Very Small or Very Large Pulmonary Emboli – What Is the Best Treatment?

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Disclosures

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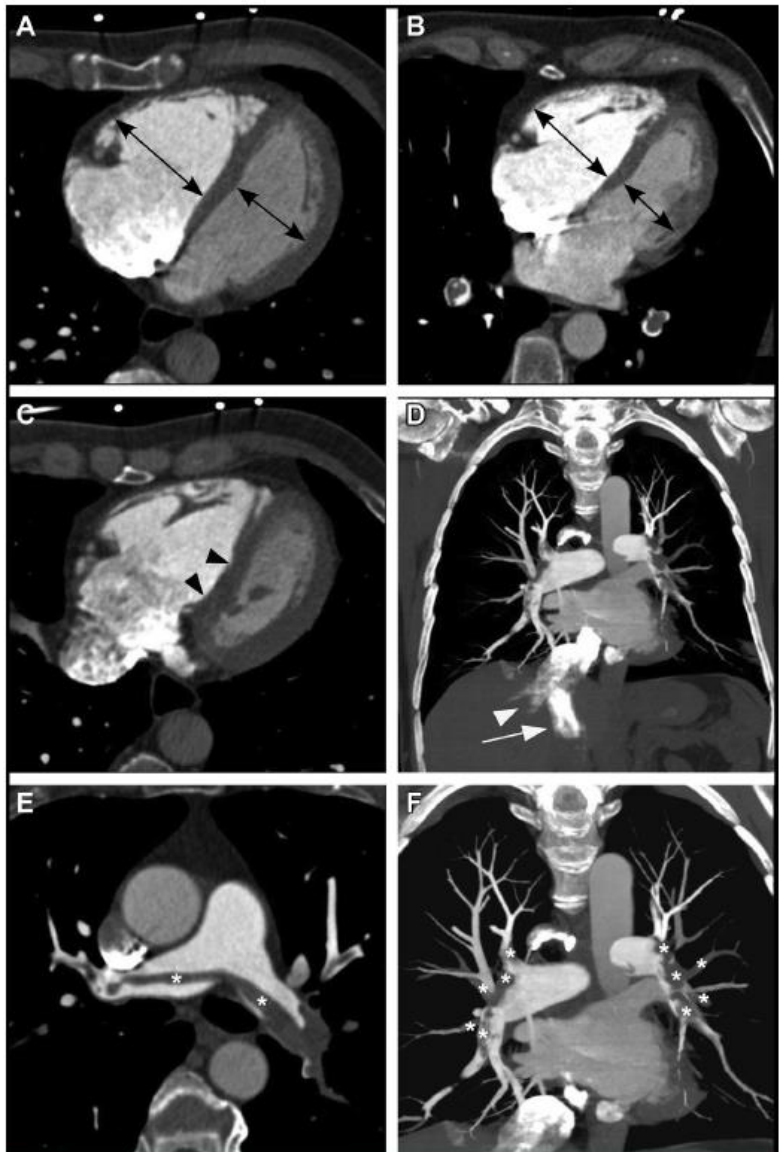
‘Small’ versus ‘large’ PE: more than thrombus size!



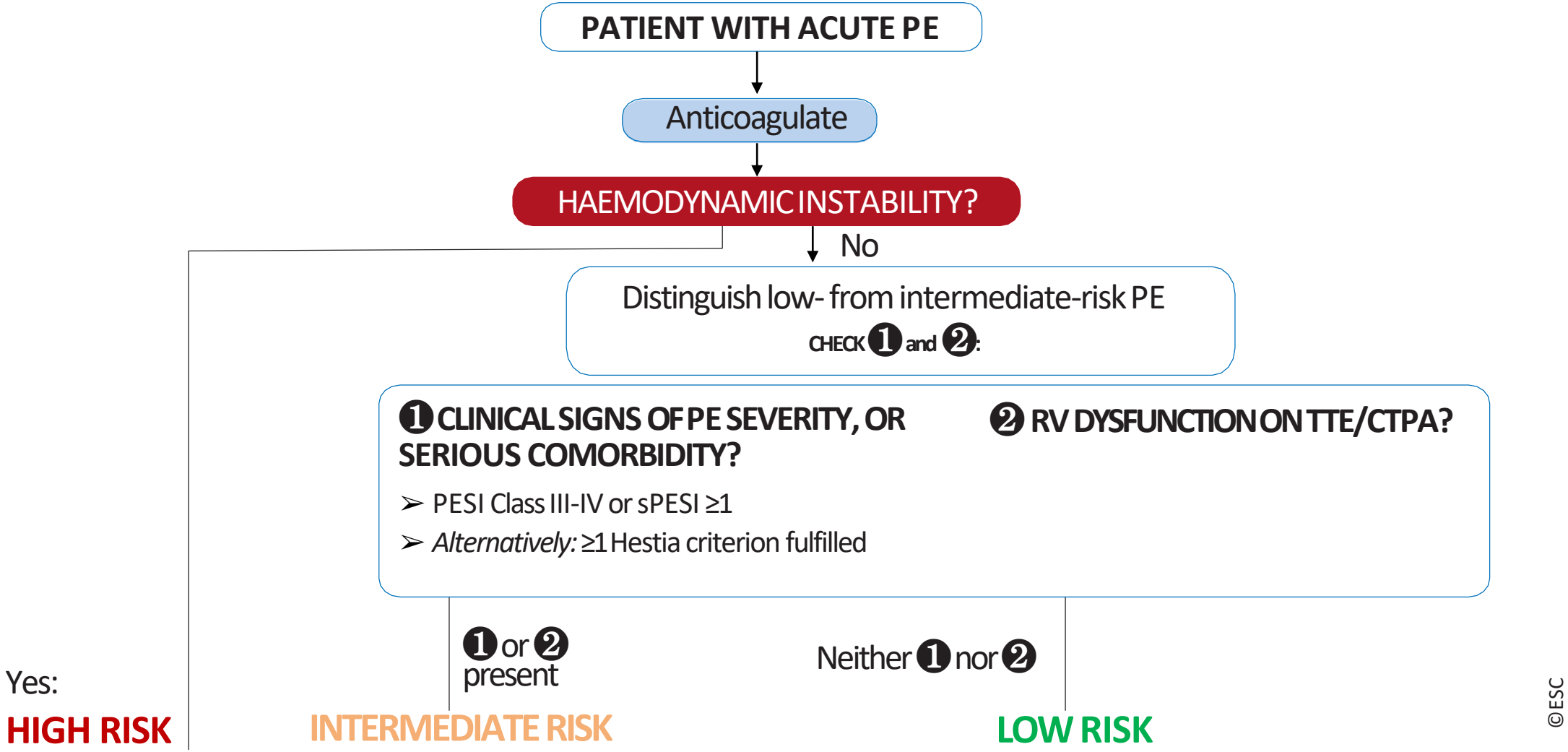
RESULTS: A total of 49 studies with 13,162 patients with acute PE.

“Abnormally **increased RV/LV diameter ratio** measured on transverse sections associated with an approximately 2.5-fold risk for all-cause mortality (pooled OR, 2.5; 95% CI, 1.8-3.5) and adverse outcome (OR, 2.3; 95% CI, 1.6-3.4) and a 5-fold risk for PE-related mortality (OR, 5.0; 95% CI, 2.7-9.2).

Thrombus load and central location were not predictive for all-cause mortality, although both were associated with adverse clinical outcome.”

Meinel MG, et al. *Am J Med* 2015;128:747-759

From defining 'size' → defining clinical severity of PE



2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2020;41(4):543-603

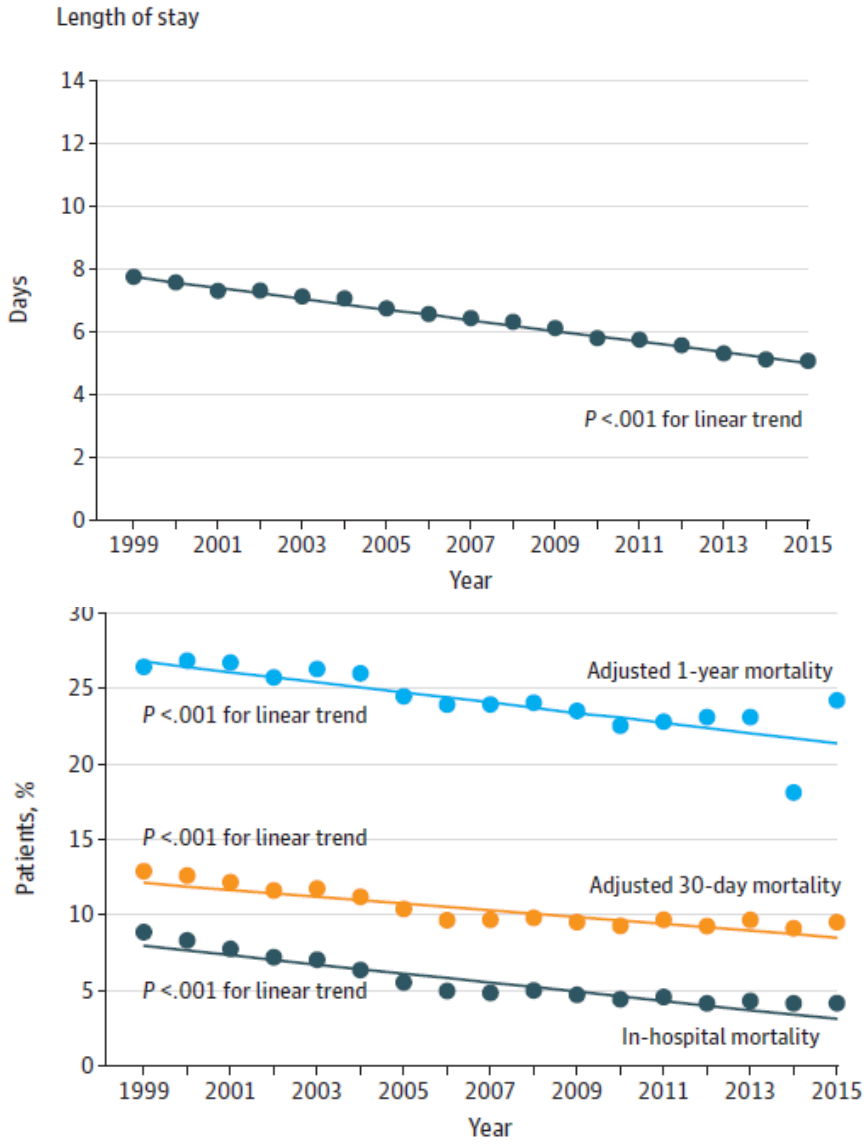
Which is the best treatment for acute ‘small’ PE?

1) The impact of ‘very small’ PE on epidemiological measures and trends
2) Uncertainties in the treatment of ‘very small' PE

PE case fatality rates: trends (US)

810,969 patients (Medicare), ≥65 yoa; principal discharge diagnosis PE (ICD-9), 1999-2015

- Mean age constant, 77.6 years
- Comorbidities (MI, stroke) ↓
- Proportion of men ↑, from 36.7% to 43.8%
- ↓ unadjusted in-hospital case fatality rate from 8.7% to 4.0%
- ↓ adjusted 30-day case fatality rate from 12.7% to 9.4%
- ↓ length of stay from 7.7 to 5.0 days

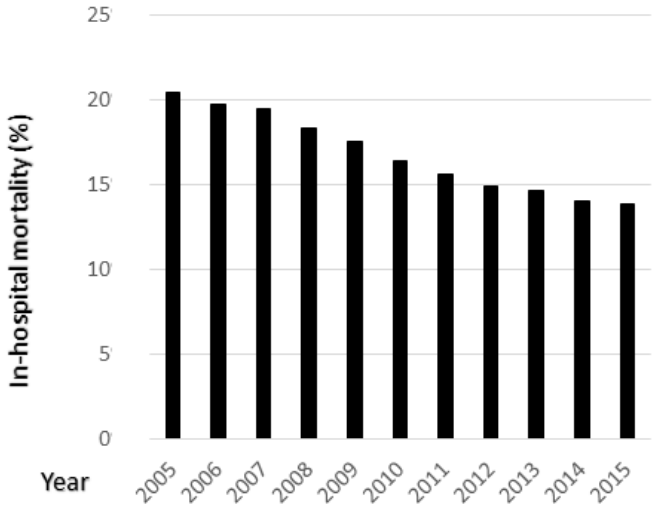


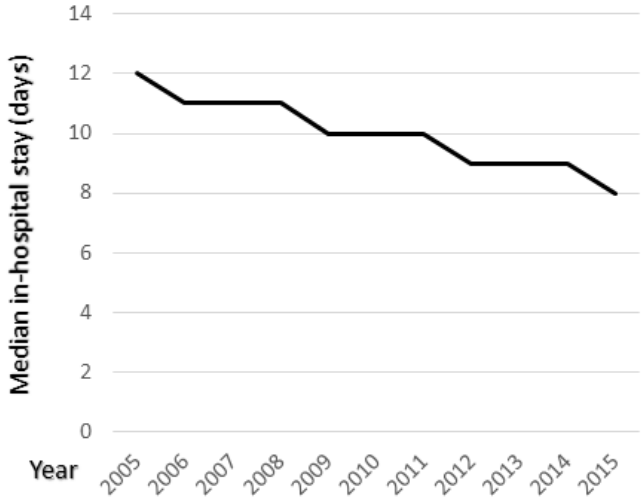
Bikdeli B, et al. *JAMA* 2019;322:574-576

PE case fatality rates: trends (Europe)

885,806 patients hospitalized for acute PE (ICD-10 I26) in Germany between 2005 and 2015

- ↓ in-hospital case fatality rate from 20.4% to 13.9%
- ↓ length of stay from 12 to 8 days





Keller K, et al. *Eur Heart J* 2019. doi:10.1093/eurheartj/ehz236

Author, Year	Country	Period covered	Registry database	Population *(N)*	30-day mortality	Length of stay
Jiménez, 2016	Europe	2001-2013	RIETE	23,858	**6.7% ↘ 4.9%**	**13.6 ↘ 9.3 days**

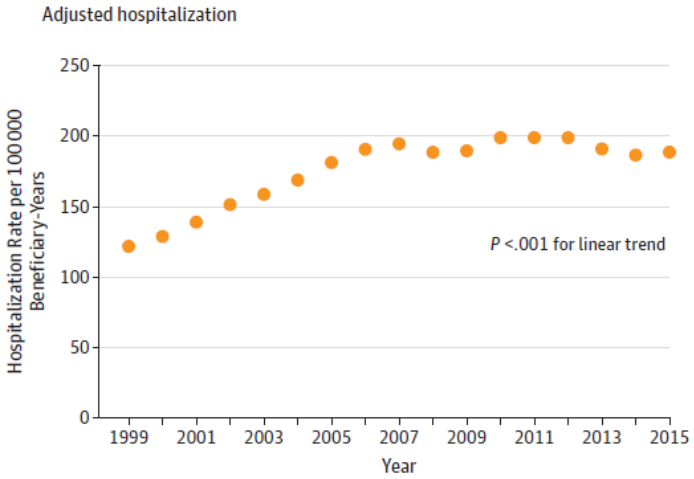
J Am Coll Cardiol 2016;67:976-990

PE incidence in US and Europe: OPPOSITE trends

810,969 patients (Medicare), ≥65 yoa, principal discharge diagnosis PE (ICD-9), 1999-2015

- ↻ annual hospitalization rate from 120 ↗ 187 per 100,000 beneficiaries

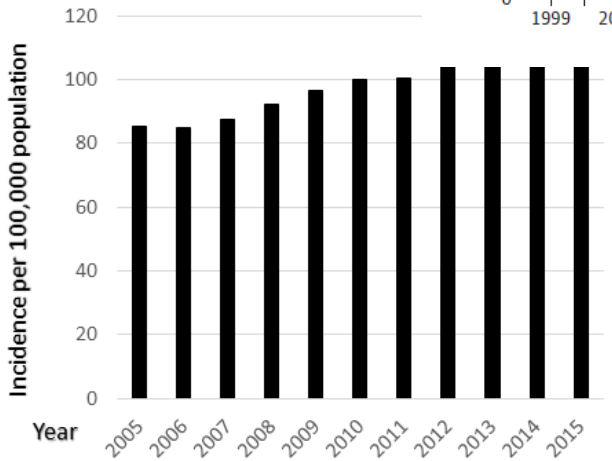
Bikdeli B, et al. *JAMA* 2019;322:574-576



885,806 patients hospitalized for PE (ICD-10 I26) in Germany, 2005-2015

- ↻ annual incidence rate from 85 ↗ 109 per 100,000 population

Keller K, et al. *Eur Heart J* 2019. doi:10.1093/eurheartj/ehz236

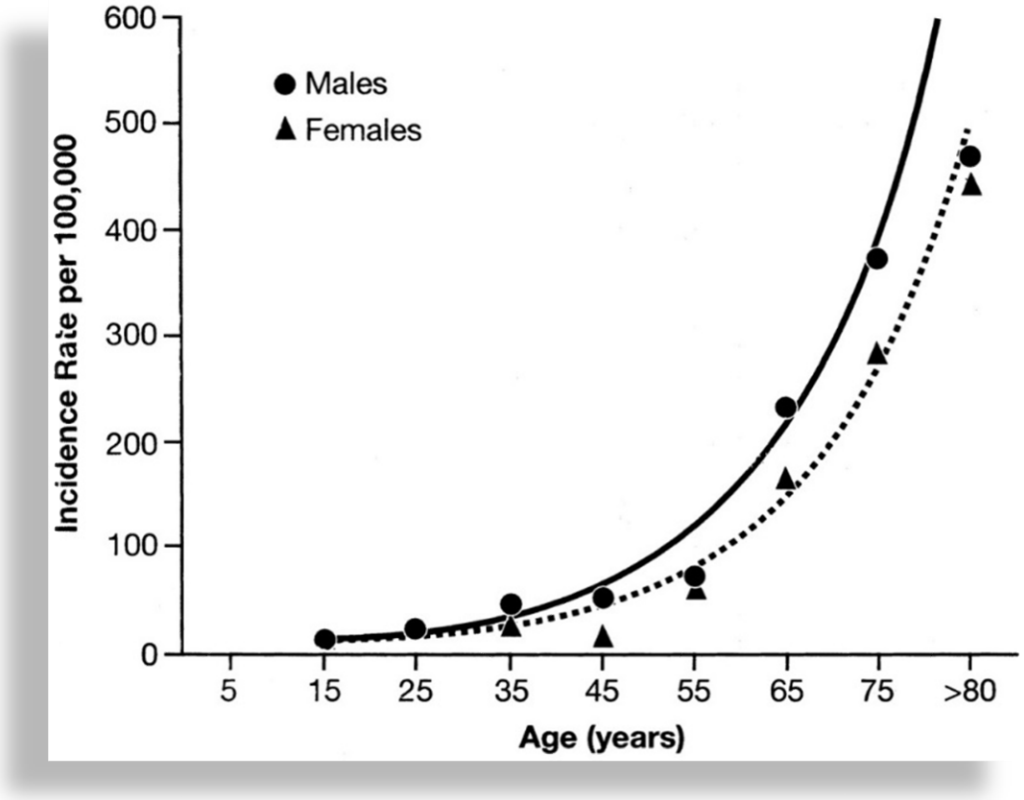


Danish population of 4,301,000, *first-time* acute PE (ICD-10 I26), 2004-2014

- ↻ annual incidence rate from 45 ↗ 84 per 100,000 population

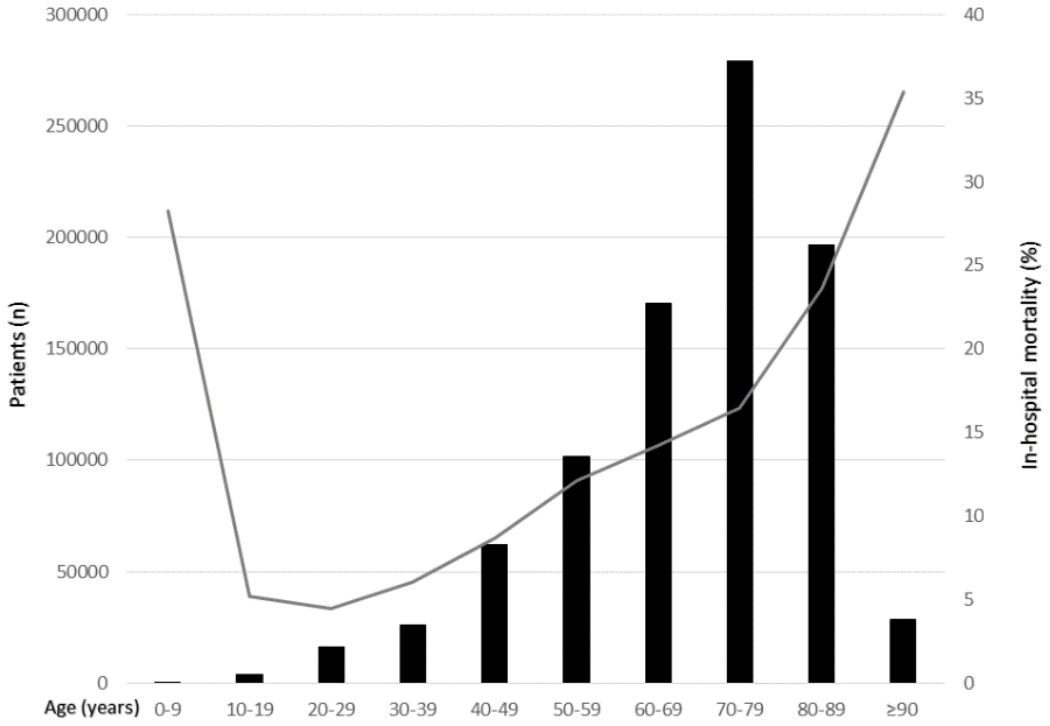
Lehnert P, et al. *Thromb Haemost* 2018;118:539-546

Why are incidence rates rising? An ageing population



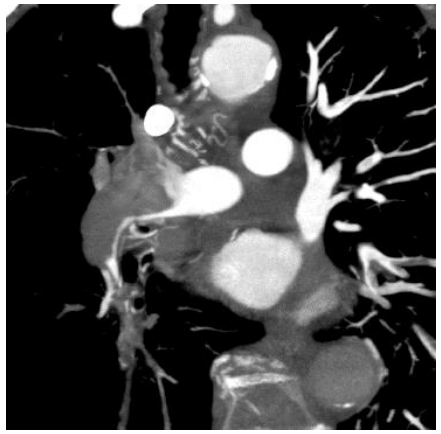
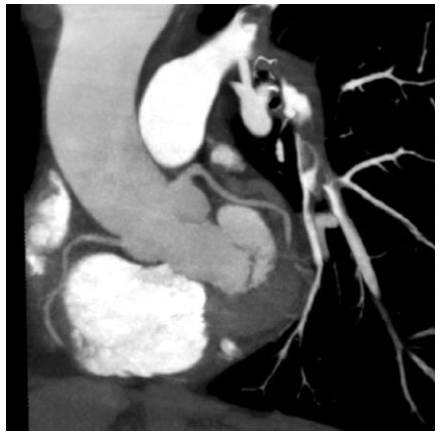
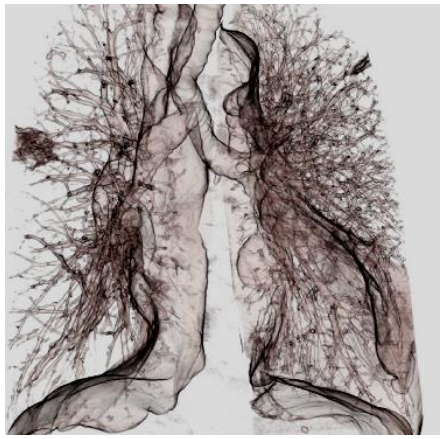
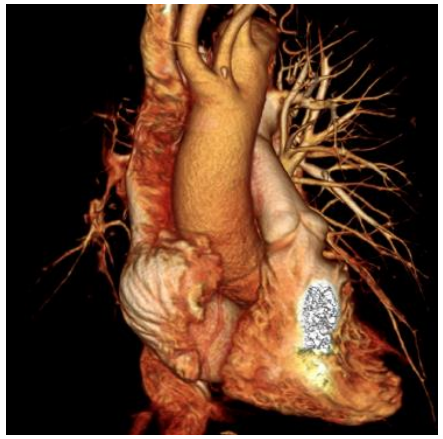
White RH et al. *Circulation* 2003;107:I-4;
Anderson FA et al. *Arch Int Med* 1991;151:933-938

Bars: numbers of patients per age group.
Line: in-hospital mortality rate



Keller K, et al. *Eur Heart J* 2019. doi:10.1093/eurheartj/ehz236

Why are incidence rates rising? Overuse of CTPA

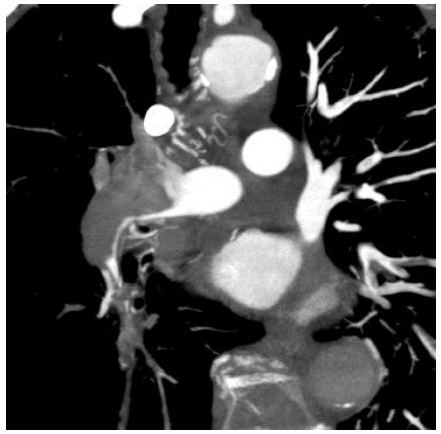
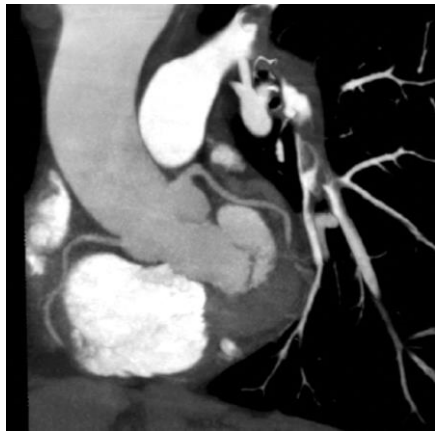
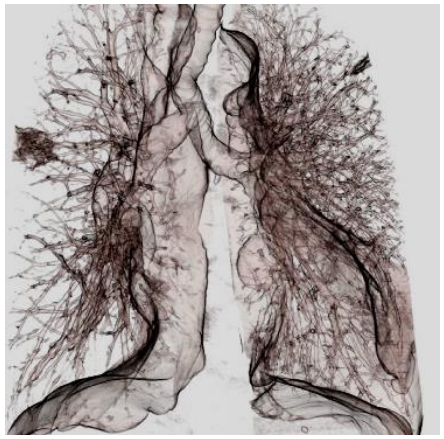
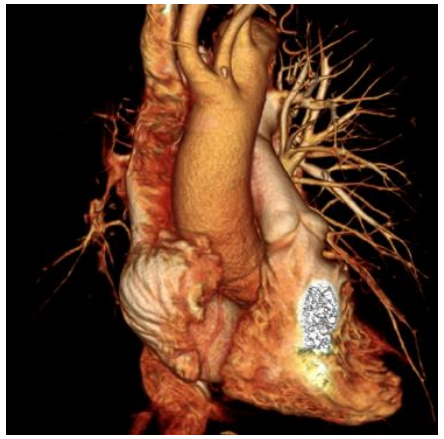
1993-1998 versus 1998-2006:

- PE incidence: unchanged before CTPA,
  ↑ 81% after CTPA
- Case fatality: ↓ before CTPA,
  ↓ 36% after CTPA
- Presumed complications of anticoagulation ↑ 71% after CTPA

Schulman S, Ageno W, Konstantinides S. *Thromb Haemost* 2017;117:1219-1229
Photos: Courtesy KF Kreitner, University Medical Center Mainz

Wiener RS. *Arch Intern Med* 2011;171:831-837

How important is *very small* PE? Does it need treatment?

Schulman S, Ageno W, Konstantinides S. *Thromb Haemost* 2017;117:1219-1229
Photos: Courtesy KF Kreitner, University Medical Center Mainz

Retrospective studies: **sub-segmental PE** on local reading, without associated DVT, no anticoagulation

Study	n	Recurrent VTE	95% CI
Eyer 2005	25*	0	(0-13.7)
Le Gal 2006	8	0	(0-32.4)
Donato 2010	22	0	(0-15.4)
Pena 2012	18	0	(0-18.5)
Goy 2015	37**	0	(0-9.5)

Eyer BA, et al. *AJR* 2005;184:623–8
Le Gal G. et al, *J Thromb Haemost* 2006; 4: 724–3
Donato AA, et al. *Thromb Res* 2010; 126: e266–70
Pena, et al. *J Thromb Haemost* 2012; 10: 496–8
Goy J, et al. *J Thromb Haemost* 2015; 13: 214–8

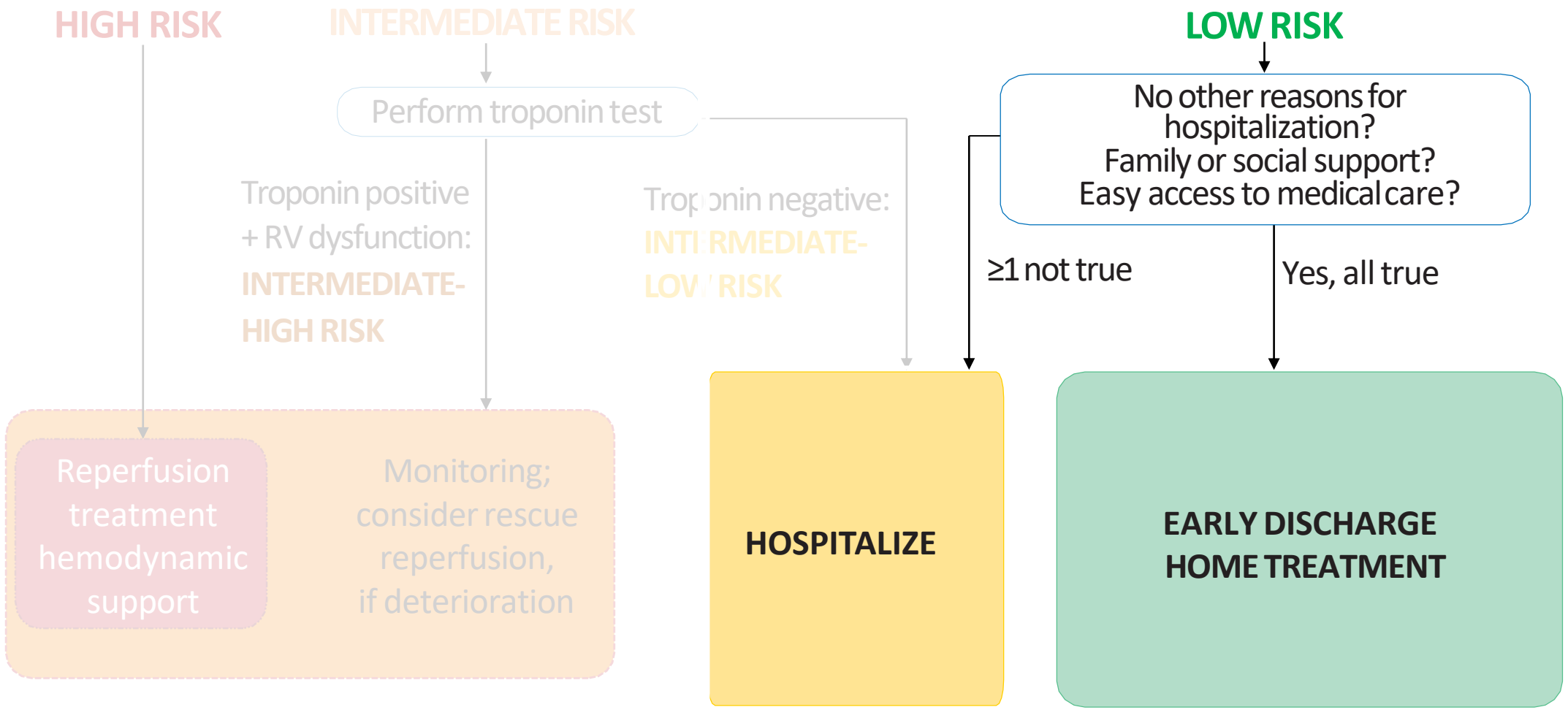
*: 25 with follow-up among 32 patients
**: no systematic search for DVT

Management of subsegmental / incidental PE

Clinical setting	Suggested management[a]	Comments
Subsegmental PE	Single subsegmental PE in an outpatient without cancer and without proximal DVT: • Clinical surveillance. Single subsegmental PE in a hospitalized patient, a patient with cancer, or if associated with confirmed proximal DVT: • Anticoagulant treatment. Multiple subsegmental PE: • Anticoagulant treatment.	• Poor interobserver agreement for the diagnosis of subsegmental PE; diagnosis to be confirmed by an experienced thoracic radiologist. • Suggestion based on indirect evidence, only limited data available.

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2020;41(4):543-603

What else is important for low-risk PE?



CTPA = computed tomography pulmonary angiography; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; TTE = transthoracic echocardiography.

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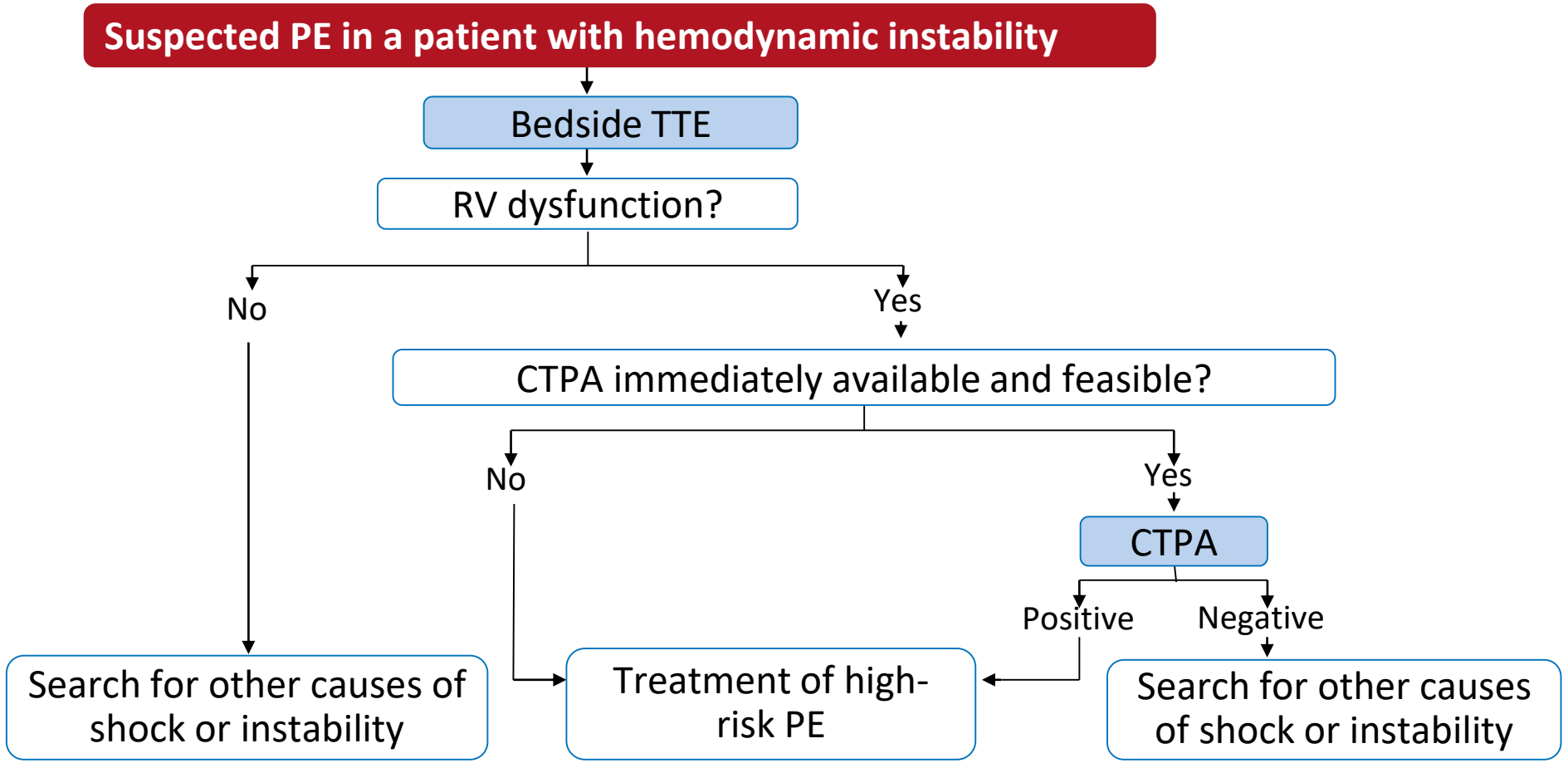
Which is the best treatment for acute ‘very large’ PE?

1) Priorities in acute PE with hemodynamic instability (high risk)
2) Priorities in acute intermediate-risk (‘submassive’) PE

Which are the priorities in acute high-risk PE?



CTPA = computed tomography pulmonary angiography; RV = right ventricular; TTE = transthoracic echocardiography

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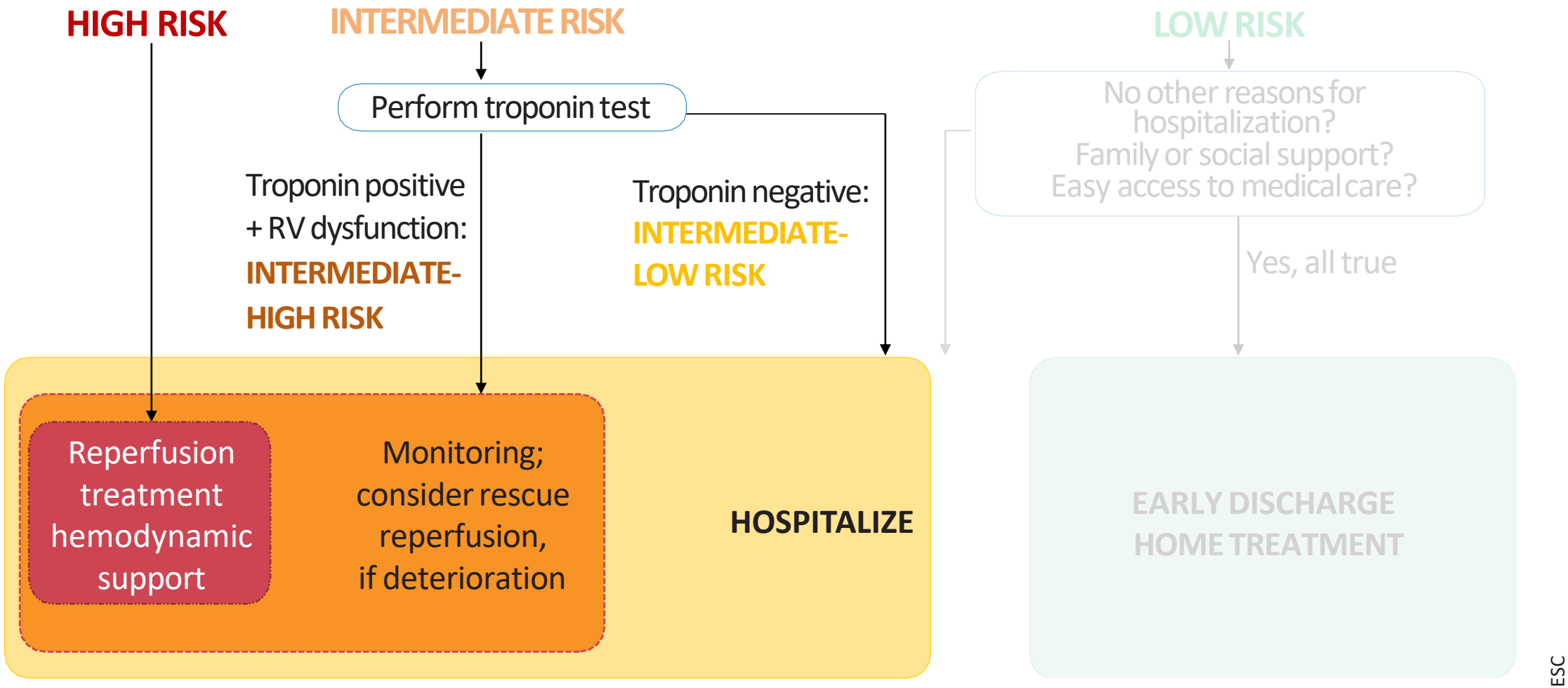
Which criteria for ‘best treatment’ in an acute situation?

- It should work in everyone and everywhere
- It should be standardized, depend as little as possible on operator
- It should be instituted promptly and work fast
- It should be safe
- It should be broadly available
- It should be affordable
- It should be backed by solid scientific and clinical evidence

Integrated risk-adapted management of PE



CTPA = computed tomography pulmonary angiography; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; TTE = transthoracic echocardiography.

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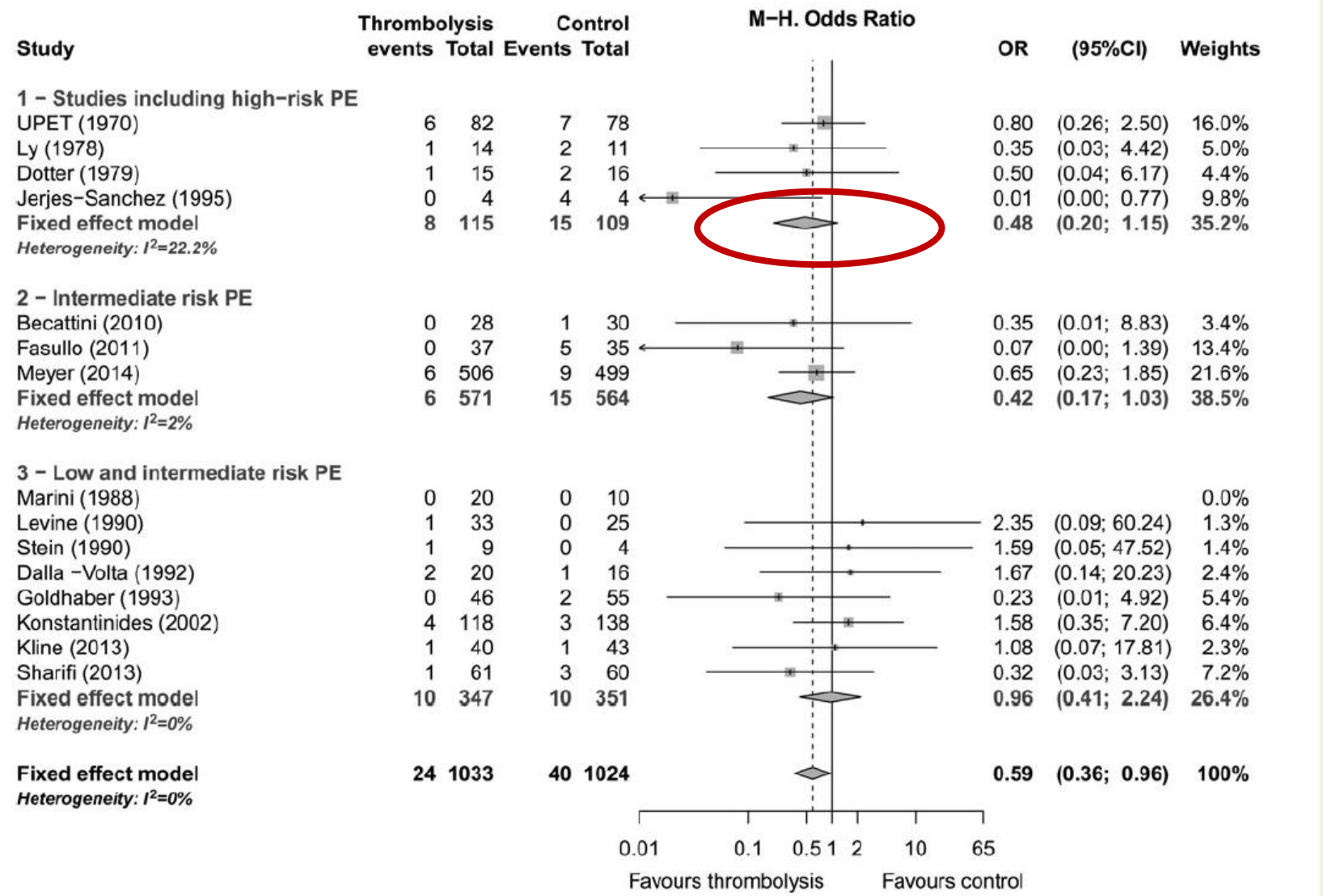
Systemic thrombolysis – efficacy (death↓): Meta-analysis



Marti C et al. *Eur Heart J* 2015; 36:605-614

Systemic thrombolysis – efficacy (all): Meta-analysis

	All studies			Studies including[a] High-risk PE	Intermediate-risk PE	Low and intermediate-risk PE	Group difference
	OR (95% CI)	*P*-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P*-value
Mortality	0.59 (0.36 to 0.96)	0.034	0	0.48 (0.20 to 1.15)	0.42 (0.17 to 1.03)	0.96 (0.41 to 2.24)	0.36
PE mortality	0.29 (0.14 to 0.60)	<0.001	0	0.15 (0.03 to 0.78)	0.17 (0.05 to 0.67)	0.63 (0.20 to 1.97)	0.23
Death or treatment escalation	0.34 (0.22 to 0.52)	<0.001	0	0.18 (0.04 to 0.79)	0.37 (0.20 to 0.69)	0.35 (0.18 to 0.66)	0.67
PE recurrence	0.50 (0.27 to 0.94)	0.031	0	0.97 (0.31 to 2.98)	0.25 (0.06 to 1.03)	0.46 (0.17 to 1.21)	0.33

[a]Not exclusively.

Marti C et al. *Eur Heart J* 2015; 36:605-614

Systemic thrombolysis – safety (bleeding): Meta-analysis

	All studies			Alteplase	Tenecteplase	Other thrombolytics	Group difference
	OR (95% CI)	*P*-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P*-value
Major bleeding	2.91 (1.95 to 4.36)	<0.001	25	1.07 (0.43 to 2.62)	5.02 (2.72 to 9.26)	2.16 (1.03 to 4.54)	0.02
Fatal/intracranial haemorrhage	3.18 (1.25 to 8.11)	0.008	0	1.09 (0.27 to 4.40)	7.32 (1.64 to 32.63)	NA	0.07

Marti C et al. *Eur Heart J* 2015; 36:605-614

Thrombolysis ‘first-line treatment’ in high-risk PE?

- ✓ It works in everyone and everywhere
- ✓ It is standardized, depends as little as possible on individual operator
- ✓ It can be instituted promptly and works fast
- ☹ It is safe
- ✓ It is broadly available
- ✓ It is affordable
- 😐 It is backed by solid scientific and clinical evidence

Recommendations for high-risk PE

Recommendations	Class	Level
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.[a]	I	C
Systemic thrombolytic therapy is recommended for high- risk PE.	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.	I	C

[a] After haemodynamic stabilization of the patient, continue anticoagulation as in intermediate- or low-risk PE.

UFH = unfractionated heparin.

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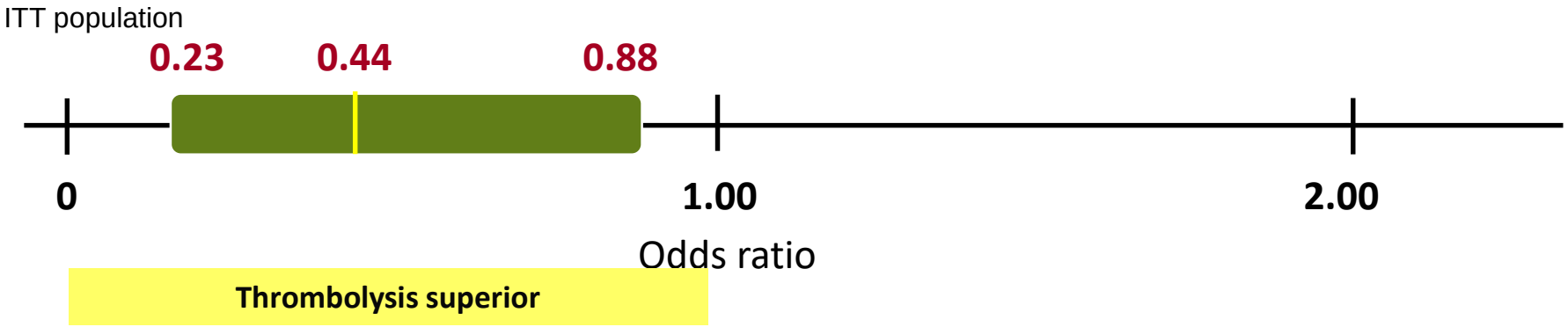
Which is the best treatment for acute ‘large’ PE?

1) Priorities in acute PE with hemodynamic instability (‘massive’)
2) Priorities in acute intermediate-risk (‘submassive’) PE

PEITHO: Systemic thrombolysis is effective

	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 *et al*, for the PEITHO Investigators. *N Engl J Med* 2014;370:1402-11

PEITHO: Systemic thrombolysis is unsafe

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
Non-intracranial bleeding					
Major	32	(6.3)	6	(1.5)	<0.001
Minor	165	(32.6)	43	(8.6)	<0.001
Strokes by day 7	**12**	**(2.4)**	**1**	**(0.2)**	**0.003**
Hemorrhagic	10		1		
Ischaemic	2		0		

Meyer G *et al*, for the PEITHO Investigators. *N Engl J Med* 2014;370:1402-11

No helpful ‘thrombolysis bleeding scores’ exist

Derived from 9,703 patients of the *nationwide in-patient sample database* (NIS) 2003-2012

1.8% suffered intracranial bleeding

Prognostic variable	Odds ratio	Upper 95 % CI	Lower 95 % CI	P-value	Points assigned in PE-CH
Peripheral vascular disease	1.59	2.90	1.12	0.049	1
Prior myocardial infarction	1.80	1.99	1.33	0.046	1
Age>65 (Elderly)	1.99	1.97	2.01	0.007	1
Prior CVA	30.90	36.5	27.21	<0.001	5

Chatterjee S, et al. *Thromb Haemost 2017;*117:246-251

Thrombolysis as ‘first-line treatment’ in intermediate risk?

- ✓ It works in everyone and everywhere
- ✓ It is standardized, depends as little as possible on individual operator
- ✓ It can be instituted promptly and is fast
- ☹ It is not safe
- ✓ It is broadly available
- ✓ It is affordable
- ☹ It is not backed by solid evidence

Recommendations for intermediate-risk PE

Recommendations	Class	Level
Reperfusion treatment		
Rescue thrombolytic therapy is recommended for patients with haemodynamic deterioration on anticoagulation treatment.	I	B
As an alternative to rescue thrombolytic therapy, surgical embolectomy or percutaneous catheter- directed treatment should be considered for patients with haemodynamic deterioration on anticoagulation treatment.	IIa	C
Routine use of primary systemic thrombolysis is not recommended in patients with intermediate- or low-risk PE.	III	B

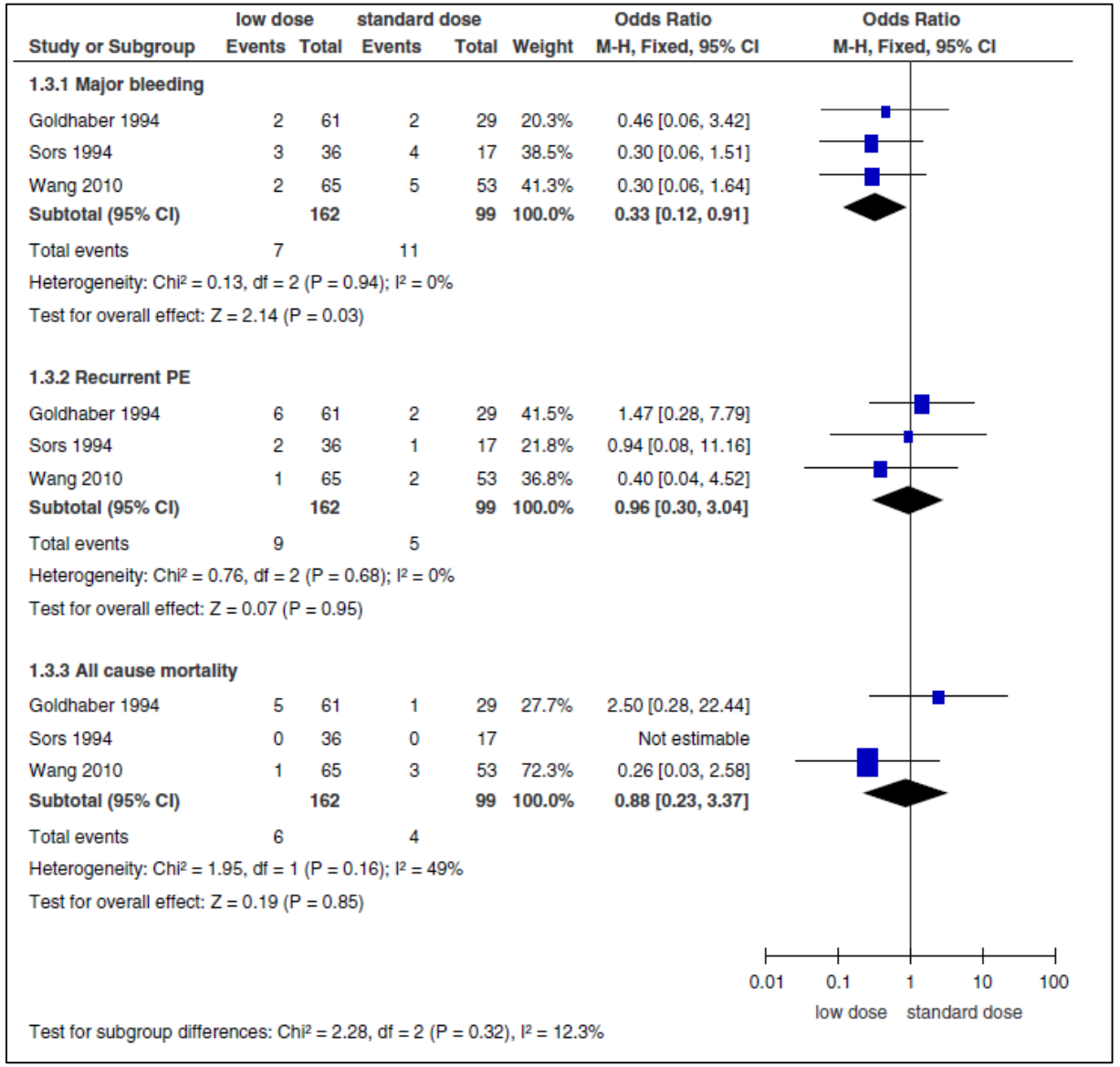
2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2020;41(4):543-603

Improving safety with systemic reduced-dose lysis?

Hardly available data

Reduced versus standard dose

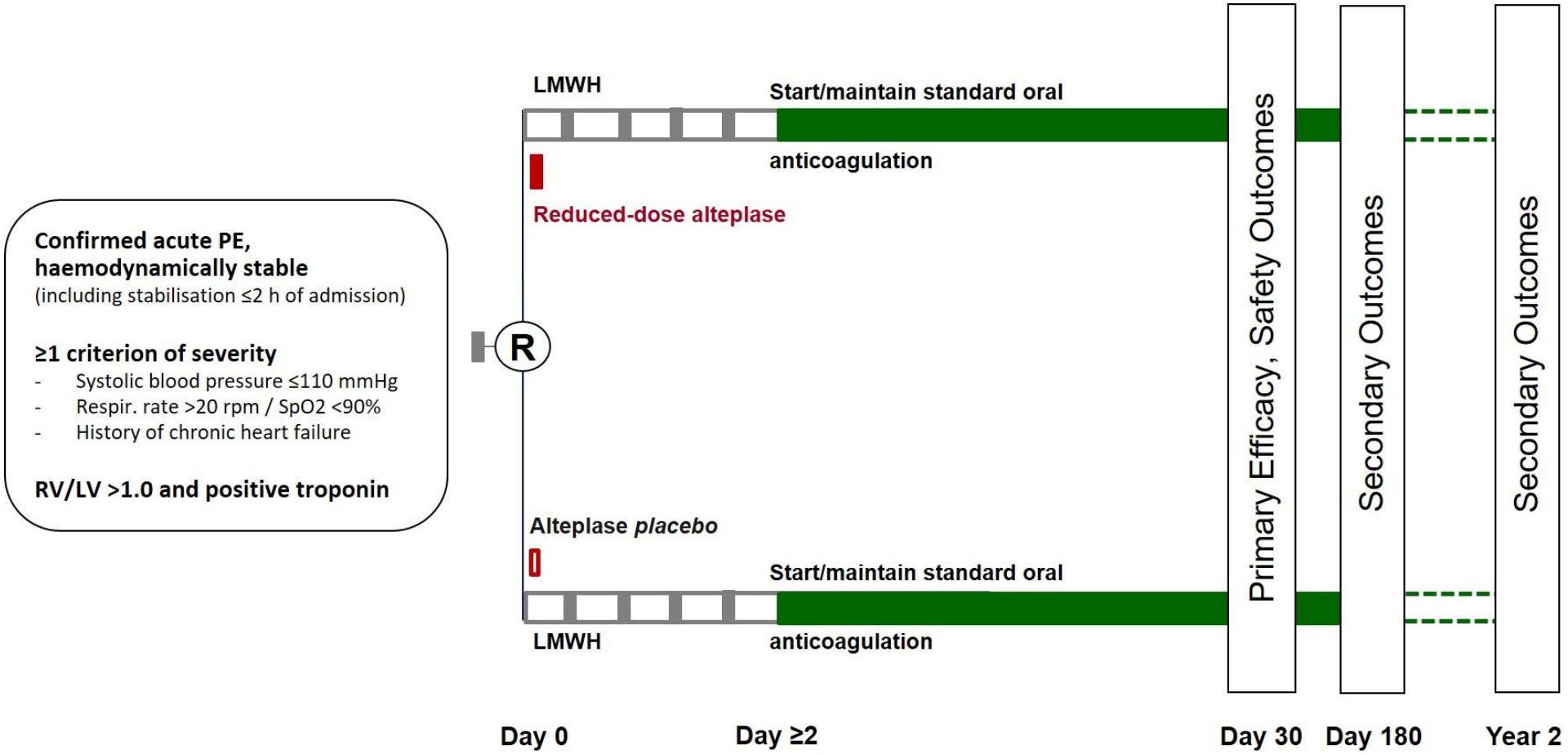
Meta-analysis of 3 studies



Zhang Z, et al. *Thromb Res* 2014;133:357-363

PEITHO III: Trial flow

A **reduced dose of intravenous thrombolytic treatment** for patients with intermediate-high-risk acute pulmonary embolism



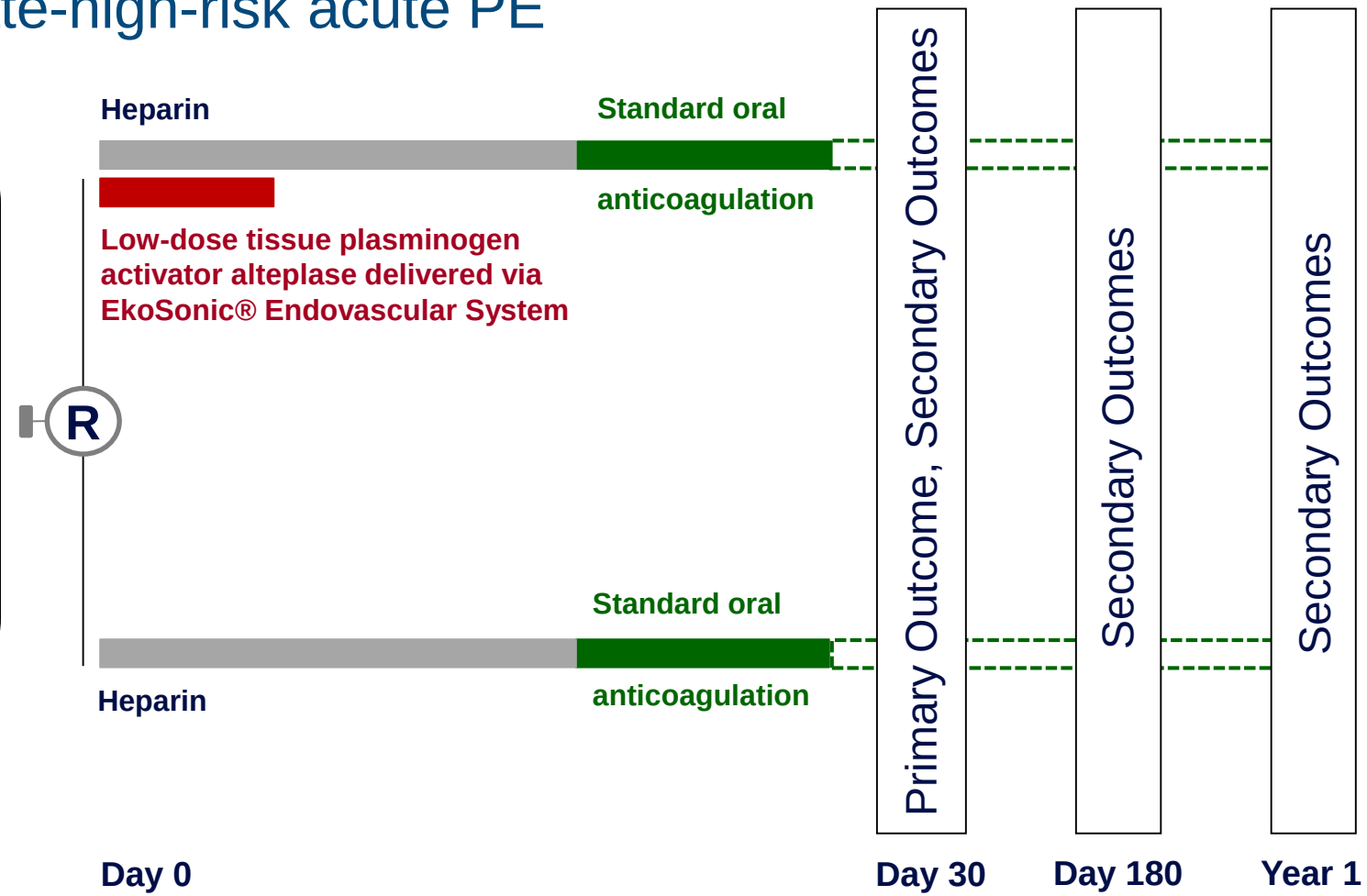
HI-PEITHO: Study flow

Catheter-directed, ultrasound-assisted low-dose thrombolytic treatment for patients with intermediate-high-risk acute PE

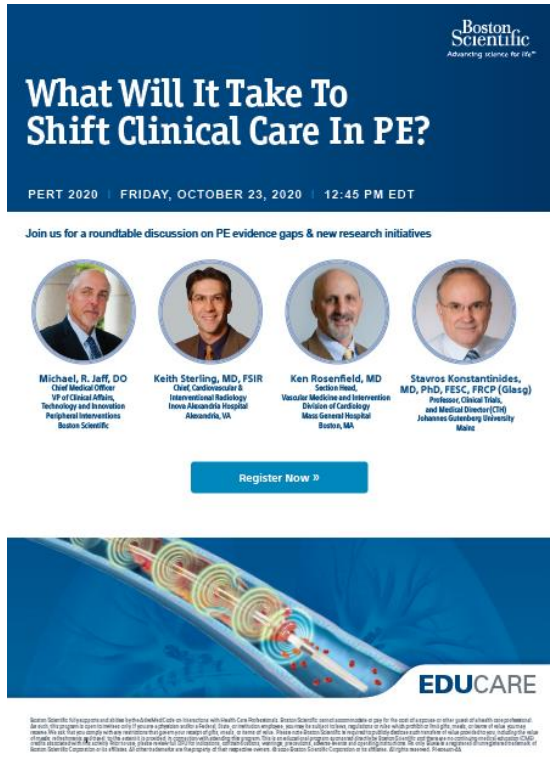
RV/LV ≥1.0 and positive troponin

Elevated risk of early hemodynamic decompensation:

- **At least two clinical criteria of severity**
  - SBP ≤110 mmHg
  - Respiratory rate >20 / SpO2 <90%
  - History of chronic heart failure
  - Heart rate ≥100 beats per minute



HI-PEITHO Promotions



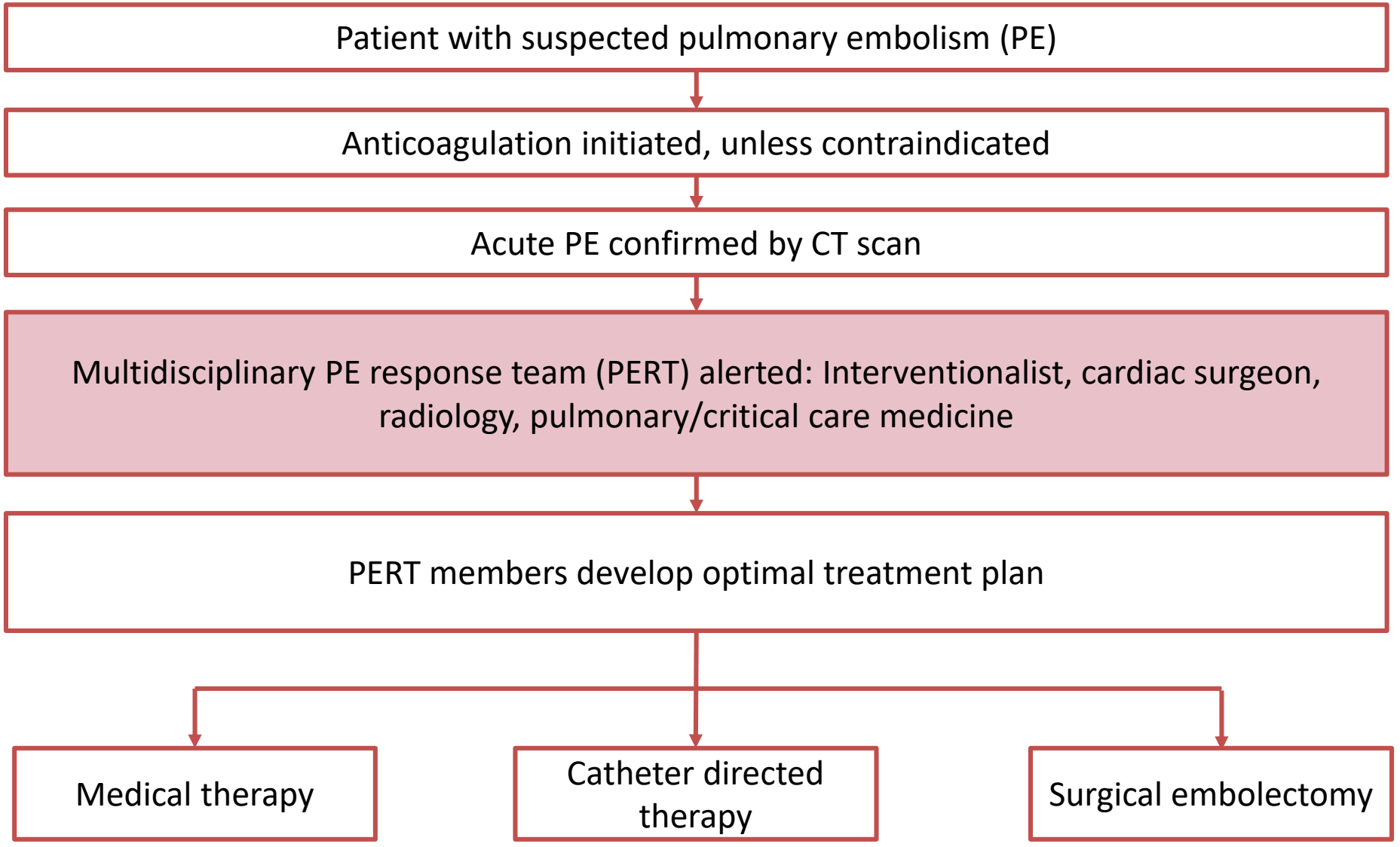
PERT Symposia Announcement

E-Blast

Website

Social

PE 2020: Multidisciplinary approach by the Pulmonary Embolism Response Team



Jaber WA, et al. *J Am Coll Cardiol* 2016;67:991-1002