TREATING ACUTE DVT WITH DOACs
ADVANCES AND CHALLENGES

Armando Mansilha MD, PhD, FEBVS

Disclosure

Speaker name:

Armando Mansilha

I have the following potential conflicts of interest to report:

- ☑ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company

- Alfa Wassermann
- Bard
- Bayer
- BMS
- Boehringer
- Boston Scientific
- Leo
- Medtronic
- Pfizer
- Pierre Fabre
- Sanofi
- Servier

Principles of VTE treatment

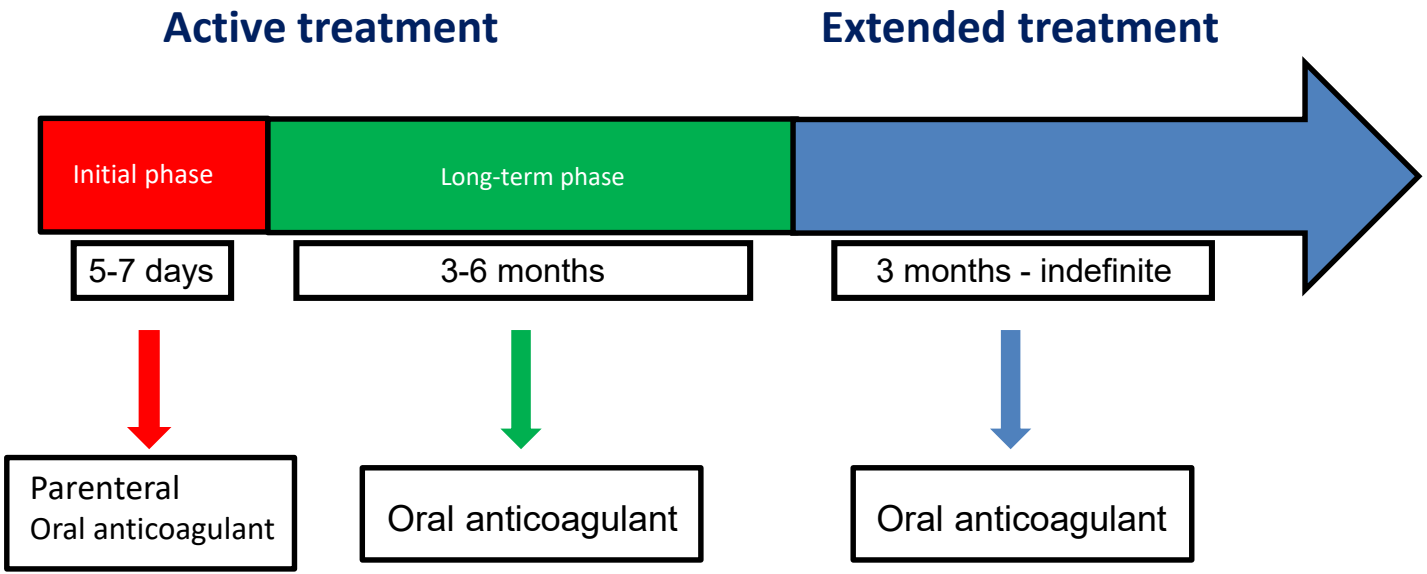
PREVENT short-term and long-term sequelae

PREVENT clot extension, including PE

PREVENT
- Post-thrombotic syndrome
- Chronic thromboembolic pulmonary hypertension

PREVENTION of recurrence

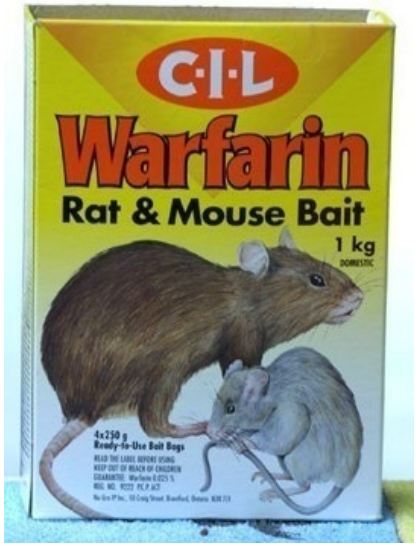
Stages of VTE treatment



Agnelli et al. Hematology 2013; 471-47,
Kearon C , and Akl E A Blood 2014;123:1794-1801

Wisconsin Alumni Research Foundation-arin
+ 50 years of experience

- Unpredictable Response
- Routine Monitoring
- Frequent dose adjustments
- Narrow therapeutic window (INR 2-3)



- Slow onset and off-set of action
- Multiple drug interactions
- Multiple diet interactions
- Warfarin resistance

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137; Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

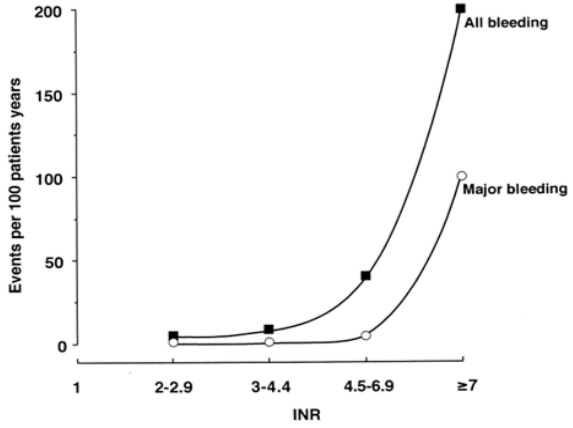
Oral Anticoagulation and Bleeding Risk

Risk of Bleeding in Oral Anticoagulation Patients

Any hemorrhage	3-6% per year
Major hemorrhage requiring admission or transfusion	1% per year
Fatal hemorrhage	0.3% per year

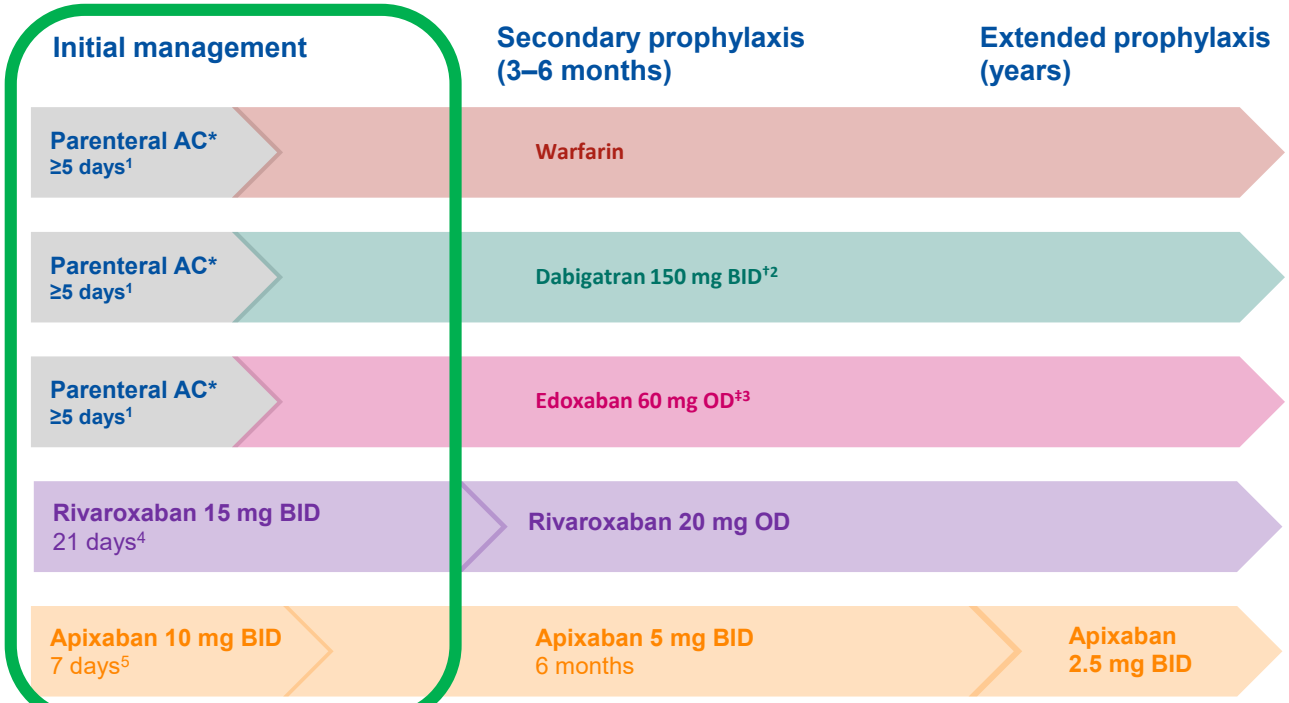
ie 1 in 300 patients on warfarin dies from bleeding every year

Rate of bleeding according to INR – ISCOAT study



Palareti G et al, Lancet 1996

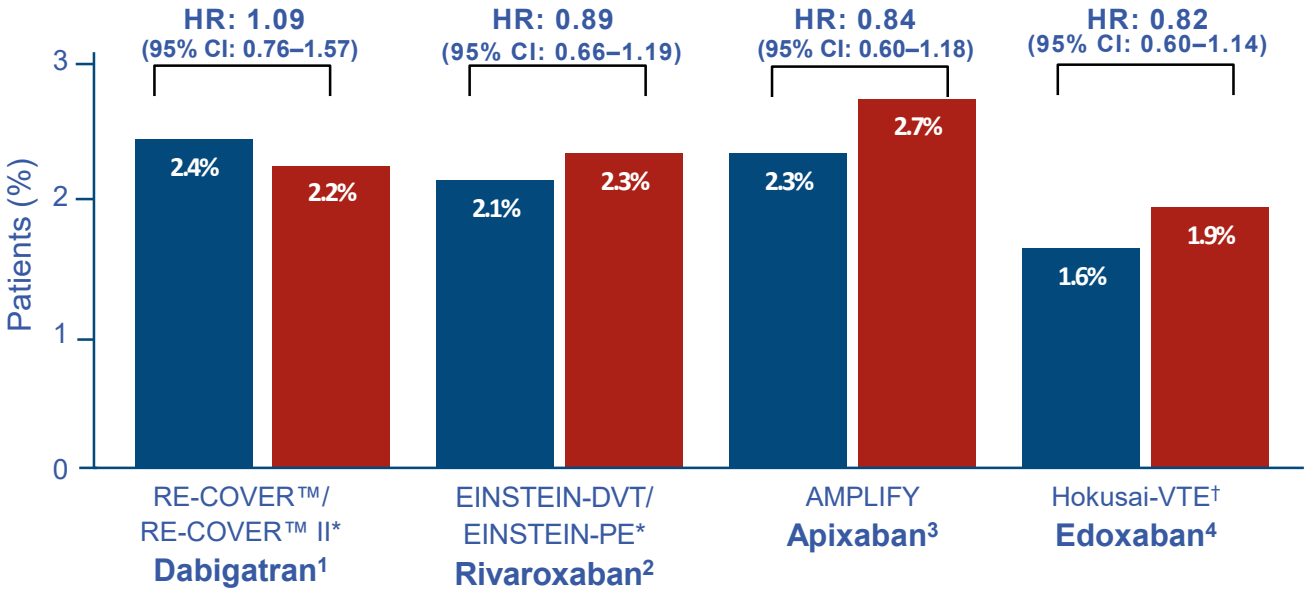
VTE requires acute and extended treatment for prevention of recurrence



*LMWH, fondaparinux or UFH; †Dabigatran 110 mg BID for aged ≥80 years, concomitant verapamil, or based on individual assessment of thromboembolic/bleeding risk; ‡Edoxaban 30 mg OD for CrCl 15–50 mL/min, weight ≤60 kg, certain concomitant P-gp inhibitors

1. Kearon et al. Chest 2012;141(2 Suppl):e419S-94S; **2.** Pradaxa SPC; **3.** Savaysa SPC; **4.** Xarelto SPC; **5.** Eliquis SPC. Current versions available online at: http://www.medicines.org.uk/emc/

Acute treatment of DVT/PE: DOACs non-inferior to warfarin for prevention of recurrent DVT/PE in their Phase III trials

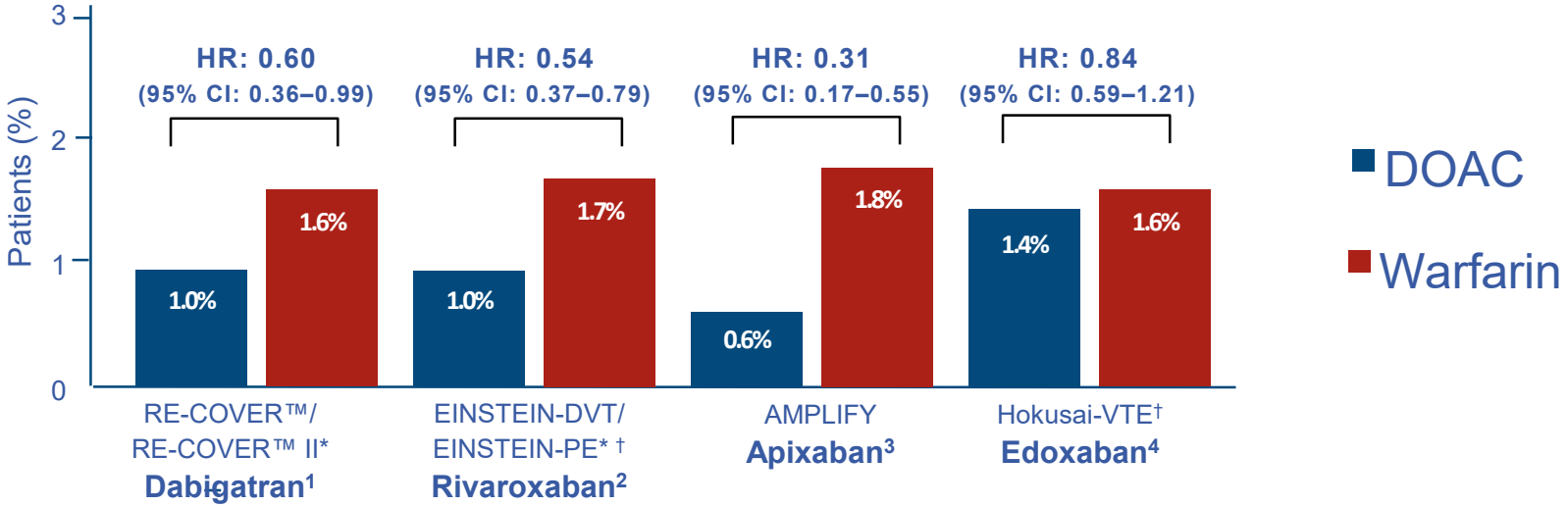


Direct comparisons cannot be made as no head to head data is available

*Pooled data; oral drug treatment period only; †On treatment

1. Schulman S et al. Circulation 2014;129:764-72; **2.** Prins MH et al. Thromb J 2013;11:21; **3.** Agnelli G et al. N Engl J Med 2013;369:799-808; **4.** The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406-15

Acute treatment of DVT/PE: DOACs associated with less major bleeding versus warfarin in their Phase III trials*



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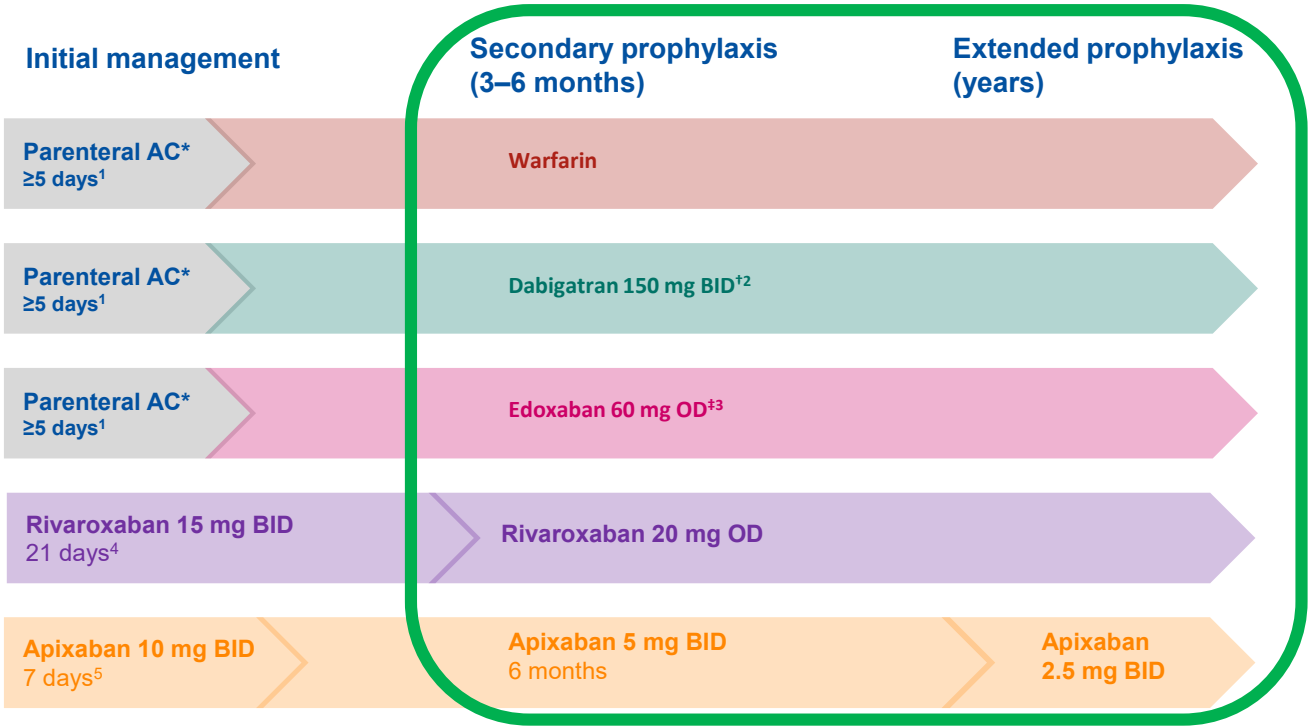
*Statistically significant reductions for dabigatran, rivaroxaban, and apixaban vs warfarin, numerical reduction for edoxaban vs warfarin; †Pooled data; oral drug treatment period only; ‡Pooled analysis; §On treatment

1. Schulman S et al. Circulation 2014;129:764-72; **2.** Prins MH et al. Thromb J 2013;11:21; **3.** Agnelli G et al. N Engl J Med 2013;369:799-808; **4.** The Hokusai-VTE Investigators. N Engl J Med 2013;369:1406-15

VTE requires acute and extended treatment for prevention of recurrence



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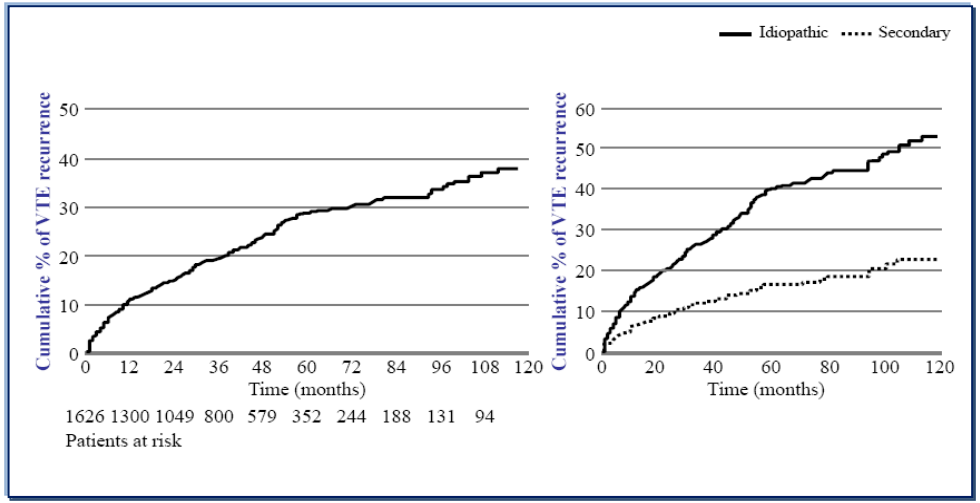
Duration of Therapy



Duration of therapy should be individualized after careful assessment of treatment benefit against risk of bleeding

Short duration (at least 3 months):

- Proximal DVT associated with transient risk factors (e.g. recent surgery, trauma, immobilization)
- Distal DVT

Extended treatment: Unprovoked DVT or DVT associated with permanent risk factors

Prandoni P et al. Haematologica. 2007;92:199-205. P. de Jong et al. BJH, 2012;158:433-441. 1. Kearon C, Akl EA, Comerota AJ, et al. Chest. 2012;141(suppl 2): e419S-e494S.

Risk of Recurrence

Provoking factor for VTE

- ❑ Major reversible risk factor
  - Surgery - very low risk
  - Non-surgical risk factors (trauma, immobilization, pregnancy, estrogens) - low risk
- ❑ Persistent or progressive risk factor (cancer) – high risk

Unprovoked VTE

- ❑ Several parameters can be evaluated - moderately high risk

Previous VTE

- ❑ A second episode of VTE has a 50% higher risk of recurrence compared with the first one

P. de Jong et al. BJH, 2012;158:433-441

Risk of Recurrence – unprovoked VTE

- Sex - Men have higher risk than women (HR – 1.9)
- Site of VTE - Proximal DVT versus distal DVT – higher risk (HR – 2.08)
- D-Dimer (1 month after stopping anticoagulation)

  When positive the risk is higher (HR – 2.27)
- Antiphospholipid syndrome

  Persistent LA or high titers of ACAS or B_2GP1 – higher risk
- Hereditary thrombophilias

  AT deficiency or multiple thrombophilias – higher risk
- Post-thrombotic syndrome

  PTS ⟺ Recurrence (ipsilateral DVT)

P. de Jong et al. BJH, 2012;158:433-441

Risk of Bleeding

Patients characteristics

- Older age (>75 ys)
- Previous bleeding
- Cancer
- Hypertension
- Diabetes
- Cerebrovascular disease
- Renal insufficiency
- Liver disease

Antithrombotics

- Poor INR control
- Antiplatelet agents
- NSAIDs

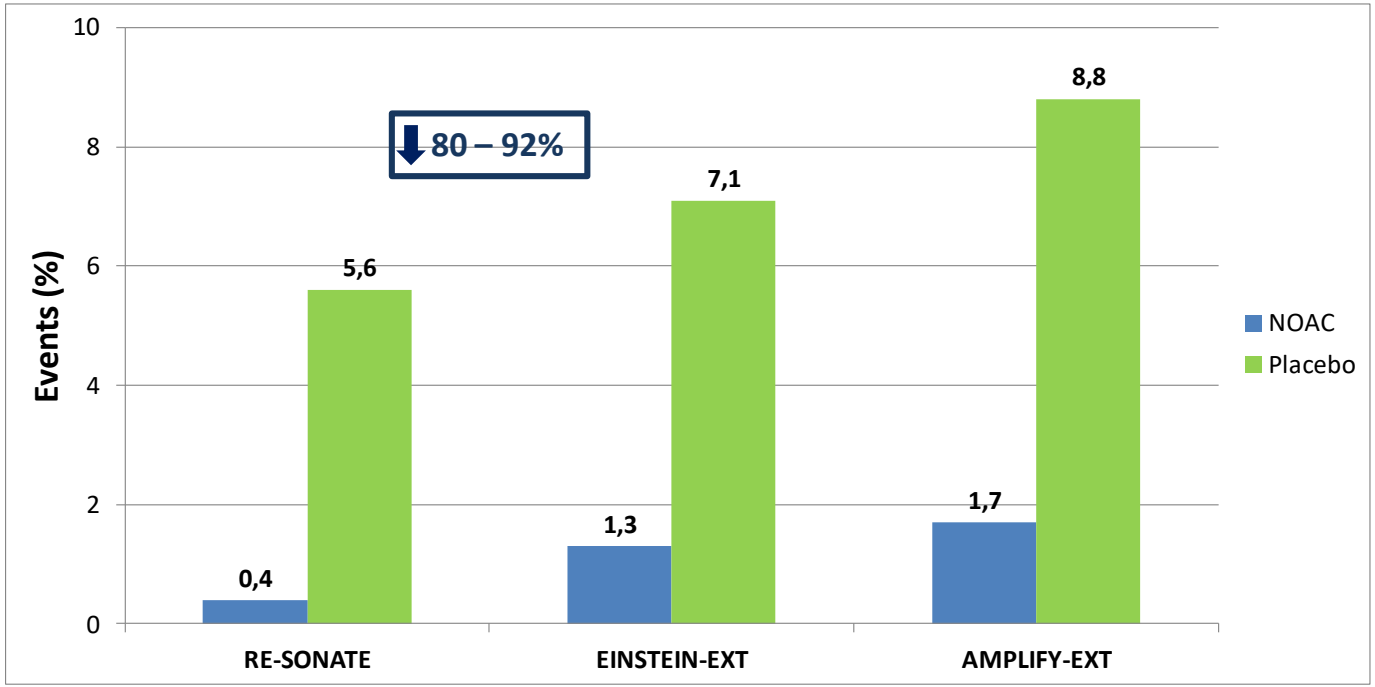
Recent surgery

Frequent falls

P. de Jong et al. BJH, 2012;158:433-441

Primary Efficacy Outcome

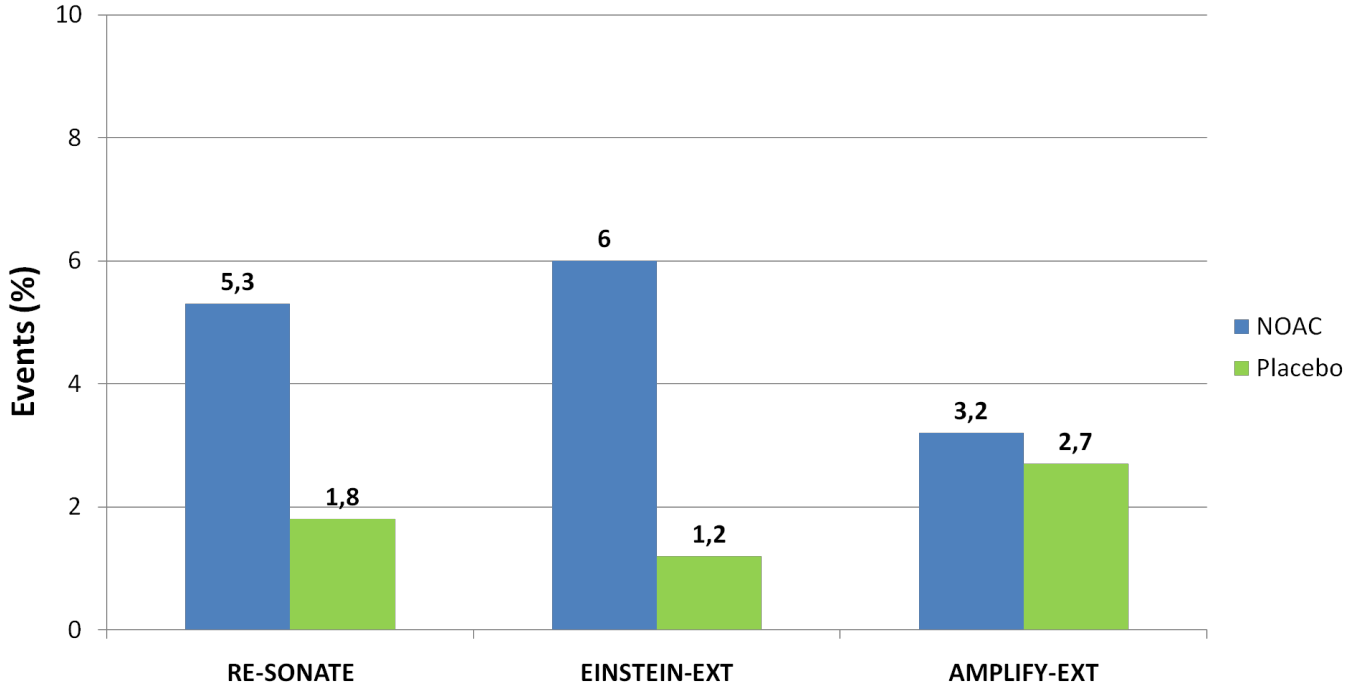
Recurrent symptomatic VTE and VTE-related deaths



1. Schulman S et al. N Engl J Med 2013;368:709–18; **2.** The EINSTEIN Investigators et al. N Engl J Med 2010;363:2499–510; **3.** Agnelli G et al. N Engl J Med 2013;368:699–708

Safety outcome

Major or CRNM bleedings



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Conclusions

- DOACs are non-inferior to warfarin for active VTE treatment - prevention of recurrent or fatal VTE and present a favourable safety profile - significant reductions in major or clinically-relevant non major bleedings with NOACs vs warfarin.
- DOACs can be used for extended treatment with high efficacy and low bleeding risk.
- Easier management

Not approved for:

- VTE associated with cancer
- VTE associated with high-risk thrombophilia (AFS)

Contra-indications:

- Pregnant women
- Patients with severe renal impairment or severe liver disease

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