Con il patrocinio di

Associazione Italiana Pneumologi Ospedalieri

Ospedale San Giuseppe
MultiMedica S.p.A.

PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

Clinica e laboratorio della malattia tromboembolica

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Ospedale Maggiore Policlinico di Milano

Milano, 18 Giugno 2016

Anticoagulant treatment in PE

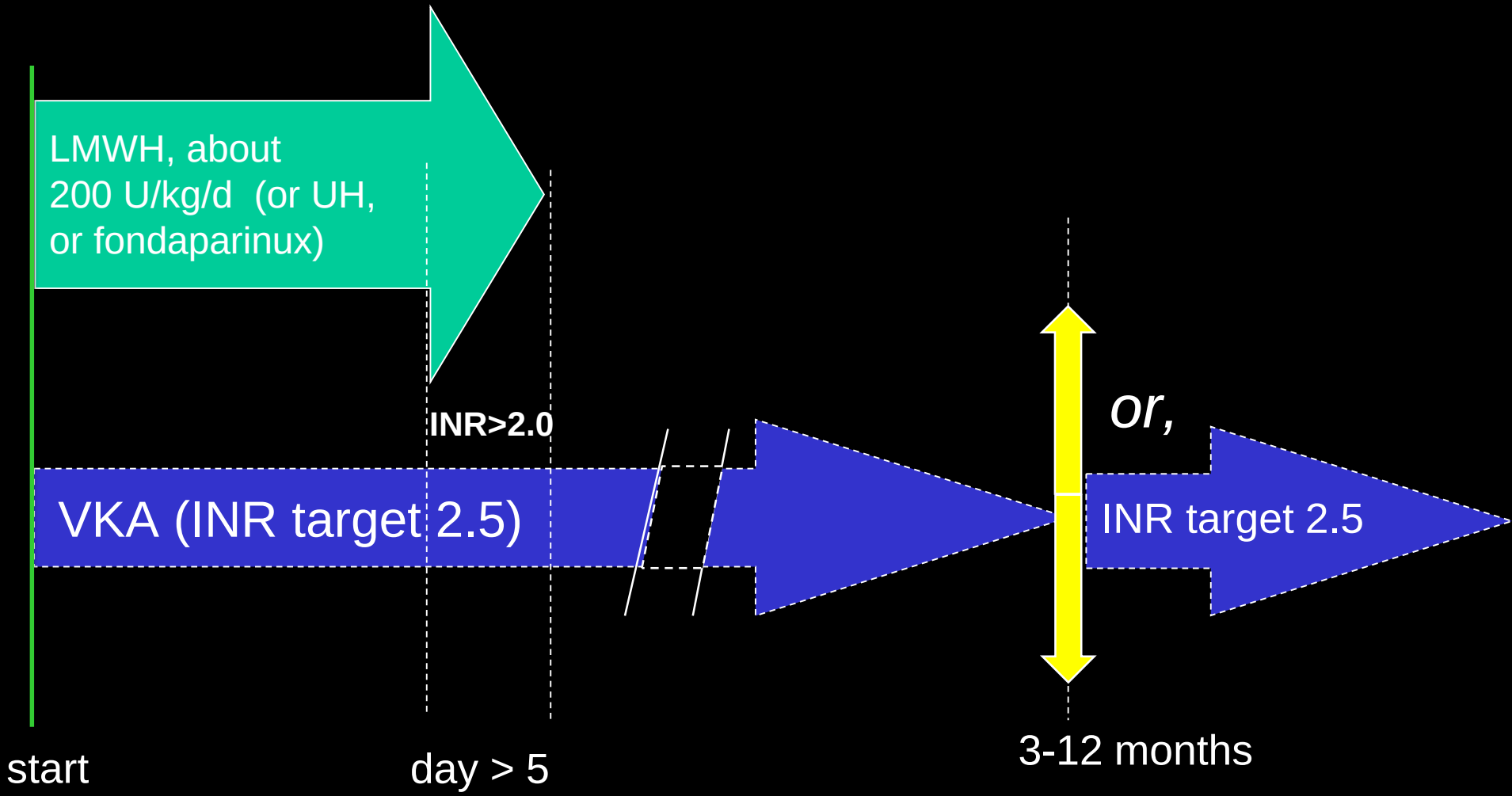
Goals

- To reduce the risk of death
- To reduce the risk of recurrence and pulmonary hypertension

by

- Reducing thrombus formation
  - At low risk of bleeding
  - Without admission

PE: standard treatment



Advantages of DOAC

- Rapid onset of action
- Specific coagulation enzyme target
- Low potential for food interactions
- Low potential for drug interactions
- **Predictable anticoagulant effect**

No need for bridging

Low risk of off-target adverse effects

No dietary precautions

Few drug restrictions

NO need for routine coagulation monitoring

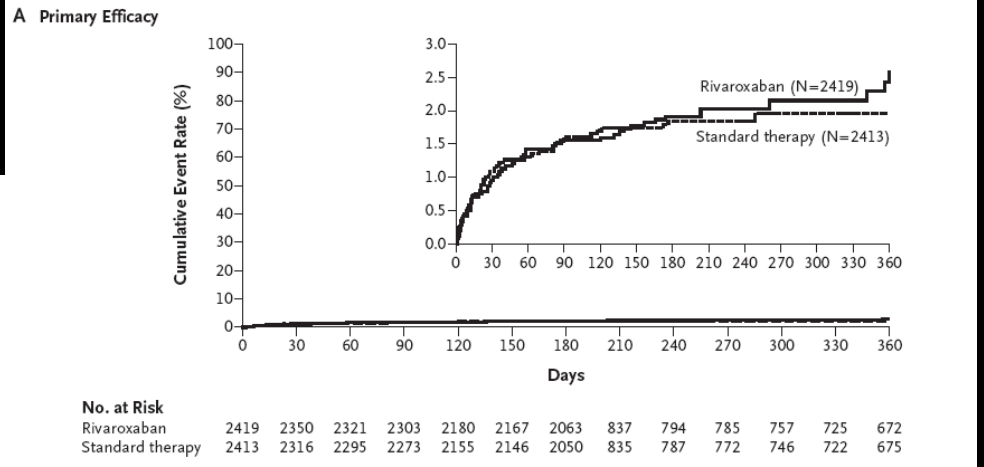
The NEW ENGLAND JOURNAL of MEDICINE

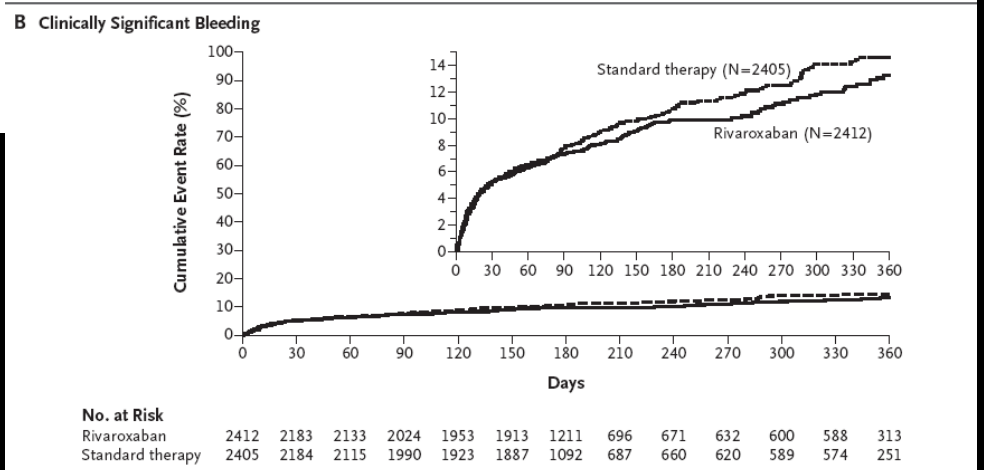
ORIGINAL ARTICLE

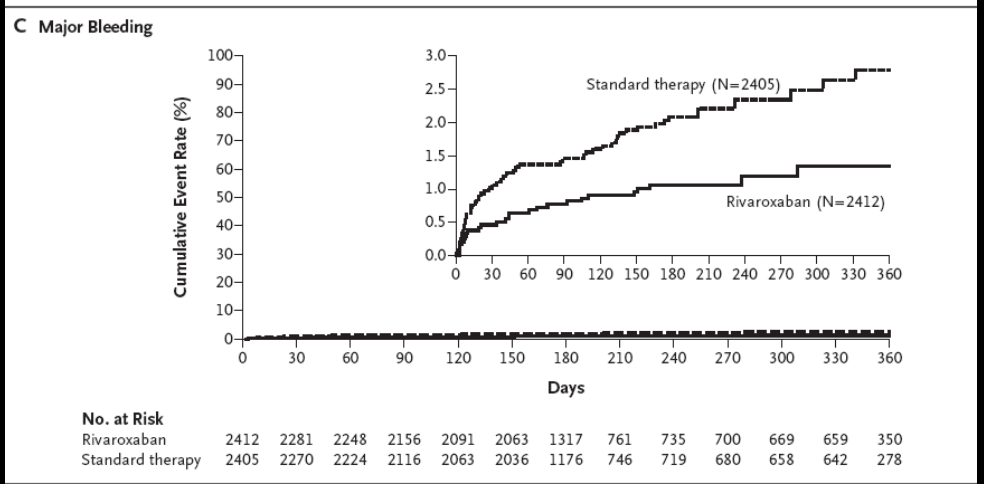
Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The EINSTEIN–PE Investigators*

N Engl J Med 2012







Study (DOAC)	N (patients)	Age (yrs)	Male sex (%)	Index PE, n (%)	Anatomical extent of PE (%)*	Design	Experimental treatment	Control treatment	Planned duration	TTR (%)
Acute treatment										
RE-COVER I (Dabigatran)	2,564	55	58	786 (31)	NR	DBRCNI	Heparin ≥5 days followed by DAB 150 mg BID	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)	6 months	60
RE-COVER II (Dabigatran)	2,589	55	61	816 (32)	NR	DBRCNI	Heparin ≥5 days followed by DAB 150 mg BID	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)	6 months	57
EINSTEIN DVT (Rivaroxaban)	3,449	56	57	23 (1)	NA	OLRCNI	RIV 15 mg BID for the first 3 weeks, followed by RIV 20 mg OD	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)	3, 6, or 12 months‡	57.7
EINSTEIN PE (Rivaroxaban)	4,833	58	53	4,833 (100)	Extensive: 24; intermediate: 58; limited: 13; missing: 5	OLRCNI	RIV 15 mg BID for the first 3 weeks, followed by RIV 20 mg OD	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)	3, 6, or 12 months‡	62.7
AMPLIFY (Apixaban)	5,400	57	59	1,836 (35)	Extensive: 37; intermediate: 43; limited: 9; missing: 11	DBRCNI	API 10 mg BID 7 days, followed by API 5 mg BID	Enoxaparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)	6 months	61
HOKUSAI-VTE (Edoxaban)	8,292	56	57	3,319 (40)	Extensive: 46; intermediate: 41; limited: 7; missing: 6	DBRCNI	Heparin ≥5 days followed by EDO 60 mg OD#	Heparin ≥5 days + warfarin dose-adjusted (INR: 2.0–3.0)	3 to 12 months‡	63.5
Extended treatment										
RE-MEDY (Dabigatran)	2,866	55	61	994 (35)	NR	DBRCNI	DAB 150 mg BID	Warfarin dose-adjusted (INR: 2.0–3.0)	18 months§	65
RE-SONATE (Dabigatran)	1,343	56	55	443 (33)	NR	DBRCS	DAB 150 mg BID	Placebo	6 months§	NA
EINSTEIN-EXTENSION (Rivaroxaban)	1,197	58	58	454 (38)	NR	DBRCS	RIV 20 mg OD	Placebo	6 or 12 months§	NA
AMPLIFY-EXT (Apixaban)	2,486	57	57	34	NR	DBRCS	API 2.5 mg and 5 mg BID	Placebo	12 months§	NA

Efficacy of DOAC in PE:
initial/long-term therapy *vs* standard treatment

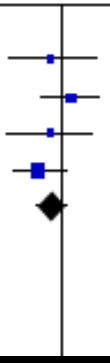
A

Study or subgroup	DOAC Events	DOAC Total	Standard treatment Events	Standard treatment Total	Weight	Risk ratio M-H, random, 95% CI
1 Index PE						
0102. POOL RE-COVER I–II	18	795	21	807	5.6%	0.87 (0.47, 1.62)
04. EINSTEIN PE	50	2,419	44	2,413	13.4%	1.13 (0.76, 1.69)
05. AMPLIFY	21	930	24	906	6.4%	0.85 (0.48, 1.52)
06. HOKUSAI-VTE	47	1,650	65	1,669	15.8%	0.73 (0.51, 1.06)
Subtotal (95% CI)		**5,794**		**5,795**	**41.2%**	**0.88 (0.70, 1.11)**
Total events	136		154			

Heterogeneity: tau^2 =0.00; chi^2 =2.51, df =3 (P=0.47); I^2 =0%

Test for overall effect: Z =1.06 (P=0.29)

Risk ratio M-H, random, 95% CI



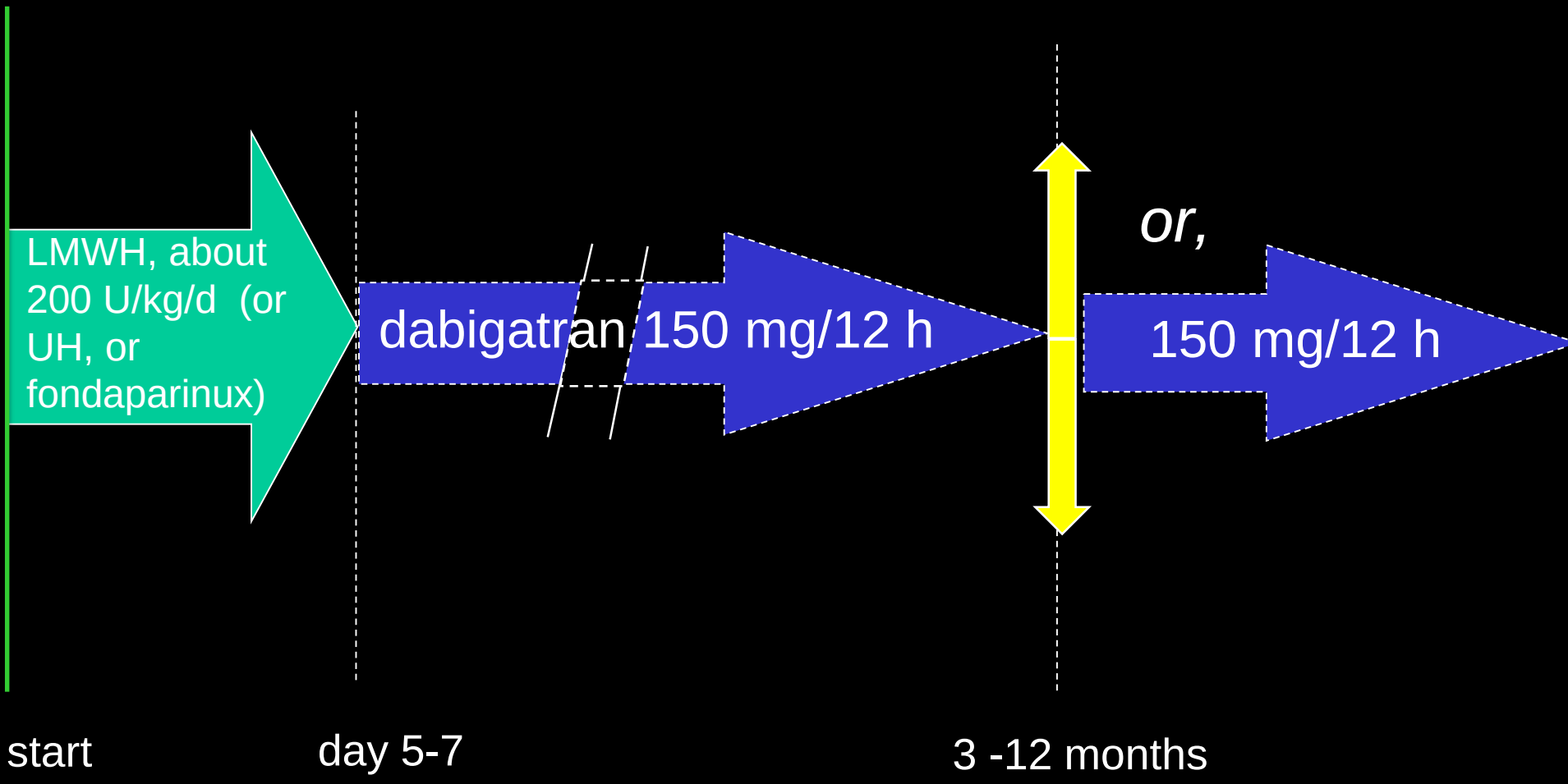
Are DOAC effective and safe in patients with PE ?

Yes !

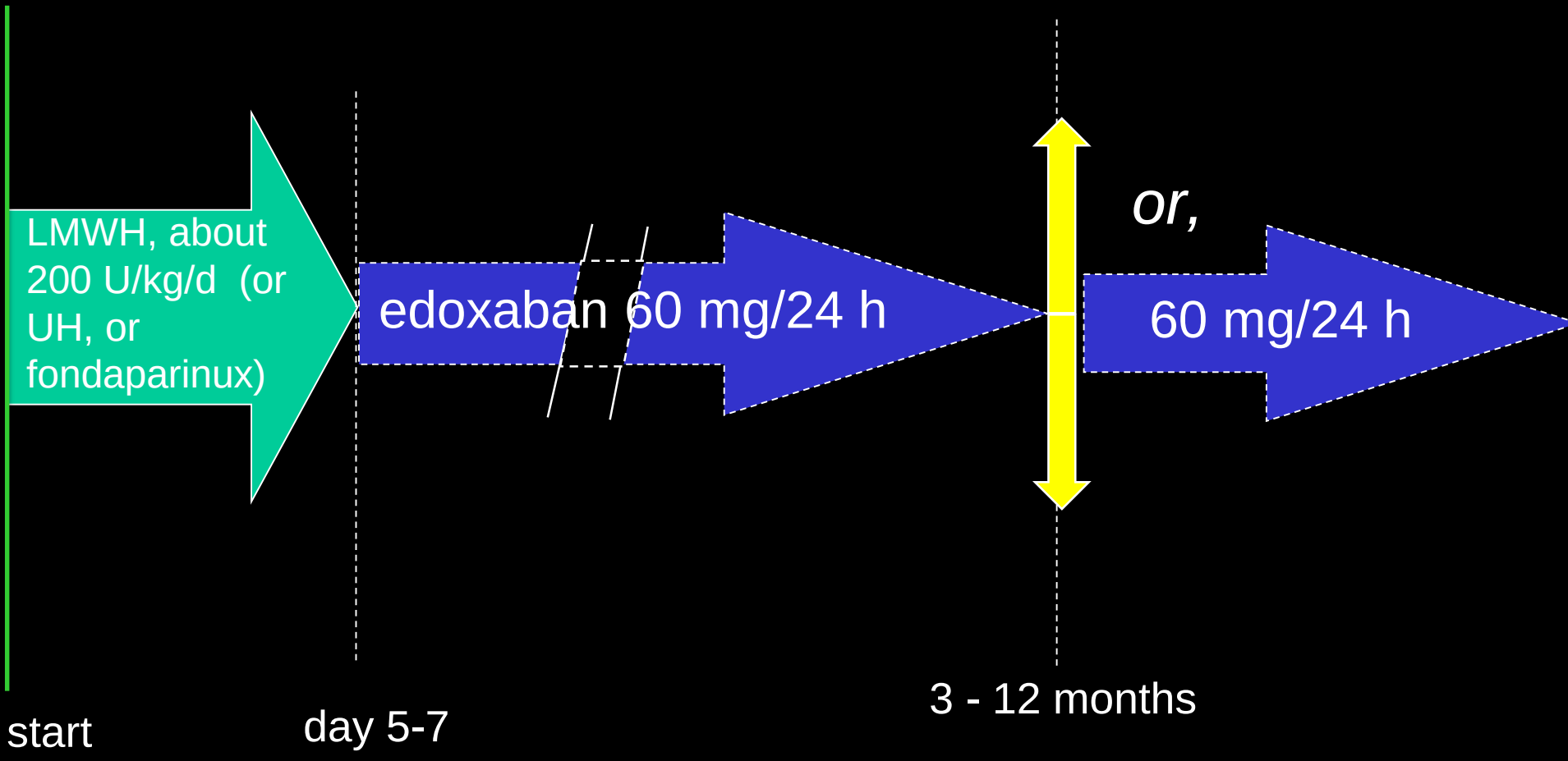
Heparin lead-in approach

dabigatran, edoxaban

Dabigatran


LMWH, about 200 U/kg/d (or UH, or fondaparinux)
dabigatran 150 mg/12 h
or,
150 mg/12 h
start
day 5-7
3 -12 months

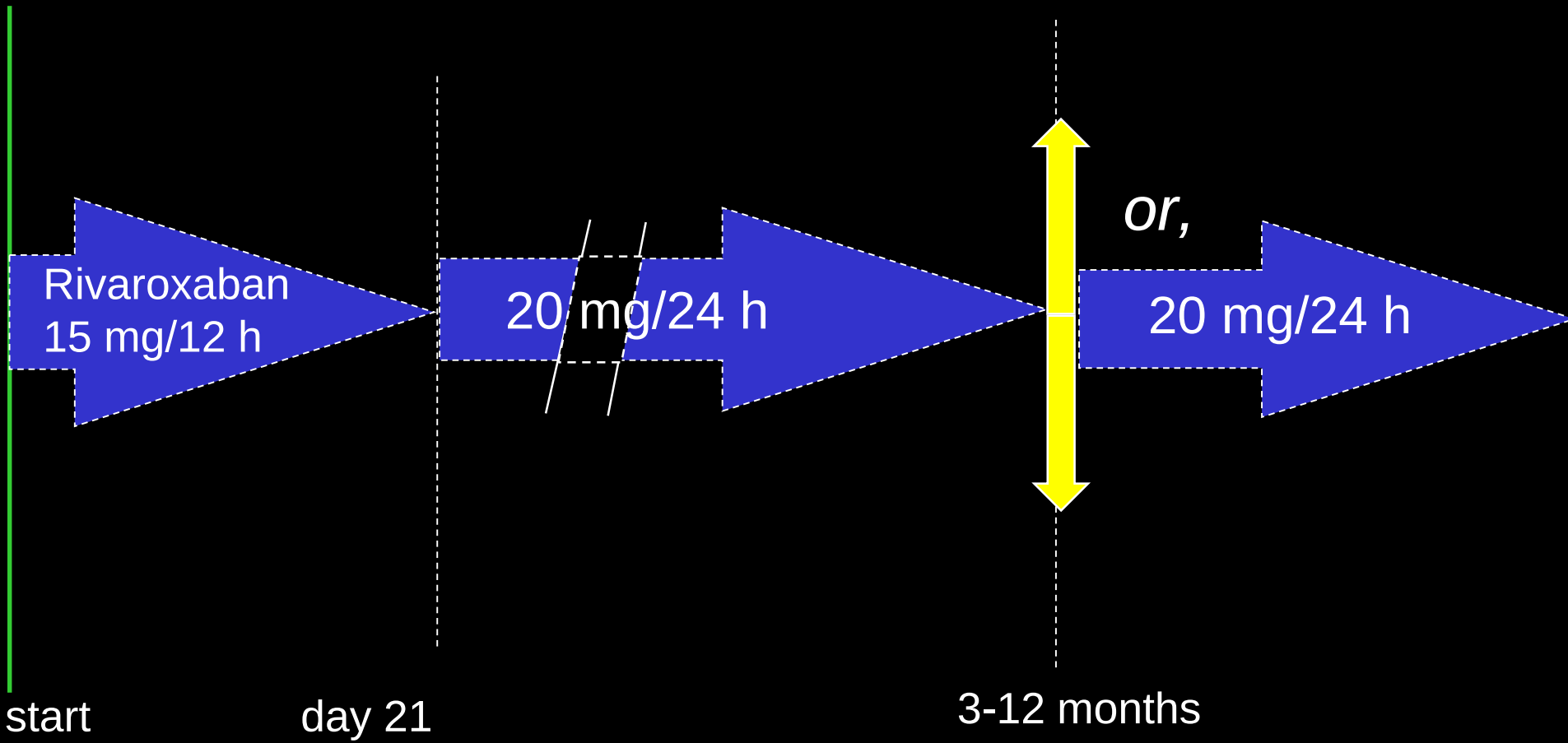
Edoxaban


LMWH, about 200 U/kg/d (or UH, or fondaparinux)
edoxaban 60 mg/24 h
or,
60 mg/24 h
start
day 5-7
3 - 12 months

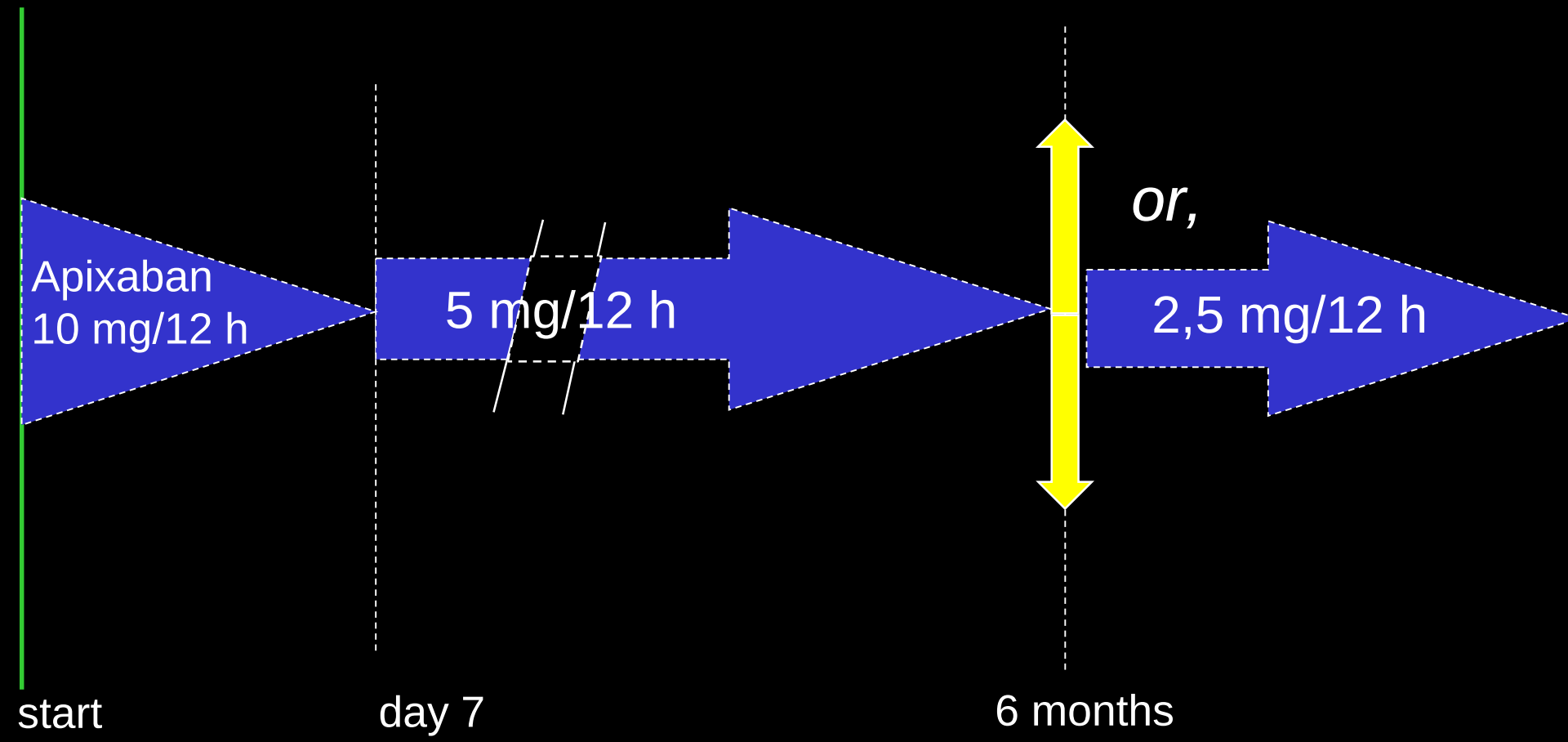
Single drug approach

rivaroxaban, apixaban

Rivaroxaban



Apixaban



Which patients should NOT be treated with DOAC

- Patients with prosthetic heart valves
- Patients with contraindications to DOAC (severe renal failure, severe liver diseases, thrombocytopenia,…)
- Patients with active bleeding or indication to surgery
- Pregnant and breast-feeding mothers

Anticoagulant treatment in PE: how long ?

- 3-6 months (removable risk factor factor, i.e surgery, pregnancy, contraceptive use…)
- Lifelong: recurrence; not-removable risk factor
- Case-by case basis (evaluate and explain the risk-benefit ratio)

To keep in mind

- Clinical conditions
- Quality, and adherence to treatment
- Side-effects of treatment
- Severity of PE, and of a possible recurrence
- Patients' preferences and environment
- Costs, availability
- Risk factors for recurrence

Prevalence of congenital defects

	general population	unselected VTE cases
Antithrombin defect	0.02 - 0.2 %	1 %
Protein C defect	0.1 - 0.5 %	3 %
Protein S defect	?	1 - 2 %
Factor V Leiden	**3 - 7 %**	**15 - 20 %**
Prothrombin G20210A	**2 - 5 %**	**6 - 15 %**

Relative risk

	Relative Risk increase
Antithrombin defect	5 - 50
Protein C defect	7 - 15
Protein S defect	6 - 10
Factor V Leiden	**5 - 8**
Prothrombin G20210A	**2 - 4**

Antiphospholipid syndrome (APS): a clinical and laboratory challenge

Antiphospholipid Antibodies

Definition

- *Lupus Anticoagulant (LA)*

  Heterogenous category of Ig able to prolong phospholipid-dependent clotting tests

- *Anti-cardiolipin, anti-β_2GPI*

  Heterogenous category of Ig able to bind protein-PL complexes, immobilized on solid-phase surfaces

Antiphospholipid Syndrome

Laboratory Diagnosis

- LA ***and*** solid-phase antiphospholipid antibodies (aCL and β_2-GPI) coexist in a limited proportion of patients with the syndrome

Diagnosis must be based on both LA and solid-phase antibodies detection

Why LA Laboratory detection is important/difficult ?

- *Important*

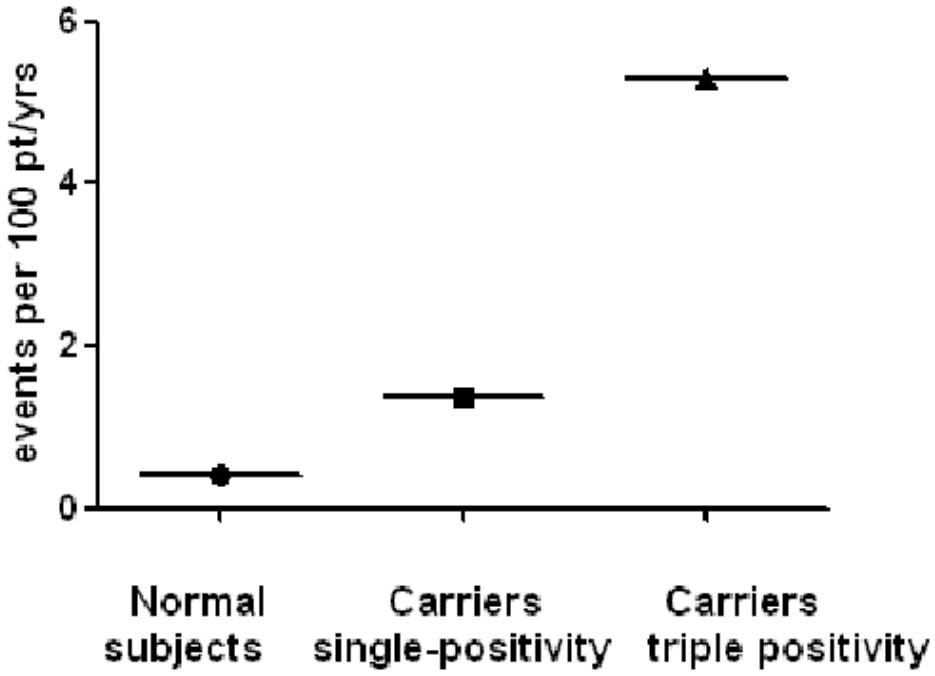
- Patients who are persistently LA-positive are candidates *for long term anticoagulation*

- *Difficult*

- There are no specific tests to detect LA
- Diagnosis is based on phospholipid-dependent clotting tests that are difficult to standardize

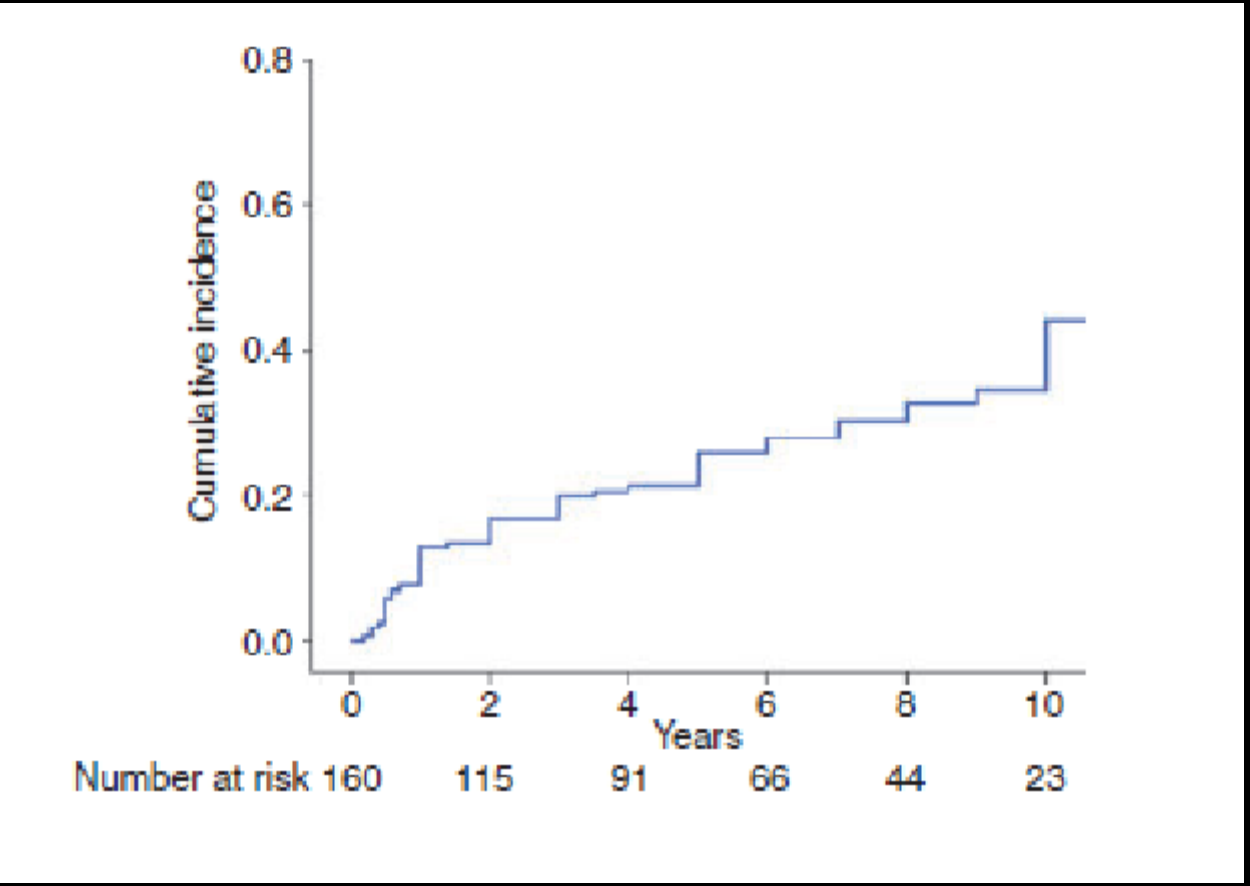
Risk for thrombosis in antiphospholipid antibody carriers

Pengo V et al, Blood 2011;118:4714-8



Average annual rates of first cardiovascular events (including VTE) in caucasian normal population (•); in single aPL positive carriers (■); and that shown in triple positive carriers in this study (▲).

Cumulative incidence of thromboembolic events in high risk triple positive APS patients (n=160)



Pengo V et al, JTH 2010;8:237-42

APS treatment in patients with VTE

- Heparin, LMWH, fondaparinux
- VKAs
  - Intensity (INR 2.0-3.0)
    - *Crowther M et al, NEJM 2003;349:1133-8*
    - *Finazzi JTH 2005;3:848-53*
- DOAC (case reports, ongoing studies)
- Duration of treatment ?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