From Acute Pulmonary Embolism to Chronic Thromboembolic Disease

Implications for follow-up after PE

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Disclosures

- Lecture honoraria: Bayer AG, Boehringer Ingelheim, MSD, Pfizer – Bristol-Myers Squibb, BTG Group, Servier
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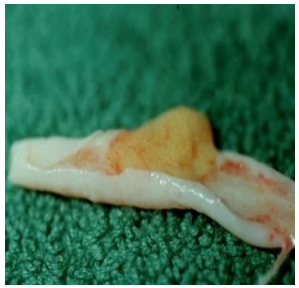
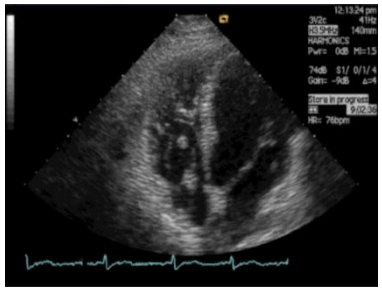
- Institutional research support: Actelion, Bayer AG, Boehringer Ingelheim, Daiichi-Sankyo

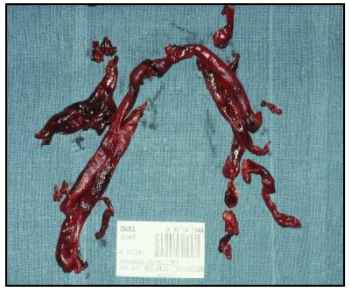
Is CTEPH a complication of PE?



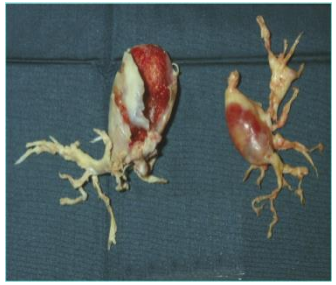
DVT



Embolus in transit



Acute PE



CTEPH

As many as 75% of patients with CTEPH report a history of previous symptomatic DVT or PE (data from 679 patients)

International CTEPH Registry. Pepke-Zaba J. *Circulation* 2011;124:1973–81.

VTE a risk factor for CTEPH (?)

Inclusion of 687 patients (433 CTEPH, 254 non-thrombotic PH) at four European referral centers for CTEPH/PH between 1996 and 2007

Risk factor	Adjusted Odds ratio	95% CI, *p* value
Previous VTE	4.5	2.4–9.1; $p<0.001$
Recurrent VTE	14.5	5.4–43.1; $p<0.001$
Thyroid hormone replacement	6.1	2.7–15.1; $p<0.001$
Malignancy	3.8	1.5–10.4; $p=0.005$
Antiphospholipid antibodies / lupus anticoagulant	4.20	1.6–12.2; $p=0.004$
Ventriculo-atrial shunt or infected pacemaker	76.4	7.7–10350.6; $p\leq0.001$
Splenectomy	17.9	1.6–2438.1; $p=0.017$

CI, confidence intervals. Bonderman D *et al. Eur Respir J* 2009;33:325–31.

Incomplete thrombus resolution after PE

Author	Patients	Design	Follow-up	Imaging method	Persistent thrombi
Cosmi (2011)[1]	173	Prospective	9 months	CT (n=80), Lung scan (n=93)	**15%** by CT **28%** by lung scan
Sanchez (2010)[2]	254	Prospective	12 months	Lung scan	**29%**
Nijkeuter (2006)[3]	268	Meta-analysis	8 days – 6 months	Lung scan (2 studies: n=187) CT (2 studies: n=81)	**Up to 65%** after 3 months

1. Cosmi B *et al. Intern Emerg Med* 2011;6:521. 2. Sanchez O *et al. J Thromb Haemost* 2010;8:1248–55. 3. Nijkeuter M *et al. Chest* 2006; 129:192–7.

[Presumed] pathophysiology of CTEPH

Inadequate anticoagulation large thrombus mass

Infection and inflammation

Immunity

Genetics

In situ thrombosis

Acute PE

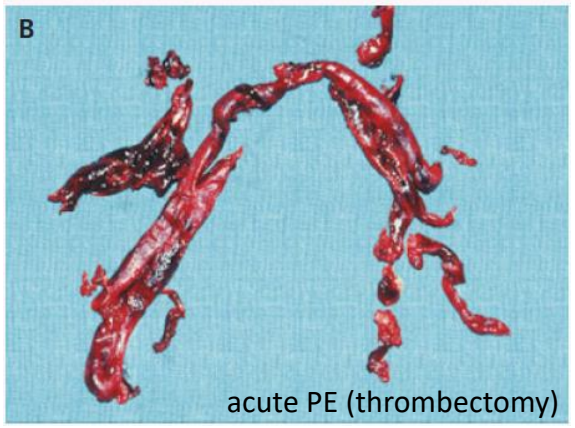
Incomplete resolution and organization of thrombus

Lack of thrombus angiogenesis

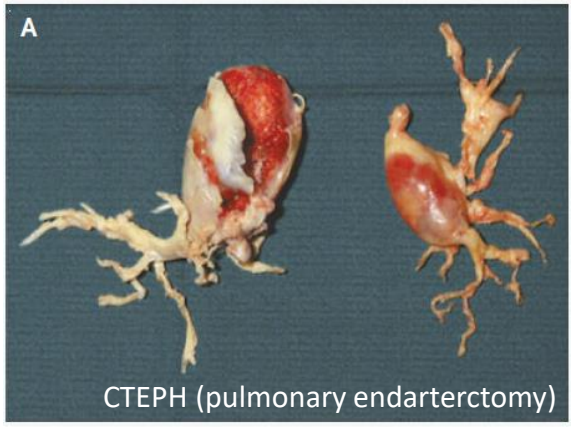
Development of fibrotic stenoses/occlusions

Remodelling of resistance vessels (shear stress)

Increase of PA pressure and PVR (CTEPH)



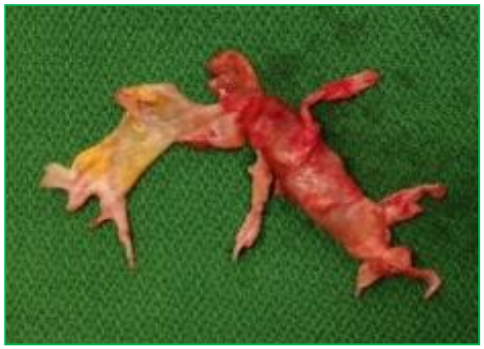
acute PE (thrombectomy)



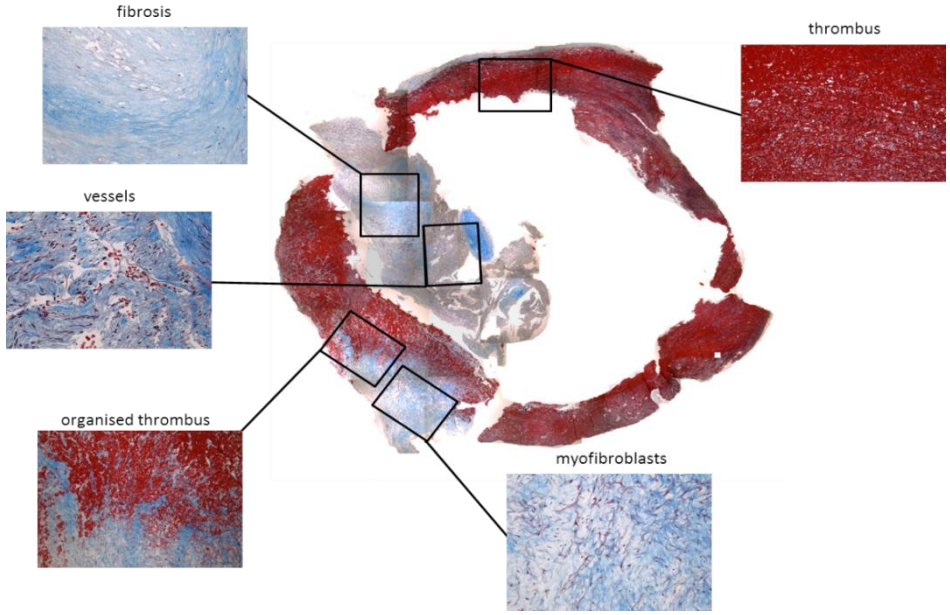
CTEPH (pulmonary endarterctomy)

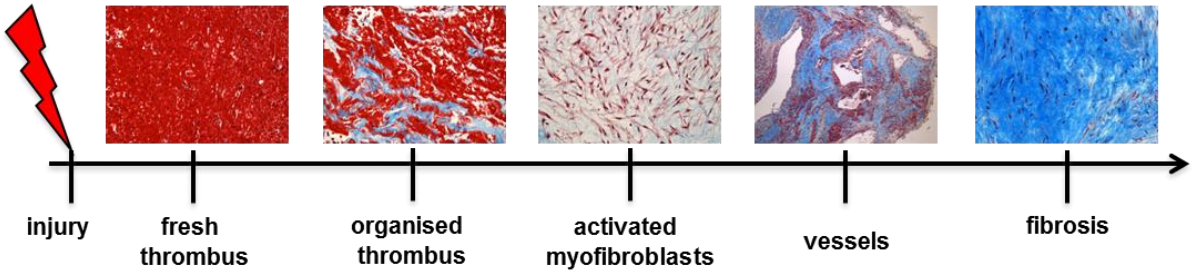
modified accorcing Lang IM et al. *Eur Respir J* 2013;41:462–8; Lang IM, *N Engl J Med* 2004;350:22

Histological classification of CTEPH specimens



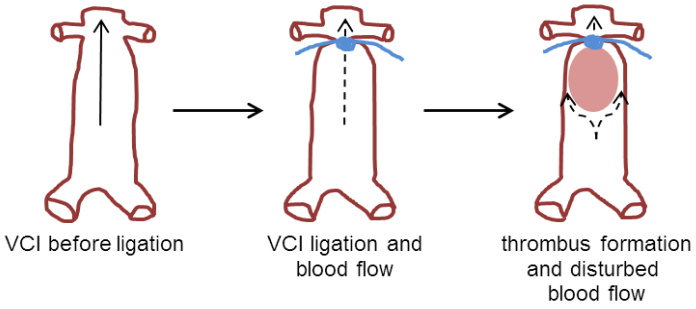
HISTOLOGICAL CLASSIFICATION	SURGICAL CLASSIFICATION		
	Type 1	Type 2	Type 3
thrombus (%)*	83.3	50	25
organised thrombus (%)*	66.7	50	41.7
myofibroblasts (%)*	100	100	100
vessels (%)*	83.3	100	66.7
fibrosis (%)*	83.3	50	100

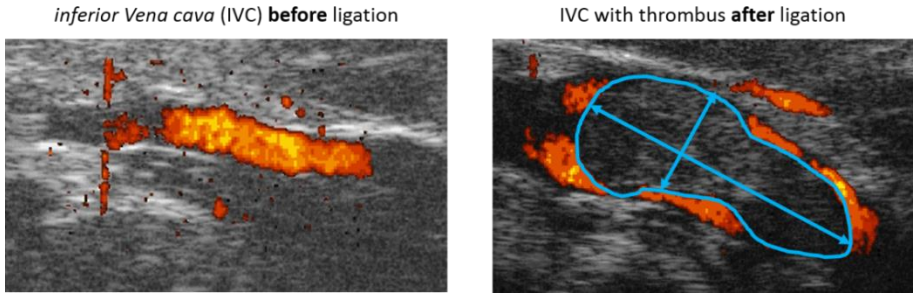




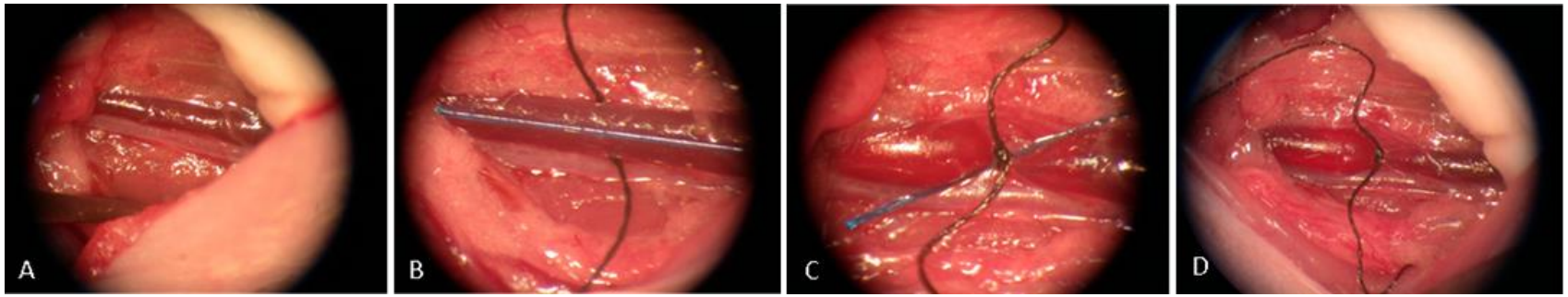
Bochenek ML et al. *Thromb Haemost* 2017; Feb 2. doi: 10.1160/TH16-10-0790. [Epub ahead of print]

Mouse model of venous thrombosis

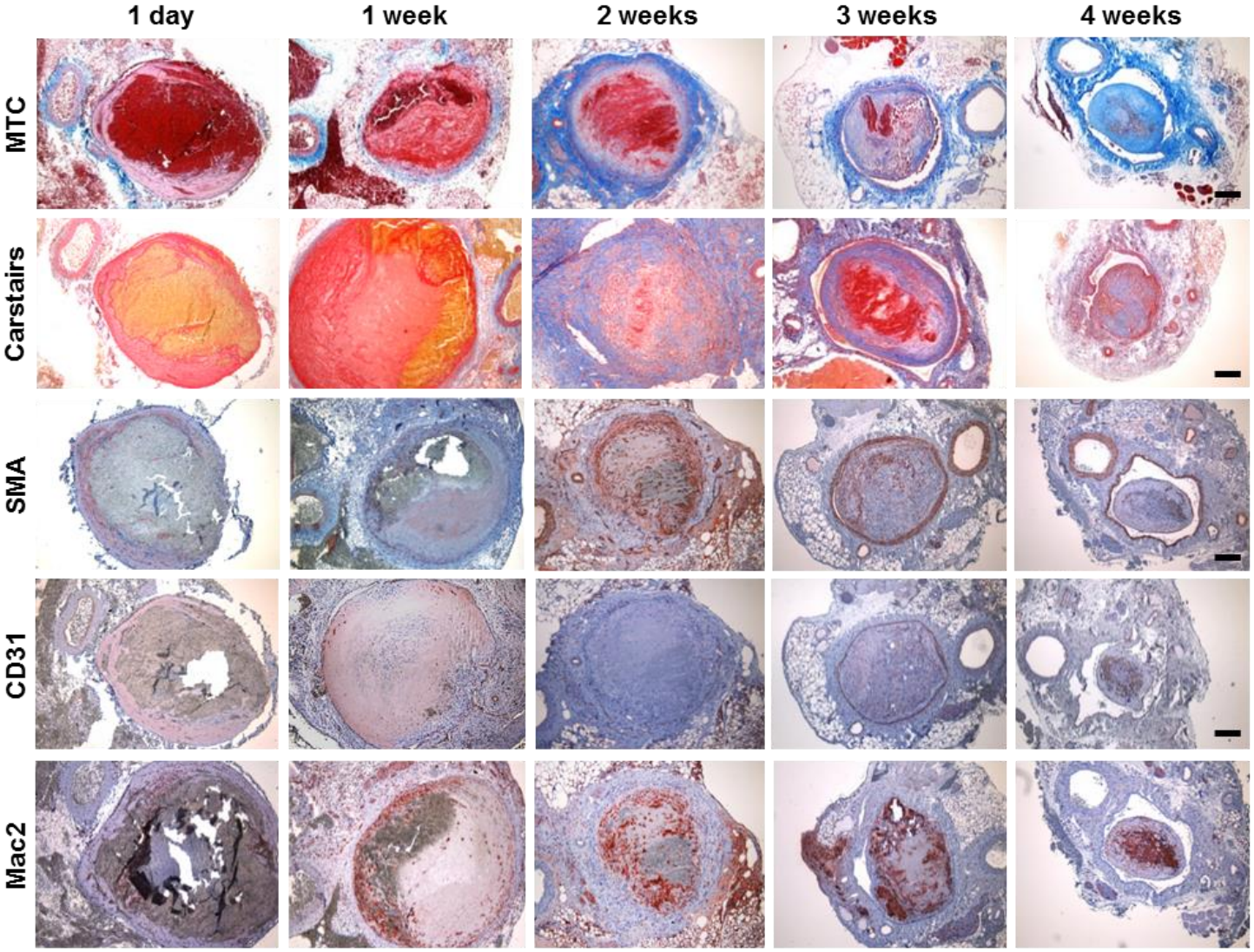




adapted after Diaz et al. 2012

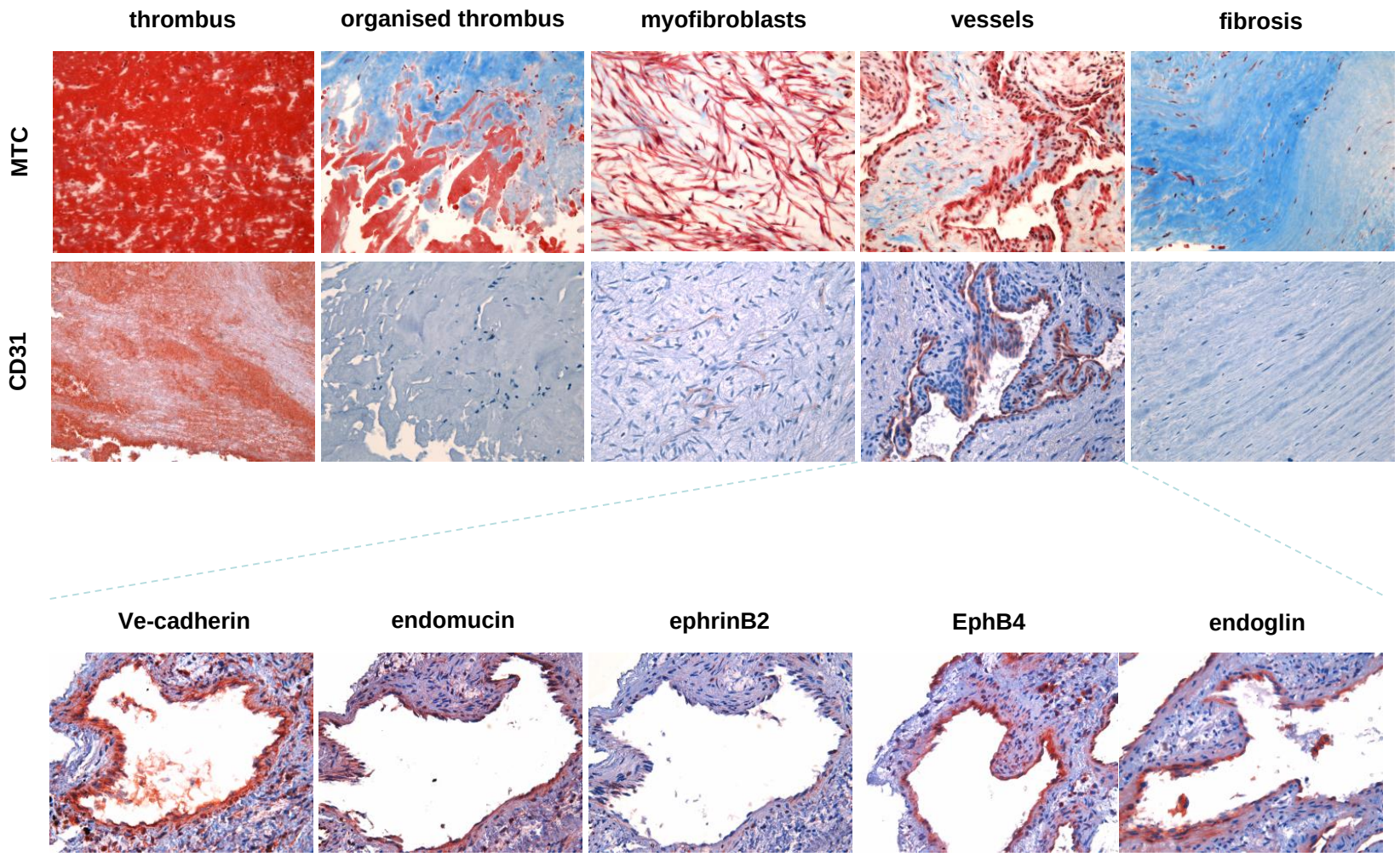


Murine venous thrombus resolution



Bochenek ML et al. *Thromb Haemost* 2017; Feb 2. doi: 10.1160/TH16-10-0790. [Epub ahead of print]

Venous endothelium in human CTEPH specimens



Bochenek ML et al. *Thromb Haemost* 2017; Feb 2. doi: 10.1160/TH16-10-0790. [Epub ahead of print]

ESC Guidelines 2014: Uncertainties on CTEPH

Recommendations	Class	Level
In PE survivors with persistent dyspnea, diagnostic evaluation for CTEPH should be considered	IIa	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended	III	C
It is recommended that, in all patients with CTEPH, the assessment of operability, and decisions regarding other treatment strategies, are made by a multidisciplinary team of experts	I	C
Life-long anticoagulation is recommended in all patients with CTEPH	I	C
Surgical PEA is recommended for patients with CTEPH	I	C
Riociguat is recommended in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team, including at least one experienced PEA surgeon, or have persistent/recurrent CTEPH after surgical treatment	I	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team, including at least one experienced PEA surgeon	IIb	B

Eur Heart J 2014:35:3145–3146

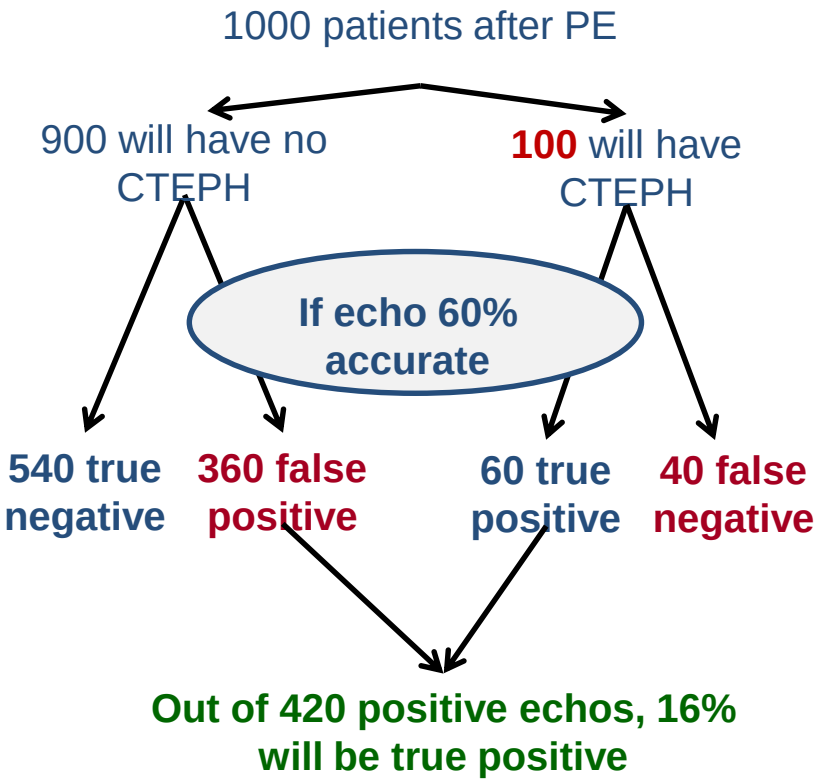
Incidence of CTEPH after acute PE: How frequent, 1% or 10%?

Study	Number of patients with acute PE	Average observation time (months)	Cumulative incidence of CTEPH (%)
Held M et al. BMC Pulmonary Medicine 2014;14:141	130	27	**6.2**
Guerin L et al. Thromb Haemost 2014;112:598-605	146	26	**4.8**
Korkmaz A et al. Clin Appl Thromb Hemost 2012;18:281–8	325	16	**4.6**
Otero R et al. Thromb Res 2011;127:303–8	744	14	**8.3**
Marti D et al. Arch Bronconeumol 2010;46:628–33	110	24	**9.1**
Klok FA et al. Haematologica 2010;95:970–5	877	34	**0.57**
Surie S et al. Thromb Res 2010;125:e202–5	110	36	**2.7**
Poli D et al. J Thromb Thrombolysis 2010;30:294–9	239	36	**0.4**
Sanchez O et al. Am J Resp Crit Care Med 2010;181: A1947	700	26	**4.7**
Dentali F et al. Thromb Res 2009;124:256–8	91	6-12	**8.8**
Becattini C et al. Chest 2006;130:172–5	259	46	**1.0**
Miniati M et al. Medicine (Baltimore) 2006;85:253–62	834	25	**1.0**
Pengo V et al. N Engl J Med 2004;350:2257–64	314	94	**3.8**
Ribeiro A et al. Circulation 1999;99:1325–30	78	12	**5.0**

CTEPH screening after PE?

The true incidence will determine the need

Scenario 1

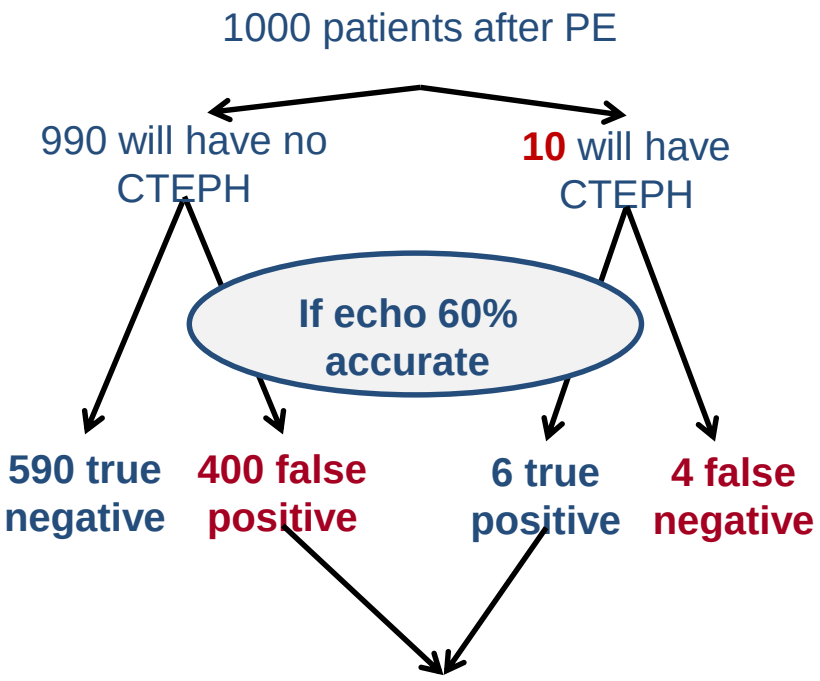


Thomas Bayes
(1702–1761)

CTEPH screening after PE?

The true incidence will determine the need

Scenario 2



Thomas Bayes
(1702–1761)

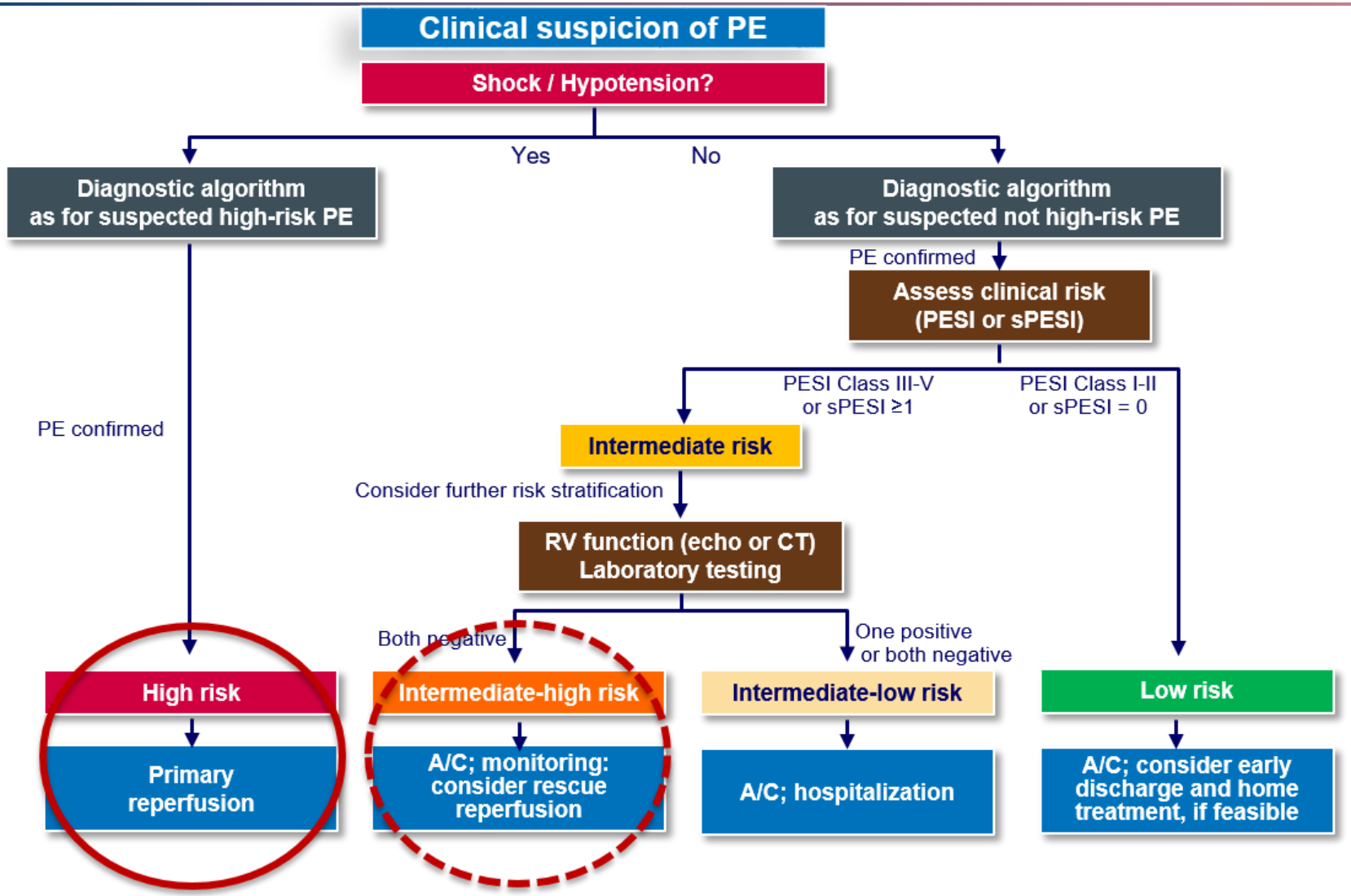
From acute PE to CTEPH: Key issues

- Can early reperfusion therapy (and which type of it) prevent CTEPH development?
- Can indefinite anticoagulation after PE prevent CTEPH?
- Which clinical, laboratory, and hemodynamic criteria can be interpreted as predictors or prodromi of CTEPH?
- On which grounds should we select patients for regular follow-up and, possibly, CTEPH screening after PE?

Can We Prevent CTEPH After Acute PE?

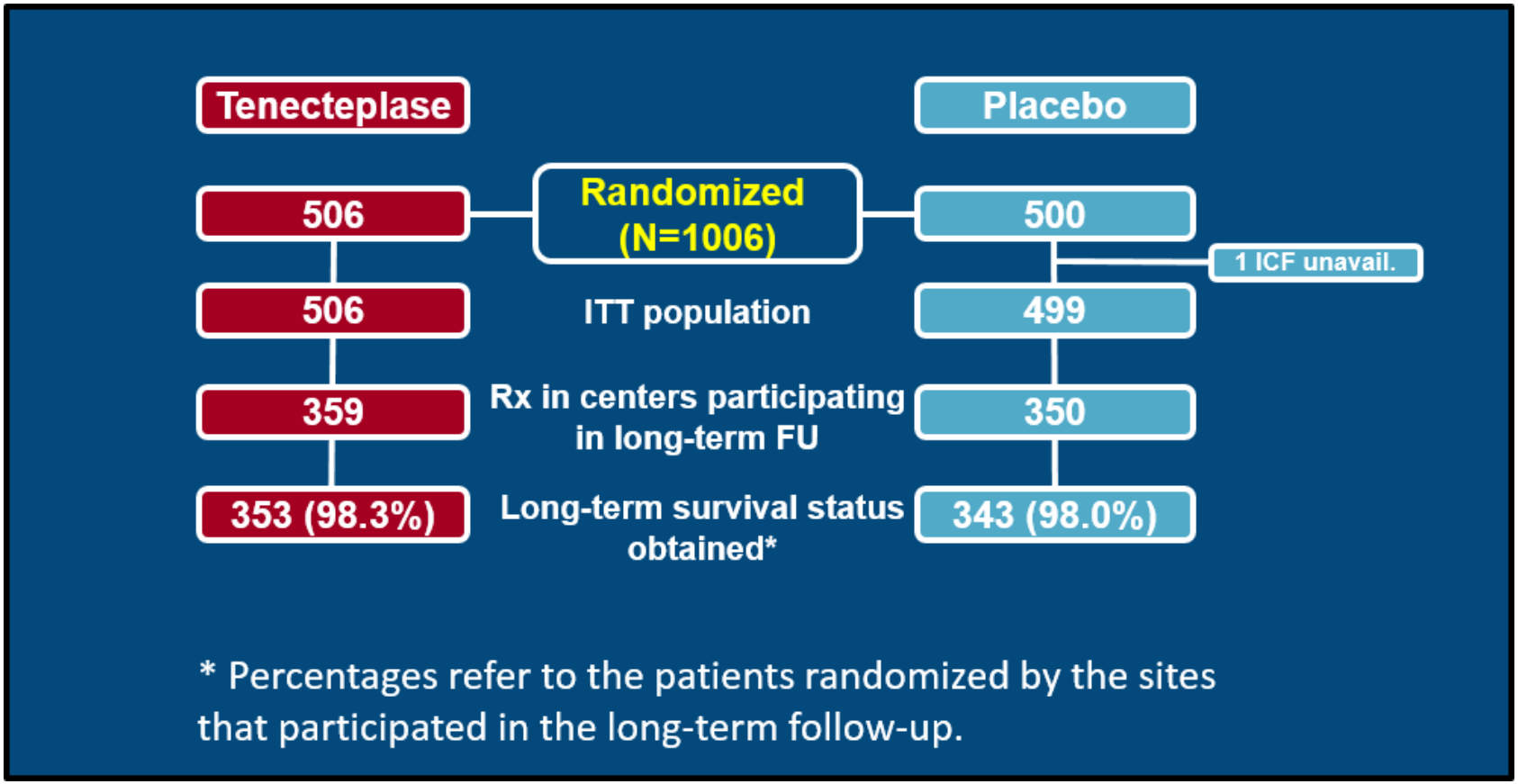
Stavros Konstantinides, CTH Mainz

ESC 2014: Candidates for reperfusion in acute PE



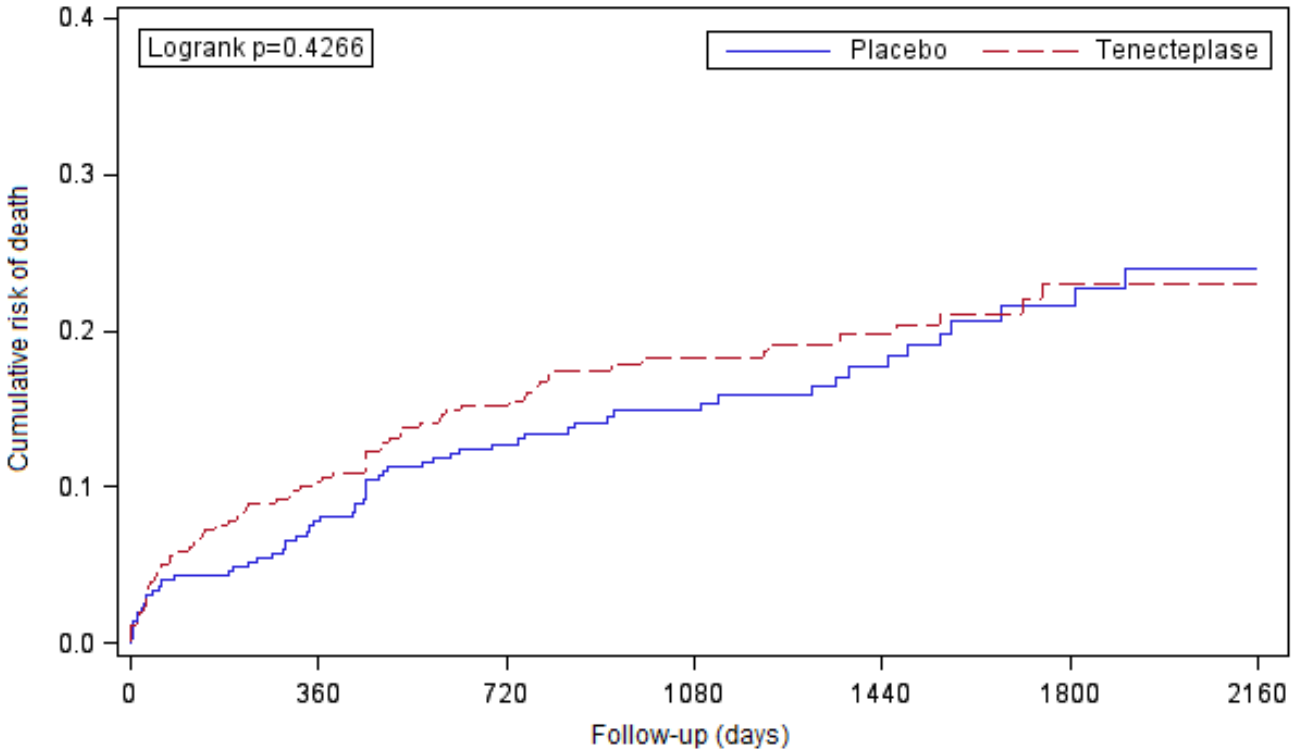
European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

PEITHO: Long-term follow-up (2016)



The PEITHO Investigators 2014-2016

PEITHO long-term FU (37.8 months [24.6.-54.8]): Probability of survival



N at risk

Placebo	350	316	299	188	120	71	38
Tenecteplase	359	317	299	198	129	69	35

The PEITHO Investigators. *J Am Coll Cardiol* 2017; in press.

Clinical and functional status after PE (41.6±15.7 month FU)

	Tenecteplase (n=175)	Placebo (n=183)	*p* value
Persisting clinical symptoms	**63 (36.0%)**	**55 (30.1%)**	**0.23**
Exertional dyspnea	55	50	
Exertional chest pain	4	0	

FU, follow-up.

PEITHO Steering Committee. *J Am Coll Cardiol* 2017;69:1536–44.

Echocardiographic parameters after PE (41.6±15.7 month FU)

	Tenecteplase (n=144)	Placebo (n=146)	*p* value
RVEDD >30 mm	34 (23.6%)	22 (15.1%)	0.058
Missing data	12 (8.3)	11 (7.5)	
RV/LV diameter ratio >0.9	34 (23.6%)	22 (15.1%)	0.834
Missing data	12 (8.3%)	11 (7.5)	
TAPSE			
Reduced, no. (%)	14 (9.7%)	7 (4.8%)	0.107
Median (interquartile range), mmHg	24.0 (20.0–27.0)	24.0 (21.0–26.0)	0.551
Missing data, no. (%)	19 (13.2)	18 (12.3)	
TR jet velocity >2.6 m/s	22 (15.3%)	27 (18.5%)	0.412
Missing data	11 (7.6)	14 (9.6)	
Systolic PAP, mmHg			
Median (interquartile range)	30.0 (24.0–35.0)	30.0 (25.0–35.0)	0.527
Missing data, no. (%)	33 (22.9)	39 (26.7)	

PAP pulmonary artery pressure; RVEDD, right ventricular end-diastolic diameter, RV/LV, right/left ventricular; TAPSE, tricuspid annulus plane systolic
excursion; TR,tricuspid regurgitation.
PEITHO Steering Committee. *J Am Coll Cardiol* 2017;69:1536–44.

Possible CTEPH incidence after PE

	Tenecteplase (n=190)	Placebo (n=186)	*p* value
CTEPH confirmed	**4 (2.1%)**	**6 (3.2%)**	**0.79**

PEITHO Steering Committee. *J Am Coll Cardiol* 2017;69:1536–44.

VTE recurrence: substantial, decreasing over time

Cohort data 1980s -1990s	**Cumulative incidence**	***Projected annual* incidence rate**
2 weeks	2%	55%
3 months	6,4%	30%
6 months	8%	18%
2 years	17%	8,5%
5 years	24%	4,8%
8 years	30%	3,8%

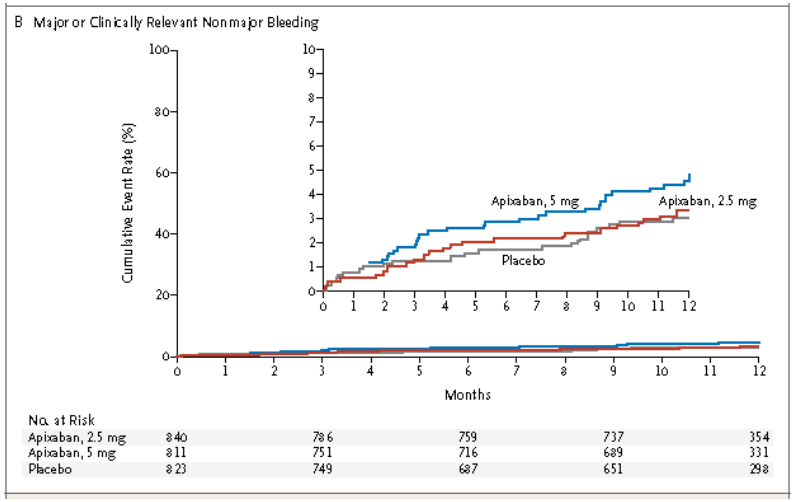
Prandoni P. *Haematologica* 1997; 82: 423-428

Prandoni P. *Ann Intern Med* 1996;125:1-7

Extended prophylaxis with low-dose NOAC

AMPLIFY-EXT

- Two doses of apixaban (2.5 mg and 5 mg, twice daily) versus placebo
- Pts with VTE who had completed 6-12 months of anticoagulation
- study drugs given for 12 months
- 2482 pts included in ITT
- **Primary EP**: 8.8% in placebo vs. 1.7% in EACH apixaban dose



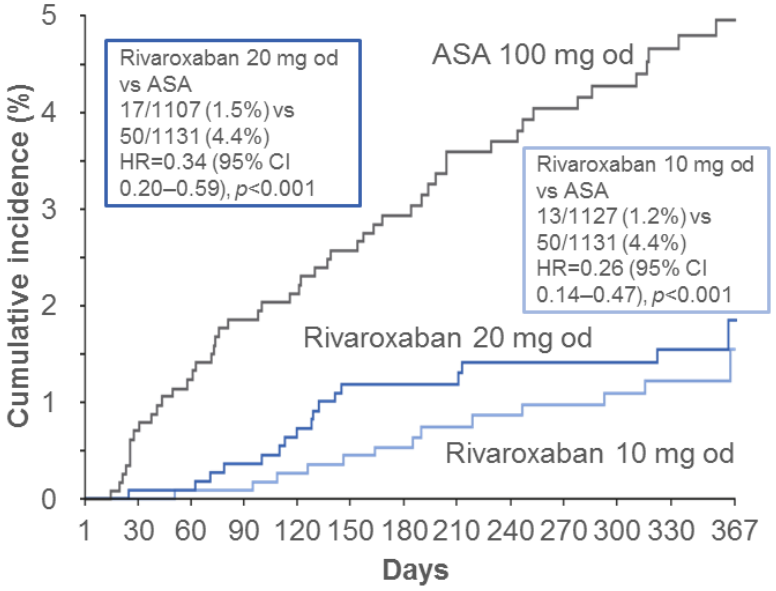
Major / CRNM bleeding:
2.7% vs. 3.2% (2.5 mg) vs. 4.3% (5 mg)

Agnelli G, for the AMPLIFY Investigators. *N Engl J Med* 2013;368:799-808

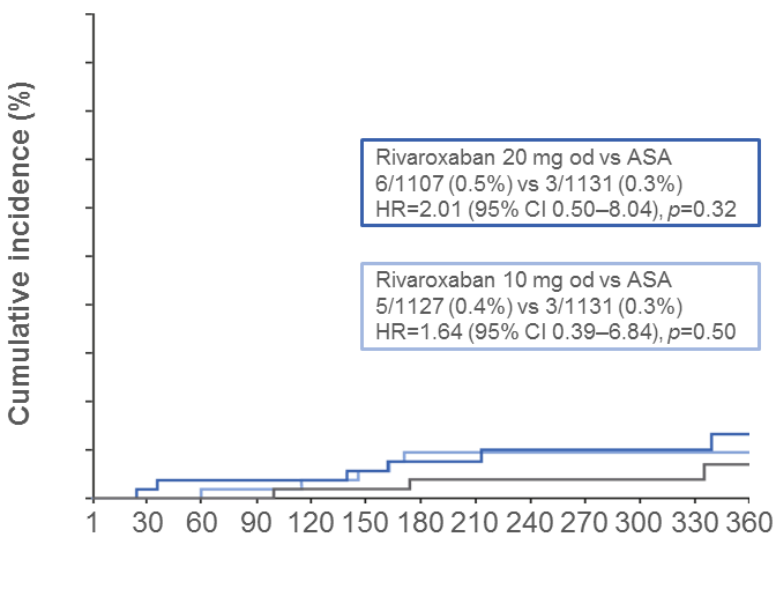
Extended prophylaxis with low-dose NOAC

EINSTEIN-Choice

Efficacy*



Major bleeding#



*Intention-to-treat analysis; #safety analysis; ‡no events after Day 360 up to Day 480

Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

Remaining challenges in anticoagulation: For whom half dose, for whom full dose?

Early recurrence[1]

- Poor quality of anticoagulation (failure to achieve therapeutic aPTT and INR)
- Cancer

Late recurrence[2,3]

Strong established factors

- Unprovoked (vs provoked) VTE
- More than one VTE event
- On-going hormonal therapy
- Elevated D-dimer levels after/during VKA treatment

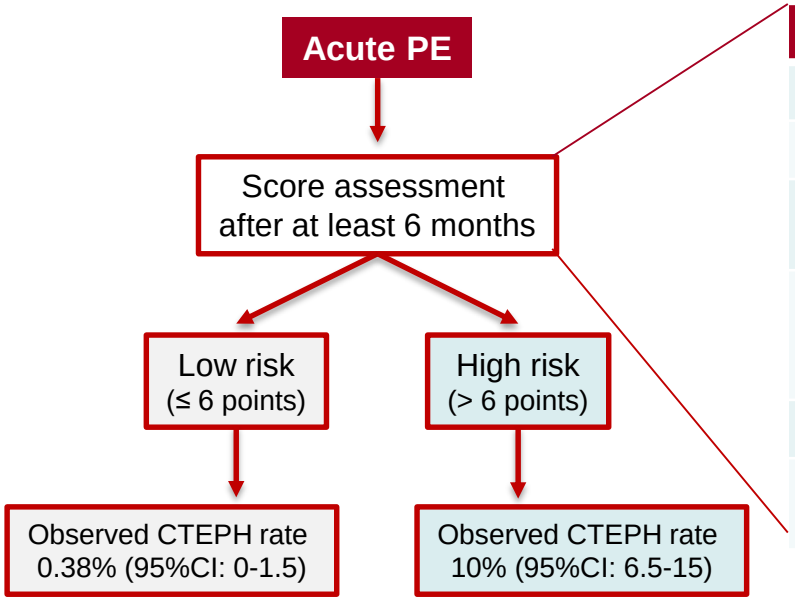
Weaker/controversial factors

- Male sex
- Location: PE/proximal DVT vs distal DVT
- Age
- Family history of VTE
- Obesity (increased BMI)
- Cancer
- Antiphospholipid syndrome
- Hereditary thrombophilia

aPTT, activated partial thromboplastin time; BMI, body mass index; INR, international normalized ratio.

1. Heit JA, *et al. Blood* 2011;118:4992–99. 2. Heit JA, *et al. Am J Hematol* 2012;87:S63–7.
3. Zhu T, *et al. Arterioscler Thromb Vasc Biol* 2009;29:298–310.

Clinical prediction scores for CTEPH
Derivation and validation studies



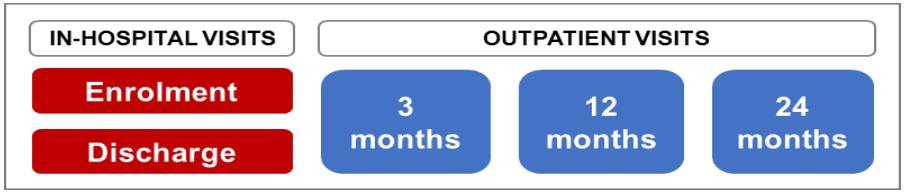
Predictors	Points
Unprovoked PE	+6
Known hypothyroidism	+3
Symptom onset > 2 weeks before PE diagnosis	+3
Right ventricular dysfunction on CT or echocardiography	+2
Known diabetes mellitus	-3
Thrombolytic therapy or embolectomy	-3

Derivation cohort of 772 patients with acute PE from 3 centers (overall CTEPH rate 2.8%)

Klok FA et al. *JTH* 2016;14:121-128

Structured follow-up after acute PE: A multicenter prospective cohort study

FOCUS.



Study objectives	To determine, over a 2-year follow-up period, the incidence of **CTEPH** or **post-PE impairment** after an index episode of acute PE
Co-primary outcomes	1) Confirmed diagnosis of CTEPH at any time during 2-year follow-up **2) 'Post-PE impairment' at ≥1 FU visit**: deterioration (compared with the previous visit or findings at discharge) by at least one category in ≥1 of *'a'* (echocardiographic) parameters plus deterioration in ≥1 of *'b'* (clinical, functional or laboratory) parameters
Number of patients/sites	1000/15
Estimated FPI/LPO	June 2014 – end 2018

FPI/LPO, first patient in, last patient out.

German Clinical Trials registry: DRKS00005939. Konstantinides SV *et al. J Thromb Thrombol* 2016;42:600–9.

Structured follow-up after acute PE: A multicenter prospective cohort study

Echocardiographic parameters of *post-PE impairment* between 2 visits (≥1 present):

Parameter		Classification
a1	RV basal diameter	≤4.2 cm *vs* >4.2 cm
a2	Right atrial (RA) end-systolic area	≤18 cm^2 *vs* >18 cm^2
a3	TAPSE	≤1.5 cm *vs* >1.5 cm
a4	Eccentricity index of the left ventricle	≤1.0 *vs* >1.0
a5	Estimated RA pressure	Normal *vs* intermediate *vs* high (based on inferior vena cava diameter and collapse with sniff)
a6	Tricuspid regurgitant (TR) velocity	<2.8 m/s *vs* 2.9–3.4 m/s *vs* >3.4 m/s
a7	Pericardial effusion	No *vs* yes

German Clinical Trials registry: DRKS00005939. FOCUS Steering Committee. *J Thromb Thrombol* 2016;42:600–9.

Structured follow-up after acute PE: A multicenter prospective cohort study

FOCUS.

Clinical, functional or laboratory parameters of *post-PE impairment* between 2 visits (≥1 present):

Parameter		Classification
b1	Clinical evidence of RV failure	No *vs* yes
b2	Rate of progression of symptoms	Slow (or none) *vs* rapid
b3	Syncope	No *vs* yes
b4	WHO functional class	I or II *vs* III or IV
b5	Cardiopulmonary exercise testing	Normal *vs* moderate *vs* severe impairment based on peak O_2 uptake and systolic BP
b6	Six-minute walking distance	>500 m *vs* 300–500 m *vs* <300 m
b7	BNP or NT-proBNP plasma levels	Normal or near-normal *vs* moderately elevated *vs* high

BNP, brain natriuretic peptide; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.
German Clinical Trials registry: DRKS00005939. FOCUS Steering Committee. *J Thromb Thrombol* 2016;42:600–9.

Systematic long-term follow-up after PE: Rationale for defining post-PE impairment

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65 % pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35 % pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65 %	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60 %

6MWD, 6-minute walking distance; CI, cardiac index; CMR, cardiac magnetic resonance; RAP, right atrial pressure; SVO_2, mixed venous oxygen saturation; VE/VCO_2, ventilatory equivalents for carbon dioxide; VO_2, oxygen consumption. Galiè N *et al. Eur Heart J* 2016;37:67–119.

Long-term follow-up after PE: CTEPH and ‘prodromi’ - preliminary data

	Tenecteplase (n=190)	Placebo (n=186)	*p* value
‘Post-PE impairment’	**16 (15.5%)**	**13 (13.4%)**	**0.67**

The PEITHO Investigators. *Unpublished data*.

PE follow-up protocol at Mainz University 2017

	Baseline	Discharge	3 months	12 months	24 months
Enrollment – informed consent	X				
Medical history	X				
Demographic data	X				
Clinical examination	X		X	X	X
Confirmation of pulmonary embolism (imaging)	X				
Echocardiography	X	X	X	X	X
Cardiopulmonary exercise testing			X	X	X
Laboratory diagnostic and safety tests	X		X	X	X
Hemodynamic collapse		X			
Death		X	X	X	X
Rehospitalization			X	X	X
Stroke		X	X	X	X
Symptomatic recurrent DVT/PE		X	X	X	X
Major bleeding/clinically relevant non-major bleeding		X	X	X	X
Functional status			X	X	X
Diagnostic work-up for CTEPH			X	X	X
Generic quality of life (EQ-5D questionnaire)			X	X	X
Disease-specific quality of life (PEmb-QoL questionnaire)			X	X	X

EQ-5D, EuroQol five dimensions questionnaire; PEmb-QoL, pulmonary embolism quality of life.

General recommendations on FU after PE in 2017

Recommendations	Class	Level
In PE survivors with persistent dyspnea, diagnostic evaluation for CTEPH should be considered	IIa	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended	III	C
It is recommended that, in all patients with CTEPH, the assessment of operability, and decisions regarding other treatment strategies, are made by a multidisciplinary team of experts	I	C
Life-long anticoagulation is recommended in all patients with CTEPH	I	C
Surgical PEA is recommended for patients with CTEPH	I	C
Riociguat is recommended in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team, including at least one experienced PEA surgeon, or have persistent/recurrent CTEPH after surgical treatment	I	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team, including at least one experienced PEA surgeon	IIb	B

Eur Heart J 2014:35:3145–3146

From acute PE to CTEPH: Where do we stand in 2017?

- Ongoing studies in animal models help to dissect the mechanisms mediating transition from acute PE to chronic ‘venous’ thrombosis and CTEPH.
- Early reperfusion therapy appears unable to prevent CTEPH development.
- Prevention of CTEPH is not, at present, an argument for indefinitely continuing anticoagulation after PE.
- Large prospective cohort studies with systematic follow-up and biobanking after PE may help determine which baseline or follow-up parameters may be **predictors or prodromi** of CTEPH, and possibly help to select patients for CTEPH screening after PE.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