Krankenhaus
Dresden-Friedrichstadt
Städtisches Klinikum

20th Cardiology Update 2013

Edoxaban in Venous Thromboembolism

The HOKUSAI VTE study

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Medizinische Klinik 2
Kardiologie – Angiologie – Intensivmedizin - stroke

Risk factors for VTE (not exhaustive)

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Age	Surgical therapy
Obesity	Malignancy
Varicose veins	Cardiac/respiratory failure
Immobility / Hospital stay	Myocardial infarction
Pregnancy	Paralysis of lower limb(s)
Biologic thrombophilia	Infection
Hormone therapy	Inflammatory bowel disease
Previous VTE	Nephrotic syndrome
Long-haul flights	Polycythaemia

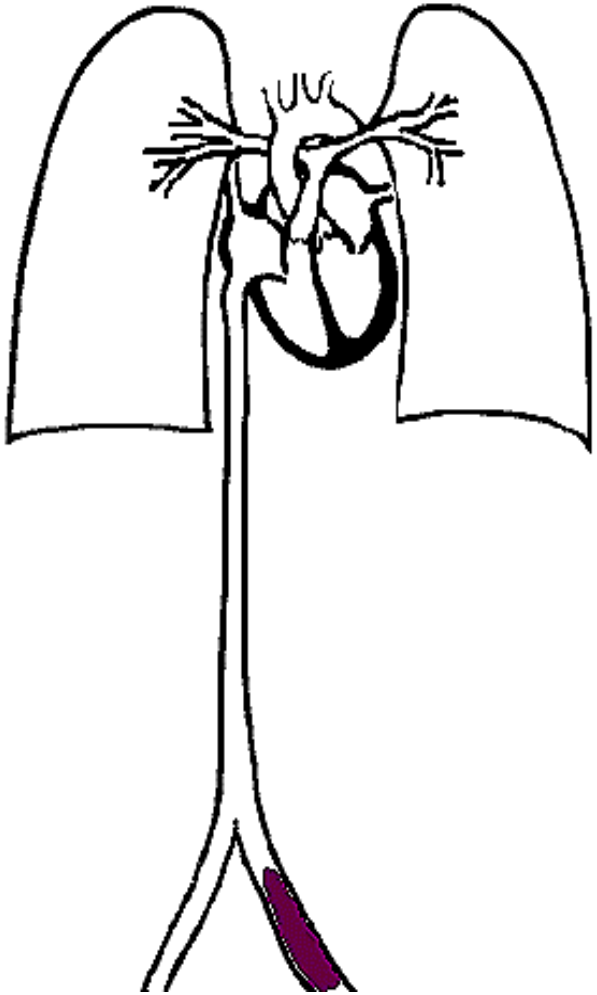
Attributable risk for DVT/PE

Risk factor	AR (%)	(95% CI)
Hospitalisation with surgery	**23.8**	**(20.3–27.3)**
Hospitalisation without surgery	**21.5**	**(17.3–25.6)**
Malignant neoplasm	**18.0**	**(13.4–22.6)**
Congestive heart failure	**9.5**	**(3.3–15.8)**
Neurological disease with extremity paresis	**6.9**	**(3.5–10.2)**

59% Medical

Heit JA et al. Arch Intern Med 2002;162:1245-8

Sequelae of venous thromboembolism



Immediate consequence of DVT

Pulmonary embolism

Late consequences

Chronic pulmonary hypertension (PE

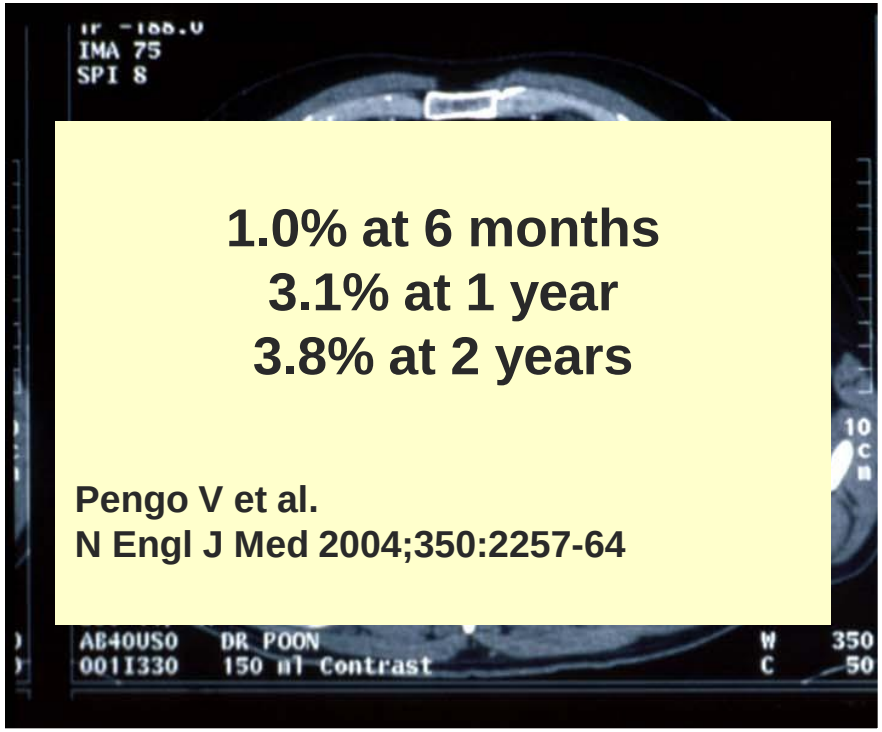
Postthrombotic syndrome (DVT)

10% of hospital deaths are due to PE

1% of all hospital admissions die from PE

Late sequelae

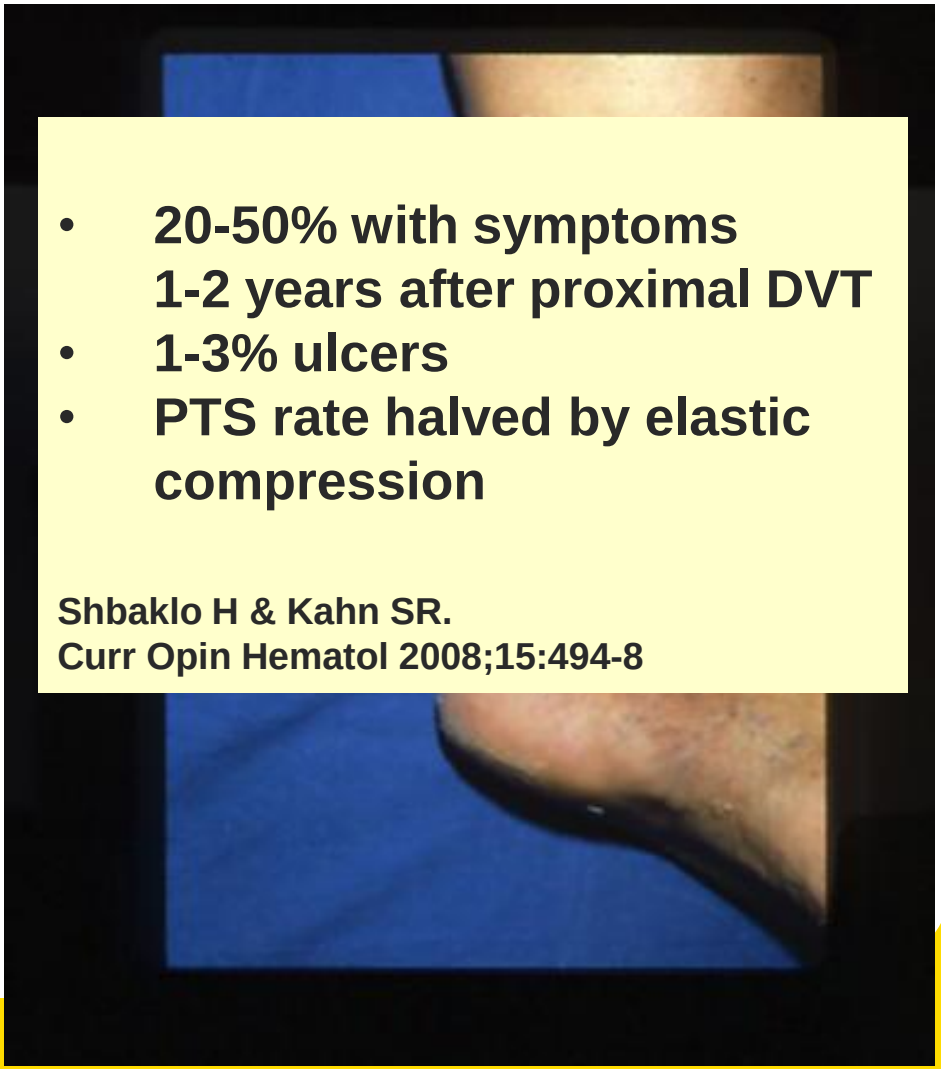
Pulmonary hypertension



1.0% at 6 months
3.1% at 1 year
3.8% at 2 years

Pengo V et al.
N Engl J Med 2004;350:2257-64

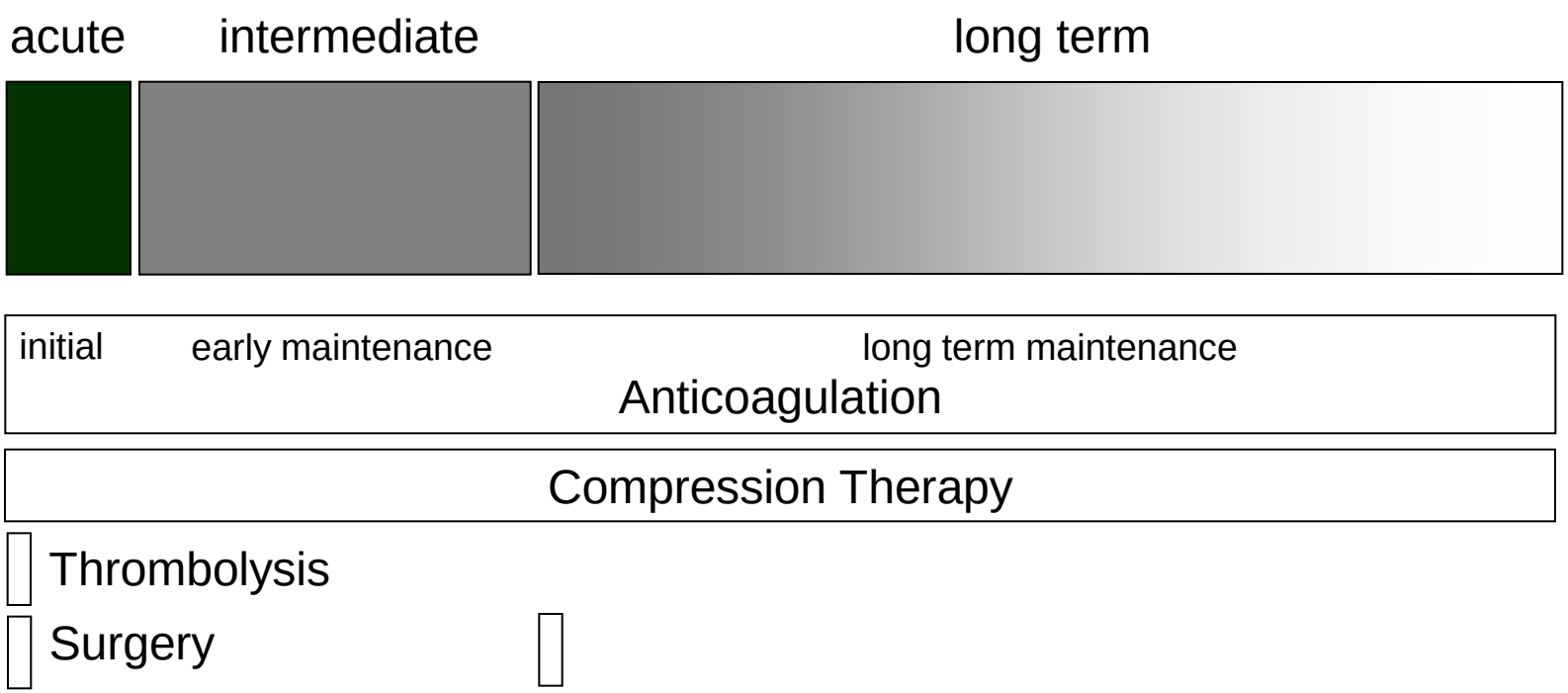
Postthrombotic syndrome



- 20-50% with symptoms 1-2 years after proximal DVT
- 1-3% ulcers
- PTS rate halved by elastic compression

Shbaklo H & Kahn SR.
Curr Opin Hematol 2008;15:494-8

Therapy of VTE



Anticoagulation in VTE

Initial therapy

LMH, Fondaparinux

exceptions: high-risk PE, renal impairment

Early maintenance therapy

VKA

exceptions: cancer, other comorbidities, planned procedures, very elderly, compliance issues...

Prolonged maintenance therapy

VKA

exceptions: rare cases

The ideal anticoagulant drug

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- Rapidly inhibits thrombus progression
- Can be administered orally
- Exhibits a large therapeutic margin
- Has predictable pharmacokinetics and dose-response relationship
- Exhibits a low non-specific binding to plasma proteins
- Does not require laboratory monitoring
- Does not need frequent dose adjustments
- Produces few bleeding complications
- Produces few adverse events
- Exhibits few interactions with other drugs and with food

How ideal are heparins?

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Drawbacks of UFH/LMWH/fondaparinux

- Need for antithrombin to inactivate thrombin
- Inability to inactivate fibrin-bound thrombin
- **Laboratory monitoring**
- **Risk of heparin-induced thrombocytopenia (HIT)**
- **Parenteral application**
- Animal origin (except fondaparinux)
- Suboptimal efficacy/safety ratio

How ideal are vitamin K antagonists?

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Drawbacks of VKA

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The HOKUSAI VTE study

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Trial Hypotheses

1. A regimen of LMW(Heparin)/edoxaban is **non-inferior** (=not worse than) to the standard treatment regimen of LMW(Heparin)/warfarin in the treatment/prevention of VTE
2. The incidence of bleeding of LMW(Heparin)/edoxaban is equal or better to LMW(Heparin)/warfarin

Rationale and Background

The study is designed to reflect the current standard-of-care treatment of a VTE event

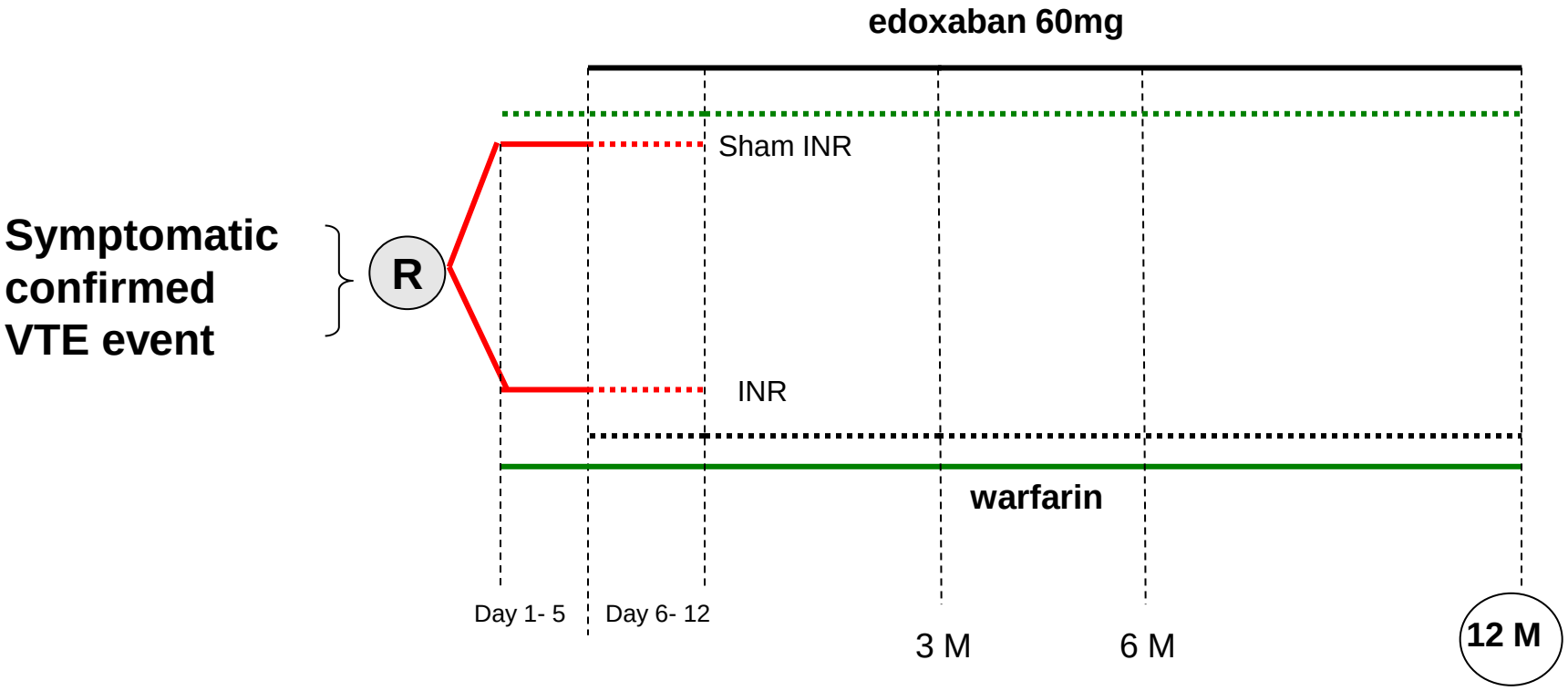
Double-blind study

Dose selection

- Phase 1 PK/PD
- Phase 2: prophylaxis and AF studies
- Population-PK modeling, logistic regression of PK exposure to bleeding events; and clinical trial simulations.

HOKUSAI Design

Randomized double blind study
with clinical outcomes



Heparin based initial treatment

..... **placebo warfarin**

..... **placebo edoxaban**

12 months of treatment or shorter ~ mitigating factors in subject's clinical status
But efficacy and safety data will need to be collected during the entire 12-month study period

Inclusion criteria

1. Male or female subjects older than the adult legal lower age limitation (country specific)
2. Site confirmed acute symptomatic proximal deep vein thrombosis (DVT) of the leg and/or symptomatic pulmonary embolism (PE)
3. Able to provide written informed consent

Stratification

1. Index event PE/DVT (≥40% PE patients)
2. Dose reduction
   a) Body weight ≤ 60 Kg
   b) Calculated CrCl 30 – 50 mL/min
   c) Concomitant use of strong PgP inhibitors
3. Transient (reversible) risk factors vs. idiopathic

A balanced randomization by region (local clinical practice) will be produced via the IXRS system

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Flexible treatment duration

At least 3 months

Risk-benefit in individual patient

Possibility to prolong or shorten intended duration

Active approach to ensure VKA quality

- POC device
  - Standardisation of test and reagent
- DMC review: TTR per center
- Time between INR measurements and time since out of range INR
- Blinded feedback to centers, plus advice and education
- Feedback on improvement
- Goal TTR above 60%

Unique study features

- Flexible treatment duration (3-12 months)
- Simulate usual clinical practice
- Strict INR monitoring and feedback
- Follow-up of all patients for 12 months
- Primary efficacy analysis at 12 months, regardless duration of therapy
- Large study; strict non-inferiority margin
- Global distribution

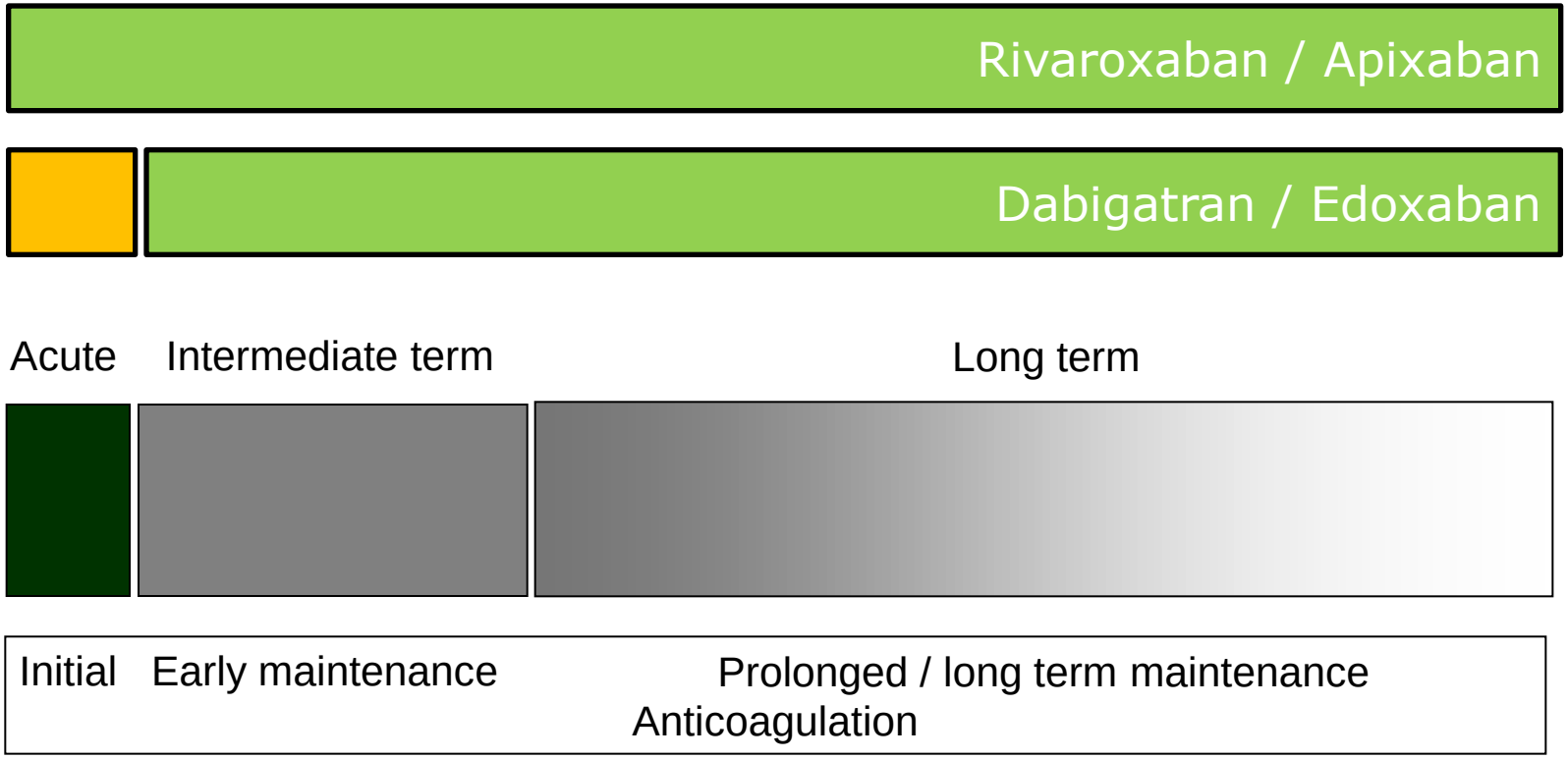
Sample size consideration

- Event driven
- Non-inferiority margin 1.5
- α = 0.05 (two-sided)
- 40% PE
- 80% power
- 7500 patients or more

Study conduct

- 437 active centers
- 37 countries (incl. Japan)
- Good distribution over Americas, Europe and Asia
- Recruitment finished in September 2012
- Follow-up almost finished
- Results to be awaited this year

Novel direct oral anticoagulants for treatment of VTE



Thank you

for your attention