Connecting acute pulmonary embolism with CTEPH

Implications for the follow-up strategy after PE

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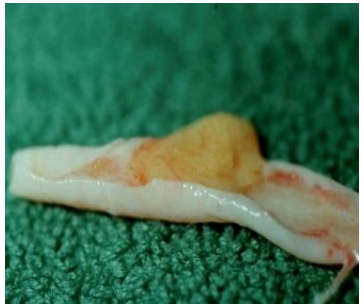
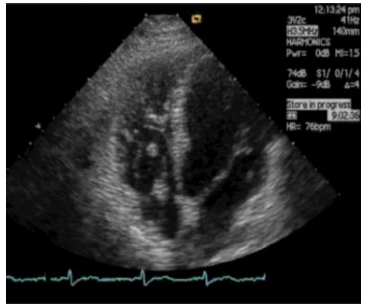
Connecting (?) acute PE to CTEPH

- Is CTEPH really a long-term complication/sequela of acute PE? Or is it a different disease?

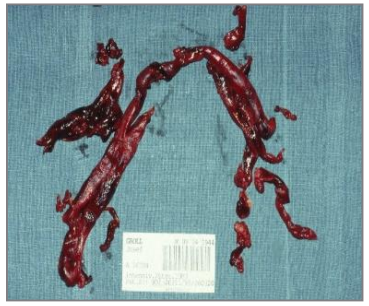
Is CTEPH a complication of PE?



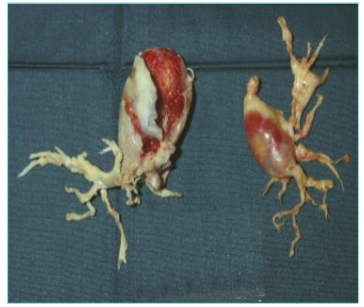
DVT



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.

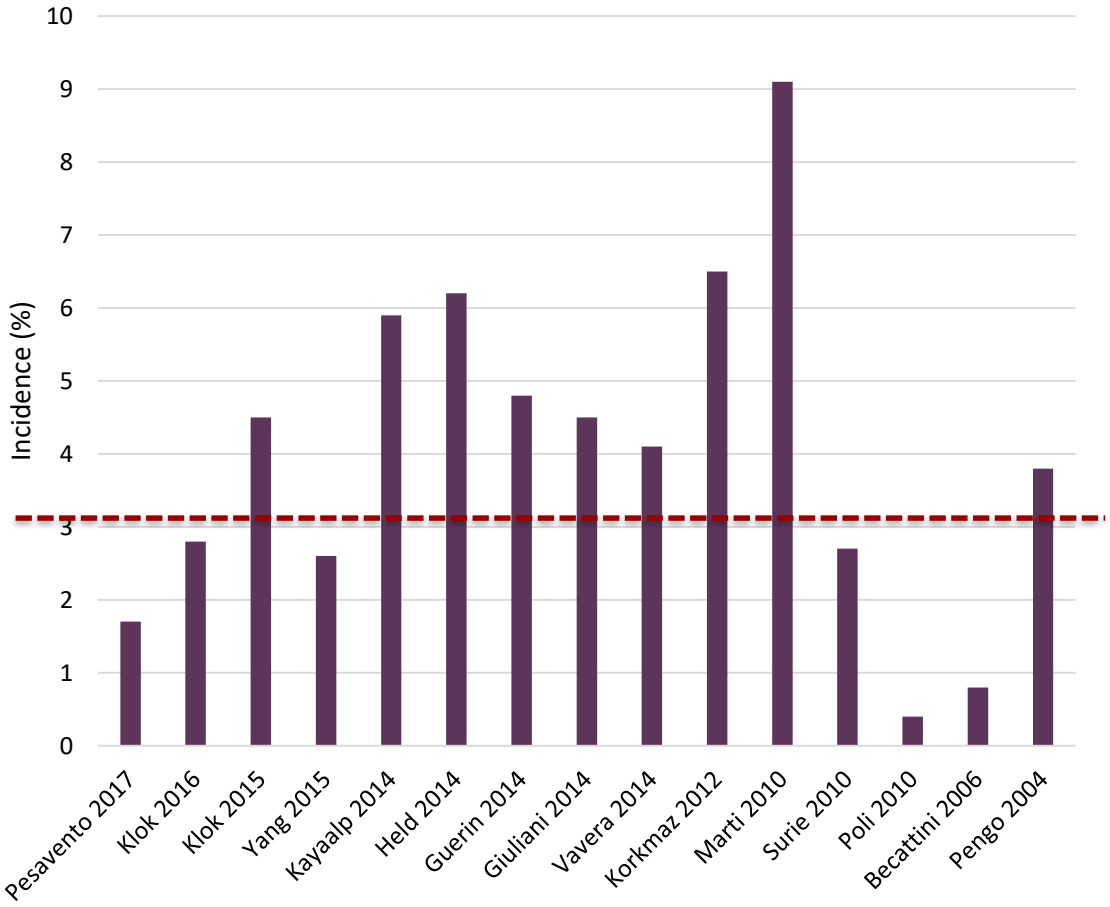
VTE a risk factor for CTEPH (?)

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; $p<0.001$
Antiphospholipid syndrome	4.20	1.6–12.2; $p=0.004$
Splenectomy	17.9	1.6–2438.1; $p=0.017$

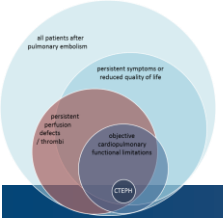
CI, confidence intervals. Bonderman D *et al. Eur Respir J* 2009;33:325–31.

How frequent is CTEPH after acute PE?



- large heterogeneity of published studies
- incidence ranges **from 0.4 to 9.1%**
- a meta-analysis reported an incidence of **3.2%** in survivors of pulmonary embolism

Ende-Verhaar YM et al., Eur Respir J 2017; 49:1601792
Konstantinides S, […] Lankeit M et al., J Thromb Thrombolysis 2016; 42:600-609



Not related to frequency of residual perfusion defects

Study	Patients	Follow-up	Imaging technique	Perfusion defects
Pesavento 2017	647	6 months	V/Q-scan	50%
Meysman 2017	46	6 months	Q-SPECT	52%
den Exter 2015	157	6 months	MDCT	16%
Pesavento 2014	113	6 months	MDCT	15%
Poli 2013	235	median 11 months	Q-scan	26%
Alonso-Martinez 2012	120	mean 5 months	MDCT	26%
Cosmi 2011	173	mean 9 months	MDCT / Q-scan	15% MDCT 28% Q scan
Sanchez 2010	254	median 12 months	V/Q scan	29%

Factors associated with (predisposing to?) to CTEPH after PE

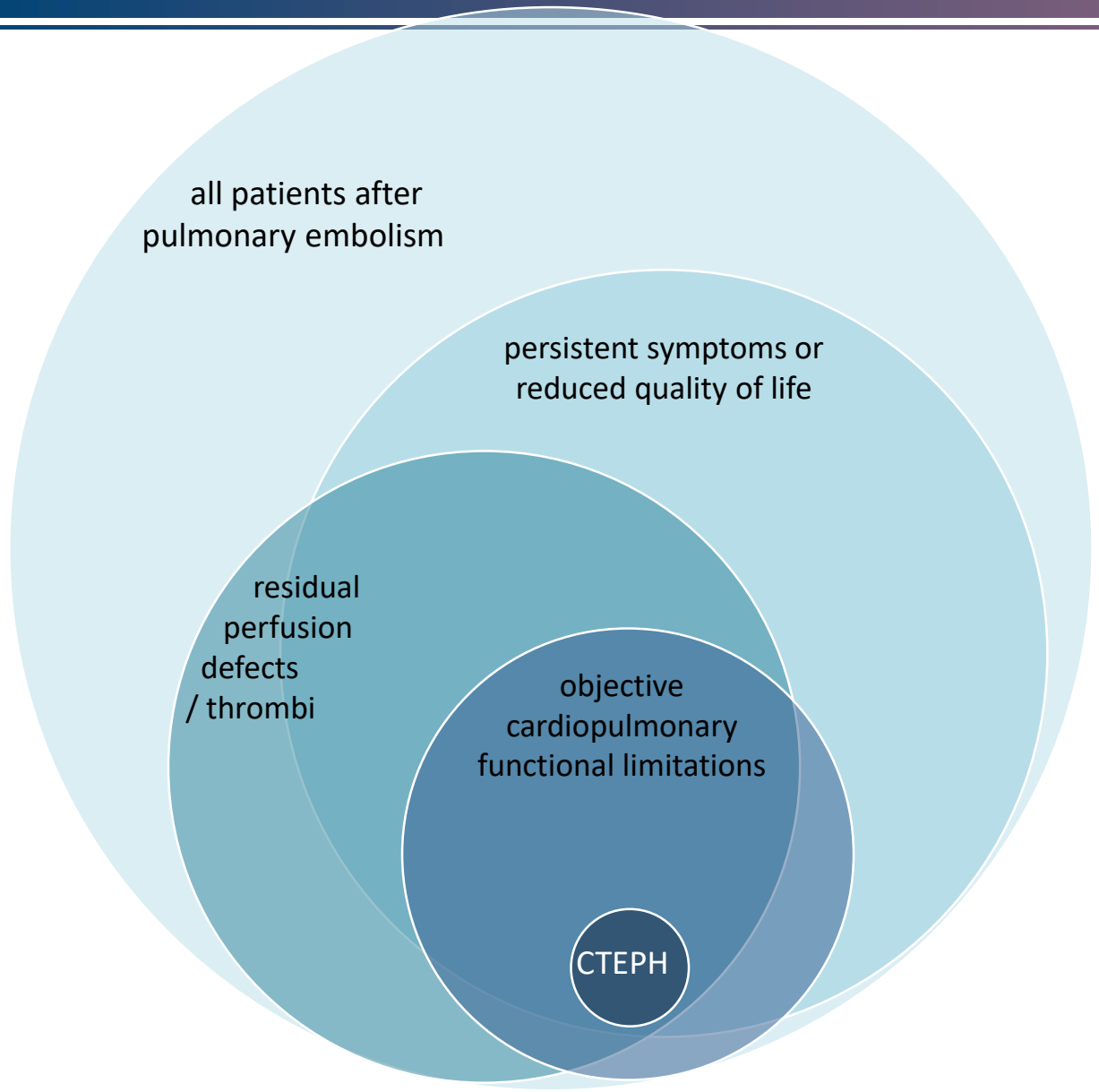
Findings at baseline (index PE event)		Conditions other than index PE	
Echo: Elevated sPAP, >60 mmHg	☐	Myeloproliferative disorders	☐
Echo/CT: RV pressure overload	☐	History of malignancy	☐
CT: Central thrombi	☐	Splenectomy	☐
CT: signs of pre-existing CTEPH*	☐	Inflammatory bowel disease	☐
		Chronic osteomyelitis	☐
		Antiphospholipid syndrome	☐
		Hypothyroidism	☐
		Ventriculo-atrial shunts	☐
		Chronic central venous lines	☐
		Pacemakers	☐

Pepke-Zaba J, Delcroix M, Lang I, et al. *Circulation*. 2011;124(18):1973-81.
Bonderman D, Wilkens H, Wakounig S, et al. *Eur Respir J* 2009;33(2):325-31.
Lang IM, Simonneau G, Pepke-Zaba JW, et al. *Thromb Haemost* 2013;110(1):83-91.

Connecting (?) acute PE to CTEPH

- Which are the patients‘ most frequent problems after PE?

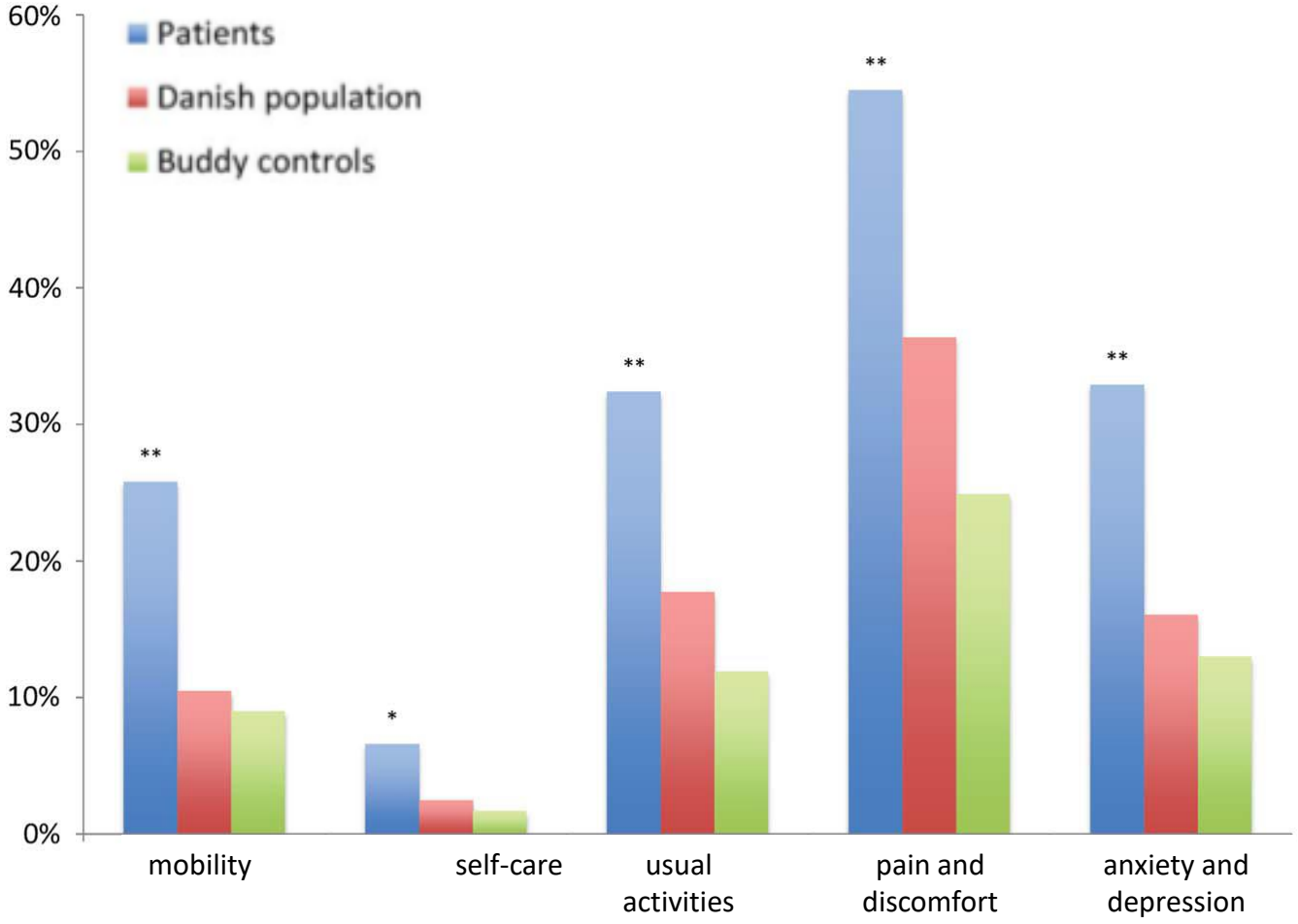
Persisting symptoms and functional limitation



- 50 % of patients report persistent symptoms or reduced quality of life
- 10-30 % of patients have cardiopulmonary functional limitation
- 25-33 % of patients have residual perfusion defects / persistent thrombi
- 0.4 to 9.1 % of patients develop CTEPH

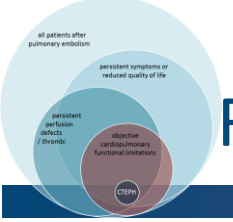
Klok FA, […], Lankeit M et al., *Blood Reviews* 2014; 28:221-226

Quality of life after pulmonary embolism

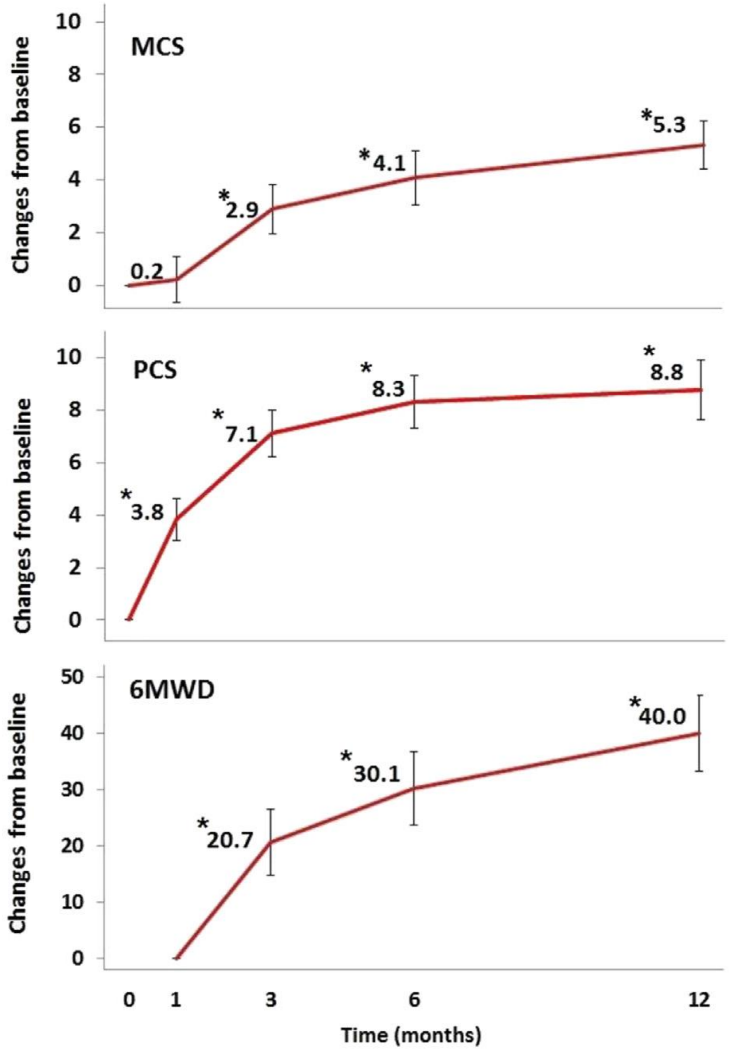


Tavoly M et al., BMJ Open 2016; 6:e013086

- Patients who survived PE have a reduced health-related quality of life.
  Tavoly M et al., BMJ Open 2016; 6:e013086, van Es J et al., Thromb Res 2013; 132:500-505
- Disease-specific quality of life can be assessed using the *Pulmonary Embolism Quality of Life* (PEmb-QoL) questionnaire.
  Cohn DM et al., J Thromb Haemost 2009; 7:1044-1046
- Quality of life is impaired by a reduced functional capacity and persistent dyspnoea



Functional limitation after pulmonary embolism



ELOPE cohort study: 100 patients followed 1, 3, 6 and 12 months after pulmonary embolism at 5 Canadian hospitals 2010-2013

- Quality of life, dyspnoea and walking distance improved during the first year after pulmonary embolism

  Kahn SR et al., Am J Med 2017; 130:e9-990.e21

- **47% of patients hat a V_{O2} peak <80% on CPET after 1 year**

  Kahn SR et al., Chest 2017; 151:1058-1068

Meta-analysis including 26 studies (3,671 patients) with 18-month follow-up

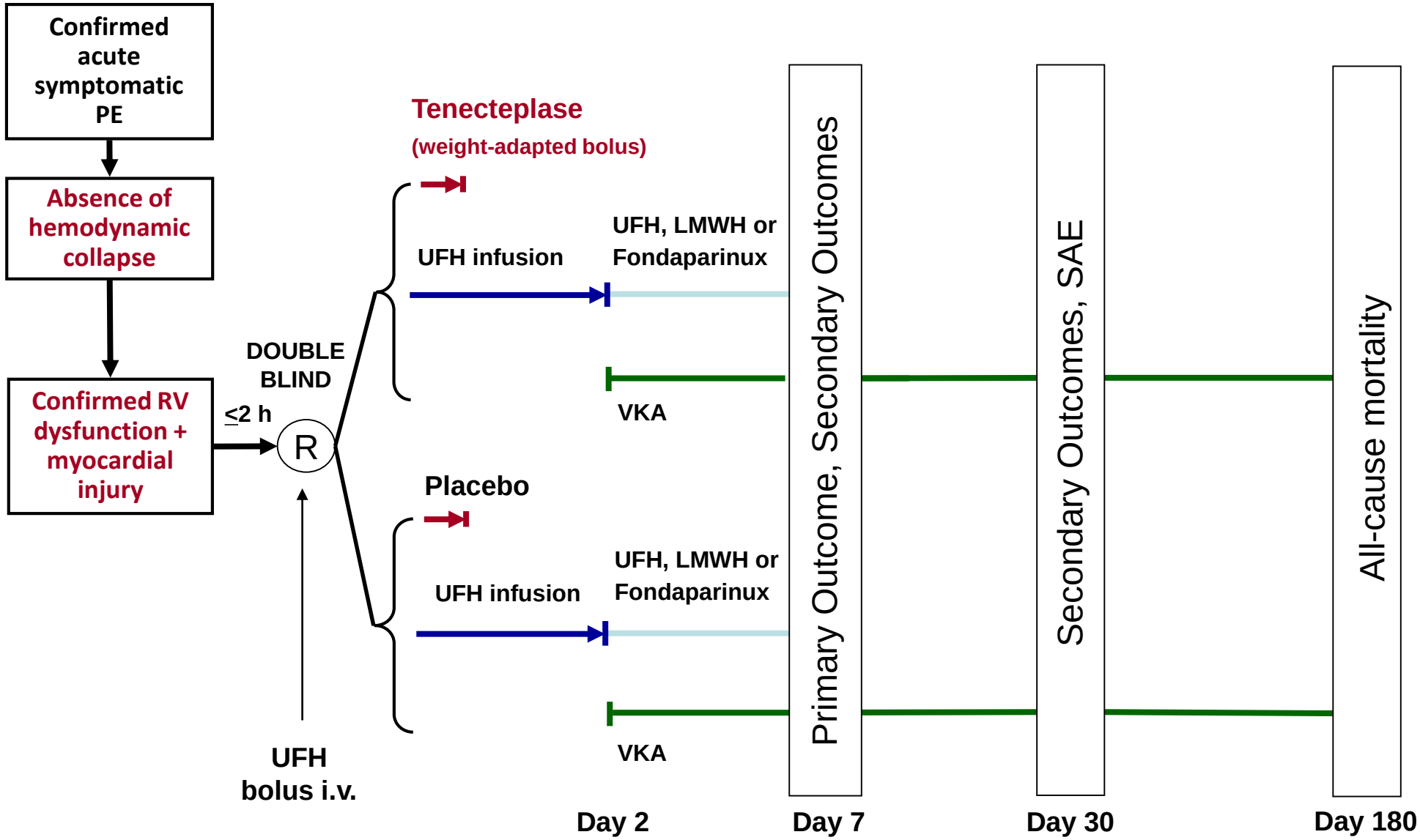
- Functional limitations after pulmonary embolism are common: 18 % had RV dysfunction and 11% NYHA III/IV
- Effects of treatment (e.g. thrombolysis, duration of anticoagulation) unclear

Sista AK et al., Vasc Med 2017; 22:37-43

The PE perspective

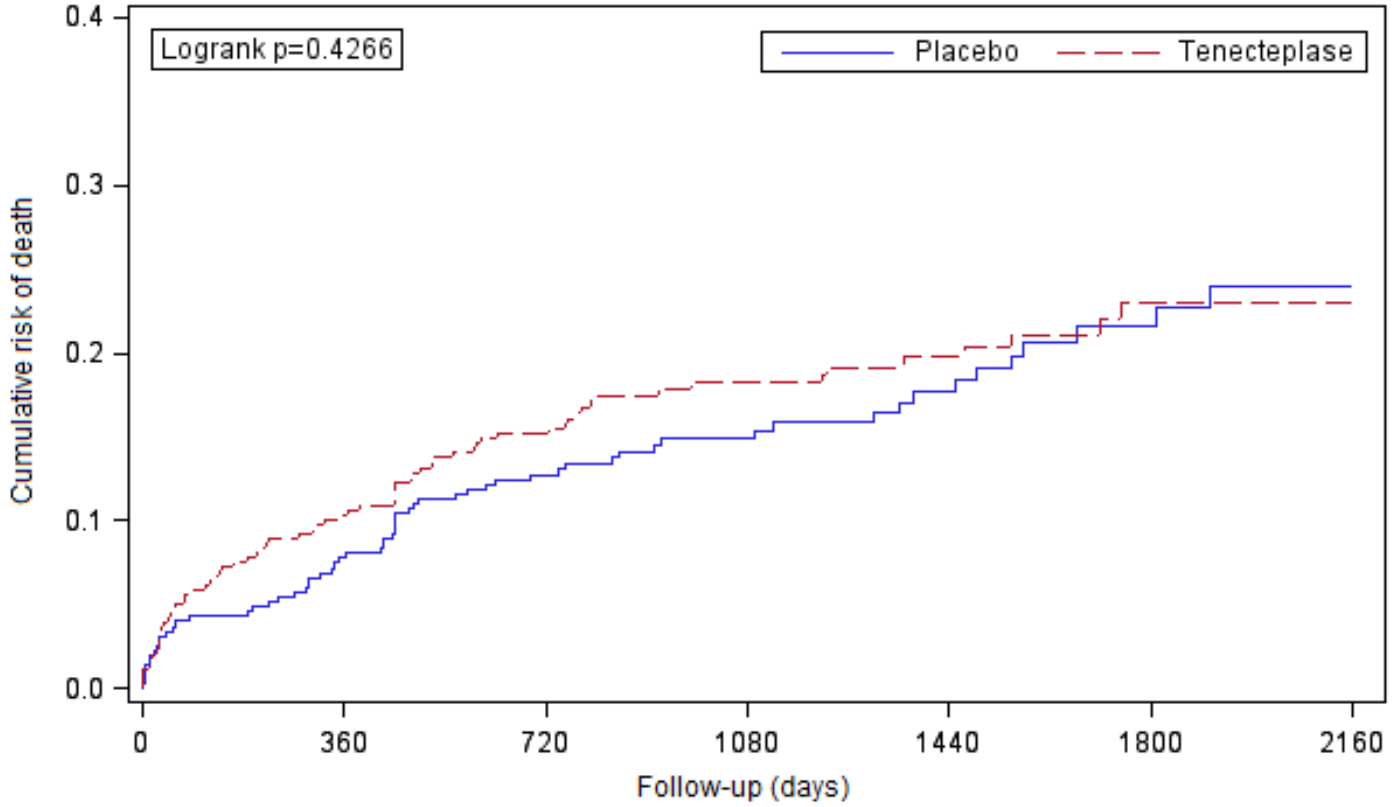
- Patient follow-up after acute PE: What did we learn from the PEITHO trial?

Reperfusion for intermediate-high risk? PEITHO



Konstantinides S *et al*, for the PEITHO Investigators. *Am Heart J* 2012;163:33-38.e1

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;69:1536-1544

PEITHO long-term FU: clinical & functional status (41.6±15.7 months)

	Tenecteplase (n=175)	Placebo (n=183)	*P* value
Persisting clinical symptoms	63 (36.0%)	55 (30.1%)	0.23
of them, exertional dyspnea	55	50	
exertional chest pain	4	0	

The PEITHO Investigators. *J Am Coll Cardiol* 2017;69:1536-1544

PEITHO long-term FU: echo findings

	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	12 (8.3%)	13 (8.9%)	0.834
Missing data	5 (3.5)	7 (4.8)	
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)	

The PEITHO Investigators. *J Am Coll Cardiol* 2017;69:1536-1544

PEITHO long-term FU: CTEPH

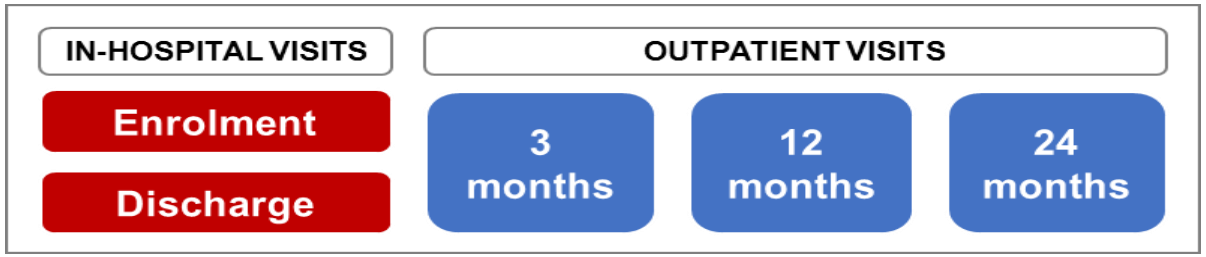
	Tenecteplase (n=190)	Placebo (n=186)	*P* value
CTEPH confirmed	**4 (2.1%)**	**6 (3.2%)**	**0.79**

The PEITHO Investigators. *J Am Coll Cardiol* 2017;69:1536-1544

The PE perspective

- What further data can we expect in the future? What can we recommend today?

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



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

German Clinical Trials registry: DRKS00005939

The FOCUS Investigators. *J Thromb Thrombol* 2016;42:600–609

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

FOCUS.

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:
Ongoing multicenter prospective cohort study

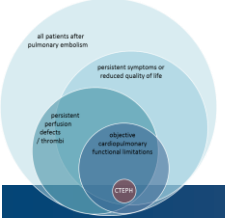
FOCUS.

Clinical, functional and 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.

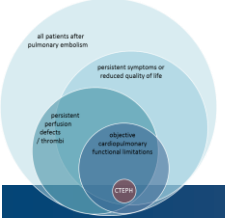
German Clinical Trials registry: DRKS00005939. FOCUS Steering Committee. *J Thromb Thrombol* 2016;42:600–9.



Selecting candidates for regular FU, CTEPH workup: Where do we stand today?

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

Eur Heart J 2014:35:3145–3146



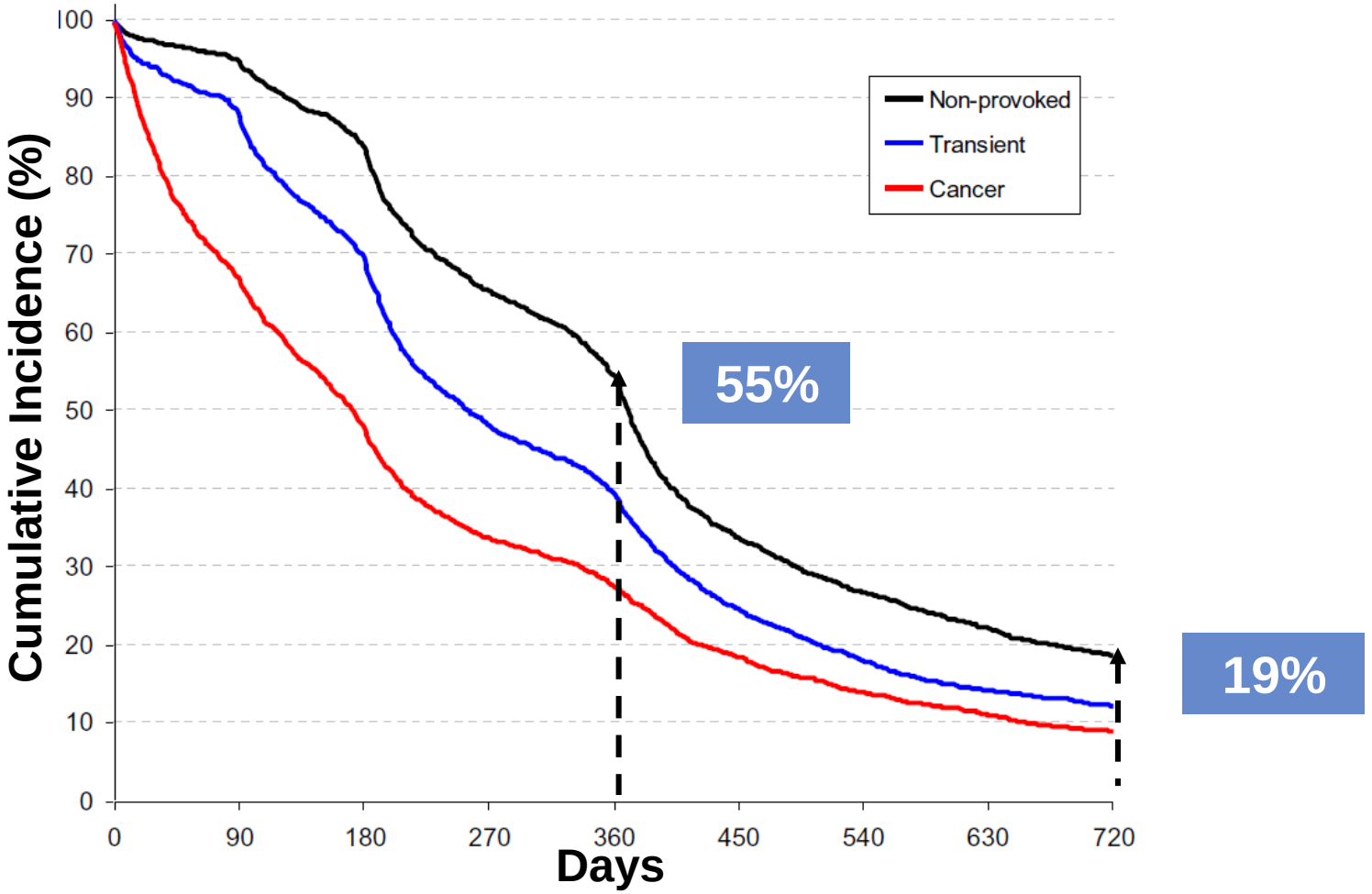
No screening for CTEPH means no follow-up?

Acute PE

Follow-up at 3-6 months, on OAC

Duration of anticoagulation after VTE in real world

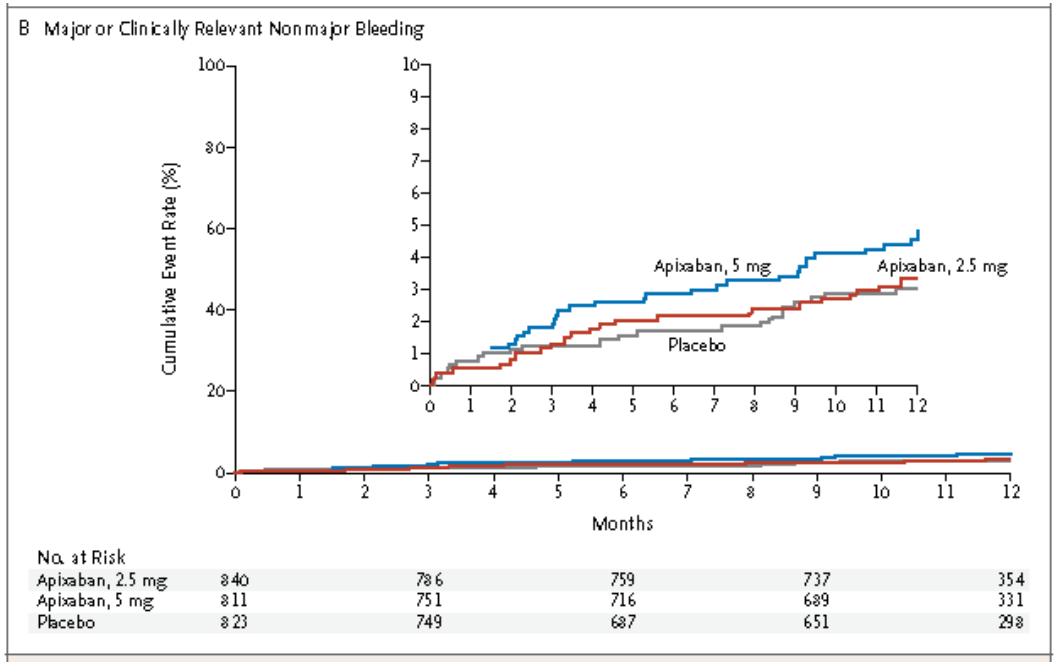
RIETE Registry (N=6944)



Ageno W, et al. *Thromb Res* 2015;135:666–672

Extended prophylaxis with *half-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 were given for 12 months
- 2482 pts included in ITT
- **Primary EP**: 8.8% in placebo vs. 1.7% in EACH apixaban dose

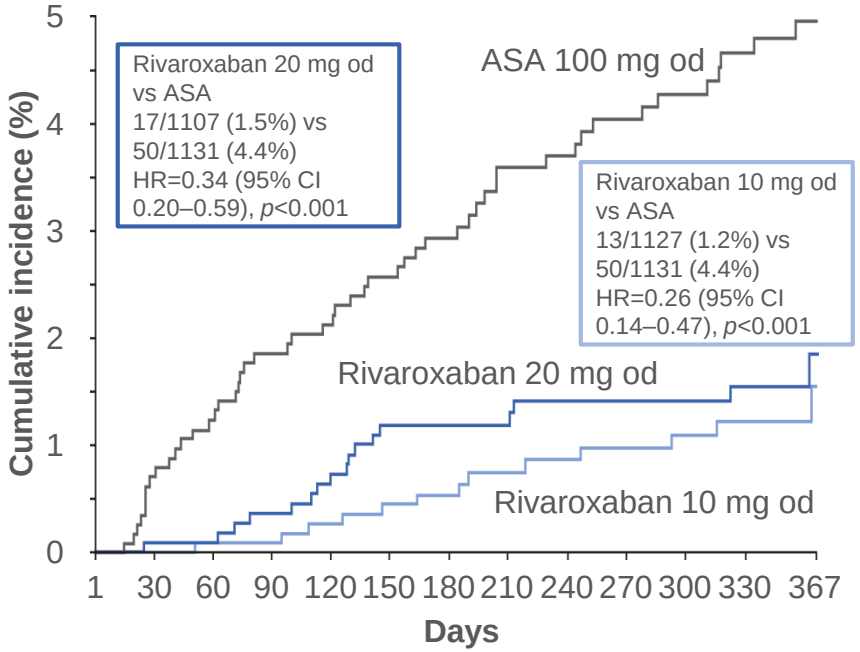


Major / CRNM bleeding:
2.7% vs. 3.2% (2.5 mg) vs. 4.3% (5 mg)

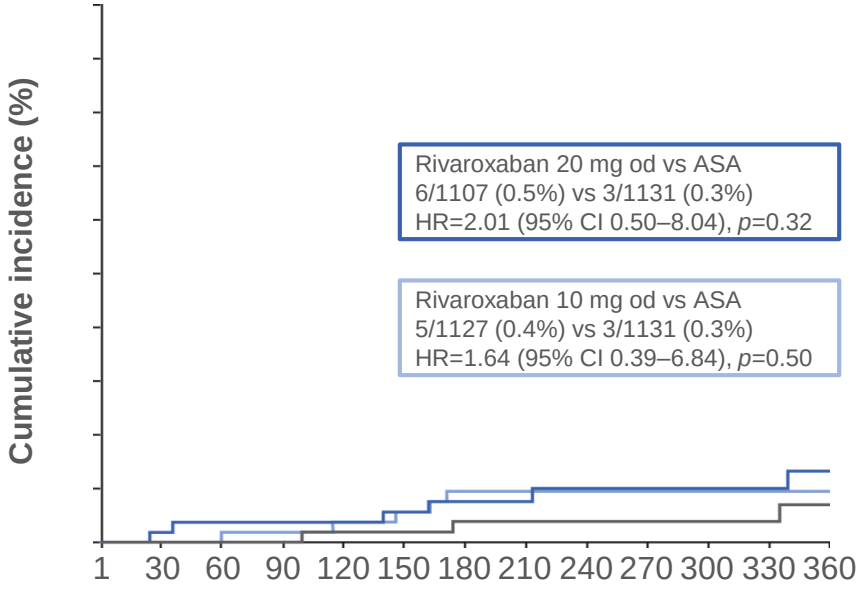
Agnelli G, for the AMPLIFY Investigators. *N Engl J Med* 2013;368:799-808

Extended prophylaxis with *half-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

Challenge: in whom to continue and with which dose?

Early recurrence[1]

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

Late recurrence[2,3]

Strong established factors

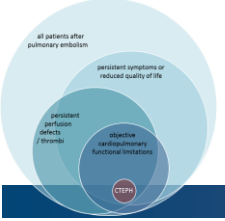
- Unprovoked (vs provoked) VTE
- More than one VTE event
- On-going hormonal therapy
- Elevated D-dimer levels after/during VKA treatment

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.



How could a ‘post-PE’ algorithm look like?

Acute PE

Follow-up at 3-6 months, ON A/C

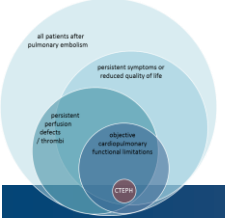
Are you short of breath? Are you limited in your daily activities? Is it worse than before PE?

YES, I have symptoms / functional limitation

Echo, lab (NT-proBNP), CPET(?)

NO, I am fine

?

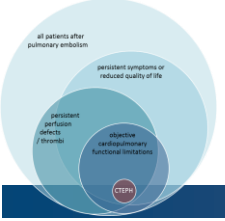


Probability of pulmonary hypertension on echo

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;



Check for ‘CTEPH risk factors’ at FU!

Findings at baseline (index PE event)		Conditions other than index PE	
Echo: Elevated sPAP, >60 mmHg	☐	Myeloproliferative disorders	☐
Echo/CT: RV pressure overload	☐	History of malignancy	☐
CT: Central thrombi	☐	Splenectomy	☐
CT: signs of pre-existing CTEPH*	☐	Inflammatory bowel disease	☐
		Chronic osteomyelitis	☐
		Antiphospholipid syndrome	☐
		Hypothyroidism	☐
		Ventriculo-atrial shunts	☐
		Chronic central venous lines	☐
		Pacemakers	☐

Pepke-Zaba J, Delcroix M, Lang I, et al. *Circulation*. 2011;124(18):1973-81.
Bonderman D, Wilkens H, Wakounig S, et al. *Eur Respir J* 2009;33(2):325-31.
Lang IM, Simonneau G, Pepke-Zaba JW, et al. *Thromb Haemost* 2013;110(1):83-91.

Acute PE --> ‘post-PE syndrome’ --> CTEPH: Where do we stand in 2018?

- Early reperfusion affects NEITHER late mortality NOR persistent symptoms in survivors of acute PE; these are determined by underlying disease/comorbidity.
- Large prospective cohort studies with systematic FU programs may help determine which baseline or FU parameters may be *predictors or prodromi* of CTEPH/CTED, and help to select patients for CTEPH screening in the future.
- For the time being, the aim of post-PE follow-up programmes should be to exclude, with simple tests, the small probability of CTEPH within the large group of patients with persisting symptoms, mostly due to **deconditioning or comorbidity**.
- In selected cases, CTEPH screening might also be performed in patients who deny symptoms but have **predisposing** factors.