Updates in venous thromboembolism

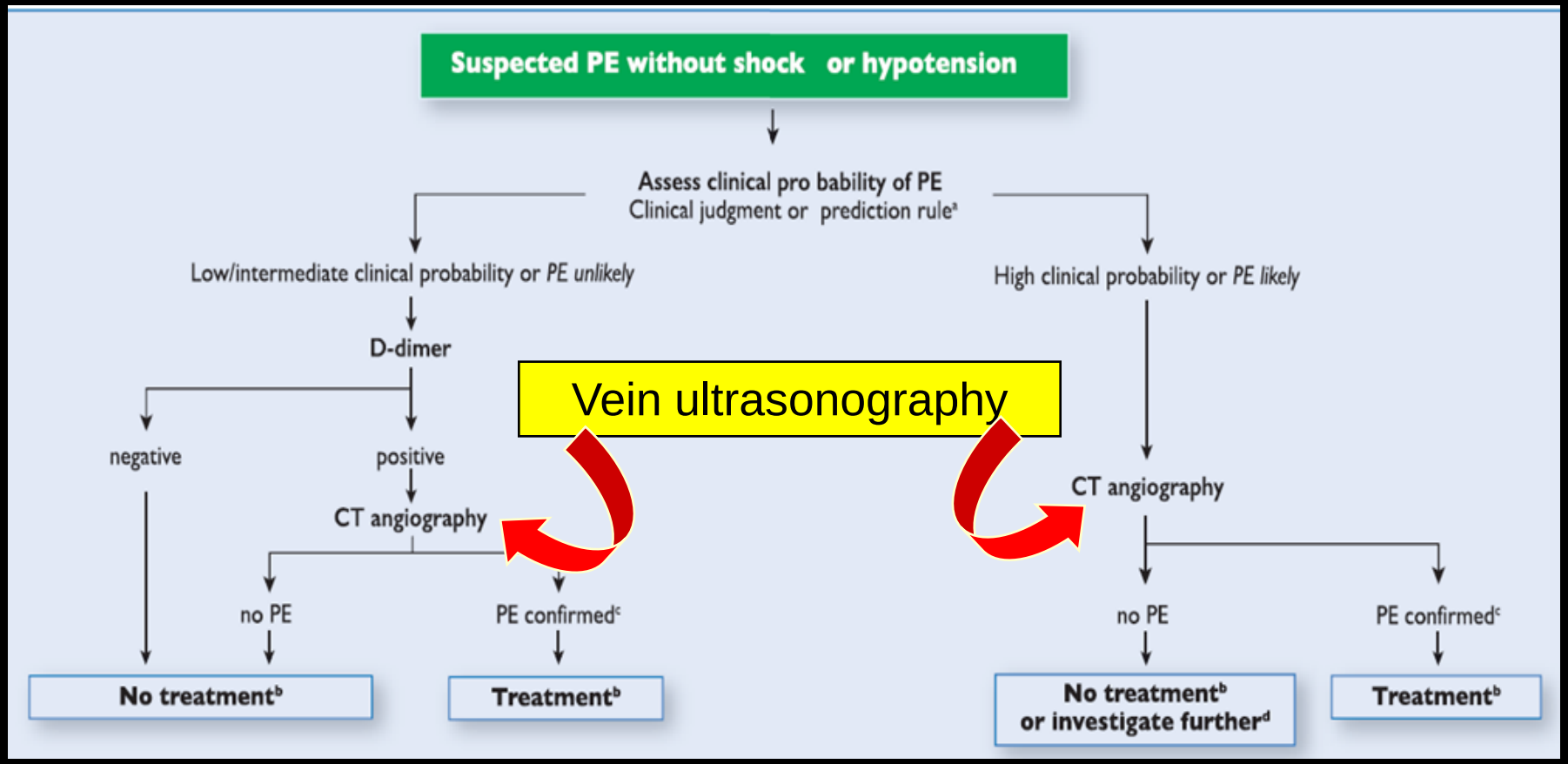
Cecilia Becattini

University of Perugia

News for VTE

- Diagnosis
- Treatment
  - the acute phase
  - the agents

Pulmonary embolism: diagnosis



Meta-analysis

15 studies, 6991 patients, 2001 (30%) had PE

Proximal CUS has low sensitivity and cannot be used to rule out PE.
Nevertheless, its high specificity allows confirming PE.

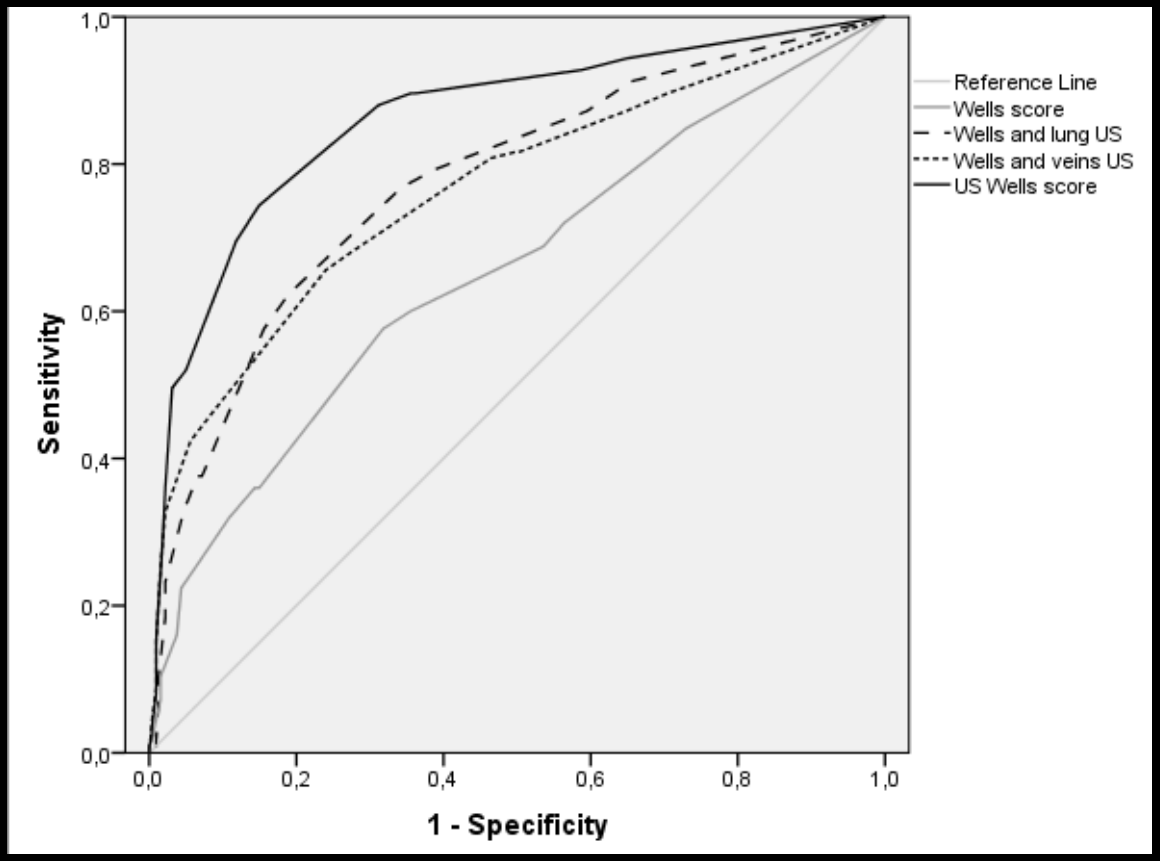
Whole-leg CUS has a higher sensitivity but low specificity for PE and can therefore not be recommended

Da Costa R, JTH 2016

PE diagnosis: US combined with Wells Score

446 patients with suspected PE

125 patients with confirmed PE



	WS	USWS
Se, %	57	69
Sp, %	68	88

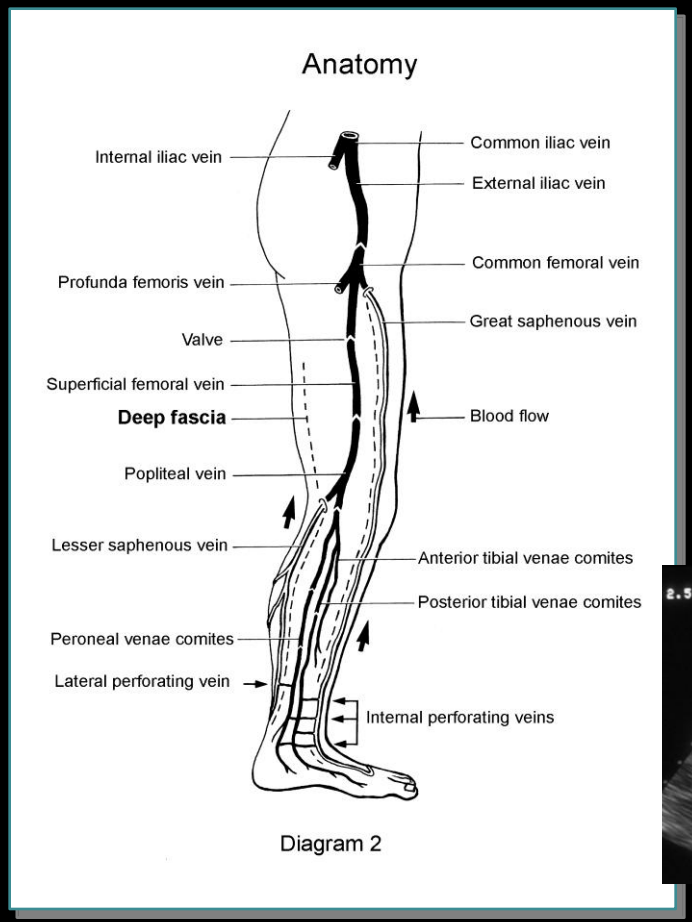
Nazerian P, in press

Venous thromboembolism: diagnosis and treatment

- Diagnosis
- Treatment : the acute phase

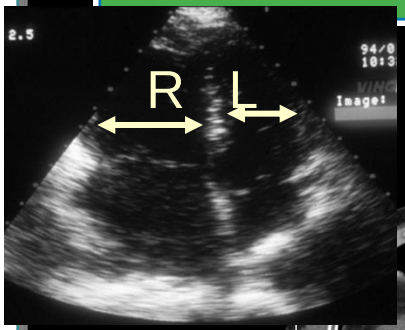
  the agents

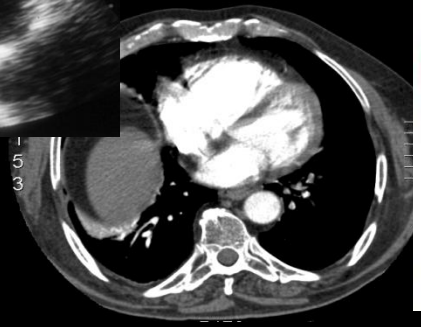
Across the VTE spectrum

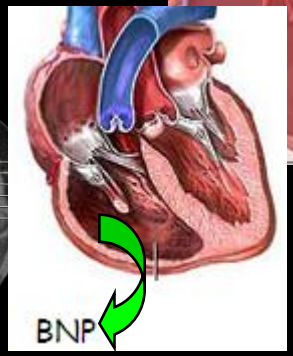


Classification of patients with acute PE based on early mortality risk

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]	







PE: ESC model for risk stratification

2014 EUROPEAN SOCIETY OF CARDIOLOGY®

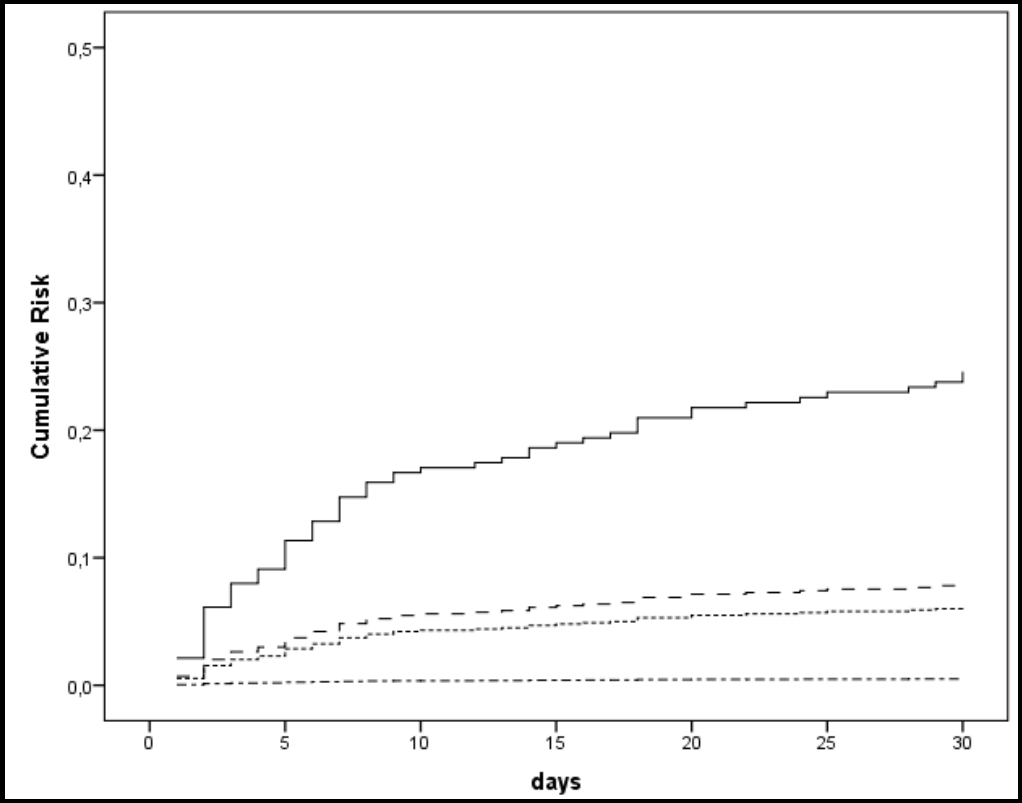
Classification of patients with acute PE based on early mortality risk

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

TNK versus placebo in patients with

acute PE, normal blood pressure

right ventricle overload and increased troponin

	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

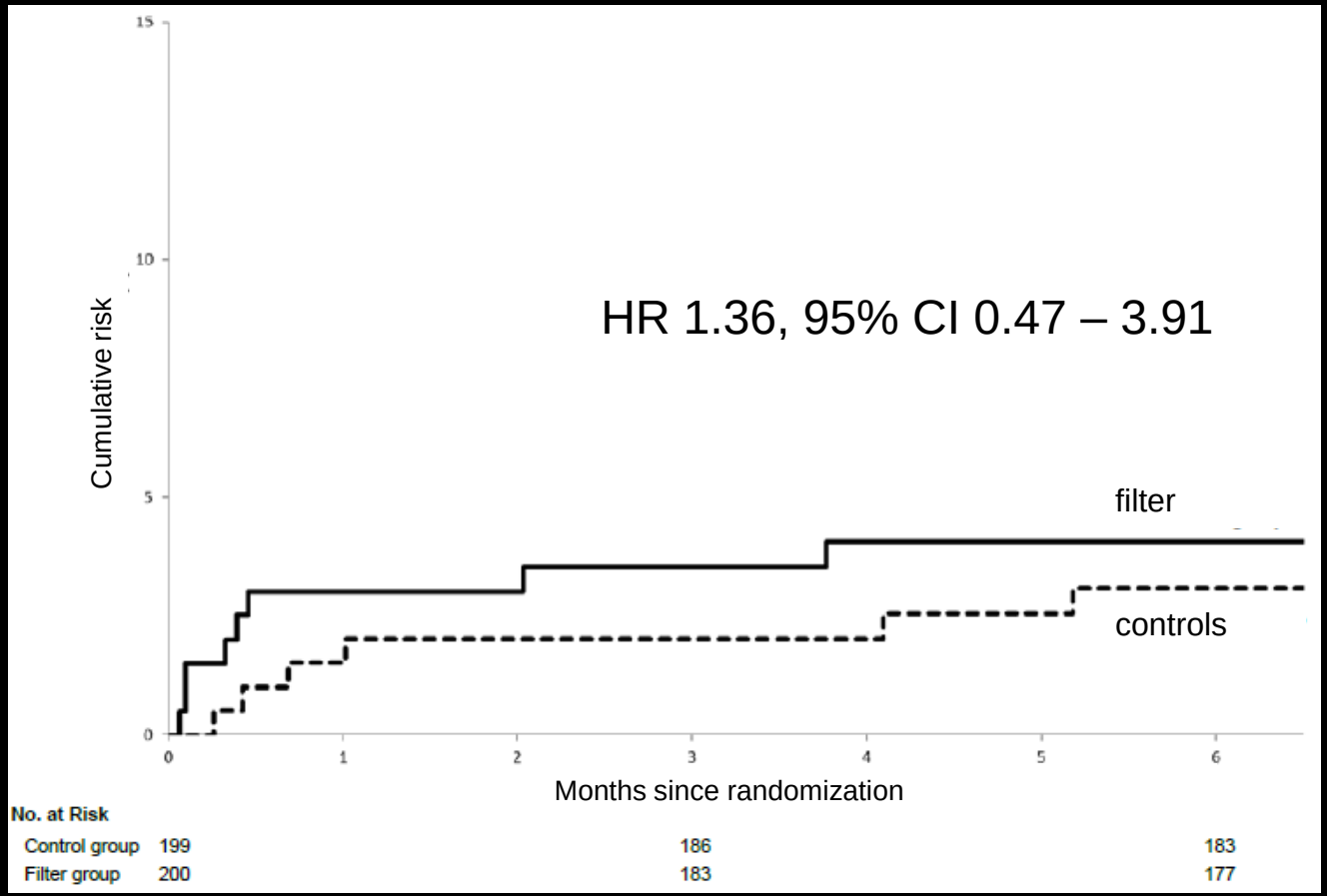
ESC Guidelines: clinical management

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

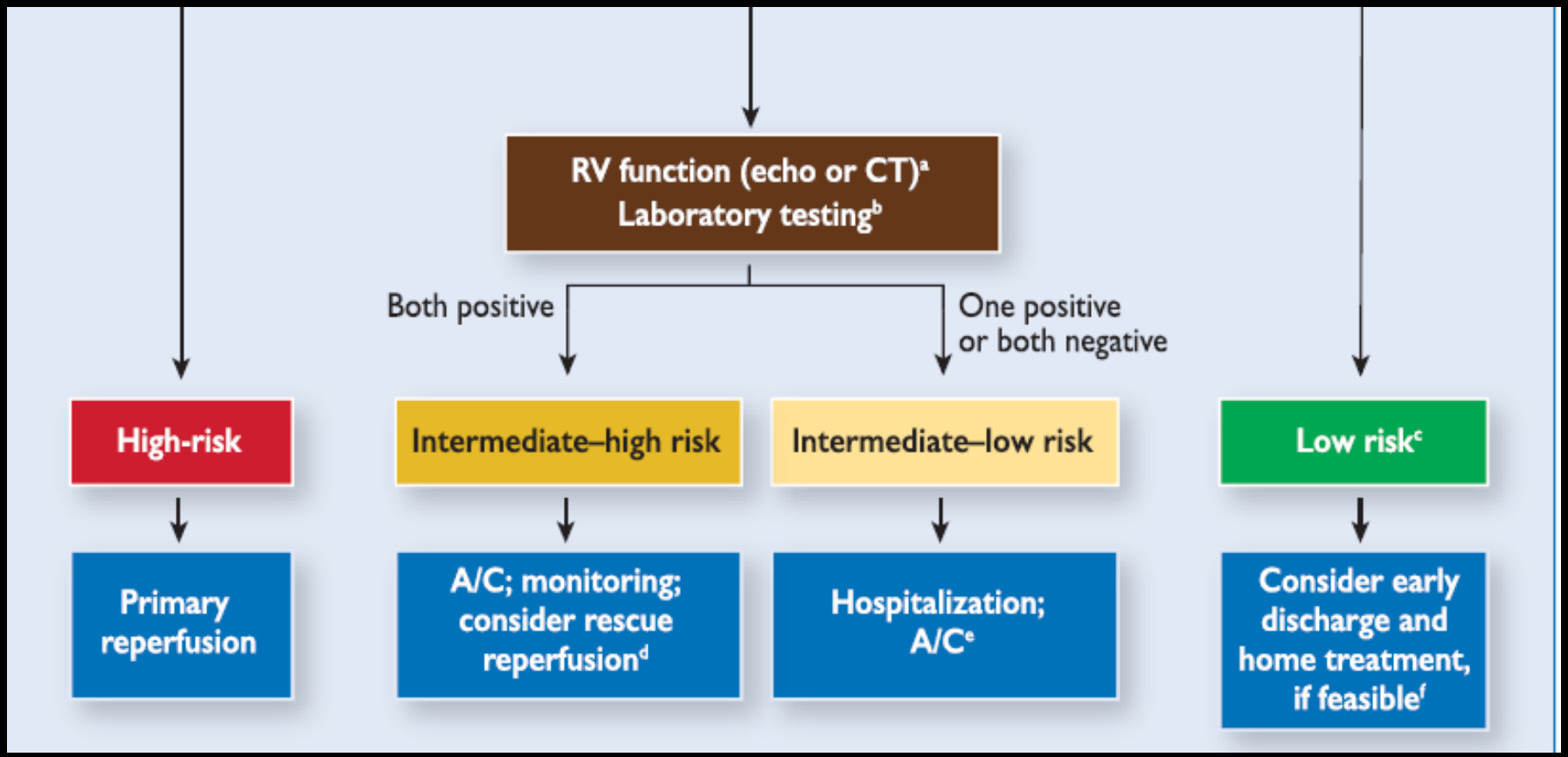
Vena cava filter for acute PE with DVT

Recurrent VTE in patients randomized to vena cava filter implantation plus anticoagulation or anticoagulation alone



Mismetti P, JAMA 2015

Treatment for pulmonary embolism



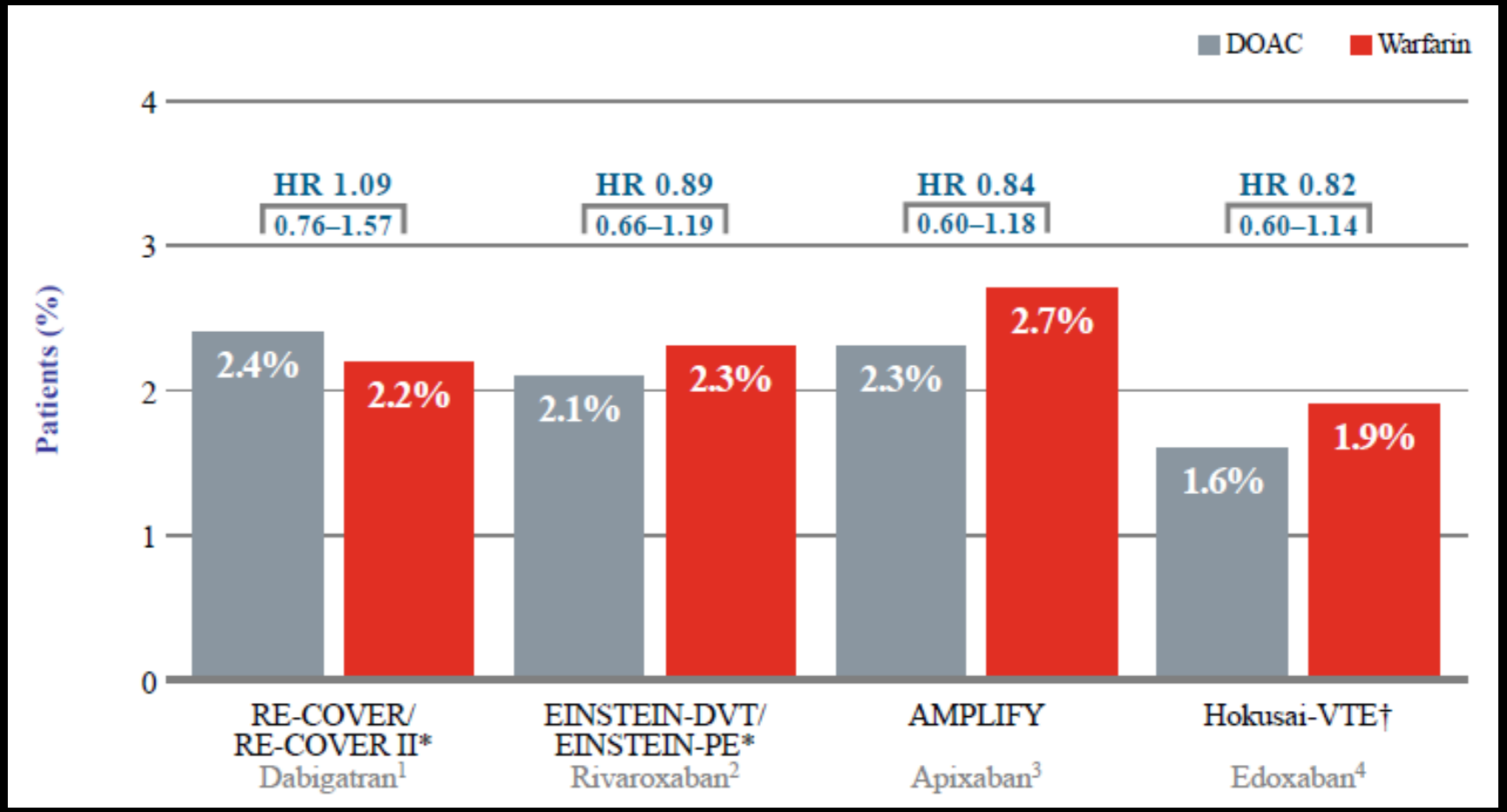
Eur Heart J 2014

Venous thromboembolism: diagnosis and treatment

- Diagnosis
- Treatment : the acute phase

  the agents

NOACs for Treatment of VTE



NOACs in pulmonary embolism

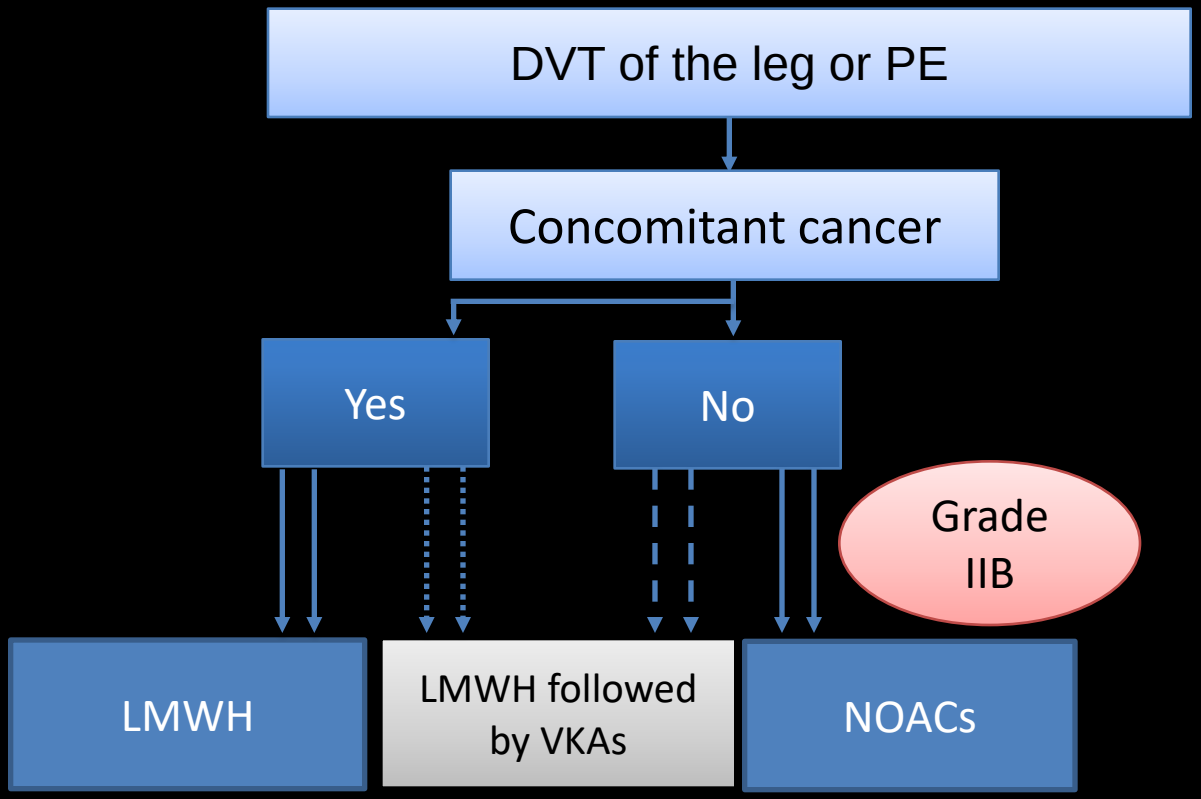
5 phase III studies included: 11,539 patients

	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

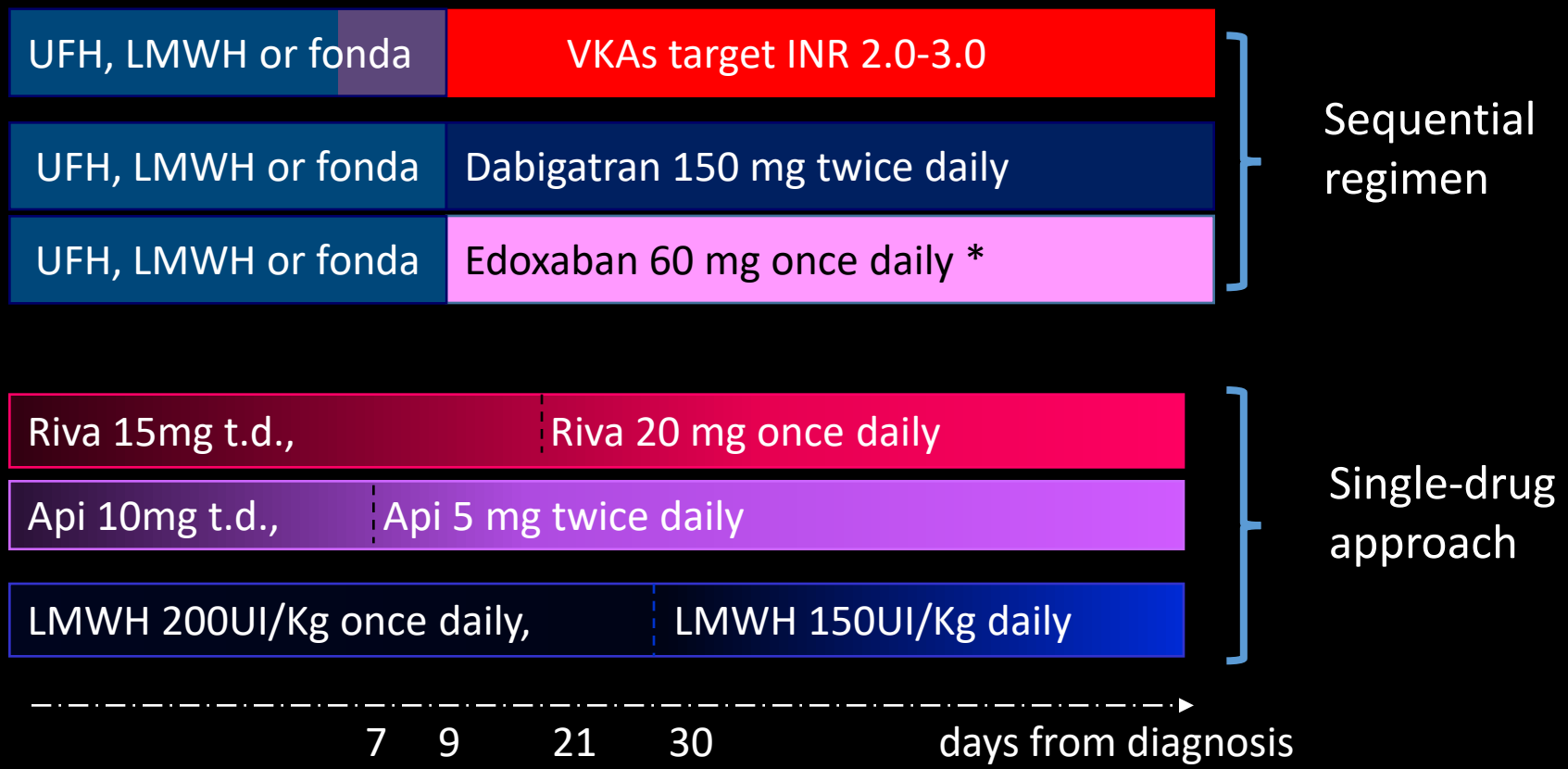
The guidelines



*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

VTE treatment: pending issues

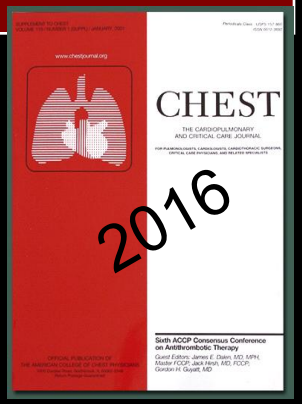
Cancer patients

Home treatment of PE

Children/pregnant women

Intermediate-high risk PE

ACCP: treatment of VTE in cancer patients



Guideline	Recommendations
2016	In patients with DVT of the leg or PE and **CANCER** ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest **LMWH over VKA** therapy (Grade 2C), **dabigatran** (Grade 2C), **rivaroxaban** (Grade 2C), **apixaban** (Grade 2C) **or edoxaban** (Grade 2C) *

*Same level of recommendation for VKAs and DOACs as alternative to LMWHs

Clive Kearon,et al. *Chest* 2016

DOACs for cancer-associated VTE: meta-analysis

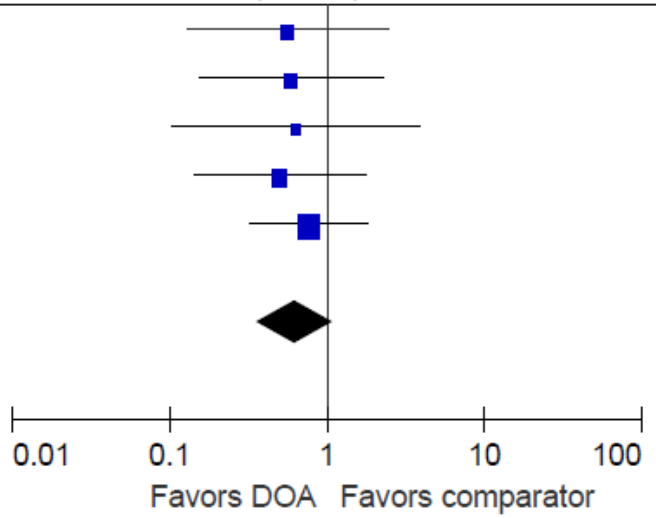
6 studies: 1132 patients with cancer at baseline

Recurrent VTE

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	3	81	5	78	15.2%	0.56 [0.13, 2.43]
EINSTEIN-DVT 2010	4	118	5	89	17.1%	0.59 [0.15, 2.26]
EINSTEIN-PE 2012	2	114	3	109	9.4%	0.63 [0.10, 3.85]
HOKUSAI 2013	4	109	7	99	22.0%	0.50 [0.14, 1.77]
RECOVER I & II 2013	10	173	12	162	36.3%	0.77 [0.32, 1.83]
Total (95% CI)		**595**		**537**	**100.0%**	**0.63 [0.37, 1.10]**
Total events	23		32			

Heterogeneity: $Chi^2 = 0.36$, $df = 4$ ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 1.62$ ($P = 0.10$)



Vedovati et al, CHEST 2015

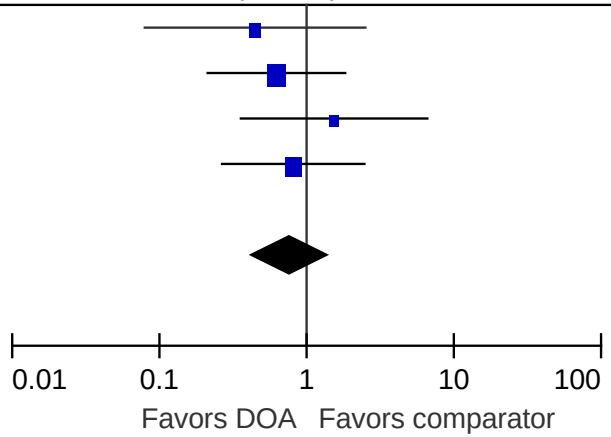
DOACs for cancer-associated VTE: meta-analysis

Major Bleeding

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	2	87	4	80	18.2%	0.45 [0.08, 2.51]
EINSTEIN DVT & PE 2013	6	232	8	196	37.7%	0.62 [0.21, 1.83]
HOKUSAI 2013	5	109	3	99	13.4%	1.54 [0.36, 6.61]
RECOVER I & II 2013	6	159	7	152	30.7%	0.81 [0.27, 2.47]
Total (95% CI)		**587**		**527**	**100.0%**	**0.77 [0.41, 1.44]**
Total events	19		22			

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.70); I² = 0%

Test for overall effect: Z = 0.81 (P = 0.42)



3.2% vs 4.2%

Vedovati Chest 2015

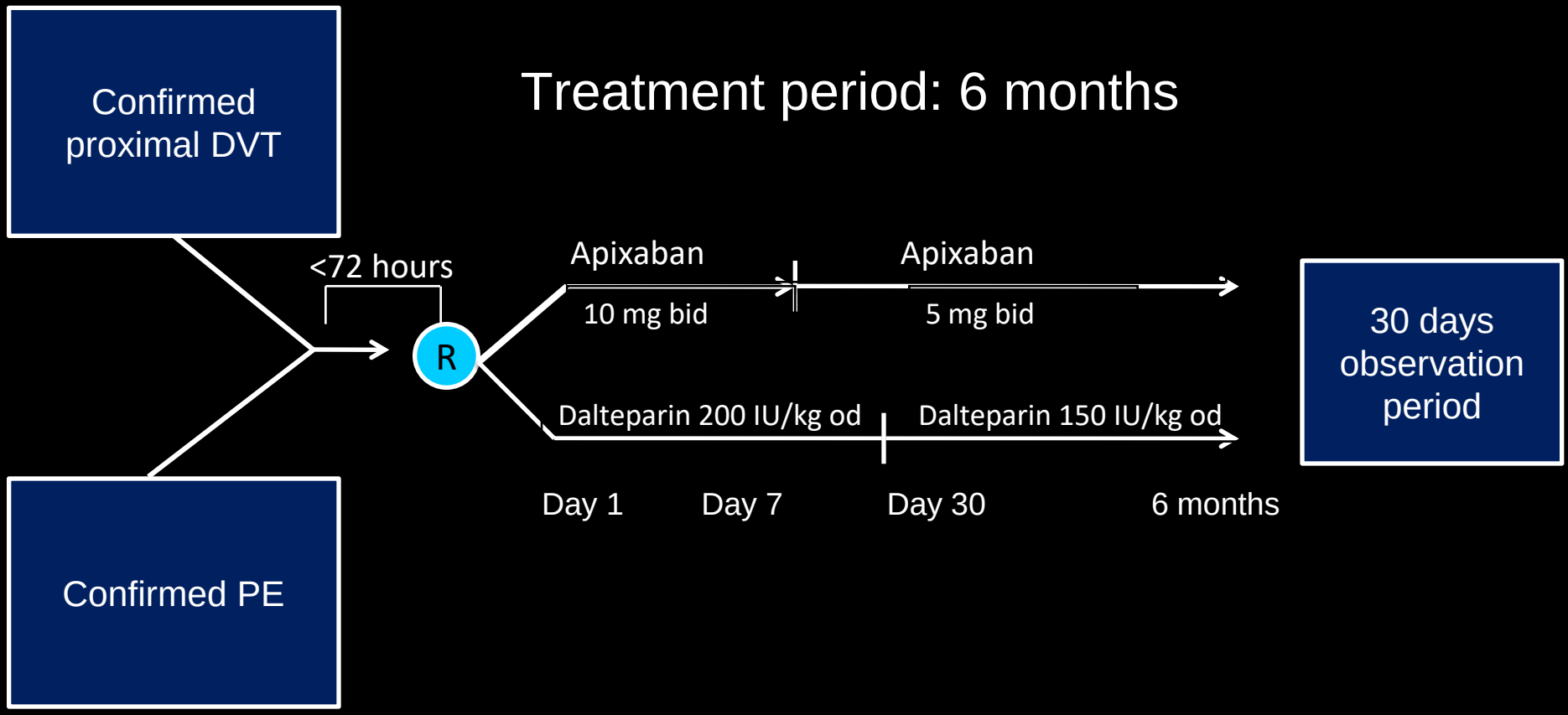
Apixaban for treatment of VTE in cancer patients: The Caravaggio study

Giancarlo Agnelli and Cecilia Becattini

University of Perugia, Italy

Study design

Randomized, open-label, PROBE, non inferiority study



VTE treatment: pending issues

Cancer patients

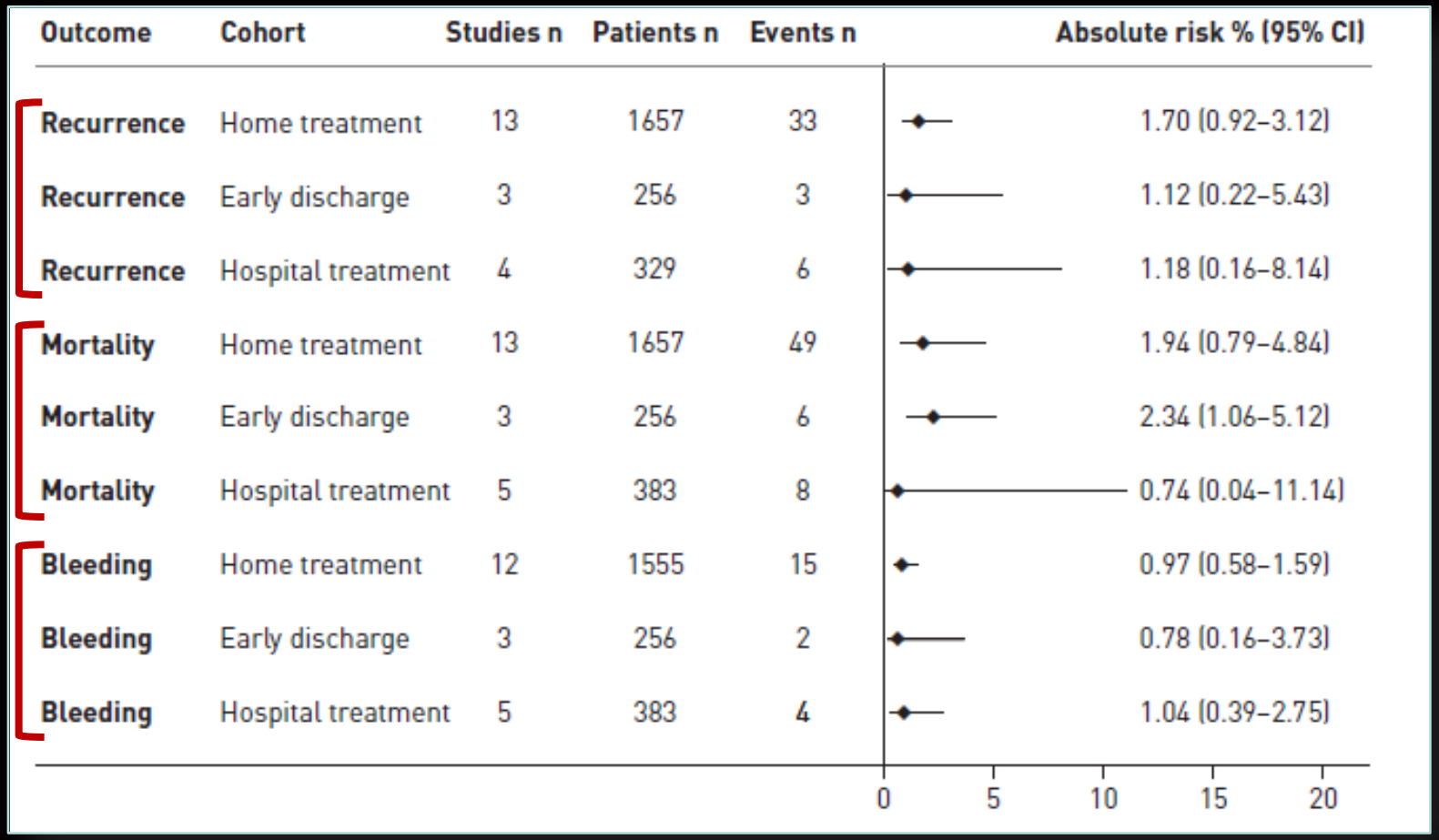
Home treatment of PE

Children/pregnant women

Intermediate-high risk PE

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

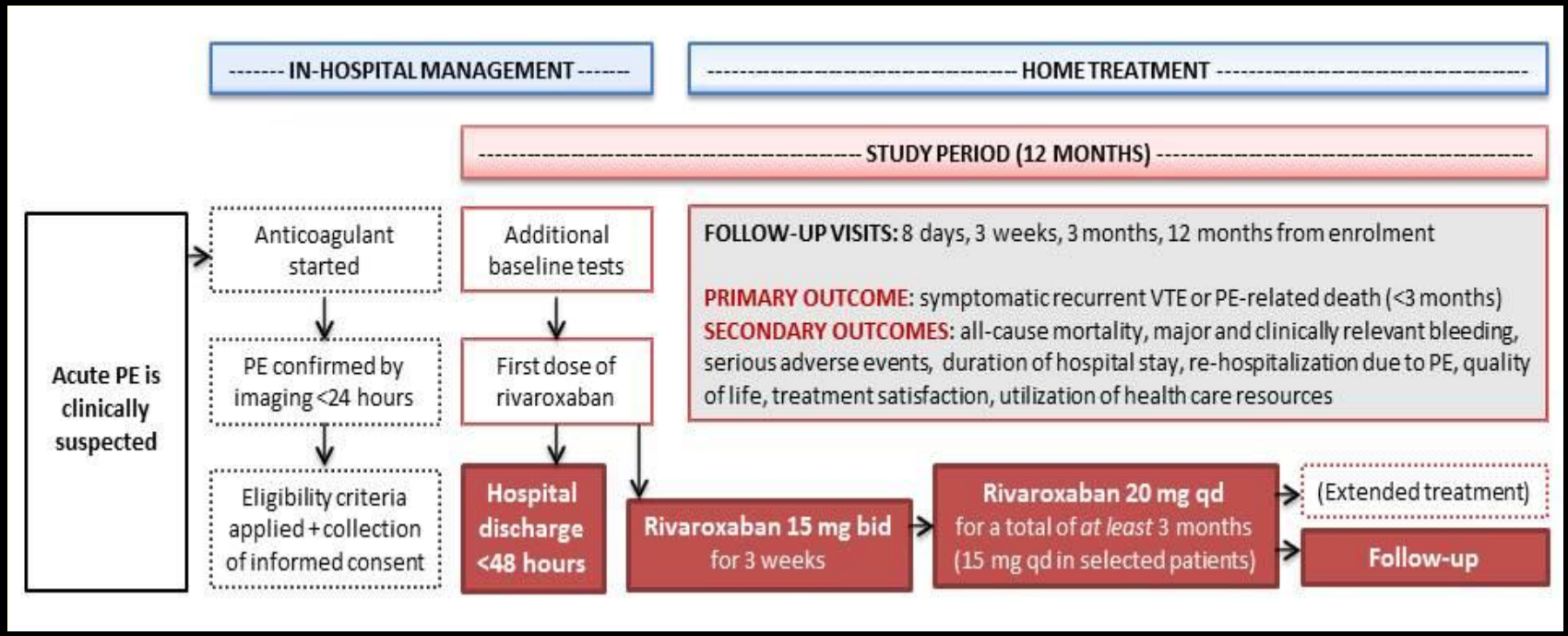


Zondag W et al., Eur Resp J 2013

PE: home treatment

	Aujesky et al	Zondag et al	Agterof et al	Otero et al
Design	Open-label, RCT	Prospective cohort	Prospective cohort	Open-label, RCT
Eligibility criteria				
Systolic BP	**≥100 mmHg**	**≥100 mmHg**	**≥90 mmHg**	**≥90 mmHg**
Clinical prediction rule	**PESI class I or II**	**Hestia**	**-**	**Uresandi 0-2**
Biomarkers	No	No	**NT-proBNP**	**Troponin T**
Absence of RVD	No	No	No	**TTE**
Renal function	CrCl ≥30	CrCl ≥30	Creatinine <150 umol/L	No
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
Others	No history of HIT	No history of HIT; no hepatic impairment	-	No surgery <15 days
Time of discharge	<24 h vs inpatient management	<24 h	<24 h	3- to 5-day vs inpatient

Home treatment: the Hot-PE trial



Barco S, Thromb Haemost 2016

Updates for venous thromboembolism

- US have a good sensitivity for the diagnosis of PE
- DOACs are the treatment of choice for the majority of VTE patients
- Further evidence is awaited for cancer patients and home-treatment

Updates for venous thromboembolism

Cecilia Becattini

University of Perugia, Italy