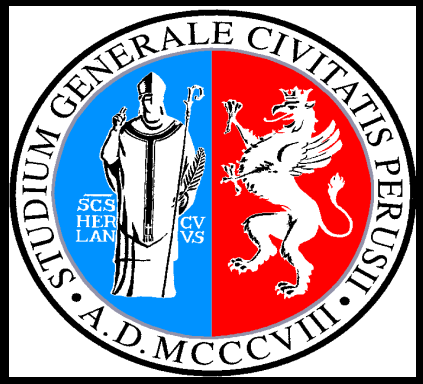
Acute and long-term treatment of PE

Cecilia Becattini

University of Perugia



Acute and long-term treatment of VTE

What is the optimal acute phase treatment for the patient?

- Intravenous thrombolysis
- One of the DOACs
- LMWH/fondaparinux
- UFH
- Perutaneous Embolectomy

PE: ESC model for risk stratification

2014 EUROPEAN SOCIETY OF CARDIOLOGY®

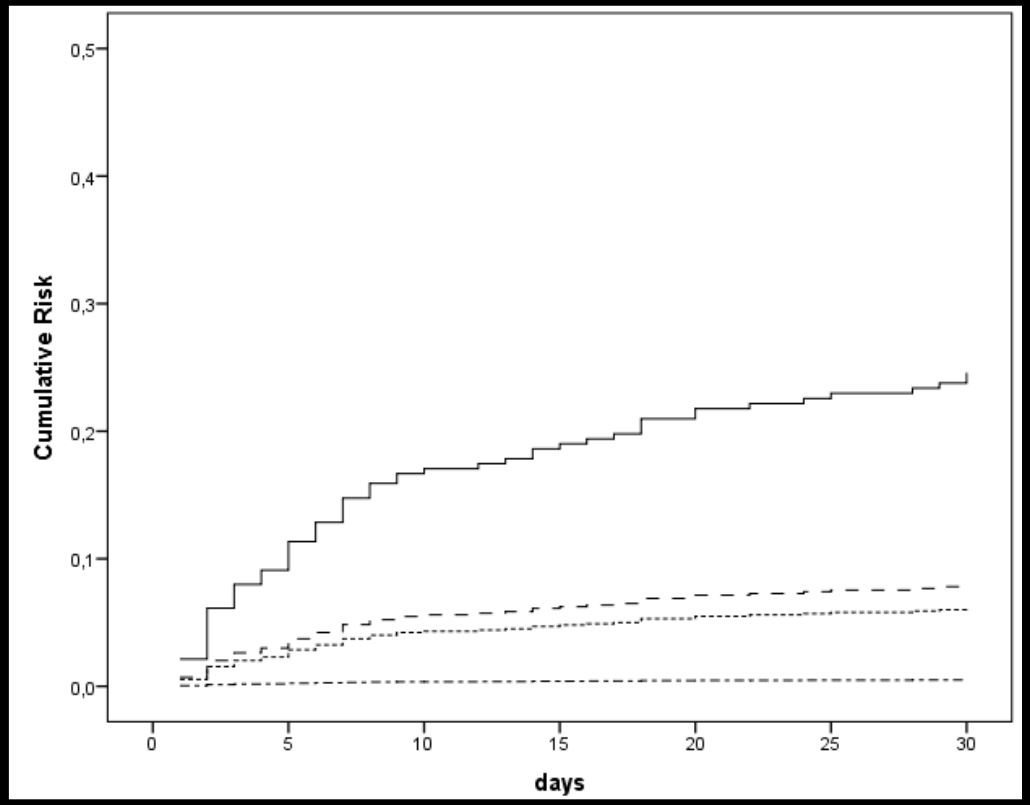
Classification of patients with acute PE based on early mortality risk

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI Class III-V or sPESI >1[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	-	+	Both positive	
	Intermediate–low	-	+	Either one (or none) positive[e]	
Low		-	-	Assessment optional; if assessed, both negative[e]	

Eur Heart J 2014

2014 ESC model… in clinical practice

906 patients with acute symptomatic objectively confirmed PE



30-day Mortality based on risk

High

Intermediate high

Intermediate low

Low

Becattini et al, *Eur Resp J 2016*

Tenecteplase for intermediate-high risk PE

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality or hemodynamic collapse within 7 days of randomization	13	(2.6)	28	(5.6)	0.015

Meyer G, N Eng J Med 2014

Tenecteplase for intermediate-high risk PE

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality within 7 days	6	(1.2)	9	(1.8)	0.43
Hemodynamic collapse within 7 days	8	(1.6)	25	(5.0)	0.002
Major	32	(6.3)	6	(1.5)	<0.001
Hemorrhagic stroke	10		1		

Meyer G, N Eng J Med2014

Ultrasound-facilitated CDT for PE

150 patients with proximal PE and right ventricle dilation at CT

	pre-procedure	48-h	p
Mean RV/LV diameter ratio	1.55	1.13	<0.0001
Mean PA systolic pressure	51.4	36.9	<0.0001
Mean modified Miller index	22.5	15.8	<0.0001

GUSTO severe bleeding	1 patient (0.5%)
GUSTO moderate bleeding	15 patients (10%)

Piazza G, JACC 2015

Interventional procedures for PE

- ✓ Limited number of controlled studies
- ✓ No evidence of reduction in mortality
- ✓ Risk for peri-procedural complications
- ✓ Long-term benefit of early HD improvement not well established

ESC Guidelines: clinical management

2014 EUROPEAN SOCIETY OF CARDIOLOGY®

PE without shock or hypotension (intermediate or low risk)[c]		
Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients without shock or hypotension.	III	B
Close monitoring is recommended in patients with intermediate-high-risk PE to permit early detection of haemodynamic decompensation and timely initiation of rescue reperfusion therapy.	I	B
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B
Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients, if the anticipated risk of bleeding under thrombolytic treatment is high.[f]	IIb	C
Percutaneous catheter-directed treatment may be considered in intermediate-high-risk patients, if the anticipated risk of bleeding under thrombolytic treatment is high.[f]	IIb	B

Acute and long-term treatment of VTE

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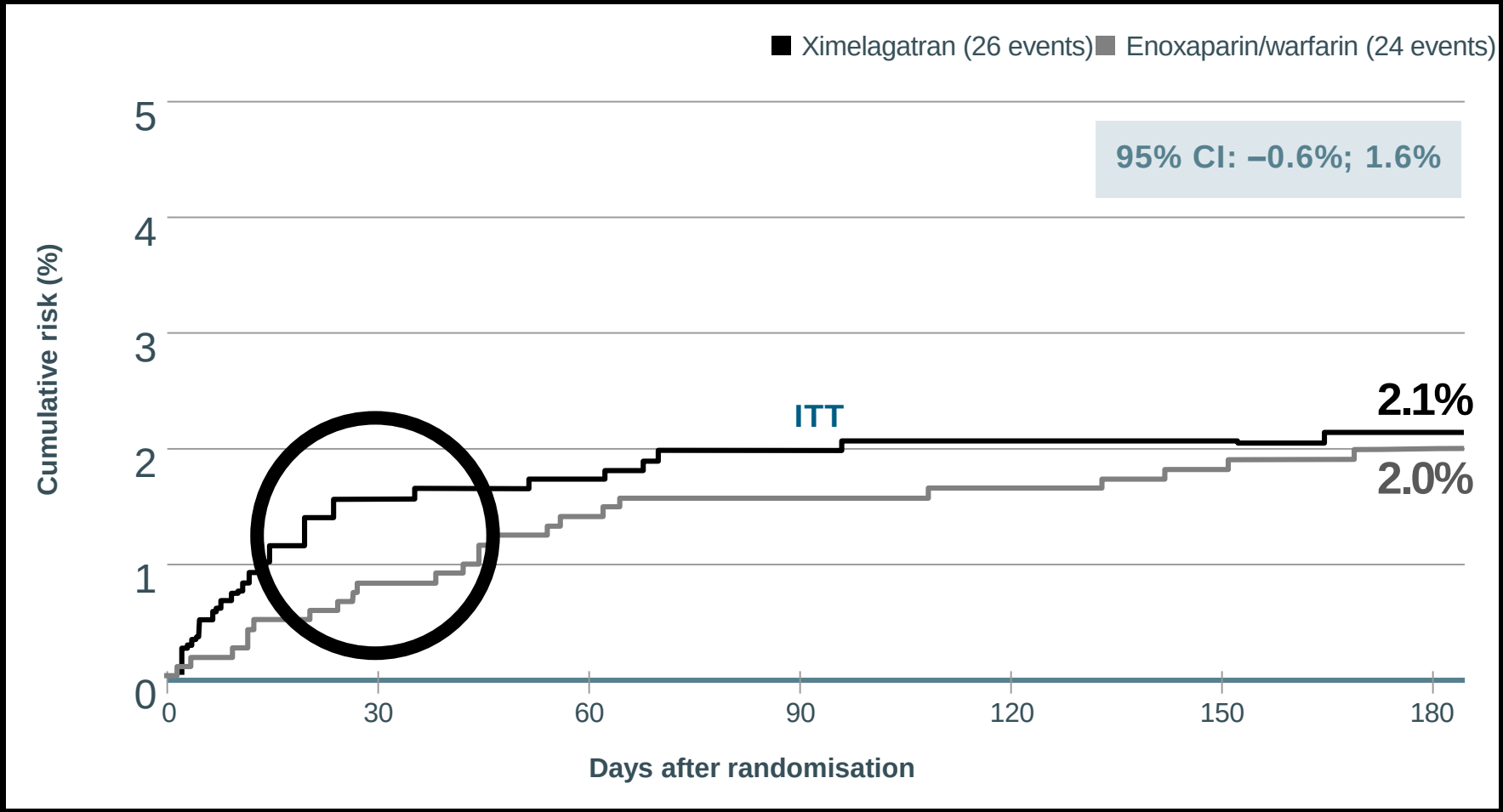
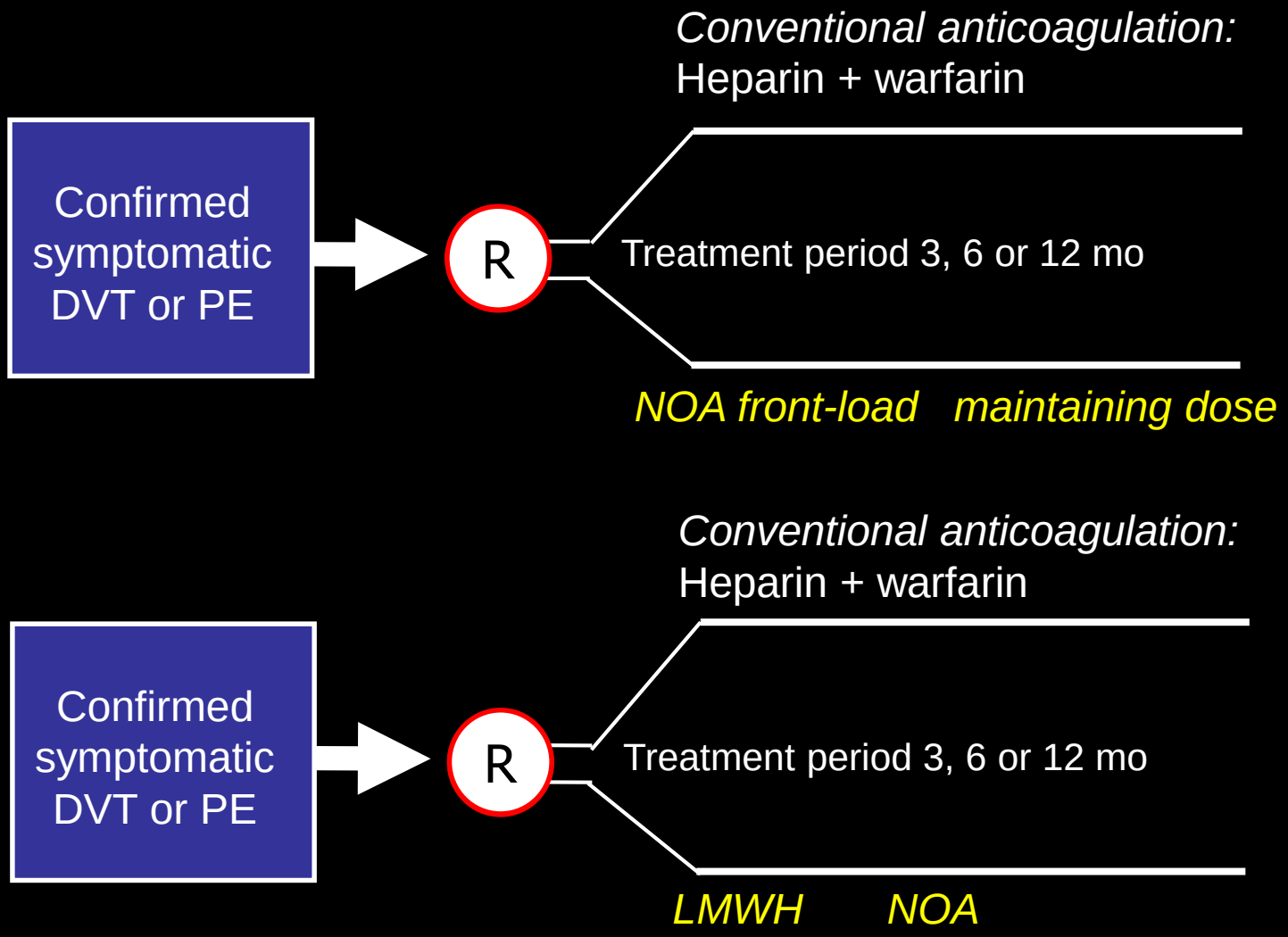
Treatment for PE & DVT

THRIVE TREATMENT



Fiessinger J-N et al. JAMA 2005;293:681–689

NOACs in VTE: study design



NOACs in pulmonary embolism

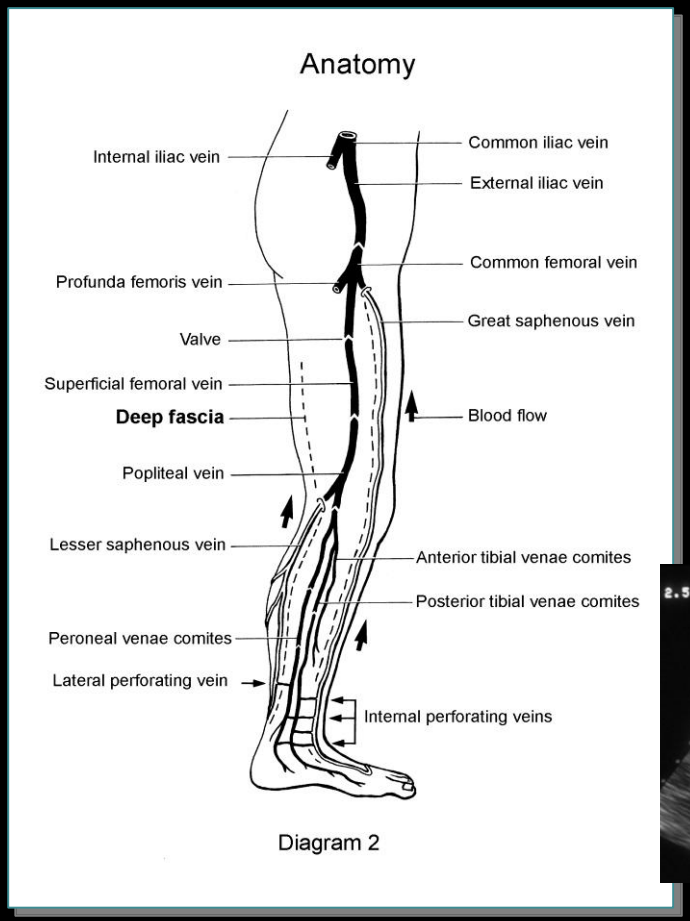
5 phase III studies included: 11,539 patients

	OR	95% CI
Recurrent VTE	0.89	(0.70-1.12)
anti-Xa	0.89	(0.69-1.15)
anti-IIa	0.87	(0.46-1.64)
Major Bleeding*	0.30	(0.10-0.95)
Clinically Relevant Bleeding*	0.89	(0.77-1.03)

* two studies included

Vedovati MC et al, Int J Cardiol 2014

NOACs: across the VTE spectrum



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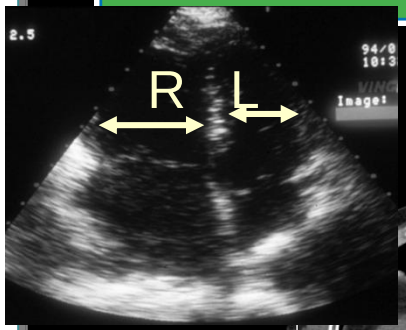
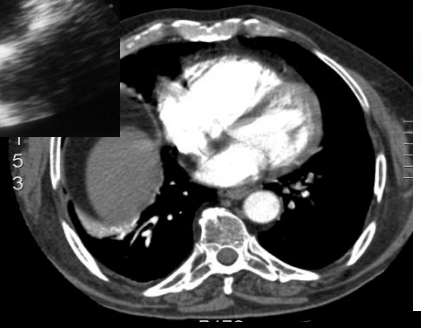
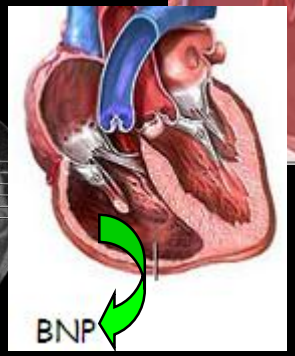
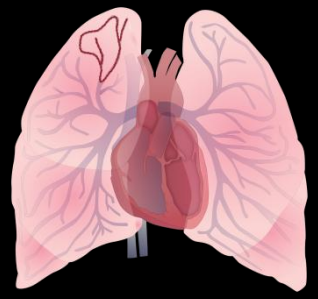




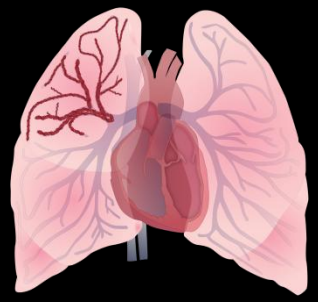


PE: anatomical extent of PE as defined in NOACs trials

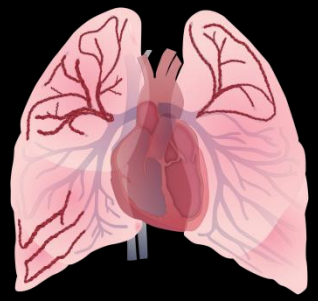
- Limited extent
  - ≤25% of the vasculature of a single lobe



- Intermediate extent
  - >25% of vasculature of a single lobe or multiple lobes with ≤25% of entire vasculature

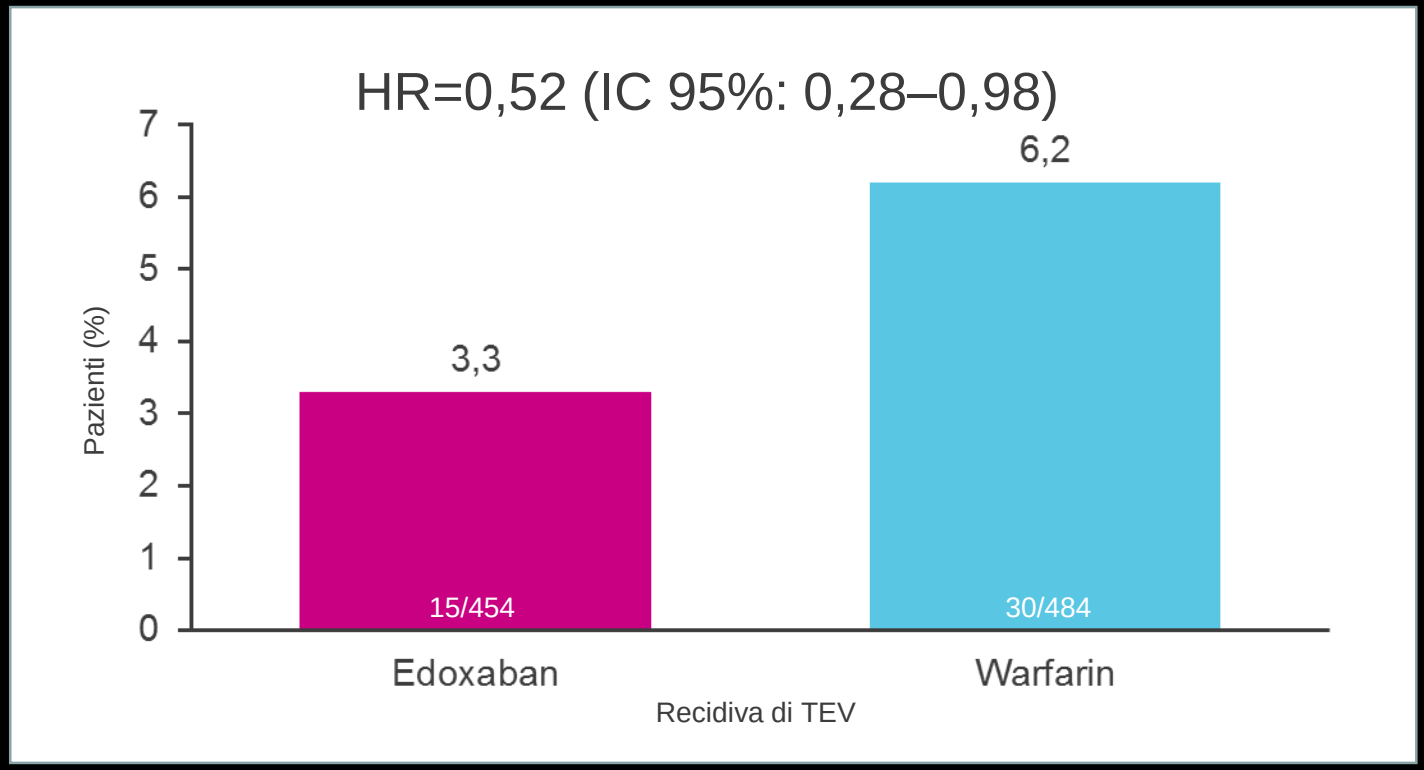


- Extensive extent
  - multiple lobes with ≥25% of entire vasculature



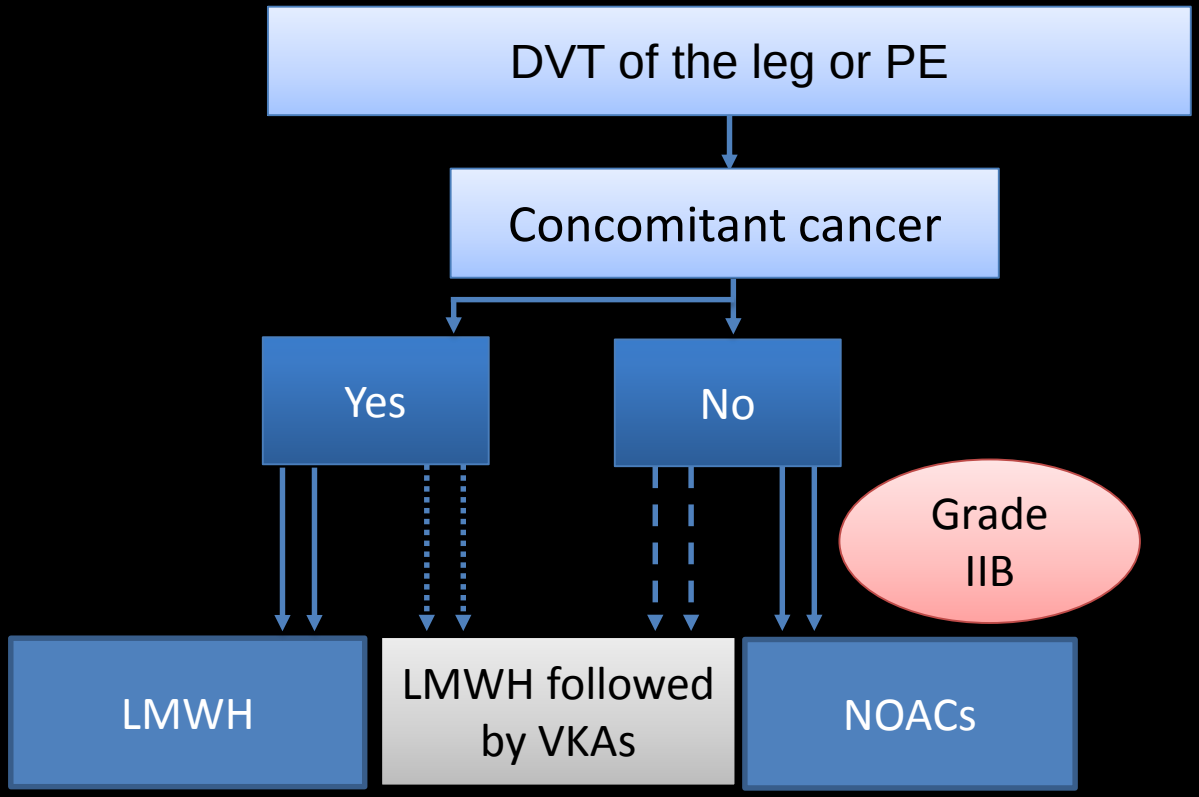
The Hokusai-VTE Investigators. N Engl J Med 2013

Edoxaban in PE patients with increased BNP



The Hokusai-VTE Investigators. N Engl J Med 2013

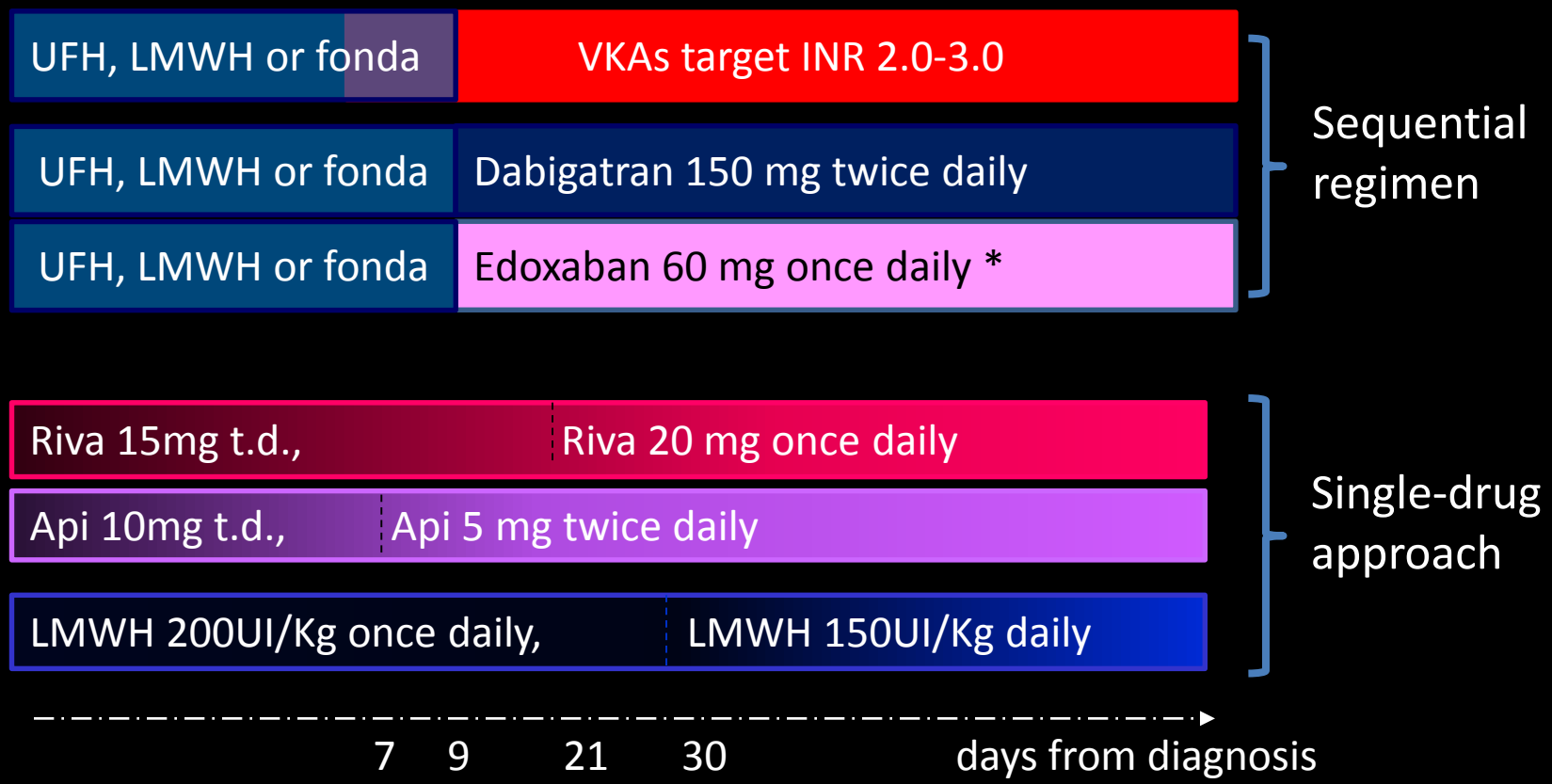
The CHEST guidelines



***Same grade of recommendation for different NOACs**

Clive Kearon,et al. Chest 2016

Treatment for VTE: agents & regimens



*To be reduced to 30mg once daily if creatinine clearance of 30 to 50 ml/min or body weight <60Kg

Becattini C, in press

Acute and long-term treatment of VTE

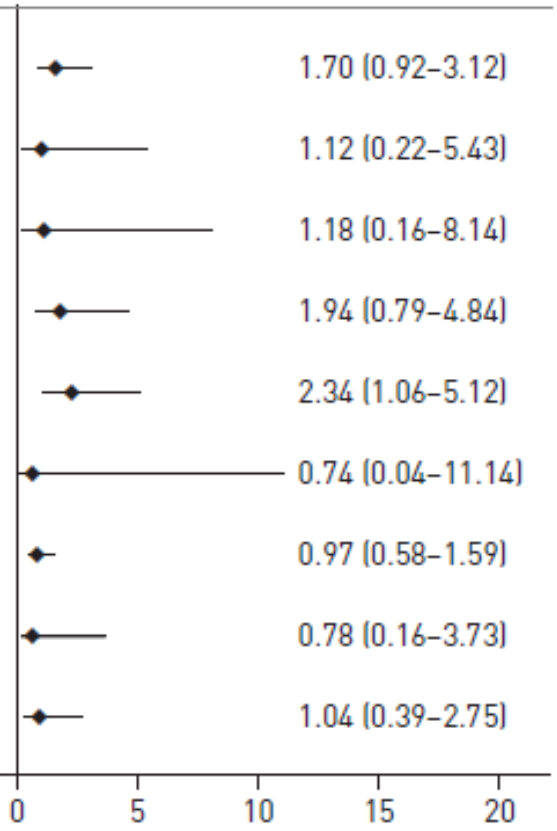
Is that the adequate patient for home

treatment?

PE: 3-month outcome of home treatment

13 studies (1657 patients) with outpatients (<24 h),
3 studies (256 patients) with early discharge (<72 h)
5 studies (383 patients) with inpatients

Outcome	Cohort	Studies n	Patients n	Events n	Absolute risk % (95% CI)
Recurrence	Home treatment	13	1657	33	1.70 (0.92–3.12)
Recurrence	Early discharge	3	256	3	1.12 (0.22–5.43)
Recurrence	Hospital treatment	4	329	6	1.18 (0.16–8.14)
Mortality	Home treatment	13	1657	49	1.94 (0.79–4.84)
Mortality	Early discharge	3	256	6	2.34 (1.06–5.12)
Mortality	Hospital treatment	5	383	8	0.74 (0.04–11.14)
Bleeding	Home treatment	12	1555	15	0.97 (0.58–1.59)
Bleeding	Early discharge	3	256	2	0.78 (0.16–3.73)
Bleeding	Hospital treatment	5	383	4	1.04 (0.39–2.75)



Zondag W et al., Eur Resp J 2013

PE: home treatment

	Aujesky et al	Zondag et al	Agterof et al	Otero et al	HoT PE ongoing
Design	Open-label, RCT	Prospective cohort	Prospective cohort	Open-label, RCT	Prospective cohort, phase IV
Eligibility criteria					
Systolic BP	≥100 mmHg	≥100 mmHg	≥90 mmHg	≥90 mmHg	≥100 mmHg
Clinical prediction rule	PESI class I or II	Hestia	-	Uresandi 0-2	Modified Hestia
Biomarkers	No	No	NT-proBNP	Troponin T	No (analysis planned)
Absence of RVD	No	No	No	TTE	CT or TTE
Renal function	CrCl ≥30	CrCl ≥30	Creatinine <150 umol/L	No	CrCl ≥15
Platelet count	≥75 000/mm^3	-	-	-	-
Body weight	≤150 kg	-	-	BMI <30 kg/m^2	
Respiratory function	SaO_2 ≥90%, or PaO_2 ≥60 mmHg	SaO_2 >90% in air	SaO_2 >90% in air	SaO_2≥ 93%; NYHA I or II; severe COPD	SaO_2 >90% in air
Others	No history of HIT	No history of HIT; no hepatic impairment	-	No surgery <15 days	No history of HIT; no severe hepatic impairment
Time of discharge	<24 h vs inpatient management	<24 h	<24 h	3- to 5-day vs inpatient	≤48 h of admission

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

5.5. In patients with low-risk PE and whose home circumstances are adequate, we suggest early discharge over standard discharge (eg, after first 5 days of treatment) (Grade 2B).

Remarks: Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment.

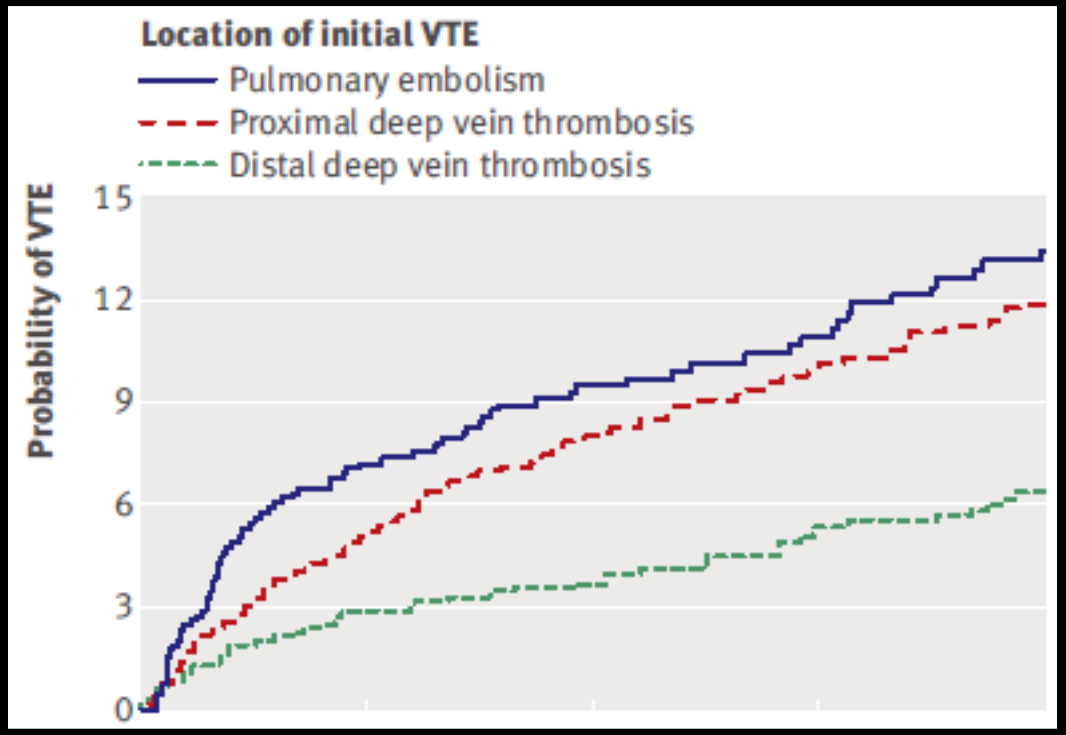
Acute and long-term treatment of VTE

How long would you treat this patient?

- 3 months
- 6 to 12 months
- indefinitely

Venous Thromboembolism: risk of recurrence

Analysis of individual data from 2925 patients from 7 trials
1177 patients with temporary risk factors for VTE

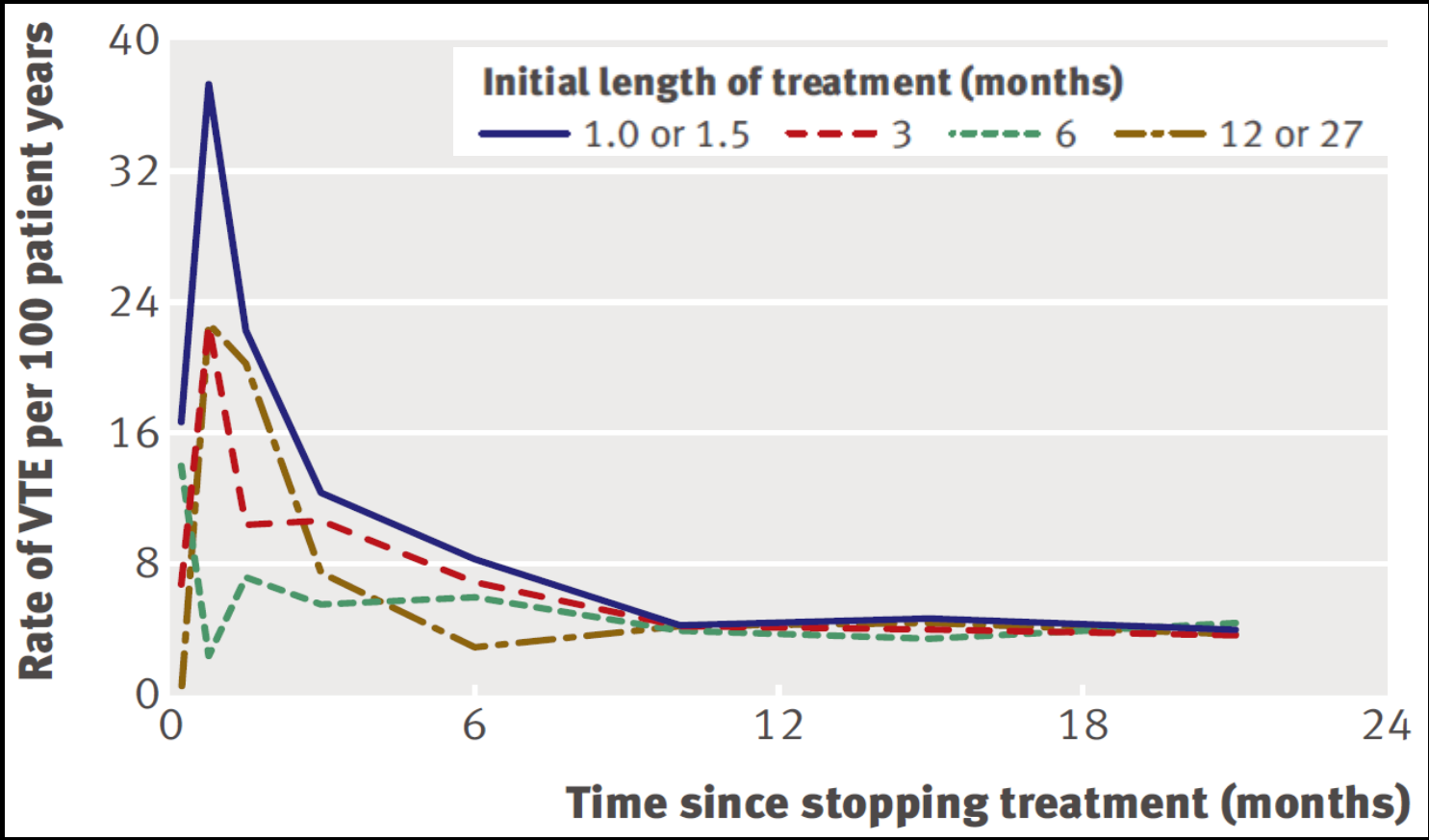


Proximal DVT vs. PE HR 1.19, 95% CI 0.87 to 1.63

Boutitie, BMJ 2011

Recurrent VTE after stopping VKAs

Individual patient-level meta-analysis of 7 RCTs on the ‘optimal duration’



Boutitie et al., BJM 2011

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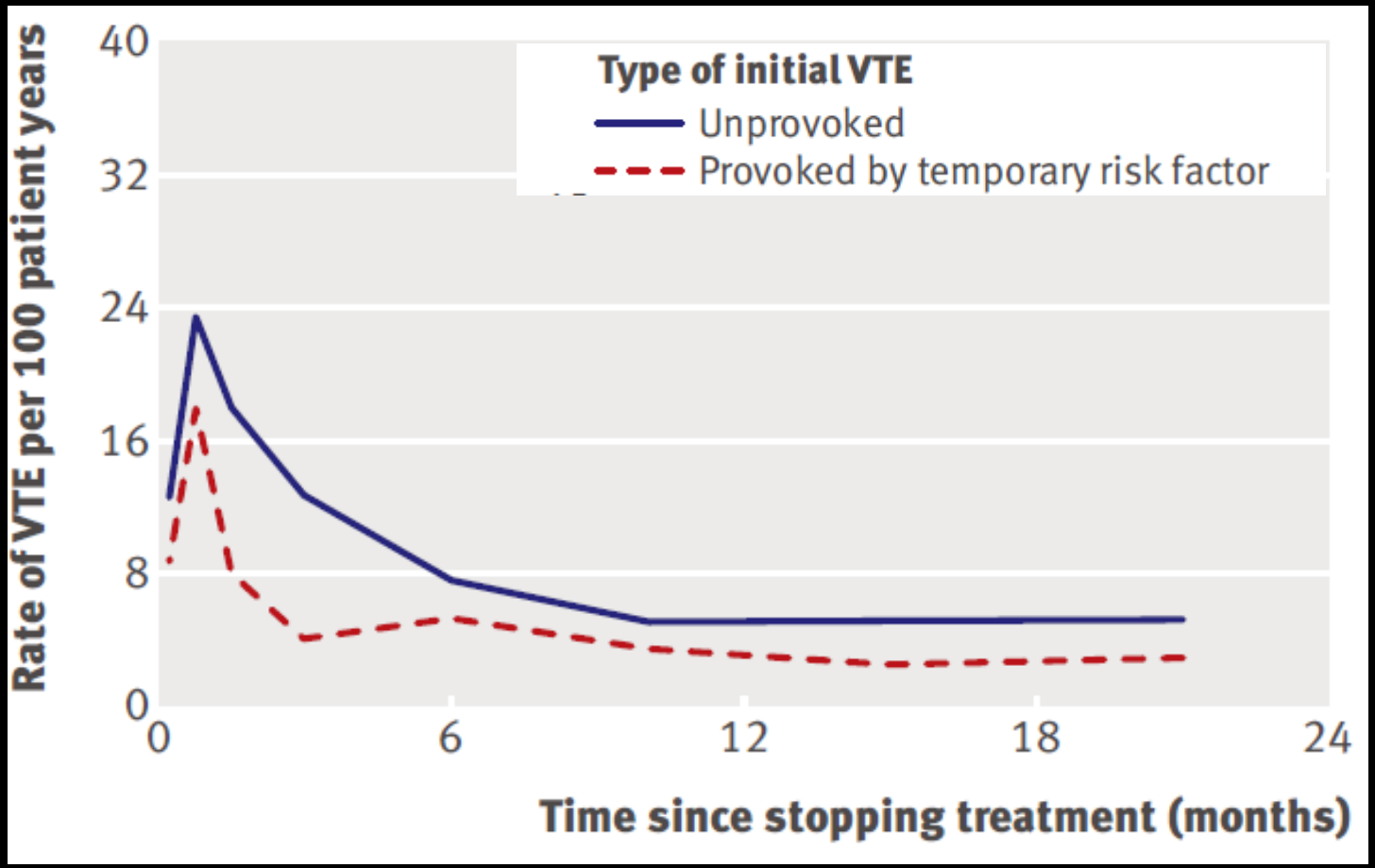
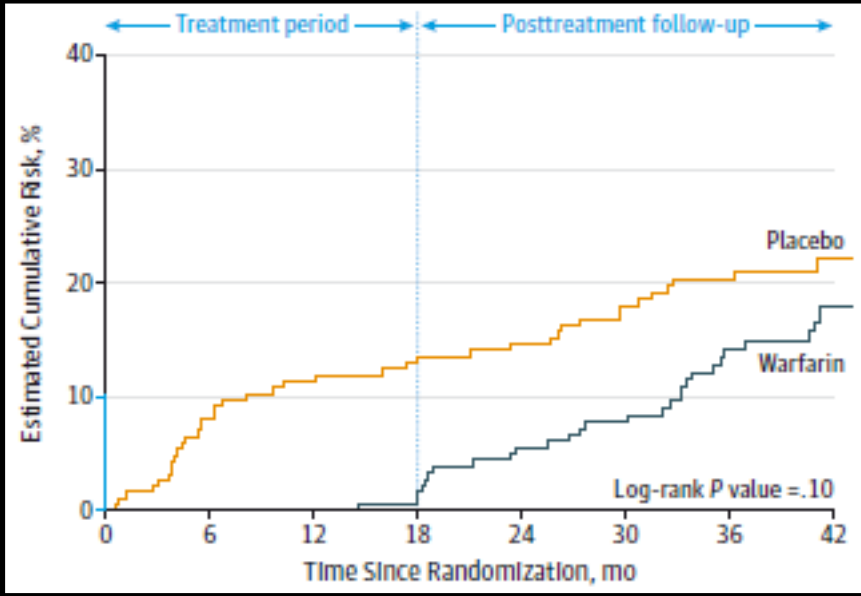


Boutitie et al., BJM 2011

Treatment duration for unprovoked PE

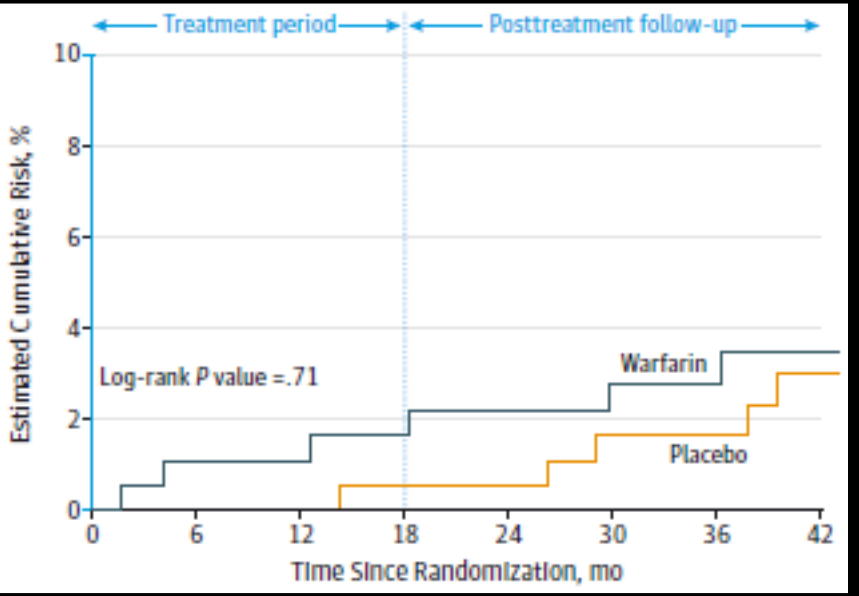
384 PE patients randomized to 18-month warfarin or placebo after 6 uninterrupted months of anticoagulant treatment

Recurrent VTE



On treat HR 0.15; 95%CI 0.05-0.43
Overall HR 0.69; 95% CI 0.42-1.12

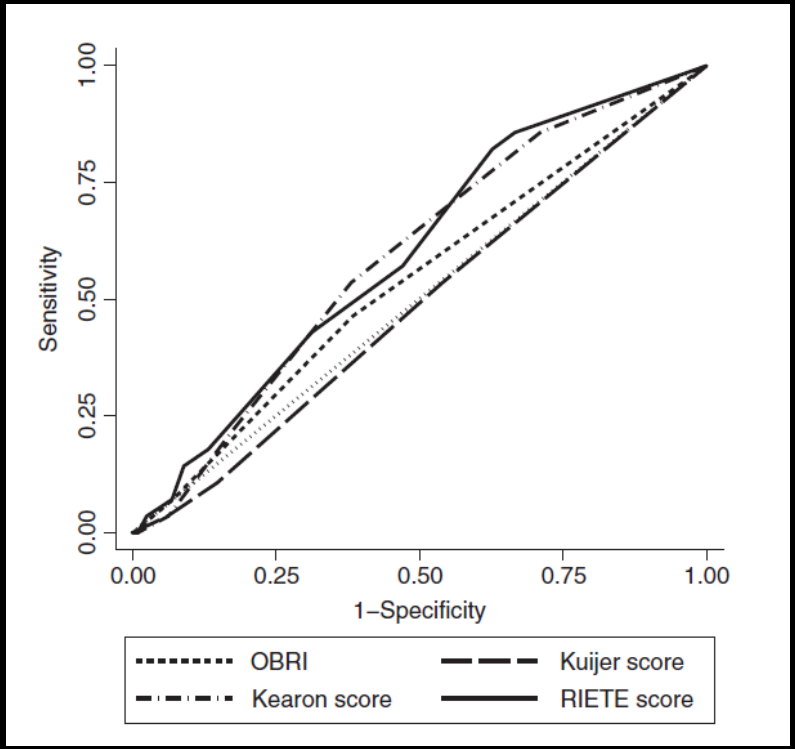
Major bleeding

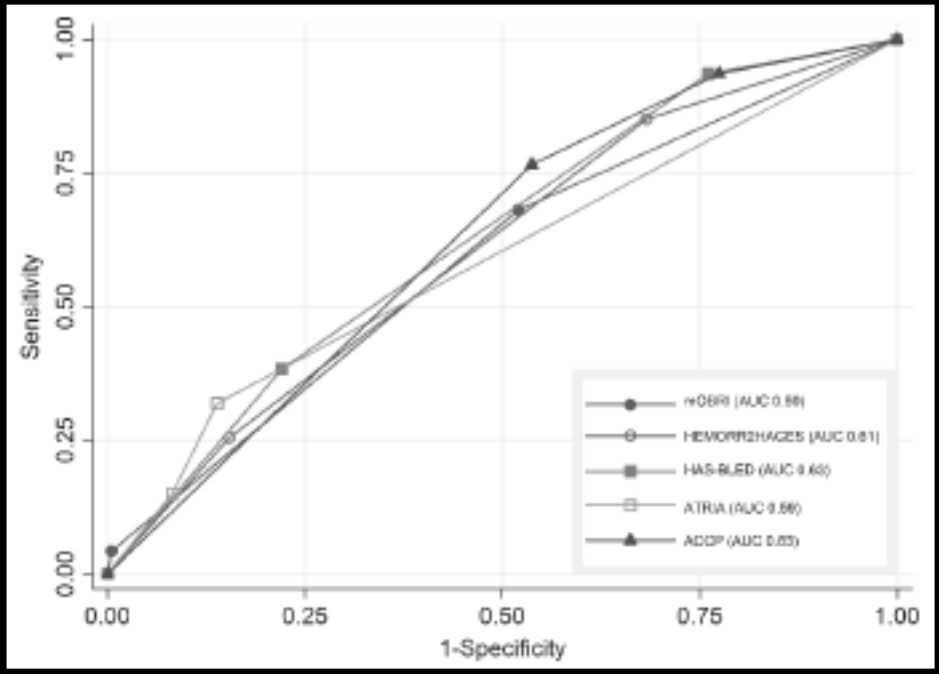


On treat HR 3.96; 95%CI 0.44-35.89
Overall HR 1.12; 95% CI 0.34-3.71

Couturaud F, JAMA 2015

Prediction of warfarin-associated bleeding in VTE





model	PPV, %	NPV, %	AUC
OBRI	**4.3**	**96**	**0.54**
Kuijer	**3.1**	**96**	**0.49**
Kearon	**5.2**	**96**	**0.59**
Riete	**6.6**	**96**	**0.60**

Scherz et al, J Thromb Haemost 2013

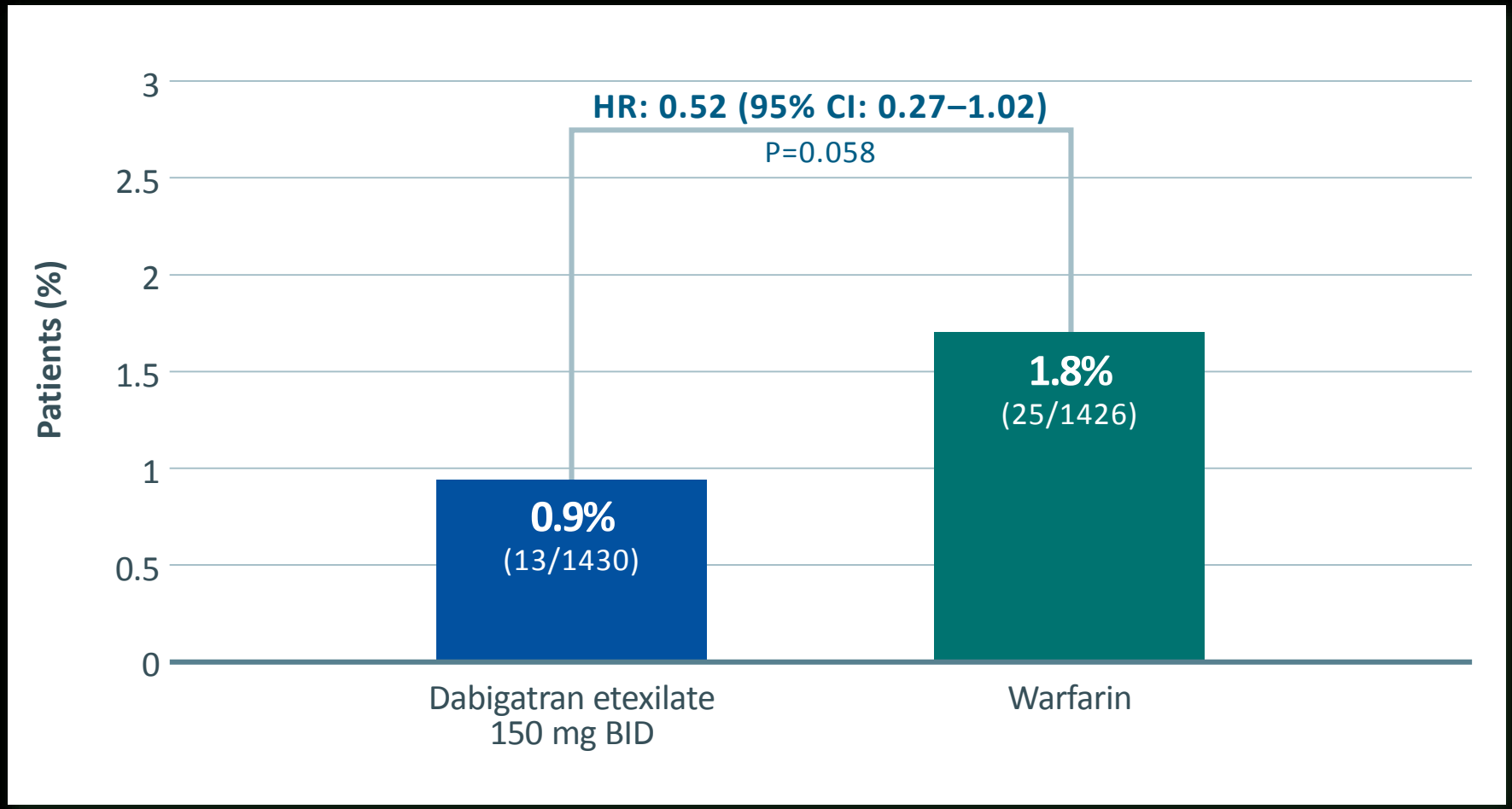
model	PPV, %	NPV, %	AUC
mOBRI	**9.4**	**95**	**0.59**
Hemorr2hages	**7.8**	**95**	**0.56**
HASBLED	**8.9**	**98**	**0.63**
ATRIA	**15.5**	**94**	**0.59**
ACCP	**8.8**	**98**	**0.63**

Riva et al, Thromb Haemost 2014

Venous Thromboembolism: risk of recurrence

First episode		Annual rec rate (%)	Recommended VKAs duration
Idiopathic/unprovoked		5	3 mos/indefinite
Associated with	Temporary RF	2	3 months
	Cancer	10	indefinite
	Thrombophilia	5	3 mos/indefinite
Recurrent episodes		10	indefnite

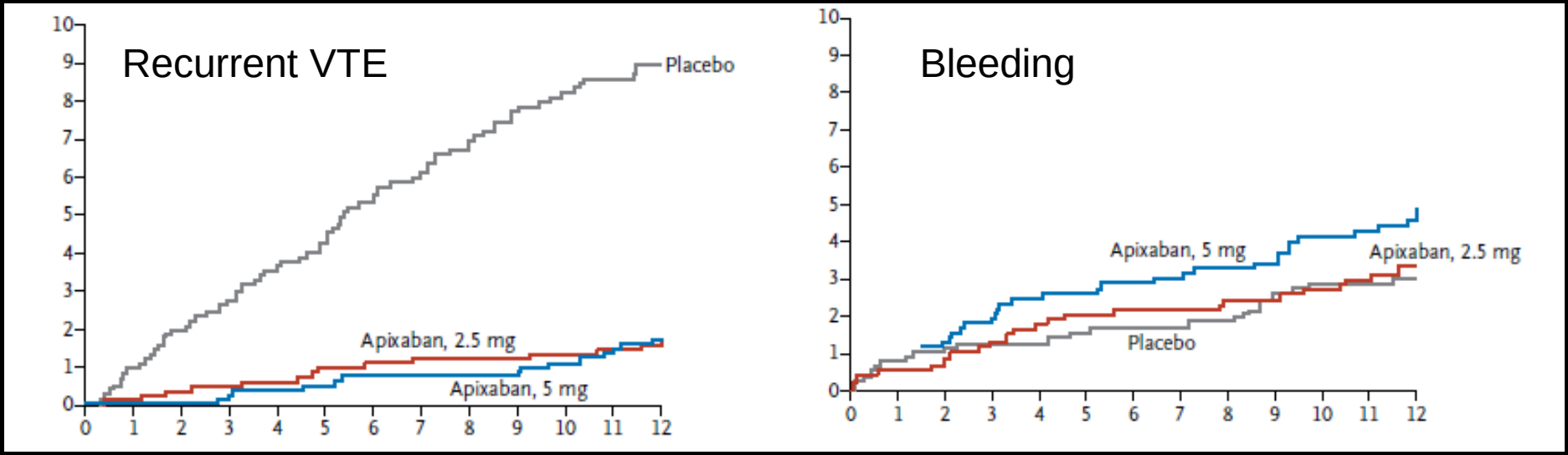
Dabigatran: safety of Extended VTE treatment



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

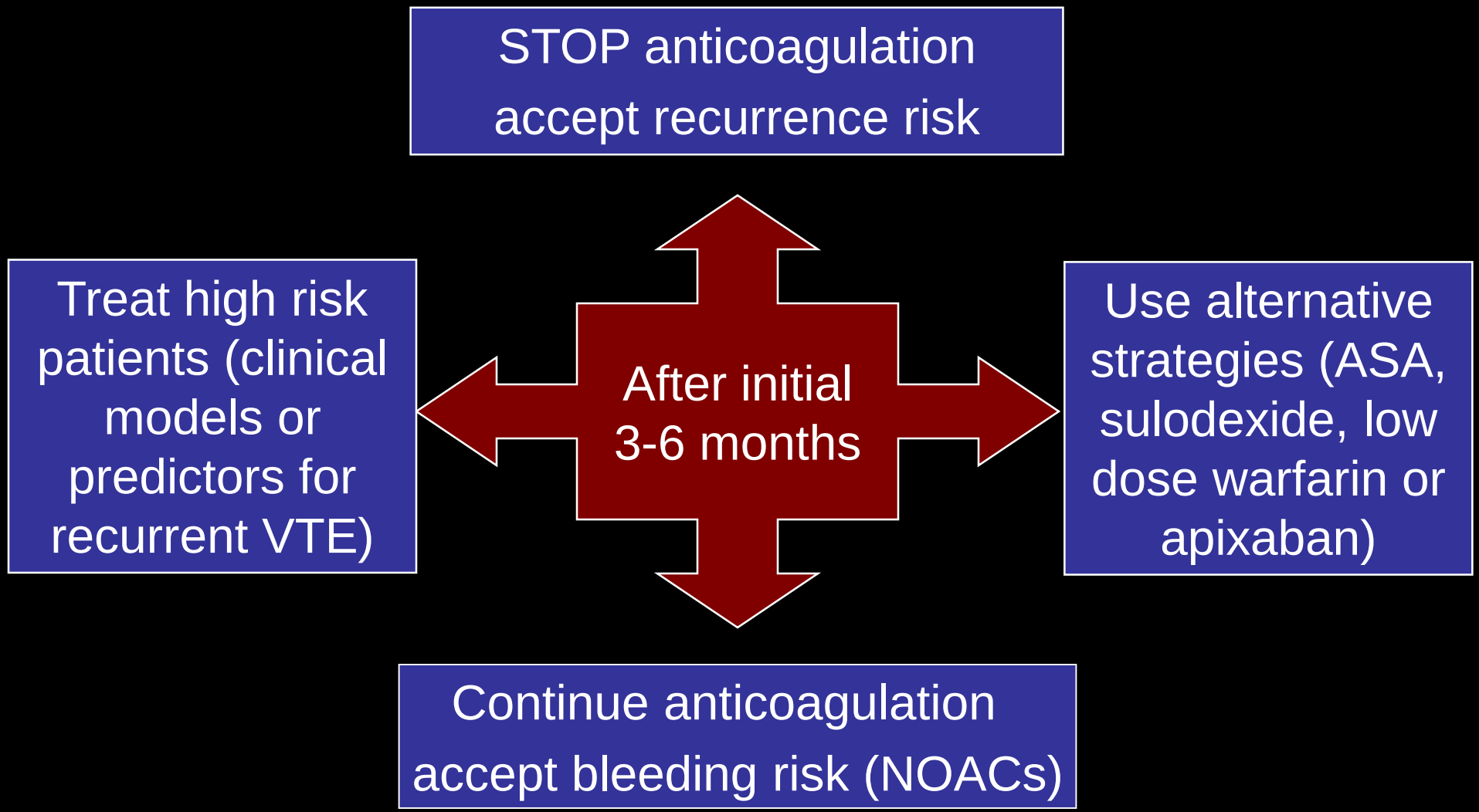
Apixaban for Extended VTE treatment

- Patients treated for VTE with clinical equipoise for discontinuation or extended treatment
- Randomized to api 5mg t.d., api 2.5mg t.d.or placebo
- Treatment period: 12 months



Agnelli et al, N Eng J Med 2013

Treatment for unprovoked VTE: the duration



Acute and long-term treatment of VTE

- ✓ Evidence not enough for treatment upgrading in HD stable
- ✓ NOACs effective and safe for treatment of VTE
- ✓ No clinical benefit by time-definite treatment extension

Management of pulmonary embolism

Cecilia Becattini

University of Perugia, Italy