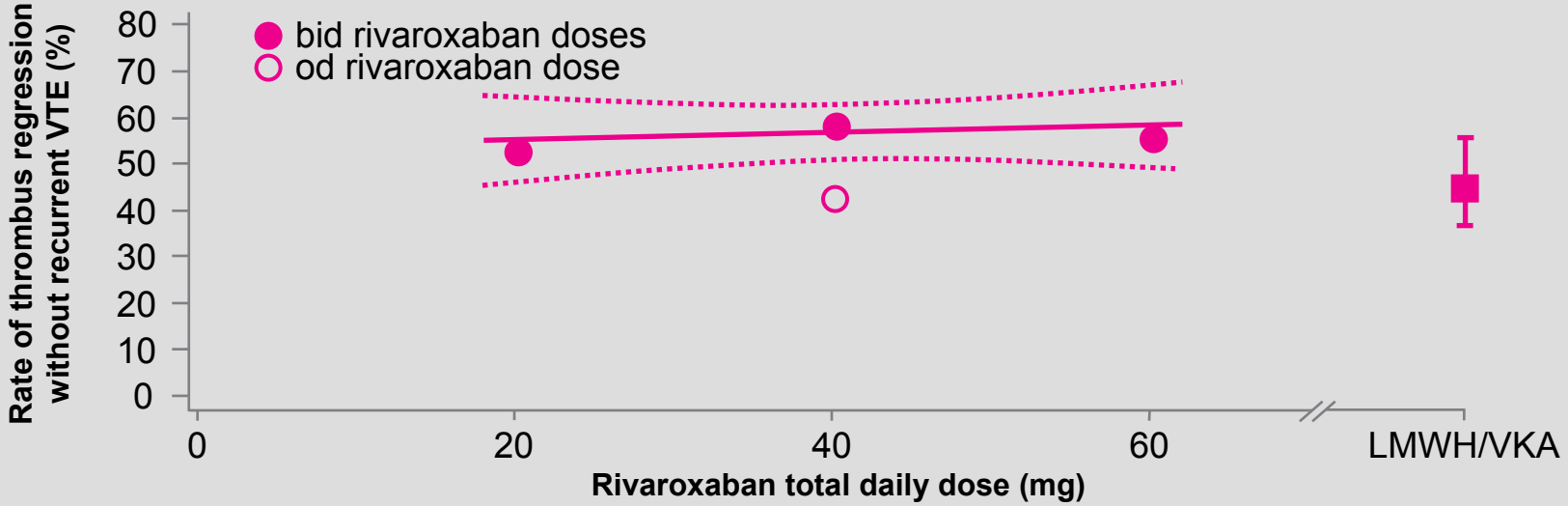
**Primary safety outcome (at 12 weeks)**

- Composite of major and clinically relevant non-major bleeding up to 48 hours after the last dose of study drug

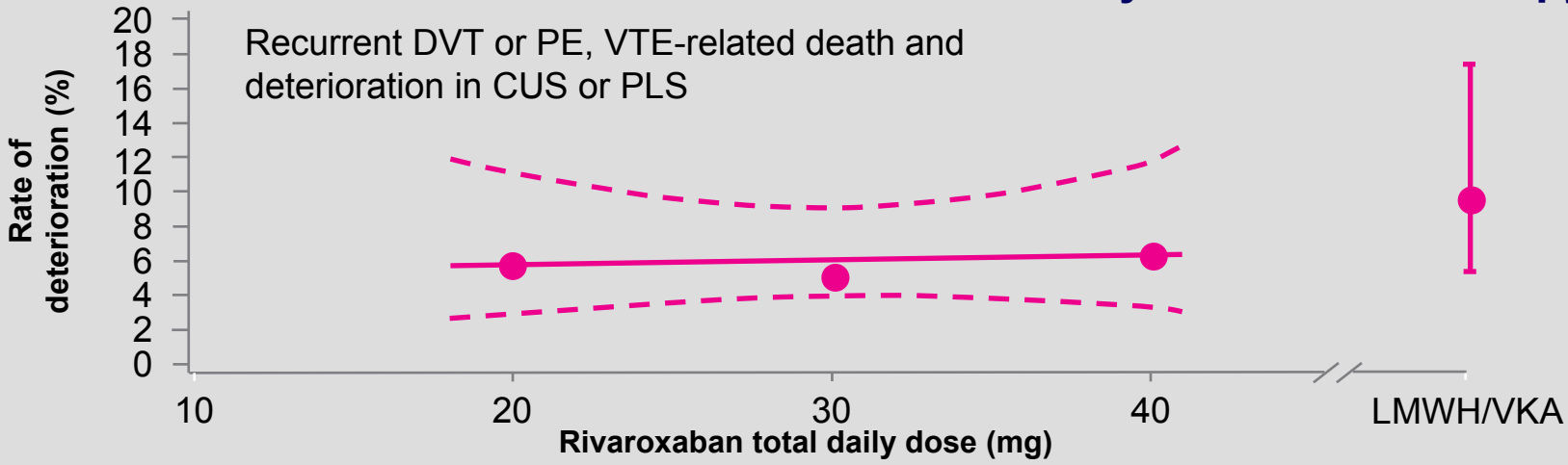
1. Agnelli G, et al. Circulation 2007;116:180–187; 2. Büller HR, et al. Blood 2008;112:2242–2247

# ODIXa-DVT and EINSTEIN DVT – efficacy outcome[1,2]

## ODIXa-DVT[1]: rivaroxaban showed similar efficacy to standard therapy




## EINSTEIN DVT[2]: rivaroxaban showed similar efficacy to standard therapy



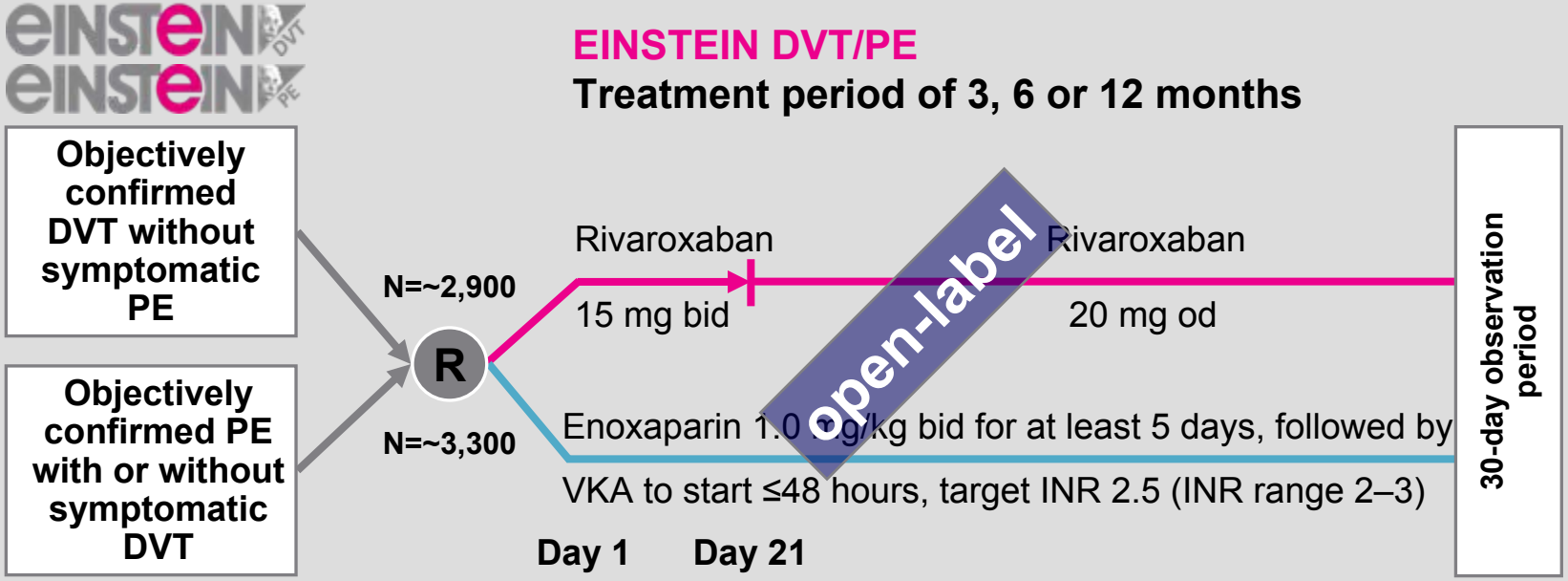

Based on data from: 1. Agnelli G, et al. Circulation 2007;116:180–187; 2. Büller HR, et al. Blood 2008;112:2242–2247

# Rationale for choice of dose for phase III

- **Efficacy results** in rivaroxaban bid and od study arms similar to LMWH/VKA comparator arms (both symptomatic recurrent VTE and asymptomatic changes in thrombotic burden)
  - higher asymptomatic improvement rate observed for the bid dose arms at 3 weeks
  - higher $C_{trough}$ levels observed for the bid regimens; intensified anticoagulant effect could be beneficial in the acute phase
- The **relative safety** in terms of bleeding compared with standard of care control treatment was better for all od regimens, compared with the bid regimen for which a slightly increased risk of bleeding was demonstrated for the 20 mg bid and the 30 mg bid doses

**The lowest od dose studied (20 mg) was selected for EINSTEIN DVT and EINSTEIN PE phase III studies, with an initial period of 3 weeks of 15 mg bid rivaroxaban**

# EINSTEIN phase III: study design




EINSTEIN DVT, PE, Extension Evaluation Study Information available at: http://clinicaltrials.gov

# EINSTEIN DVT – 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 clinically relevant non-major bleeding

## Secondary and other outcomes*:

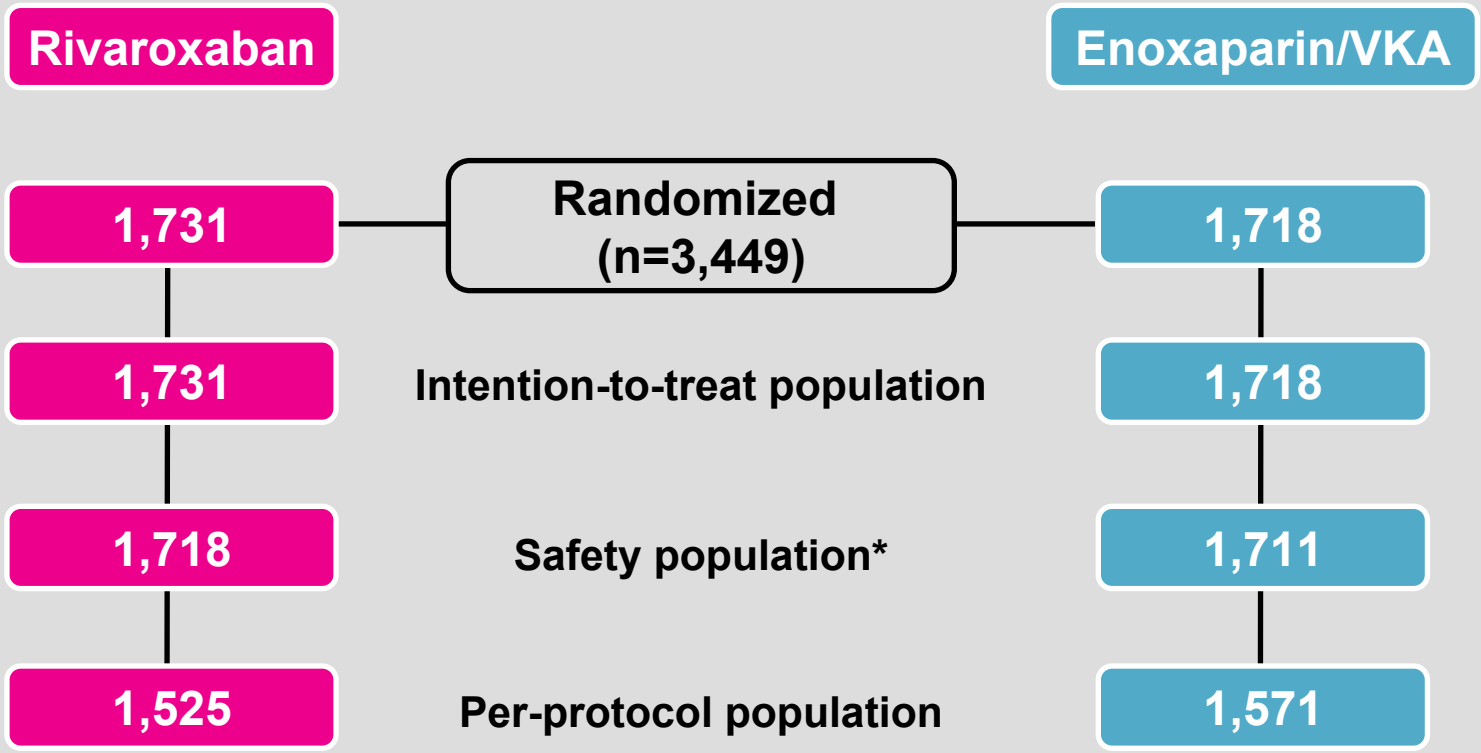
- **Net clinical benefit: primary efficacy outcome + major bleeding**
- Total mortality
- Cardiovascular events

## Central laboratory

- Monthly ALT and bilirubin testing

*Adjudicated by the central independent and blinded adjudication committee

# EINSTEIN DVT – Patient flow




*As treated

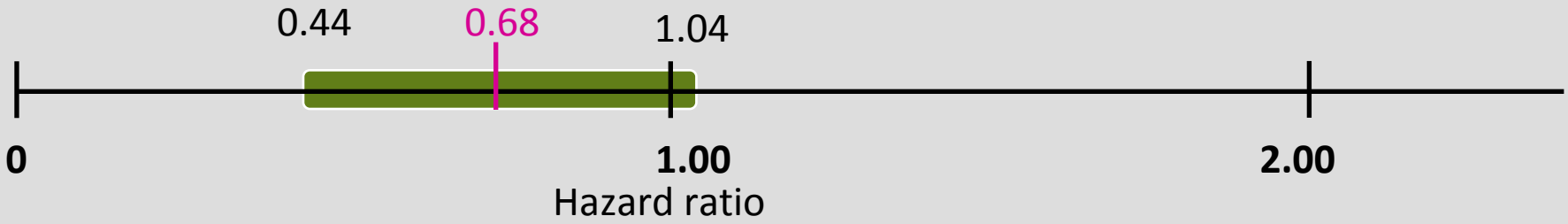
# EINSTEIN DVT – Patient characteristics

| | Rivaroxaban (n=1,731) | Enoxaparin/VKA (n=1,718) |
|---|---|---|
| **Males (%)** | 57 | 56 |
| **Age, mean (years)** | 56 | 56 |
| **Body mass index, mean (kg/m²)** | 28 | 28 |
| **Creatinine clearance (%)** | | |
| <50 ml/min | 7 | 7 |
| 50–<80 ml/min | 23 | 23 |
| ≥80 ml/min | 69 | 68 |
| **Patients with secondary DVT (%)** | 39 | 37 |
| Patients with active cancer (%) | 7 | 5 |
| **Intended treatment duration (%)** | | |
| 3 months | 12 | 12 |
| 6 months | 63 | 63 |
| 12 months | 25 | 25 |
| **Pre-treatment for maximum 48 hours with LMWH/fondaparinux (%)** | 73 | 71 |

ITT population

# Primary efficacy outcome analysis

| | Rivaroxaban (n=1,731) | | Enoxaparin/VKA (n=1,718) | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **First symptomatic recurrent VTE** | **36** | **(2.1)** | **51** | **(3.0)** |
| Recurrent DVT | 14 | **(0.8)** | 28 | **(1.6)** |
| Recurrent DVT + PE | 1 | **(<0.1)** | 0 | **(0)** |
| Non-fatal PE | 20 | **(1.2)** | 18 | **(1.0)** |
| Fatal PE/unexplained death where PE cannot be ruled out | 4 | **(0.2)** | 6 | **(0.3)** |




Rivaroxaban superior | Rivaroxaban non-inferior | Rivaroxaban inferior

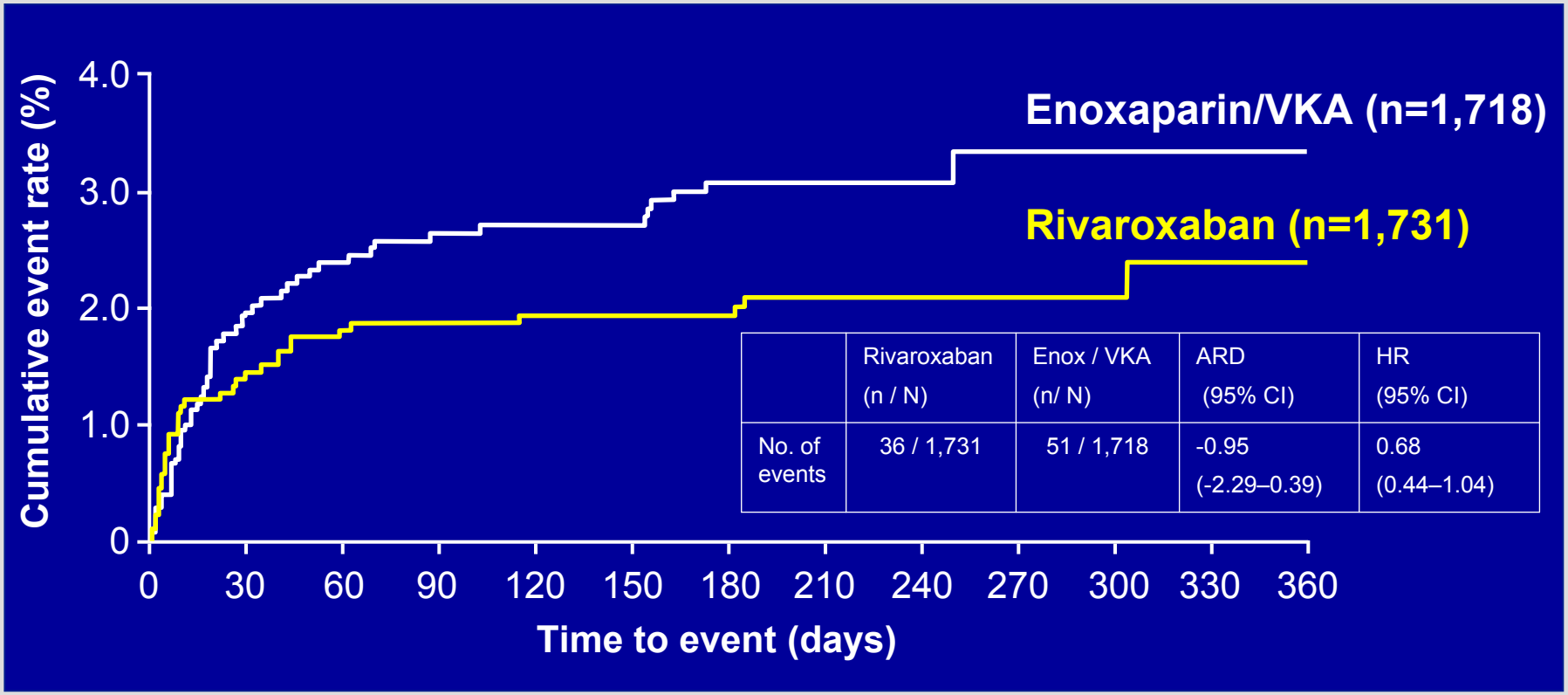
*p*=0.076 for superiority (two-sided)

*p*<0.0001 for non-inferiority (one-sided)

ITT population

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

# Primary efficacy outcome: time to first event



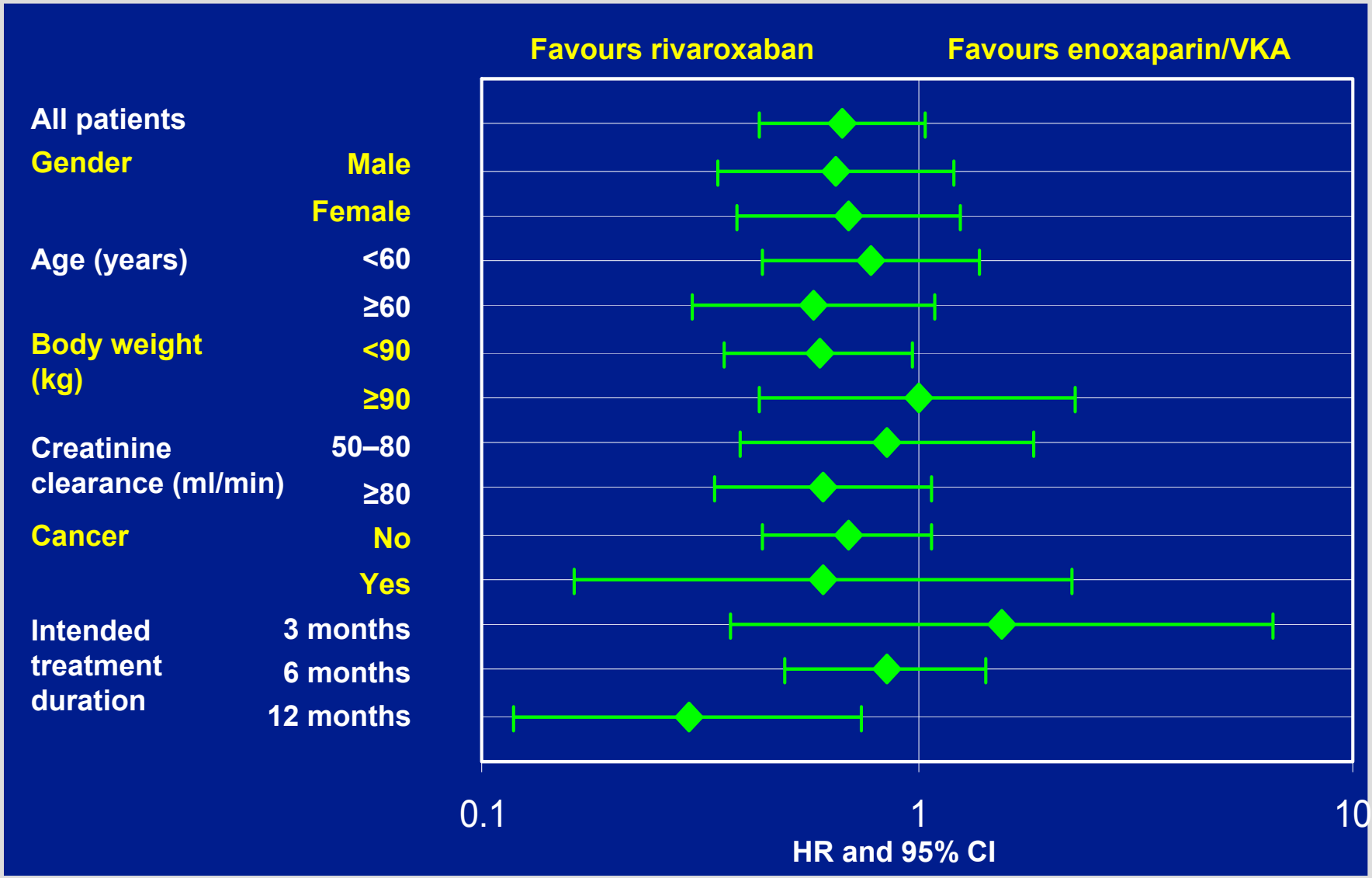

| | Rivaroxaban (n / N) | Enox / VKA (n/ N) | ARD (95% CI) | HR (95% CI) |
|---|---|---|---|---|
| No. of events | 36 / 1,731 | 51 / 1,718 | -0.95 (-2.29–0.39) | 0.68 (0.44–1.04) |

**Number of subjects at risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rivaroxaban | 1,731 | 1,668 | 1,648 | 1,621 | 1,424 | 1,412 | 1,220 | 400 | 369 | 363 | 345 | 309 | 266 |
| Enox/VKA | 1,718 | 1,616 | 1,581 | 1,553 | 1,368 | 1,358 | 1,186 | 380 | 362 | 337 | 325 | 297 | 264 |

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

# Primary efficacy outcome by subgroup




EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

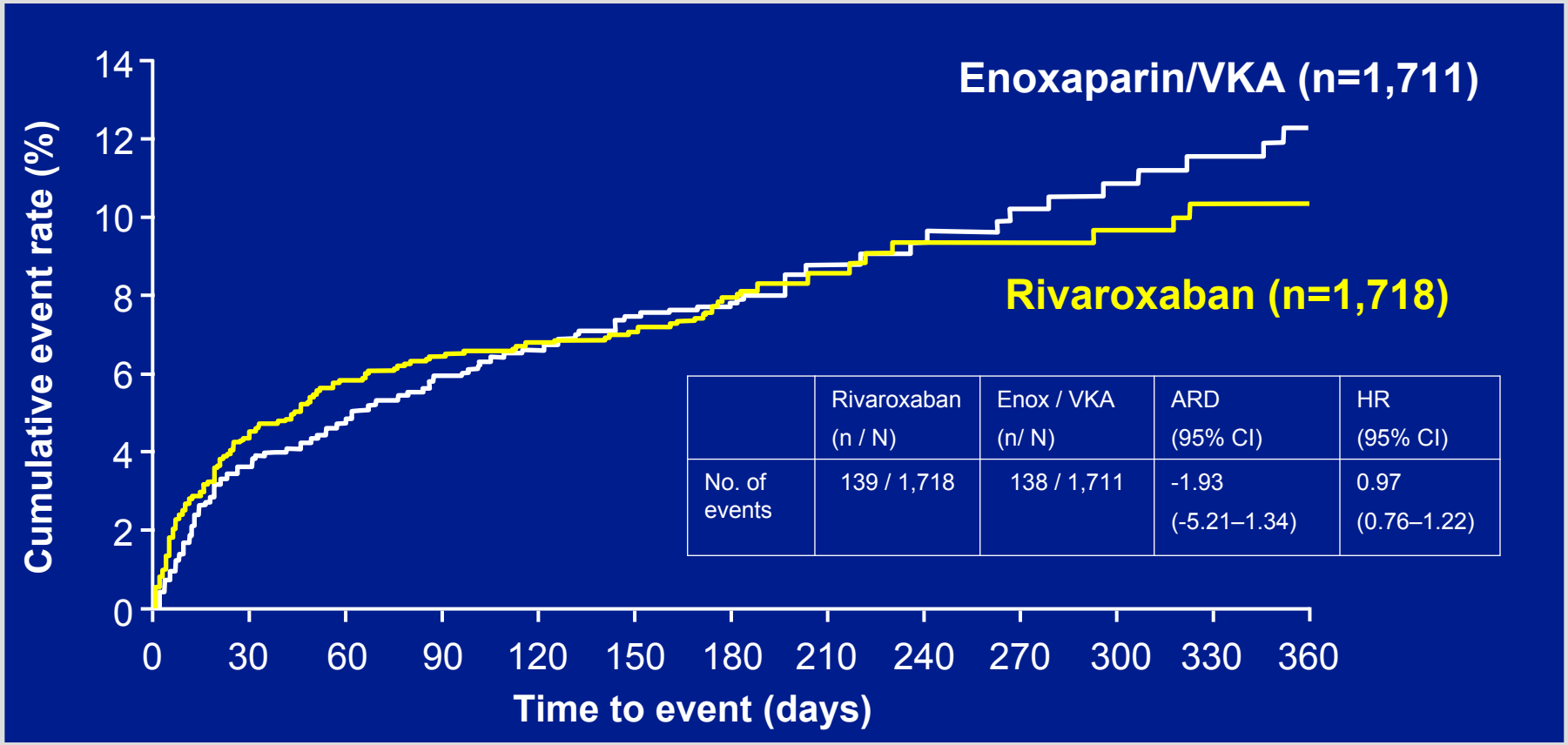
# Principal safety outcome analysis

| | Rivaroxaban (n=1,718) | | Enox/VKA (n=1,711) | | HR (95% CI) |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | *p* value |
| **First major or clinically relevant non-major bleeding** | **139** | **(8.1)** | **138** | **(8.1)** | **0.97 (0.76–1.22) *p*=0.77** |
| **Major bleeding** | **14** | **(0.8)** | **20** | **(1.2)** | |
| Contributing to death | 1 | (<0.1) | 5 | (0.3) | |
| In a critical site | 3 | (0.2) | 3 | (0.2) | |
| Associated with fall in Hb ≥2 g/dl and/or transfusion of ≥2 units | 10 | (0.6) | 12 | (0.7) | |
| **Clinically relevant non-major bleeding** | **126** | **(7.3)** | **119** | **(7.0)** | |

Safety population

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

# Principal safety outcome: time to first event




| | Rivaroxaban (n / N) | Enox / VKA (n/ N) | ARD (95% CI) | HR (95% CI) |
|---|---|---|---|---|
| No. of events | 139 / 1,718 | 138 / 1,711 | -1.93 (-5.21–1.34) | 0.97 (0.76–1.22) |

**Number of subjects at risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rivaroxaban | 1,718 | 1,585 | 1,538 | 1,382 | 1,317 | 1,297 | 715 | 355 | 338 | 304 | 278 | 265 | 140 |
| Enox/VKA | 1,711 | 1,554 | 1,503 | 1,340 | 1,263 | 1,238 | 619 | 338 | 321 | 287 | 268 | 249 | 118 |

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

# Key secondary and other outcomes

| Outcome | Rivaroxaban n/N (%) | Enoxaparin/VKA n/N (%) | HR (95% CI) |
|---|---|---|---|
| **Net clinical benefit: primary efficacy outcome + major bleeding** | **51/1,731 (2.9)** | **73/1,718 (4.2)** | **0.67 (0.47–0.95)** |
| Total mortality | 38/1,731 (2.2) | 49/1,718 (2.9) | 0.67 (0.44–1.02) |
| Cardiovascular events | 12/1,718 (0.7) | 14/1,711 (0.8) | 0.79 (0.36–1.71) |
| ALT >3x ULN + bilirubin >2x ULN | 2/1,682 (0.1) | 4/1,648 (0.2) | |
| % time INR in range | | | |
| <2.0 | | 24.4 | |
| [2.0–3.0] | | 57.7 | |
| >3.0 | | 16.2 | |

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

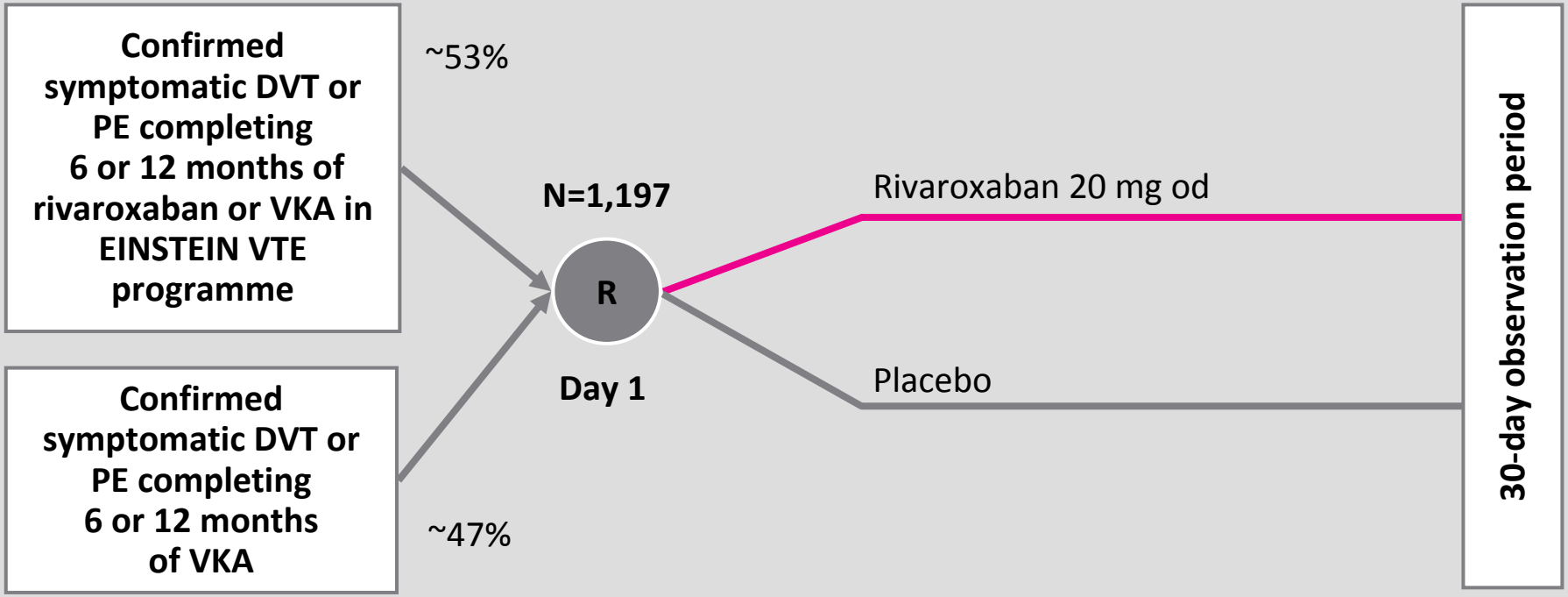
# EINSTEIN DVT – Conclusions

- In patients who had acute symptomatic proximal DVT, without symptomatic PE, rivaroxaban showed:
  - Non-inferiority to LMWH/VKA for efficacy: HR=0.68 (0.44–1.04);
    $p<0.0001$ for non-inferiority;
  - Similar findings for principal safety outcome: HR=0.97 (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.

# EINSTEIN Extension – study design

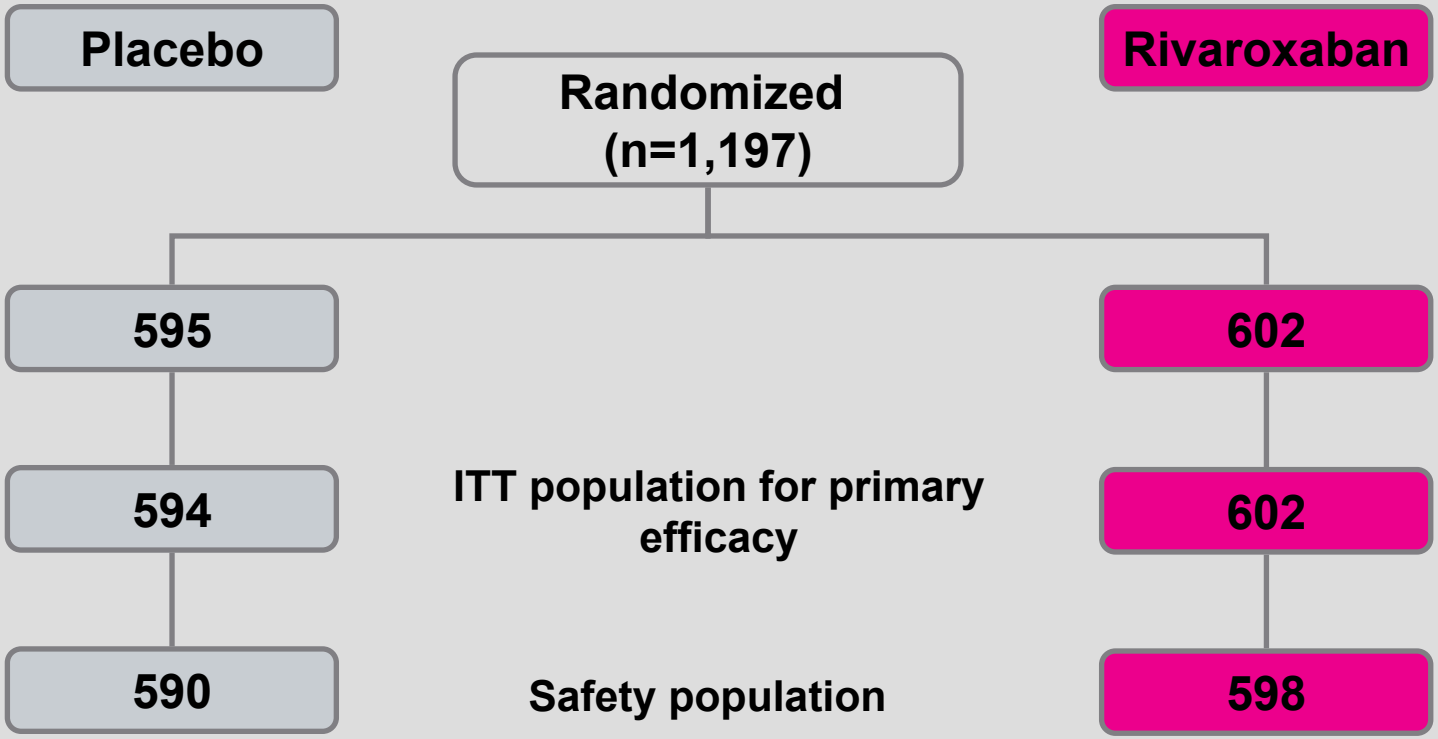
**Randomized, double-blind, placebo-controlled, event-driven (n=30), superiority study**

**Treatment period of 6 or 12 months**




EINSTEIN Extension Trial ID: NCT00439725

# EINSTEIN Extension – patient flow




- Mean duration of therapy
  - Before study entry: placebo 249 days; rivaroxaban 248 days
  - During study: placebo 190 days; rivaroxaban 190 days

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

# EINSTEIN Extension – patient characteristics

| | Placebo (n=594) | Rivaroxaban (n=602) |
|---|---|---|
| **Males (%)** | 57 | 59 |
| **Age, mean (years)** | 58 | 58 |
| **Body mass index, mean (kg/m²)** | 28 | 28 |
| **Creatinine clearance, ml/min** | | |
| <50 | 49 (8%) | 37 (6%) |
| 50–<80 | 121 (20%) | 134 (22%) |
| ≥80 | 373 (63%) | 371 (62%) |
| **Index event*** | | |
| DVT | 350 (59%) | 376 (63%) |
| PE with or without DVT | 233 (39%) | 213 (35%) |
| **Risk factors** | | |
| Patients with idiopathic DVT/PE | 358 (60%) | 344 (57%) |
| Patients with risk factors | 236 (40%) | 258 (43%) |

Intention-to-treat (ITT) population; *index event not confirmed in all patients

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

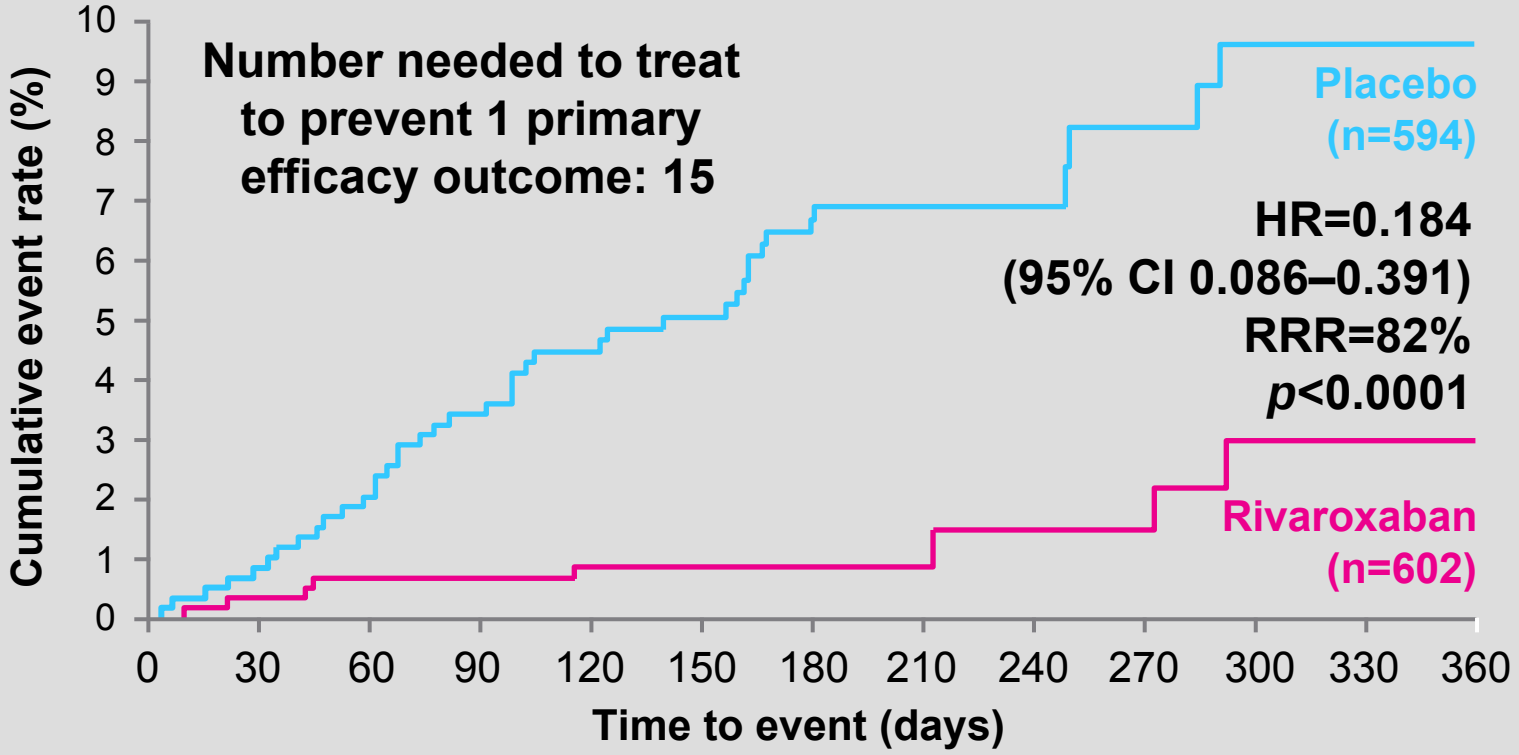
# Primary efficacy outcome and individual components

| | Placebo (n=594) | | Rivaroxaban (n=602) | |
|---|---|---|---|---|
| **Symptomatic recurrent VTE*** | 42 | (7.1%) | 8 | (1.3%) |
| Recurrent DVT | 31 | (5.2%) | 5 | (0.8%) |
| Non-fatal PE | 13 | (2.2%) | 2 | (0.3%) |
| Fatal PE | 1 | (0.2%) | 0 | |
| Unexplained death (where PE cannot be excluded) | 0 | | 1 | (0.2%) |

ITT population; *some patients experienced more than one event

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

# Primary efficacy outcome (time to first event)



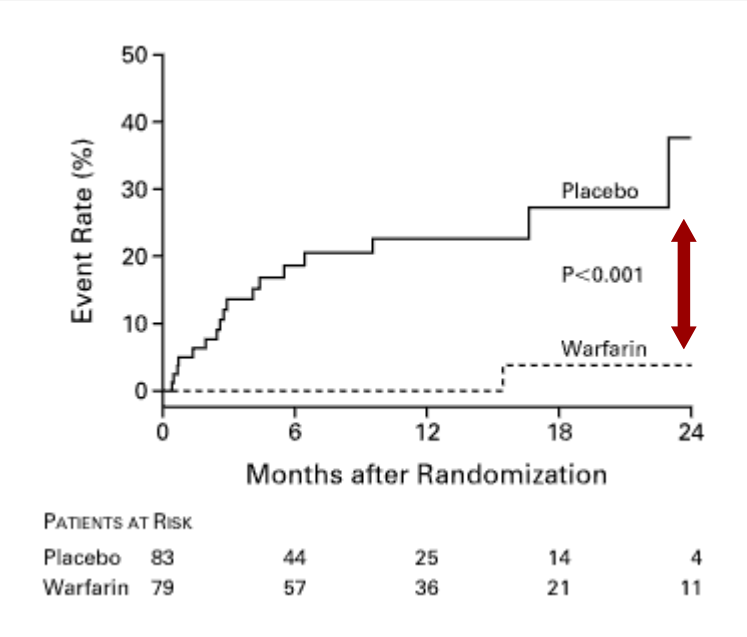

| Number of subjects at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rivaroxaban | 602 | 590 | 583 | 573 | 552 | 503 | 482 | 171 | 138 | 132 | 114 | 92 | 81 |
| Placebo | 594 | 582 | 570 | 554 | 521 | 467 | 444 | 164 | 138 | 133 | 110 | 93 | 85 |

ITT population; CI, confidence interval; HR, hazard ratio; RRR, relative risk reduction

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

# Remember warfarin?

Highly effective, BUT…




**Recurrence reduced by 90%**

**_Major bleeding_: 3,8% / year**

Study discontinued after 2 years

C Kearon. N Engl J Med 1999;340:910-907

# EINSTEIN principal safety outcome: major bleeding

| | Placebo (n=590) | Rivaroxaban (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 haemoglobin ≥2 g/dl and/or transfusion | | | |
| Gastrointestinal bleeding | 0 | 3 | (0.5%) |
| Menorrhagia | 0 | 1 | (0.2%) |

*$p$=0.11

- Number needed to harm: approximately 139

Safety population

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

# EINSTEIN other outcomes

| | Placebo (n=590) | | Rivaroxaban (n=598) | |
|---|---|---|---|---|
| **Clinically relevant non-major bleeding** | **7** | **(1.2%)** | **32** | **(5.4%)*** |
| Urogenital/uterus | 2 | (0.3%) | 12 | (2.0%) |
| Nasal | 1 | (0.2%) | 8 | (1.3%) |
| Rectal/anal | 2 | (0.3%) | 6 | (1.0%) |
| Skin | 2 | (0.3%) | 4 | (0.7%) |
| Ear | 0 | | 1 | (0.2%) |
| Gastrointestinal | 0 | | 1 | (0.2%) |
| Surgical site | 0 | | 1 | (0.2%) |

*$p<0.01$

Safety population; some patients experienced more than one event

EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

# EINSTEIN Extension – Conclusions

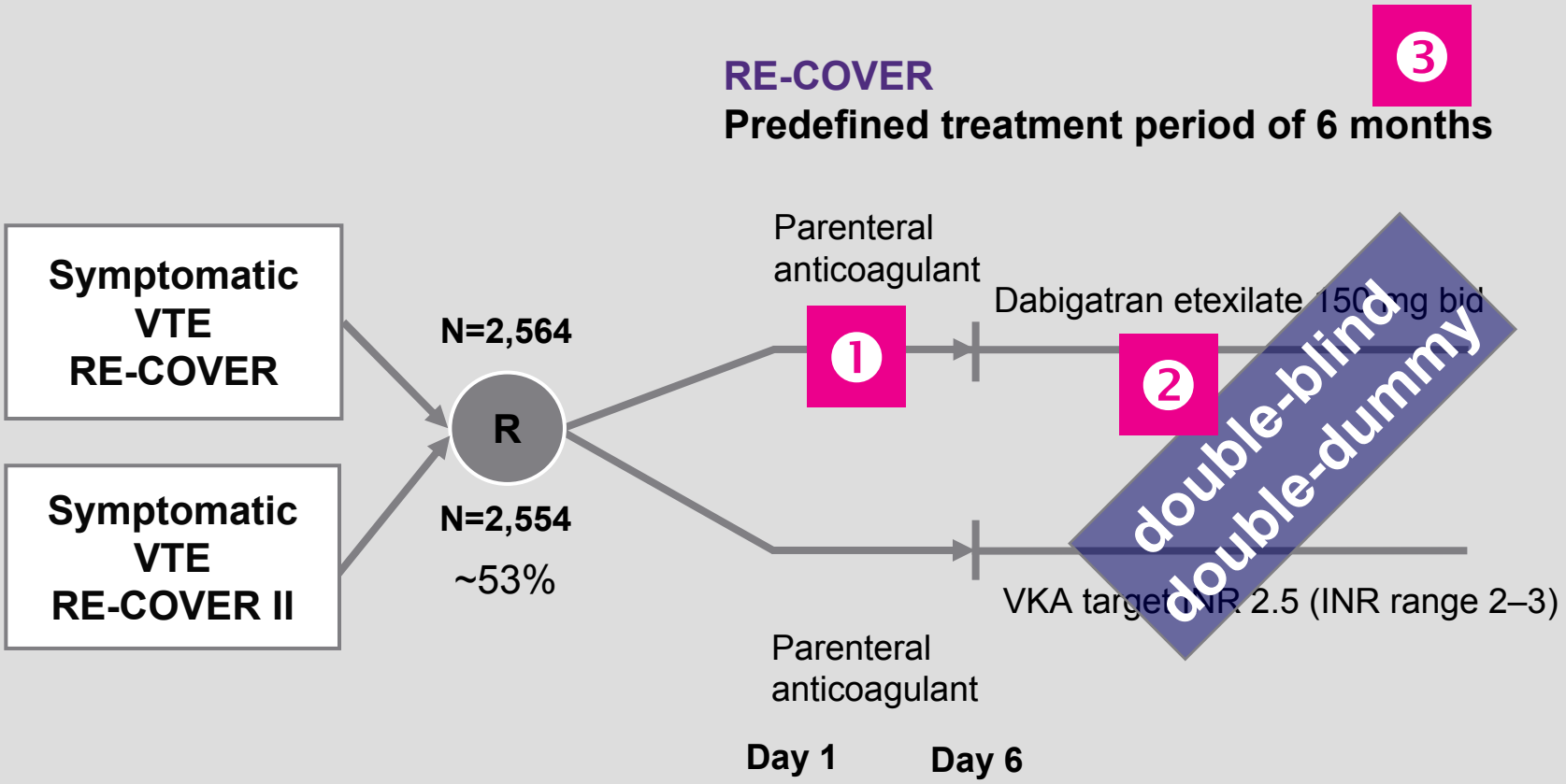
- In patients who had completed 6 or 12 months of anticoagulation rivaroxaban showed
  - An 82% relative risk reduction in the recurrence of VTE (HR=0.184; $p<0.0001$)
  - Absolute risk reduction of 5.8% ▸ 15 patients need to be treated to prevent one recurrent venous thromboembolic event
  - Low incidence of major bleeding (0.7%; $p=0.11$; number needed to harm approximately 139)
  - Modest increase in clinically relevant non-major bleeding (5.4% vs 1.2%; $p<0.01$)

# VTE treatment: clinical studies[1]

| | Phase II | Phase III |
|---|---|---|
| **Rivaroxaban**<br>Oral, direct Factor Xa inhibitor | **EINSTEIN DVT**<br>Rivaroxaban vs LMWH/UFH followed by VKA[2]<br>**ODIXa-DVT**<br>Rivaroxaban vs enoxaparin followed by VKA[3] | **EINSTEIN DVT/PE**<br>Rivaroxaban for 3, 6 or 12 months vs enoxaparin for ≥5 days followed by VKA for 3, 6, or 12 months<br>**EINSTEIN EXT**<br>Rivaroxaban or placebo for 6 or 12 months after pre-treatment with rivaroxaban or VKA for 6 or 12 months |
| **Dabigatran**<br>Oral, direct thrombin inhibitor | | **RE-COVER[5] & RE-COVER II**<br>5–10 days pre-treatment with LMWH bridging to dabigatran or VKA for 6 months<br>**RE-MEDY**<br>3–6 months treatment with approved anticoagulant; switch to dabigatran or VKA<br>**RE-SONATE**<br>6–18 months VKA followed by 6 months dabigatran or placebo |
| **Apixaban**<br>Oral, direct Factor Xa inhibitor | **Botticelli-DVT**<br>Apixaban vs LMWH or fondaparinux followed by VKA[4] | **AMPLIFY**<br>Apixaban 10 mg bid followed by 5 mg bid for 6 months vs enoxaparin followed by VKA<br>**AMPLIFY-EXT**<br>Apixaban 2.5 mg bid or 5 mg bid for extended 12 months vs placebo |

bid, twice daily; 1. http://clinicaltrials.gov; 2. Büller HR, et al. Blood 2008;112:6:2242–2247; 3. Agnelli GA, et al. Circulation 2007;116:180–187; 4. Büller HR, et al. J Thromb Haemost 2008;6;1313–1318; 5. Schulman S, et al. N Engl J Med 2009;361:2342–2352

# Dabigatran study programme in VTE treatment




1. Schulman S, et al. N Engl J Med 2009;361:2342–2352; 2. RE-COVER-II Study Information. Trial ID: NCT00680186 Available at: http://clinicaltrial.gov/ct2/show/NCT00680186

# RE-COVER: major outcomes

## Primary efficacy outcome

- Composite of symptomatic recurrent VTE and VTE-related death within 6 months

## Principal safety outcome

- Bleeding events, adverse events (AEs), discontinuation due to AEs, laboratory measures, acute coronary syndromes, electrocardiography and vital signs
  - **Major bleeding** was defined as clinically overt and associated with a fall in haemoglobin level of at least 20 g/l,
  - or requiring transfusion of 2 or more units of red cells, or involved a critical site or was fatal

1. RE-COVER Study Information. Trial ID: NCT00291330 Available at http://clinicaltrial.gov/ct2/show/NCT00291330;
2. Schulman S, et al. N Engl J Med 2009;361:2342–2352; 3. RE-COVER-II Study Information. Trial ID: NCT00680186
Available at http://clinicaltrial.gov/ct2/show/NCT00680186

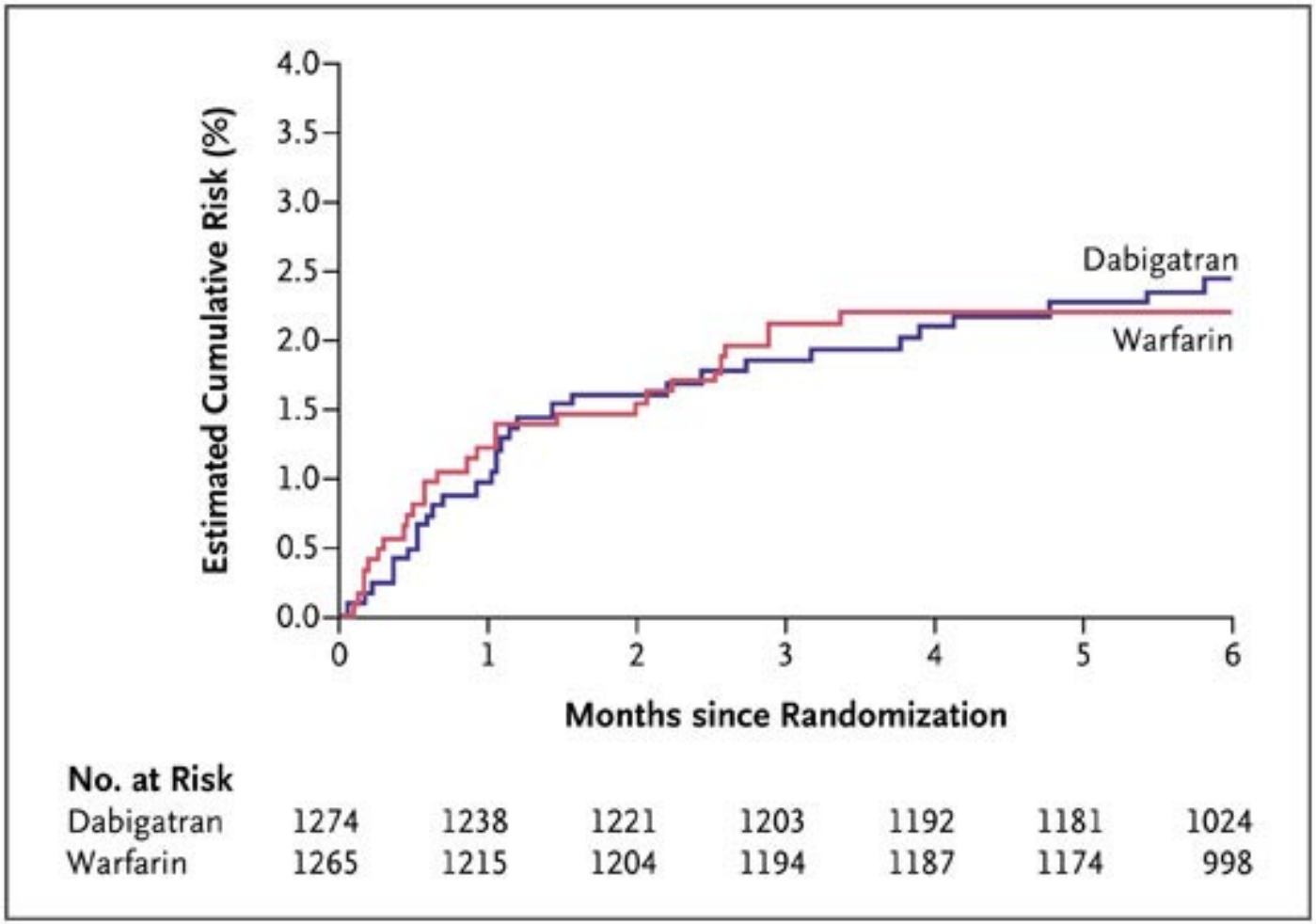
# RE-COVER: study results

| Events | Dabigatran (n=1,274) | | Warfarin (n=1,265) | | Hazard ratios and confidence intervals |
|---|---|---|---|---|---|
| Recurrent VTE or related death* | 30 | (2.4%) | 27 | (2.1%) | Risk difference = 0.4%; 95% CI –0.8 to 1.5 *p*<0.001 for **prespecified non-inferiority** |
| Recurrent VTE or related death# | 34 | (2.7%) | 32 | (2.5%) | HR=1 .05 95% CI 0.65 to 1.70 |
| Major bleeding | 20 | (1.6%) | 24 | (1.9%) | HR=0.82 95% CI 0.45 to 1.48 |
| Any bleeding | 205 | (16.1%) | 277 | (21.9%) | **HR=0.71 95% CI 0.59 to 0.85** |

*During the study period
# During the study period plus 30 day f-up

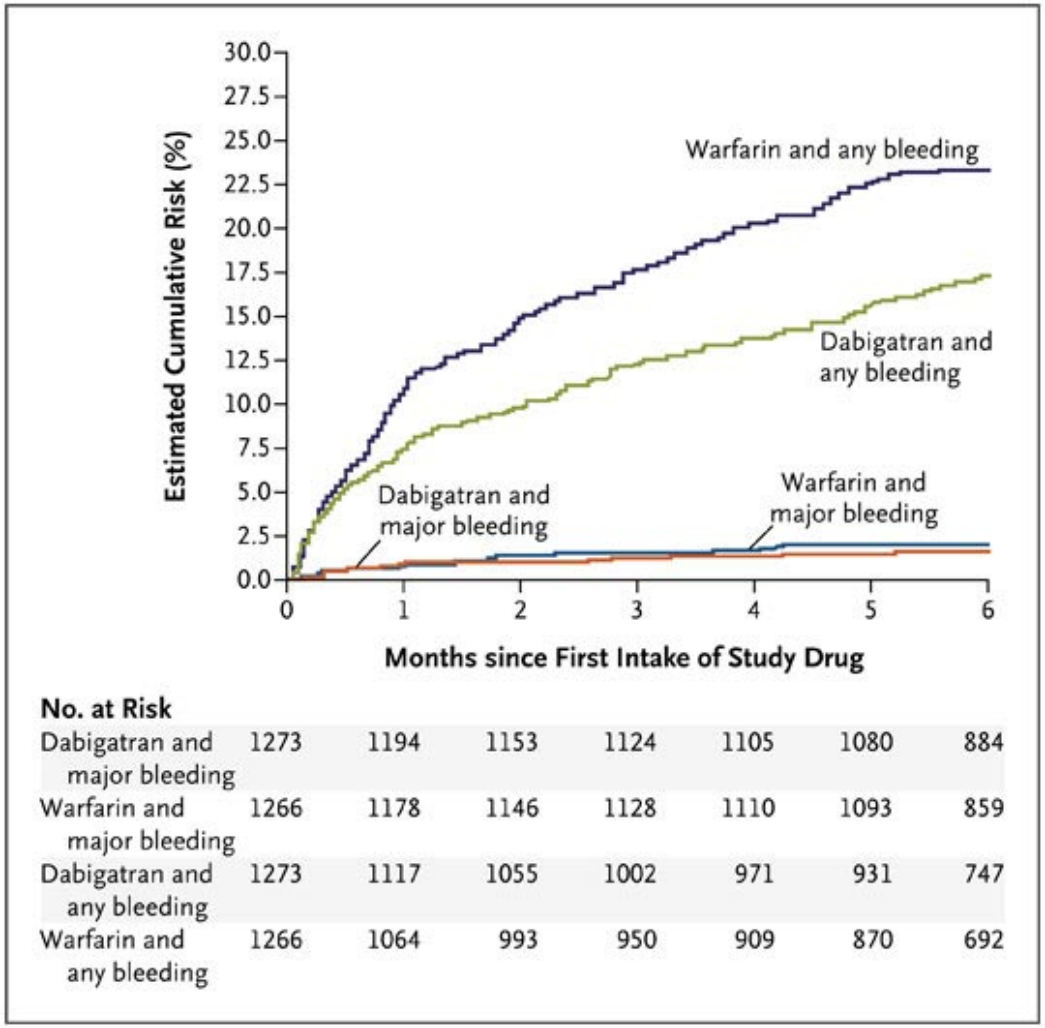
Schulman S, et al. N Engl J Med 2009;361:2342–2352

# RE-COVER: efficacy




Schulman S et al. N Engl J Med 2009;361:2342-2352

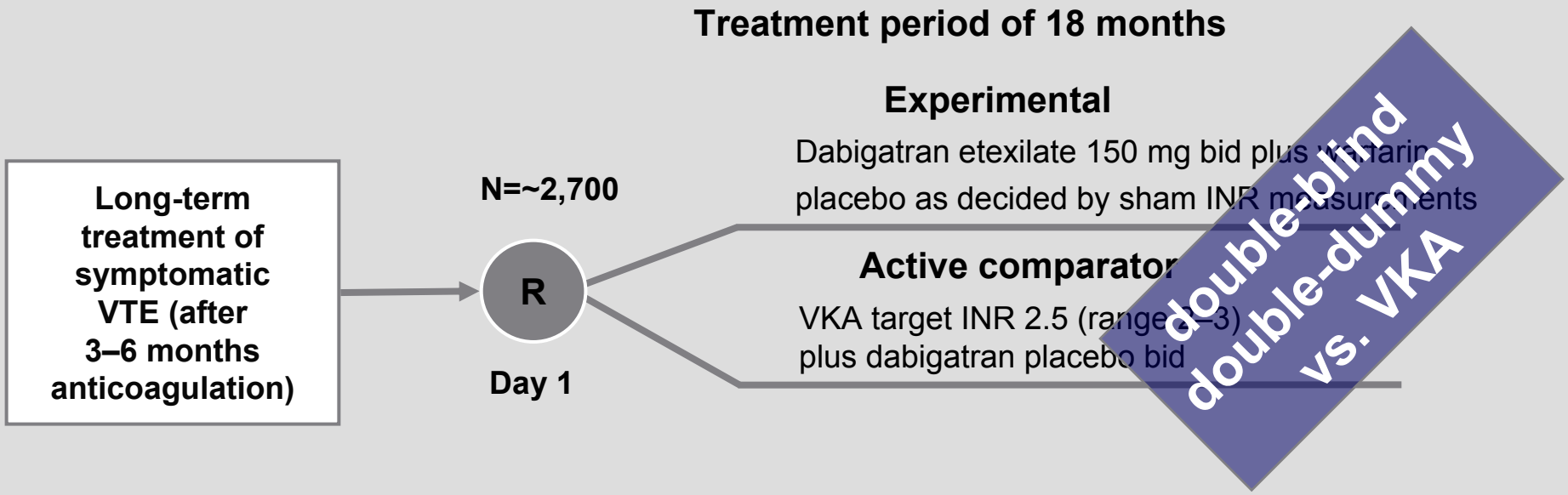
# RE-COVER: safety




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dabigatran and major bleeding | 1273 | 1194 | 1153 | 1124 | 1105 | 1080 | 884 |
| Warfarin and major bleeding | 1266 | 1178 | 1146 | 1128 | 1110 | 1093 | 859 |
| Dabigatran and any bleeding | 1273 | 1117 | 1055 | 1002 | 971 | 931 | 747 |
| Warfarin and any bleeding | 1266 | 1064 | 993 | 950 | 909 | 870 | 692 |

Schulman S et al. N Engl J Med 2009;361:2342-2352

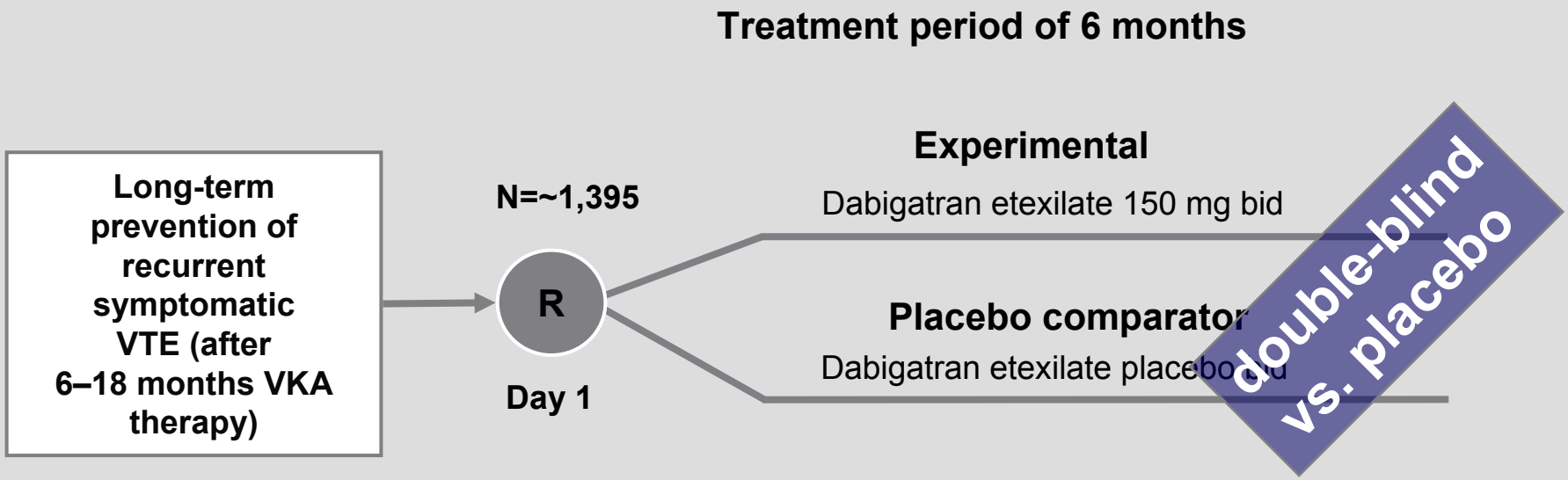
# Dabigatran study programme in prevention of secondary VTE: RE-MEDY




- **Primary efficacy outcome:** composite of recurrent symptomatic VTE (DVT and PE) and deaths related to VTE during the treatment period
- **Secondary outcome:** bleeding events during treatment


1. RE-MEDY Study Information. Trial ID: NCT00329238 Available at: http://www.clinicaltrials.gov/ct2/show/NCT00329238?term=NCT00329238&rank=1
2. Boehringer Ingelheim. RE-VOLUTION Dabigatran etexilate clinical trials. 2009. Available at: http://www.pradaxa.com/Include/media/pdf/RE-VOLUTION_dabigatran_etexilate-clinical_trials.pdf

# Dabigatran study programme in prevention of secondary VTE: RE-SONATE




- **Primary efficacy outcome:** recurrent symptomatic VTE (composite DVT, fatal and non-fatal PE) during treatment
- **Primary safety outcome:** Clinical relevant bleeding, all deaths and cardiovascular events

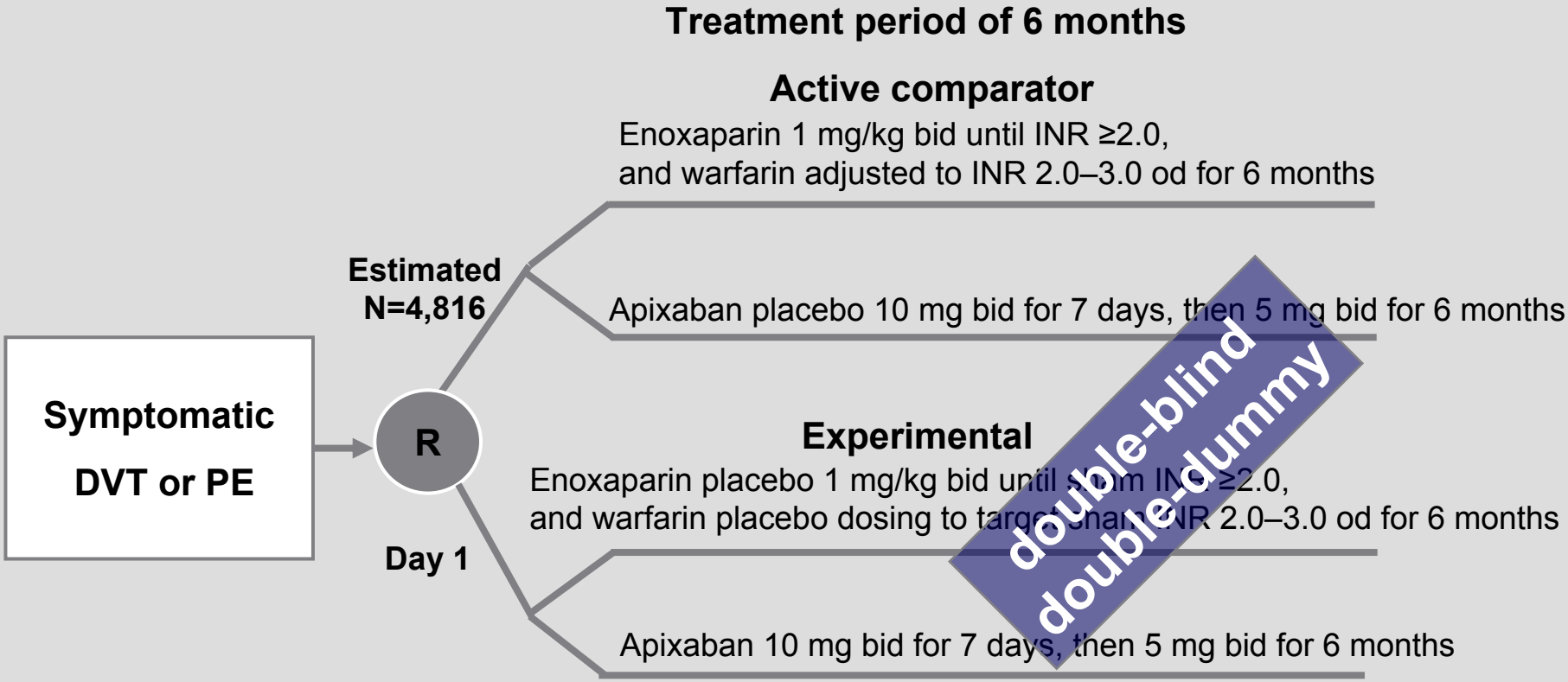
1. RE-SONATE Study Information. Trial ID: NCT00558259. Available at: http://clinicaltrials.gov/ct2/show/NCT00558259;
2. Boehringer Ingelheim. RE-VOLUTION Dabigatran etexilate clinical trials. 2009. Available at: http://www.pradaxa.com/Include/media/pdf/RE-VOLUTION_dabigatran_etexilate-clinical_trials.pdf

# VTE treatment: clinical studies[1]

| | Phase II | Phase III |
|---|---|---|
| **Rivaroxaban**<br>Oral, direct Factor Xa inhibitor | **EINSTEIN DVT**<br>Rivaroxaban vs LMWH/UFH followed by VKA[2]<br>**ODIXa-DVT**<br>Rivaroxaban vs enoxaparin followed by VKA[3] | **EINSTEIN DVT/PE**<br>Rivaroxaban for 3, 6 or 12 months vs enoxaparin for ≥5 days followed by VKA for 3, 6, or 12 months<br>**EINSTEIN EXT**<br>**R**ivaroxaban or placebo for 6 or 12 months after pre-treatment with rivaroxaban or VKA for 6 or 12 months |
| **Dabigatran**<br>Oral, direct thrombin inhibitor | | **RE-COVER[5] & RE-COVER II**<br>5–10 days pre-treatment with LMWH bridging to dabigatran or VKA for 6 months<br>**RE-MEDY**<br>3–6 months treatment with approved anticoagulant; switch to dabigatran or VKA<br>**RE-SONATE**<br>6–18 months VKA followed by 6 months dabigatran or placebo |
| **Apixaban**<br>Oral, direct Factor Xa inhibitor | **Botticelli-DVT**<br>Apixaban vs LMWH or fondaparinux followed by VKA[4] | **AMPLIFY**<br>Apixaban 10 mg bid followed by 5 mg bid for 6 months vs enoxaparin followed by VKA<br>**AMPLIFY-EXT**<br>Apixaban 2.5 mg bid or 5 mg bid for extended 12 months vs placebo |

bid, twice daily; 1. http://clinicaltrials.gov; 2. Büller HR, et al. Blood 2008;112:6:2242–2247; 3. Agnelli GA, et al. Circulation 2007;116:180–187; 4. Büller HR, et al. J Thromb Haemost 2008;6;1313–1318; 5. Schulman S, et al. N Engl J Med 2009;361:2342–2352

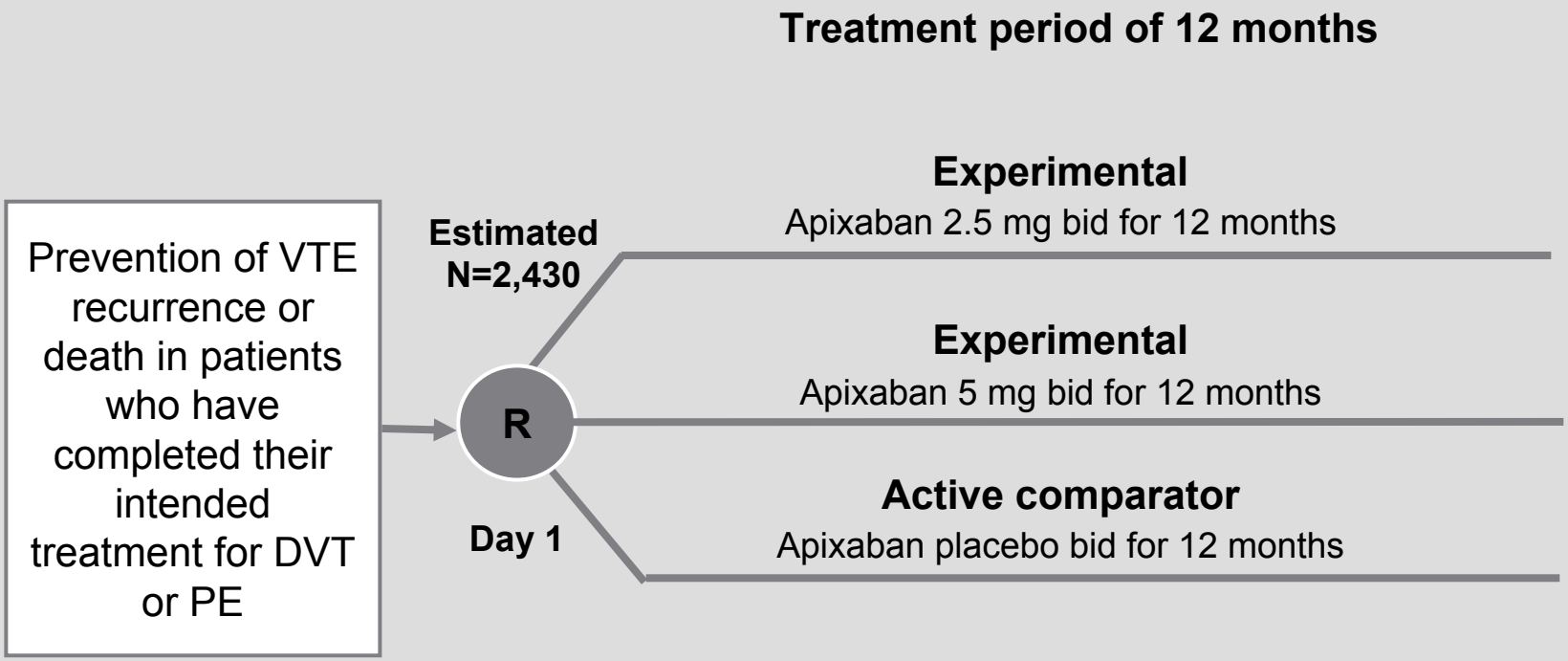
# Apixaban: AMPLIFY




- **Primary efficacy outcome:** VTE recurrence or death during study treatment
- **Secondary outcome:** bleeding during study treatment

AMPLIFY Study Information. Trial ID: NCT00643201 Available at: http://clinicaltrials.gov/ct2/show/NCT00643201?term=NCT00643201&rank=1

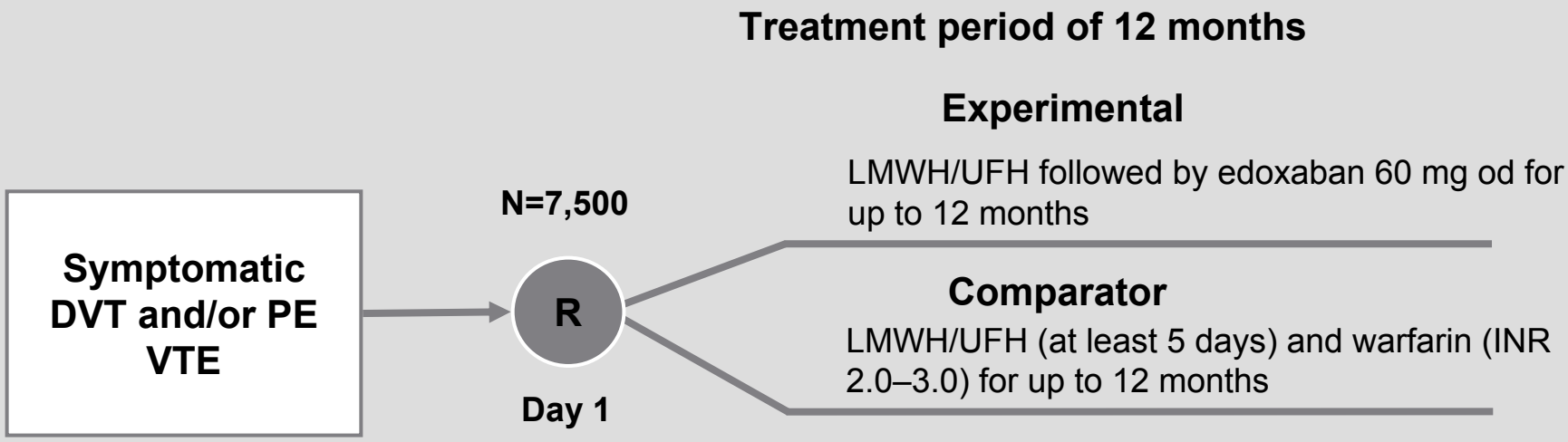
# Apixaban: AMPLIFY-EXT




- **Primary efficacy outcome:** VTE recurrence or death during study treatment
- **Secondary outcome:** bleeding during study treatment

AMPLIFY-EXT Study Information. Trial ID: NCT00633893 Available at: http://clinicaltrials.gov/ct2/show/NCT00633893?term=NCT00633893&rank=1

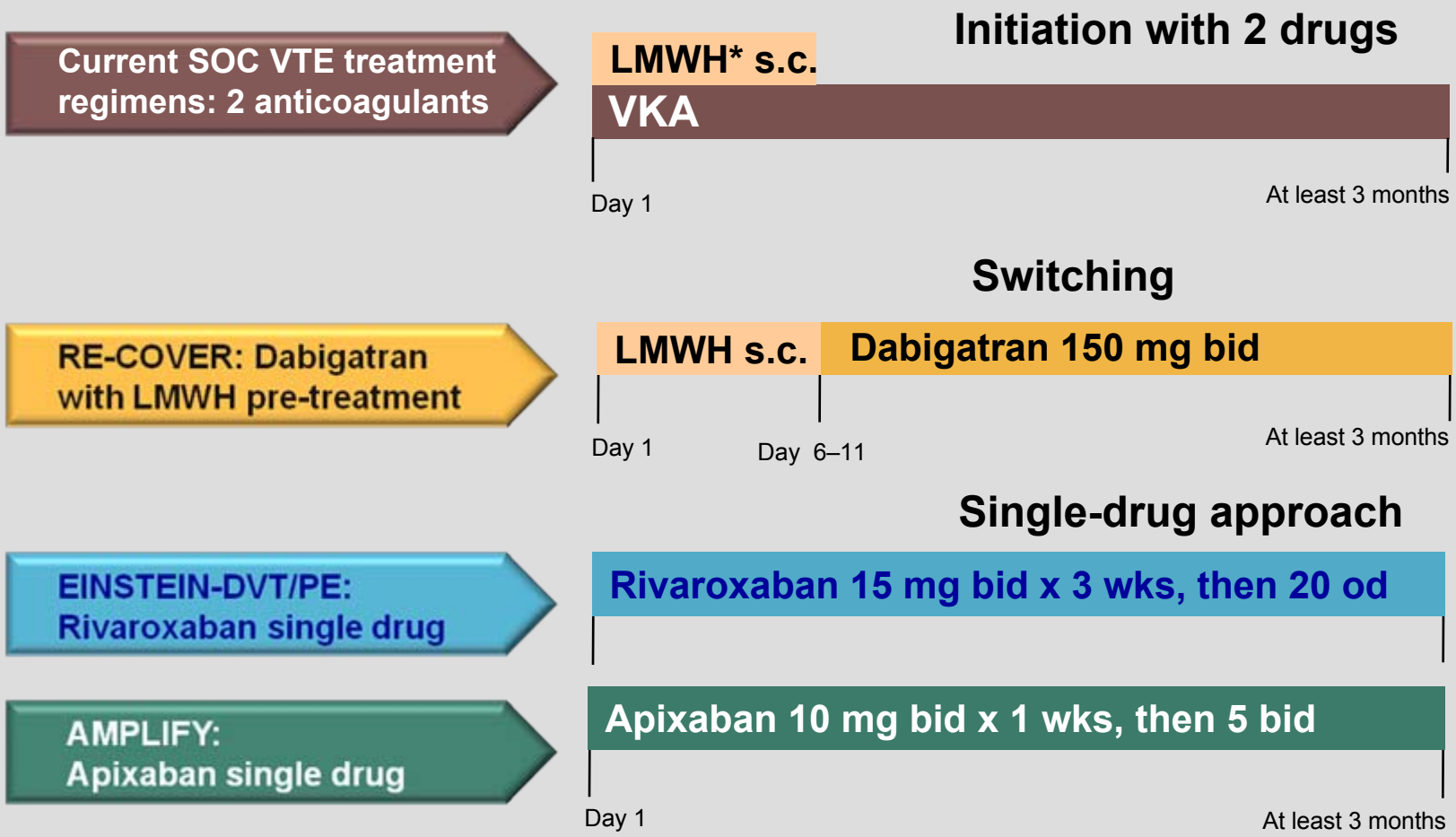
# Edoxaban: Hokusai-VTE study




- **Primary efficacy outcome:** recurrent symptomatic VTE (DVT, non-fatal and fatal PE)12 months from randomization
- **Primary safety outcome:** clinically relevant bleeding (major or clinically relevant non-major bleeding) during treatment

Hokusai-VTE Study Information. Trial ID: NCT00986154. Available at: http://clinicaltrials.gov/ct2/show/NCT00986154?term=edoxaban&rank=1

# Single drug approach vs switching in VTE treatment




*Or UFH or fondaparinux

# Summary and Conclusions

- Current standard of treatment usually requires initial parenteral LMWH/UFH/fondaparinux followed by oral VKA.
- For many patients with VTE, secondary prevention with VKA is not extended beyond 6 months.
- Patients with VTE have a major risk of recurrent VTE that may persist for many years.
- New oral anticoagulants such as apixaban, dabigatran and rivaroxaban may have the potential to improve benefit–risk and simplify acute VTE treatment and secondary prevention.
- In patients who had completed 6 or 12 months of anticoagulation rivaroxaban showed an 82% relative risk reduction in the recurrence of VTE vs placebo (Einstein EXT).