Management of Intermediate-Risk Pulmonary Embolism

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Disclosures

Advisory boards / Lecture fees (moderate):

Boehringer Ingelheim

Bayer HealthCare

Pfizer – Bristol-Myers Squibb

Daiichi Sankyo

Management of intermediate risk: the questions

1) What *options* do we have to treat PE?
2) What *is* intermediate-risk PE?
3) What is the recommended *evidence-based* treatment for intermediate-risk PE?

❶ Systemic thrombolysis for PE

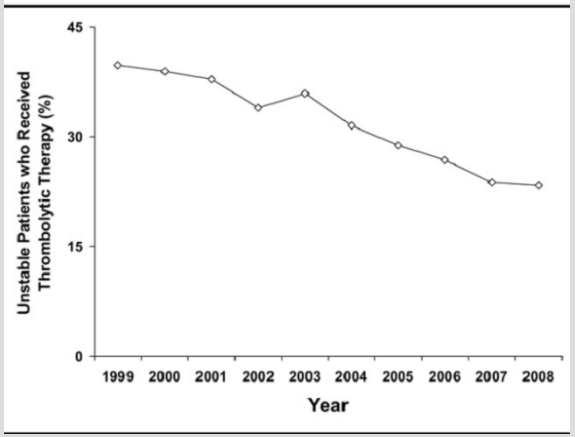
High-risk PE

Recommendation	Class	Level
Thrombolytic therapy in patients with high-risk PE presenting with cardiogenic shock and/or persistent arterial hypotension	I	A
Surgical pulmonary embolectomy if thrombolysis is absolutely contraindicated or has failed	I	C
Catheter embolectomy or fragmentation of proximal pulmonary arterial clots may be an alternative to surgical treatment	IIb	C

Thrombolysis for PE: recent epidemiological data

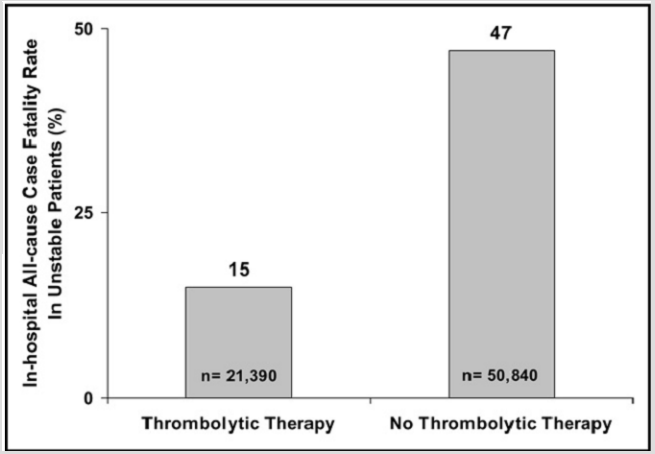
- Nationwide Inpatient Sample USA 1999-2008
- 2,110,320 patients discharged with diagnosis of PE (ICD-9-CM)
- **72,230 (3.4%) unstable (shock, ventilated)**

↘ **21,390 (30%) received thrombolytics**



In patients who received thrombolysis:

- All-cause mortality: RR, 0.31 (0.30-0.32)
- **PE-related death: RR, 0.20 (0.19-0.22)**



PD Stein. Am J Med. 2012;125:465-70. Epub 2012 Feb 10.

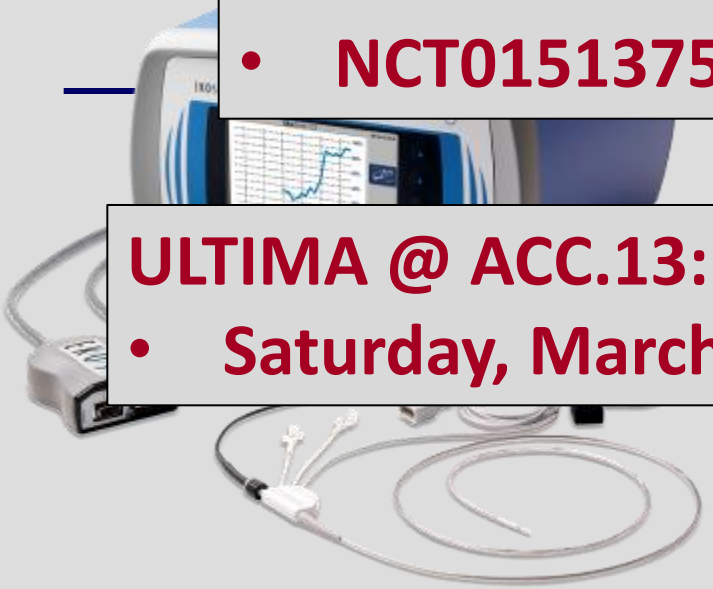
❷ Interventions for PE

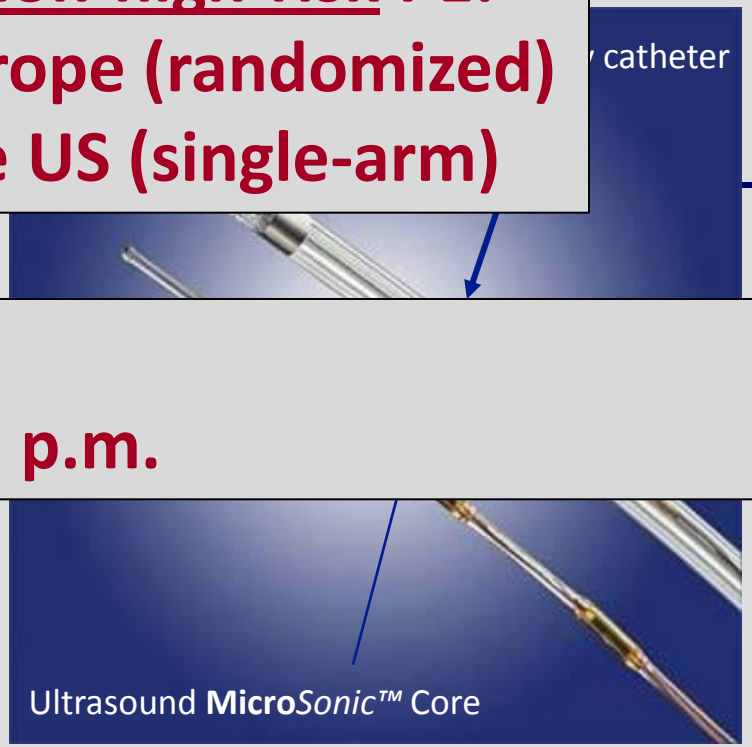
Ekosonic Control Unit

Ekosonic Mach4
Endovascular Device

Trials in patients with <u>non-high-risk</u> PE:

- **NCT01166997 in Europe (randomized)**
- **NCT01513759 in the US (single-arm)**



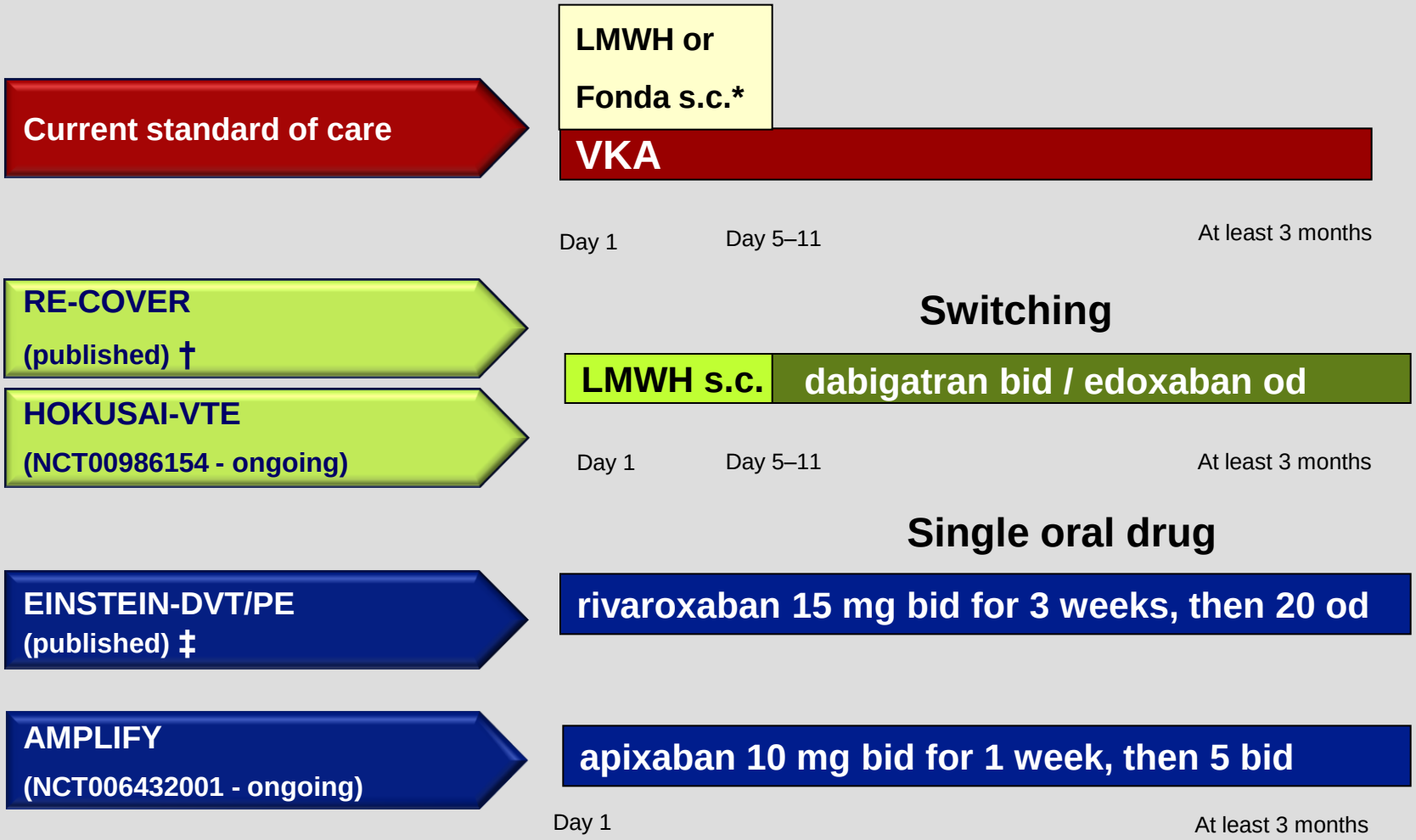


ULTIMA @ ACC.13:

- **Saturday, March 9, 3:15 p.m.**

Courtesy Prof. Nils Kucher, Bern, CH

❸ Anticoagulation for pulmonary embolism: NOAC



*Or UFH or fondaparinux

S Konstantinides and SZ Goldhaber. Eur Heart J 2012; in press

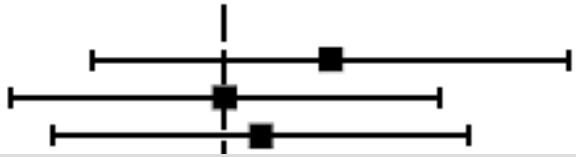
	Phase III trial	Setting	Comparator	Status (Jan 2013)
Dabigatran	**RECOVER**	VTE treatment	Parenteral anticoagulant	Published 2009
Rivaroxaban	**EINSTEIN-DVT**	DVT treatment	Enoxaparin/VKA (open-label)	Published 2010
	EINSTEIN-PE	PE ± symptomatic DVT treatment	Enoxaparin/VKA (open-label)	Published 2012
	EINSTEIN-EXT	VTE prevention after 6-12 mo. rivaroxaban or VKA	Placebo	Published 2010
Apixaban				
	AMPLIFY-EXT	VTE prevention after completed intended treatment for DVT or PE	Two doses of apixaban versus placebo	Published 2012
Edoxaban				

S Konstantinides and M Lankeit. Haemostaseol 2013 [Epub ahead of press]

Single drug approach for “severe” PE as well ?

“Anatomical extent” of PE	N (%)	
	Rivaroxaban n=2,419	Standard Tx n=2,413
Limited: <25% of vasculature of a single lobe	309 (12.8)	299 (12.4)
Intermediate	1392 (57.5)	1424 (59.0)
Extensive: multiple lobes and >25% of entire pulmonary vasculature	597 (24.7)	576 (23.9)
Not assessable	121 (5.0)	114 (4.7)

16/751	(2.1)	11/723	(1.5)
16/737	(2.2)	16/756	(2.1)
18/810	(2.2)	16/820	(2.0)

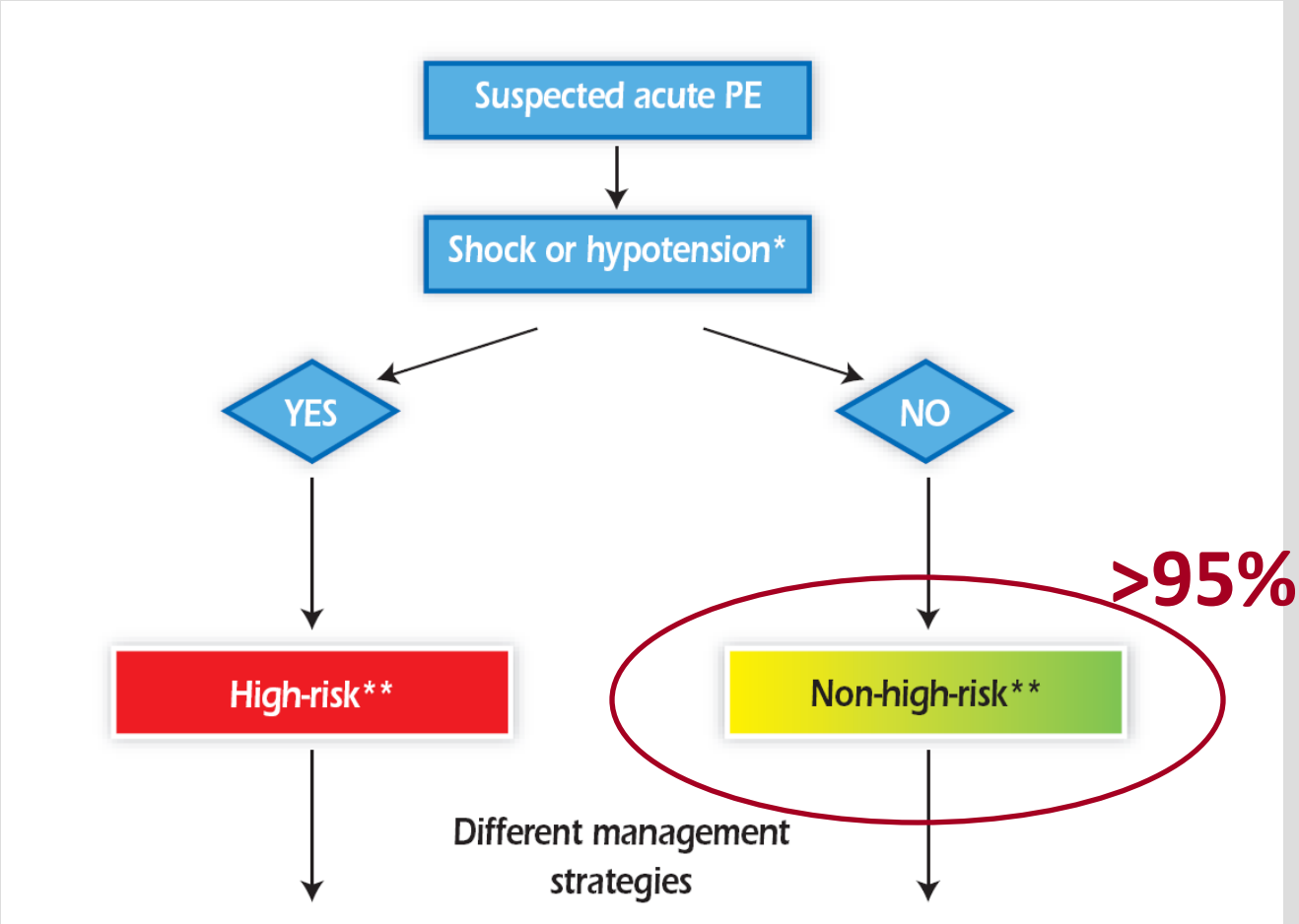


HR Büller for the EINSTEIN Investigators. N Engl J Med 2012; published online March 26

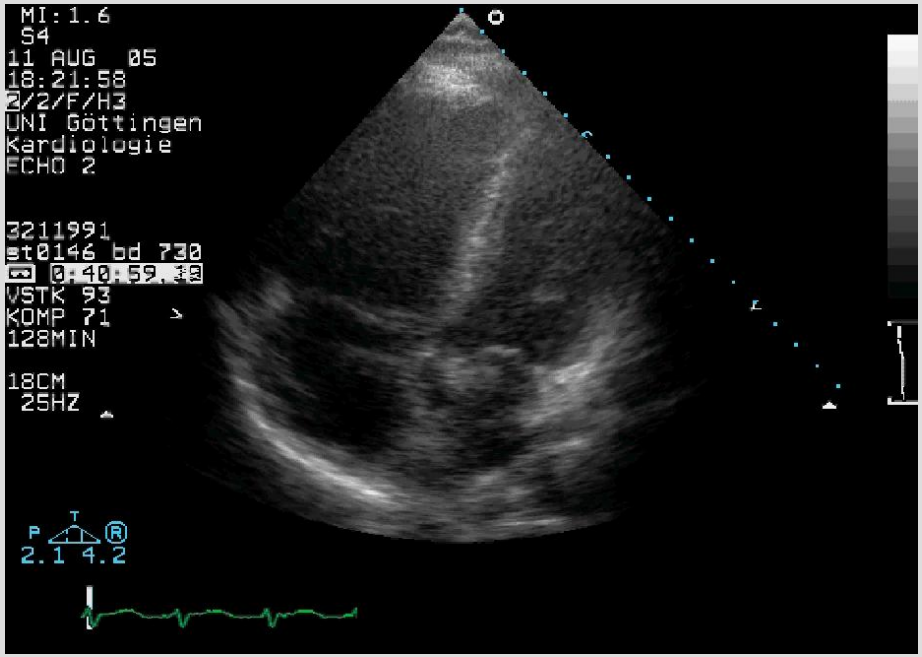
Management of intermediate risk: the questions

1) What options do we have to treat PE?
2) What *is* intermediate-risk PE?
3) What is the recommended evidence-based treatment for intermediate-risk PE?

The large group of normotensive PE patients



Echocardiographic findings in acute PE

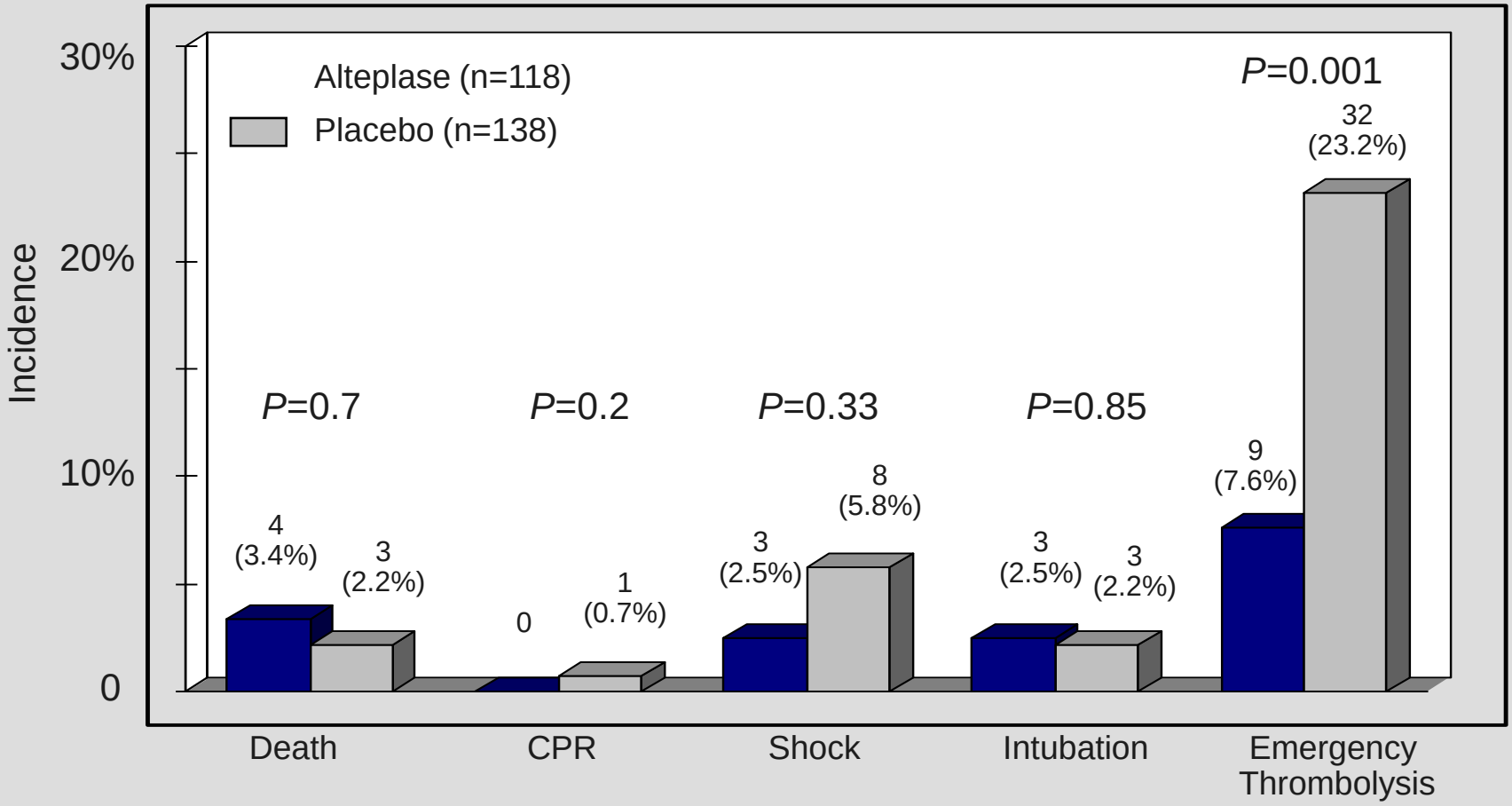


Echo criteria

- RV dilatation (RV>LV, or RVEDD >30 mm)
- RV free wall hypokinesia
- Paradoxical septal wall
- Pulmonary hypertension (RV-RA gradient >30 mm Hg, or pulmonary acceleration time <80 ms)

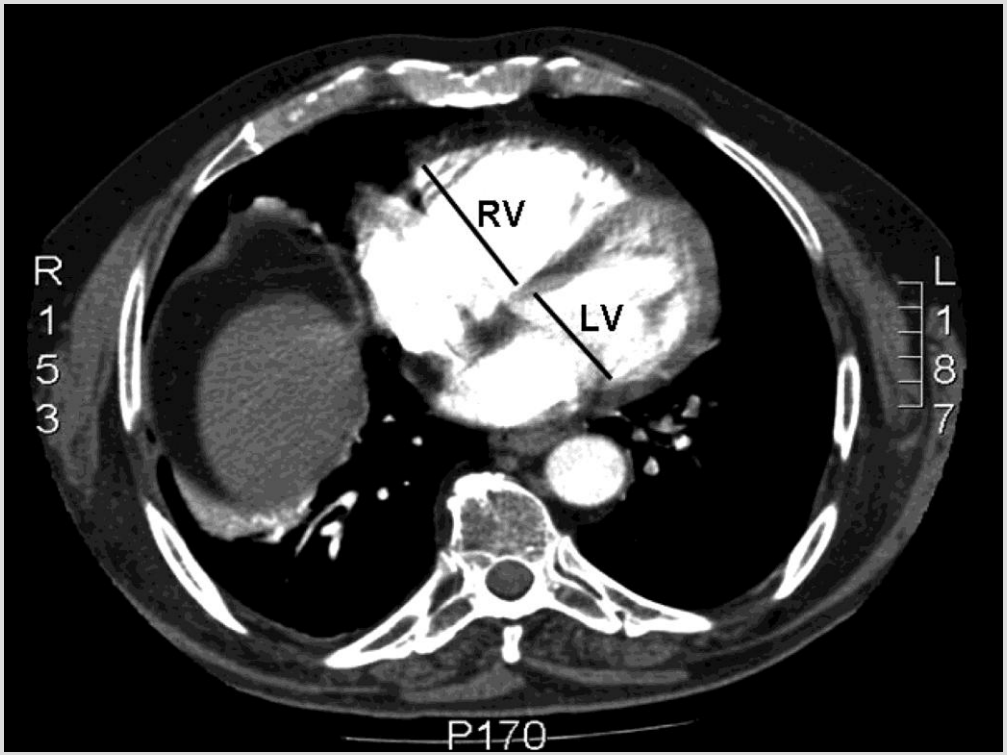
S Konstantinides. Curr Opin Cardiol 2005; N Engl J Med 2008

Echo alone probably does not indicate poor prognosis



S Konstantinides. N Engl J Med 2002;347:1143

Imaging of RV dysfunction on CT: similar information



Prospective multicenter validation (457 pts with PE):

- RV dilatation: RV:LV ≥0.9
- present in 66% of patients
- sensitivity, 92%; NPV, 100%
- **Independent predictor of adverse outcome**: HR, 3.5; 95% CI, 1.6–7.7; *P*= 0.002

C Becattini, S Konstantinides. Eur Heart J 2011;32:1657-1663

Troponins in PE: LOW positive predictive value

Author	Pts (n)	Marker	Ref. value*	Positive (%)	NPV (%)	PPV (%)
Giannitsis, 2000	56	Trop T	**0.10**	32	**97**	44
Konstantinides, 2002	106	Trop I	**0.07**	41	**98**	14
Konstantinides, 2002	106	Trop T	**0.04**	37	**97**	12
Janata, 2003	106	Trop T	**0.09**	11	**99**	34
Pruszczyk, 2003	64	Trop T	**0.01**	50	**100**	25

* in ng/mL

N Kucher. Circulation 2003;108:2191

BNP, proBNP in PE: LOW positive predictive value

Author	Pts (n)	Marker	Ref. value	Positive (%)	NPV (%)	PPV (%)
ten Wolde, 2003	110	BNP	**21.7 pmol/L**	33	**99**	17
Kucher, 2003	73	BNP	**50 pg/mL**	58	**100**	12
Krüger, 2004	42	BNP	**90 pg/mL**	40	**96**	6
Kucher, 2003	73	NT-proBNP	**500 pg/mL**	58	**100**	12
Pruszczyk, 2003	79	NT-proBNP	**153-334 pg/mL**	66	**100**	23
Binder, 2005	124	NT-proBNP	**1,000 pg/mL**	46	**100**	10

N Kucher. Circulation 2003;108:2191

Tools for risk stratification of PE: a critical look

Table I Risk assessment tools in acute pulmonary embolism

	Strengths	Weaknesses
Clinical prediction rules		
PESI	Assessment of clinical severity, comorbidity	Prognostic value for intermediate-risk PE unknown
Geneva risk score	PESI strong for defining low-risk PE, successfully employed in a randomized trial	Clinical scores do not account for RV function, a key prognostic determinant in the early phase
Imaging tests		
Echocardiography	Real-time, bedside assessment of RV size and function, PA systolic pressure	Moderate positive and NPV Poorly standardized parameters and criteria Ultrasound failed to identify candidates for thrombolysis in a randomized trial
CT	Diagnosis of PE and assessment of RV size in one test Findings correlated with PE prognosis	Implications of an enlarged RV on CT for the management of intermediate-risk PE unclear
Laboratory markers		
Cardiac troponin I, T	Troponin elevation correlated with PE prognosis Sensitive test, high NPV Widely used test	Non-specific test, positive predictive value low (positive test does not justify advanced therapy)
Natriuretic peptides (BNP, NT-proBNP)	BNP/NT-proBNP elevation correlated with PE prognosis High NPV Widely used test	Non-specific test, positive predictive value very low (positive test does not justify advanced therapy) Appropriate cut-off value(s) unclear
H-FABP	Early marker of adverse outcome	Not available for routine use at present
GDF-15	'Global' marker of myocardial injury, heart failure, comorbidity	Not available for routine use at present

PESI, Pulmonary Embolism Severity Index; CT, computed tomography; PE, pulmonary embolism; BNP, brain natriuretic peptide; GDF-15, growth differentiation factor-15; H-FABP, heart-type fatty acid-binding protein; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, pulmonary artery; RV, right ventricular; NPV, negative predictive value.

S Konstantinides and SZ Goldhaber. Eur Heart J 2012

Combine biomarkers with imaging ?

Parameter	Tests / Findings
RV Dysfunction **+?**	RV dilatation, hypokinesis or pressure overload on echocardiography RV dilatation on spiral CT [BNP or NT-proBNP elevation] [↑ right heart pressures at RHC]
Myocardial injury	Cardiac troponin T or I positive [H-FABP] [Myoglobin]

Biomarkers combined with imaging: early evidence

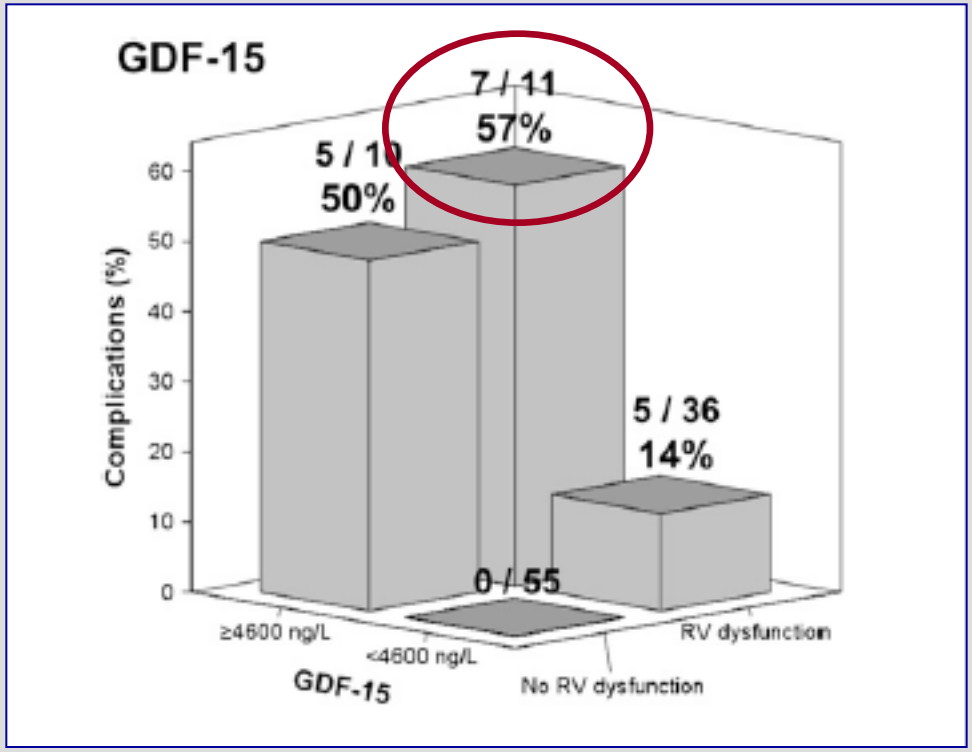
Patient group	Complication risk (OR, 95% CI)
Troponin T-negative (<0.04 ng/ml)	-------
Troponin-positive, echo-negative	3.70 (0.76-18.18) =0.107
Troponin-negative, echo-positive	(0.97-32) *P*=0.055
***Both* troponin- and echo-positive**	**10.00 (2.14-46.80)** ***P*=0.004**

~ 15% of all PE patients

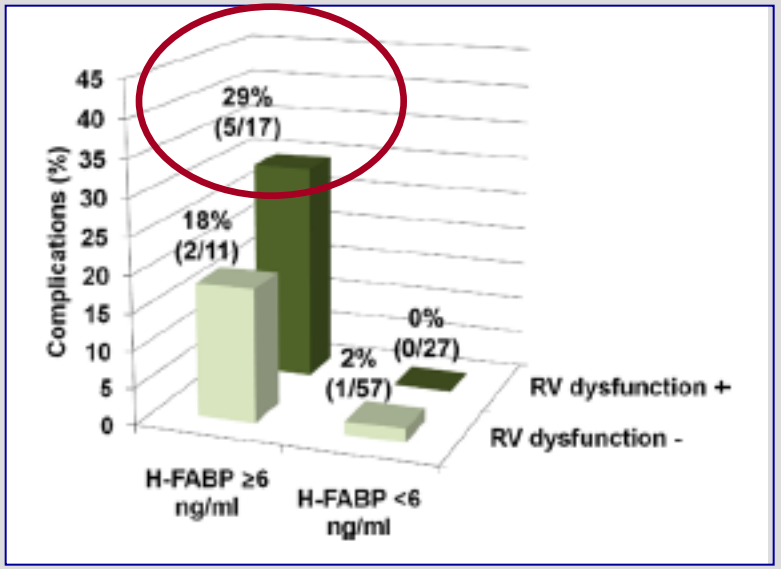
L Binder, S Konstantinides. Circulation 2005;112:1573-1579

Biomarkers combined with imaging: additive value

Echo + GDF-15



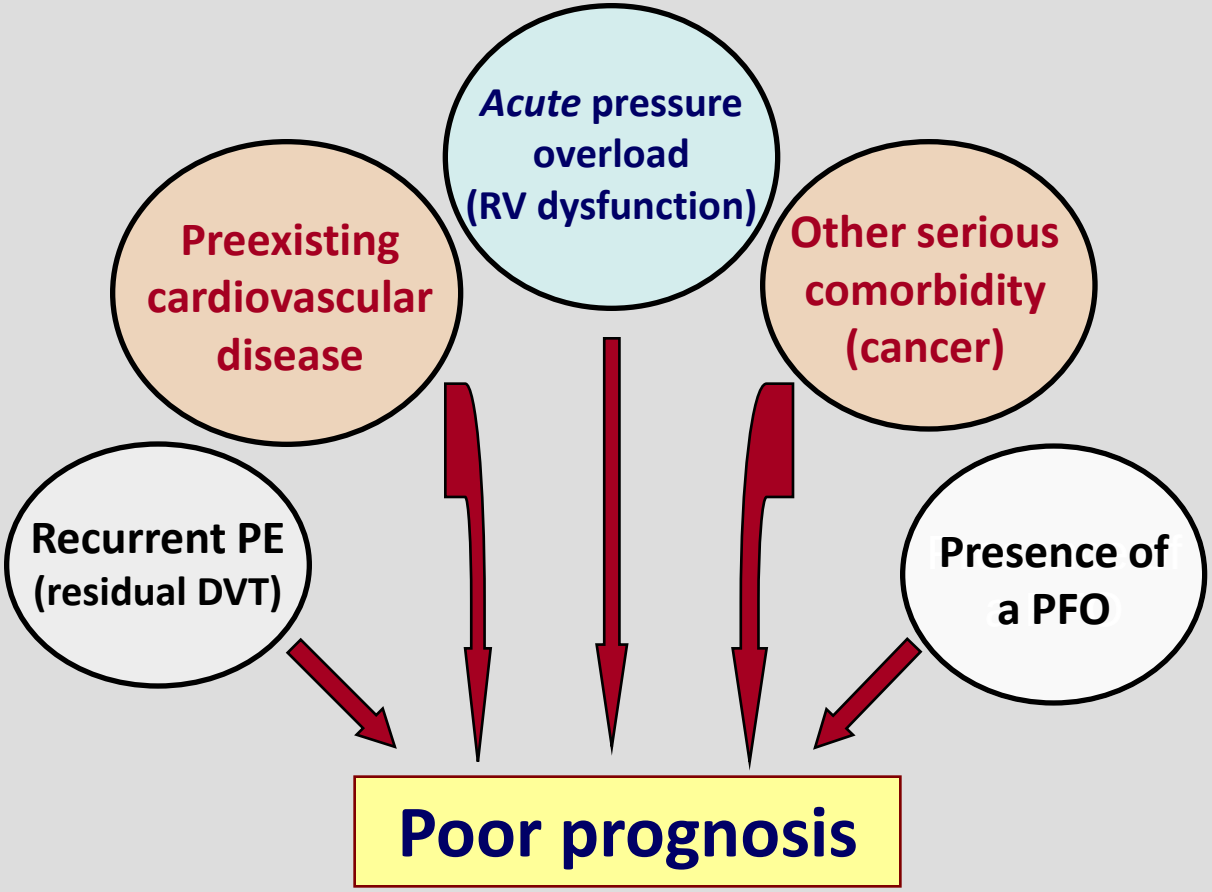
Echo + H-FABP



M Lankeit., S Konstantinides. Am J Respir Crit Care Med 2008;177:1018-1025

C Dellas, S Konstantinides. J Am Coll Cardiol 2010;55:2150

Further determinants of an adverse early outcome



Pulmonary Embolism Severity Index (PESI)

Variable	Score: Original PESI[a]	Score: Simplified PESI[b]
Age >80 y	Age in years	1
Male sex	+10	
History of cancer	+30	1
History of heart failure	+10	1[c]
History of chronic lung disease	+10	
Pulse ≥110 beats/min	+20	1
Systolic blood pressure <100 mm Hg	+30	1
Respiratory rate ≥30 breaths/min	+20	
Temperature <36°C	+20	
Altered mental status	+60	
Arterial oxyhemoglobin saturation level <90%	+20	1

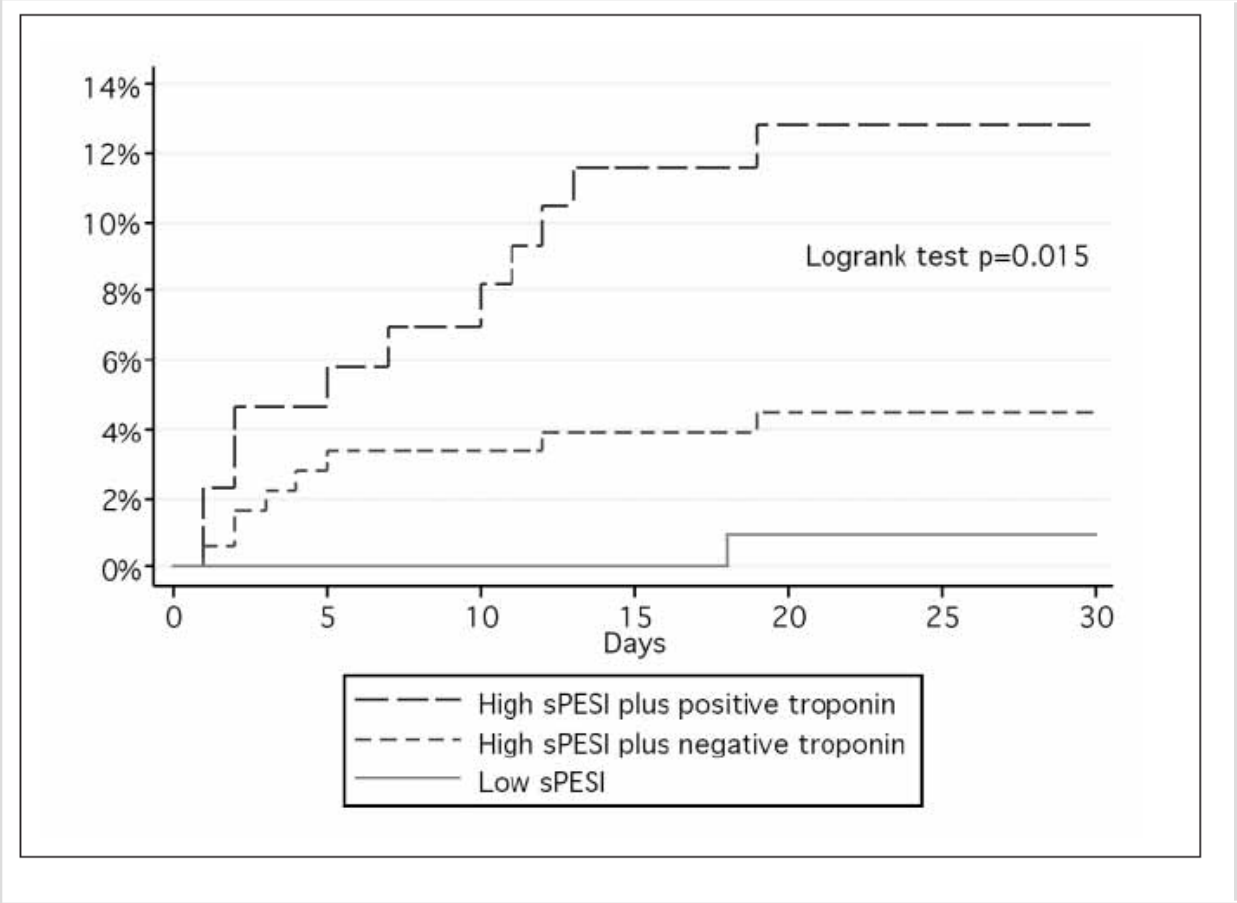
Low-risk, 0 points (30 to 36% of patients)

High-risk, 1 or more points

D Jiménez. Arch Intern Med 2010;170:1383

Cardiac troponins *on top of* sPESI (Swiss registry)

Multicentre prospective registry: 369 unselected patients
Combined endpoint: death or recurrent PE at 30-days



D Spirk. Thromb Haemost 2011;Epub ahead of print

Cardiac troponins *on top of* sPESI (Swiss registry)

Characteristics	sPESI	Any troponin	sPESI plus any troponin
Test positive, n (%)	235/332 (71)	94/332 (28)	81/332 (24)
Specificity, % (95% CI)	31 (26–36)	74 (69–79)	78 (73–82)
Positive predictive value, % (95% CI)	8 (5–12)	13 (7–21)	14 (7–23)
Sensitivity, % (95% CI)	95 (75–100)	60 (36–81)	55 (32–77)
Negative predictive value, % (95% CI)	99 (94–100)	97 (94–99)	96 (93–98)
Area under the curve (95% CI)	0.63 (0.57–0.68)	0.67 (0.56–0.78)	0.72 (0.63–0.81)

- Additive value of the combination with troponin testing

D Spirk. Thromb Haemost 2011;Epub ahead of print

Management of intermediate risk: the questions

1) What options do we have to treat PE?
2) What is intermediate-risk PE?
3) What is the recommended *evidence-based* treatment for intermediate-risk PE?

What *did* the guidelines say in 2008?

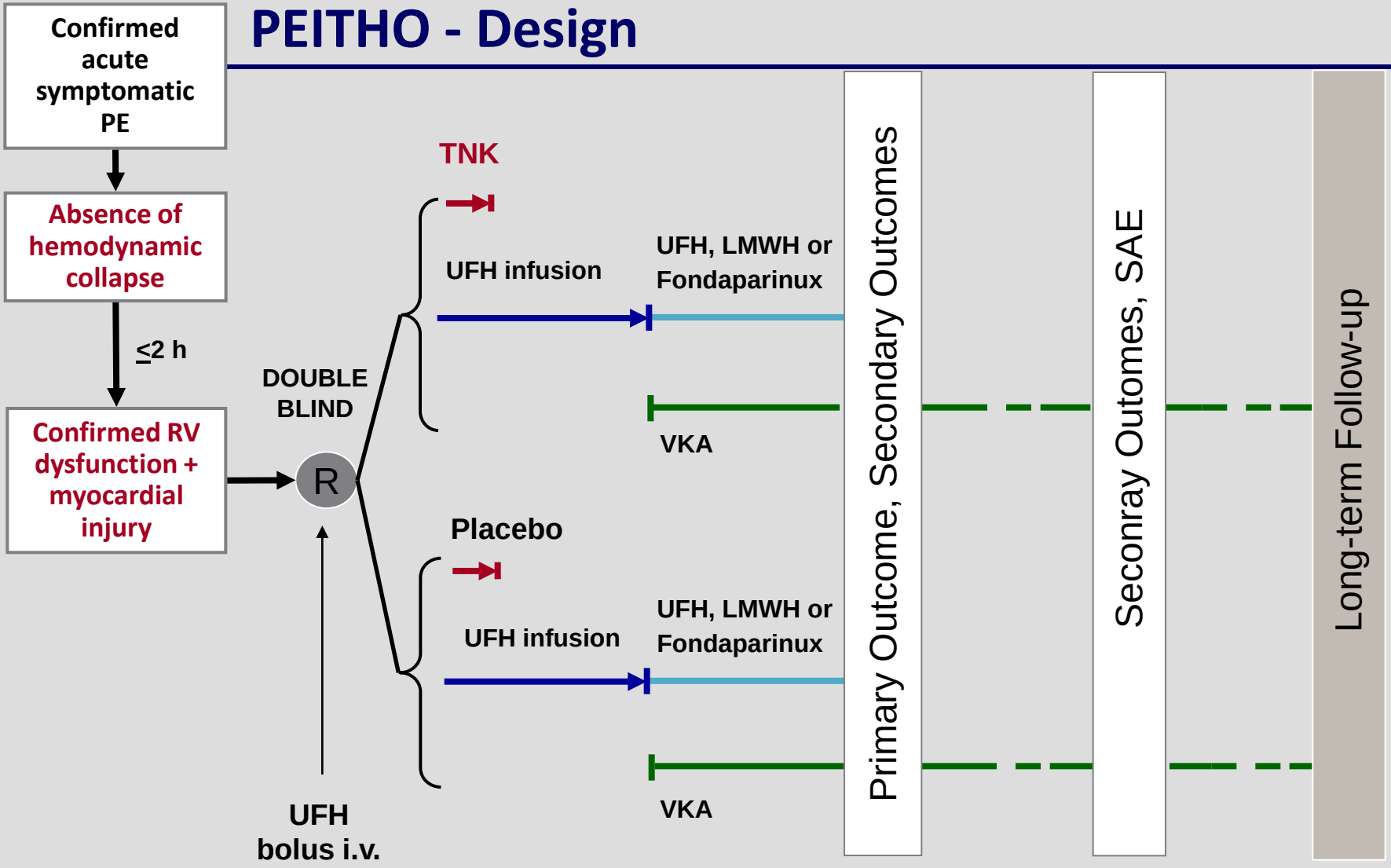
Non-high-risk PE

Recommendation	Class	Level
Anticoagulation should be initiated without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is still ongoing	I	C
LMW heparin or fondaparinux for most patients	I	A
Thrombolysis generally NOT recommended (1B) – may be considered in **selected cases**	**IIb**	**B**

Biomarkers + echo identify candidates for thrombolysis?

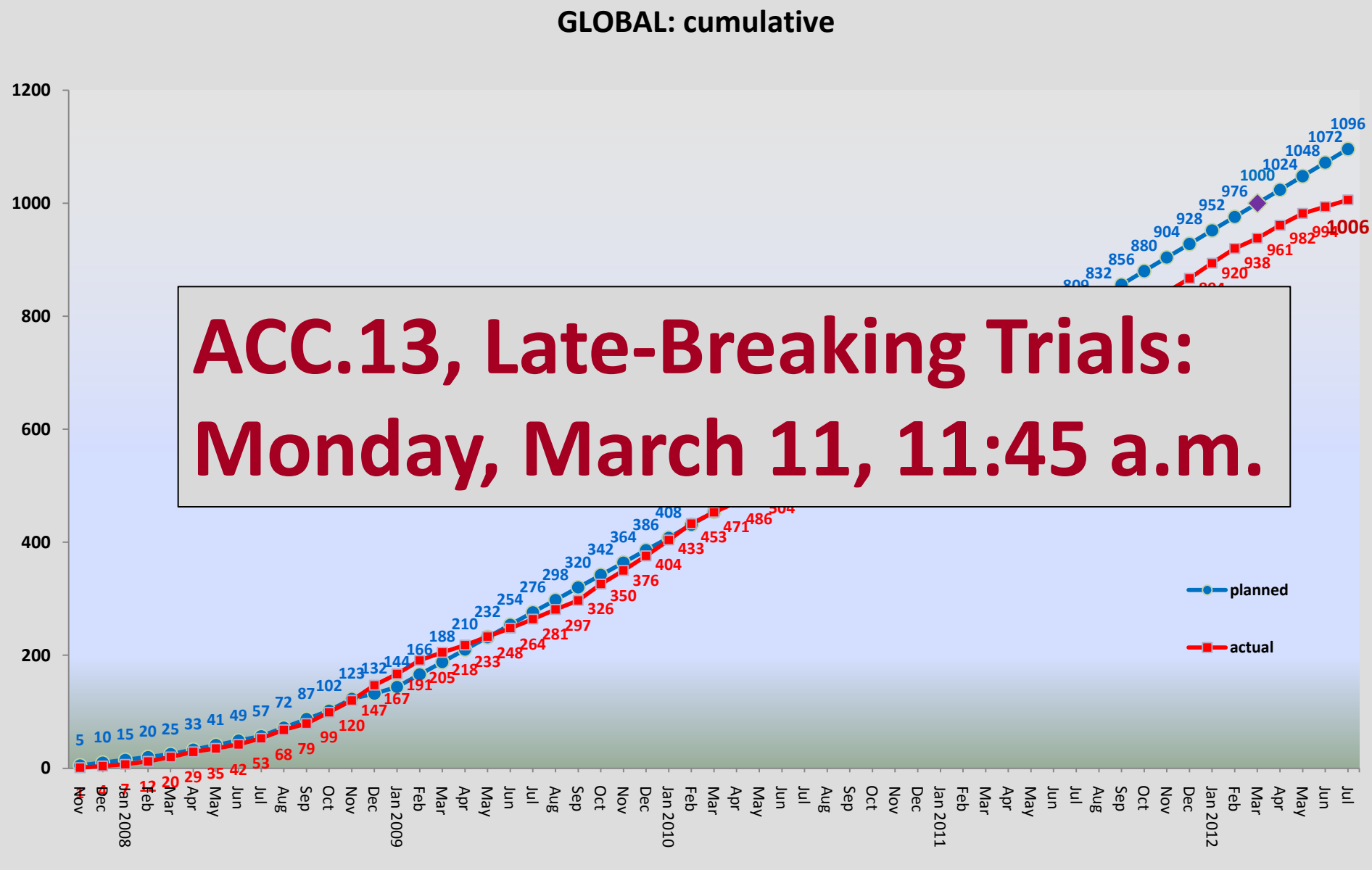
PE-related early MORTALITY RISK		RISK MARKERS: CLINICAL (Shock or hypotension)	RISK MARKERS: RV Dysfunction	RISK MARKERS: Myocardial injury	Potential treatment implications
HIGH > 15%		+	(+)*	(+)*	Thrombolysis or Embolectomy
NON HIGH	Inter mediate 3 - 15%	–	+	+	Thrombolysis? Hospital Admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

PEITHO - Design



S Konstantinides for the PEITHO Steering Committee. Am Heart J 2012;163:33-38.e1

PEITHO FINAL Status (July 31, 2012)



Intermediate-risk PE: Conclusions and outlook (1)

- Right ventricular dysfunction is an important - but not the only - determinant of prognosis in acute pulmonary embolism.
- In normotensive patients, echocardiographic and CT parameters, several biomarkers, and clinical parameters, have *individually* been correlated with poor prognosis.
- PEITHO, a large European randomized trial, will soon determine whether definition of “intermediate-risk” PE by imaging + biomarker may have **implications for acute management**, i.e. set the indication for early thrombolysis.

Intermediate-risk PE: Conclusions and outlook (2)

- Future risk stratification scores and strategies may need to include clinical data (comorbidity) and define a **smaller** proportion of patients at truly elevated risk for “advanced” early treatment (thrombolysis, intervention).
- It will need to be determined whether **new oral anticoagulants** can be given from the beginning also to patients with intermediate-risk PE.

PE classification update 2012-2014: like this?

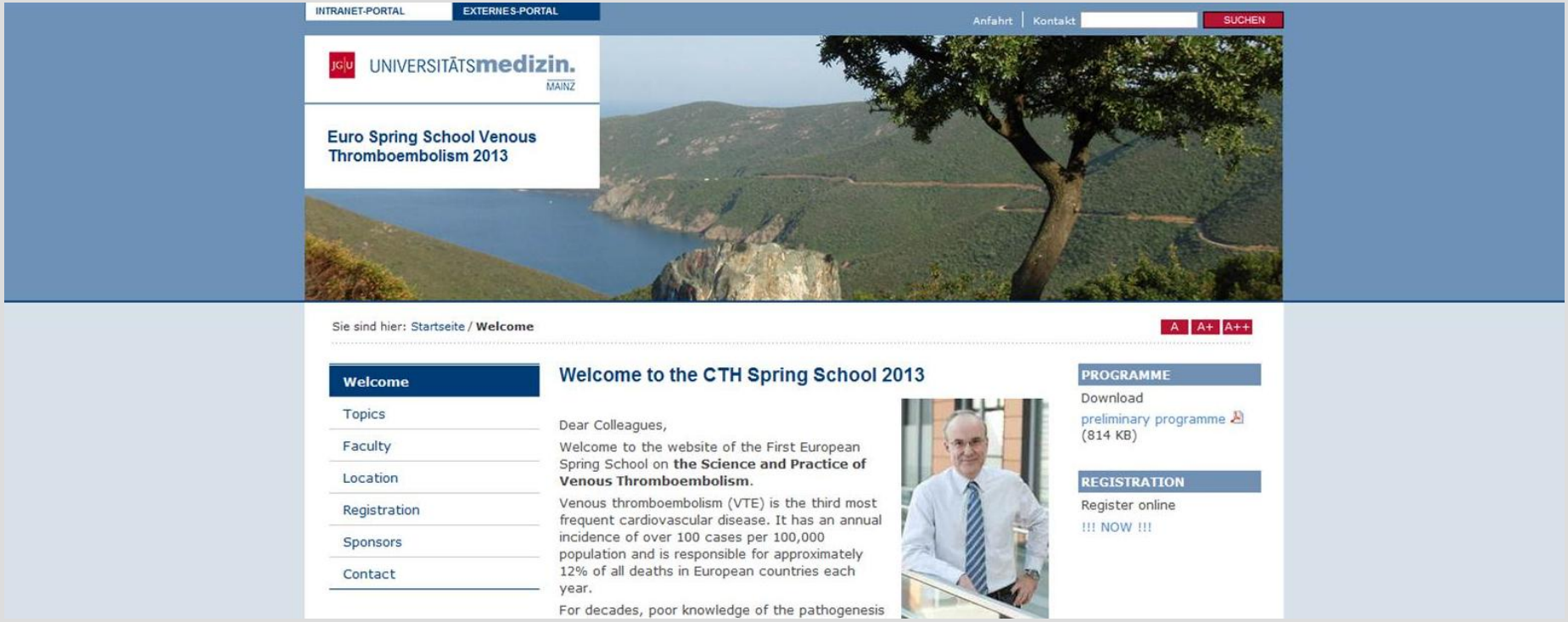
EARLY DEATH RISK	EARLY DEATH RATE	RISK MARKERS				ACUTE TREATMENT
		Clinical		Imaging/biochemical		
		Hypotension, instability	Normotensive, high clinical risk (score?)	RV dysfunction (echo, CT)	Positive biomarker (troponin, BNP)	
HIGH	>15%	+	+	+	(+)	Thrombolysis (intervention, surgery)
NON-HIGH	8-10%	-	+	+	+	Thrombolysis / Intervention
				+	-	Monitoring; initial A/C in-hospital
				-	+	
	1-2%	-	-	-	+	
				+	-	
	<1%	-	-	(-)	-	Early discharge

Or perhaps as simple as this?

EARLY DEATH RISK	EARLY DEATH RATE	RISK MARKERS				ACUTE TREATMENT
		Clinical		Imaging/biochemical		
		Hypotension, instability	Normotensive, high clinical risk (score?)	RV dysfunction (echo, CT)	Positive biomarker (troponin, BNP)	
HIGH	**>15%**	**+**	**+**	**+**	**(+)**	**Thrombolysis (intervention, surgery)**
NON-HIGH	**1-8%**	**-**	**(+)**			**Initial A/C in-hospital**
	<1%	**-**	**-**	**(-)**	**-**	**Early discharge**

1st European Spring School 2013

The Science and Practice of Venous Thromboembolism

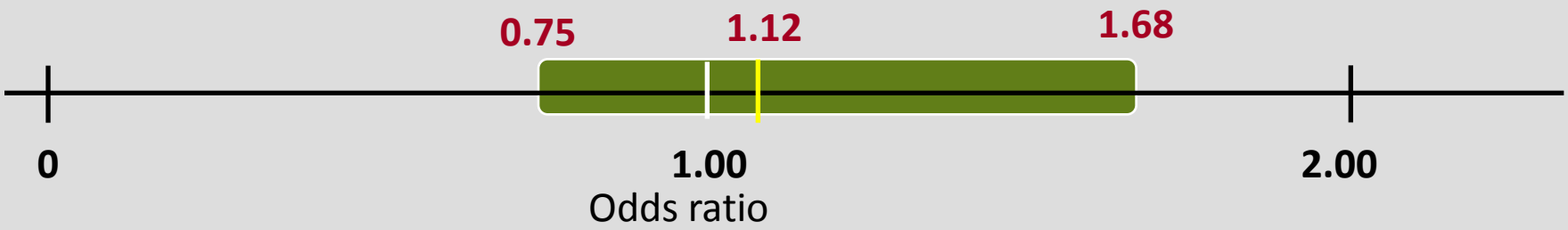


www.eurospringschool.eu


Thank you

EINSTEIN-PE: Primary efficacy outcome

	Rivaroxaban (n=2,419)		Warfarin (n=2,413)	
	n	(%)	n	(%)
First symptomatic recurrent VTE	**50**	**(2.1%)**	**44**	**(1.8%)**
Recurrent DVT	18	(0.7%)	17	(0.7%)
Non-fatal PE	22	(0.9%)	19	(0.8%)
Fatal PE	2		1	
Unexplained death where PE could not be ruled out	8	(0.3%)	5	(0.2%)



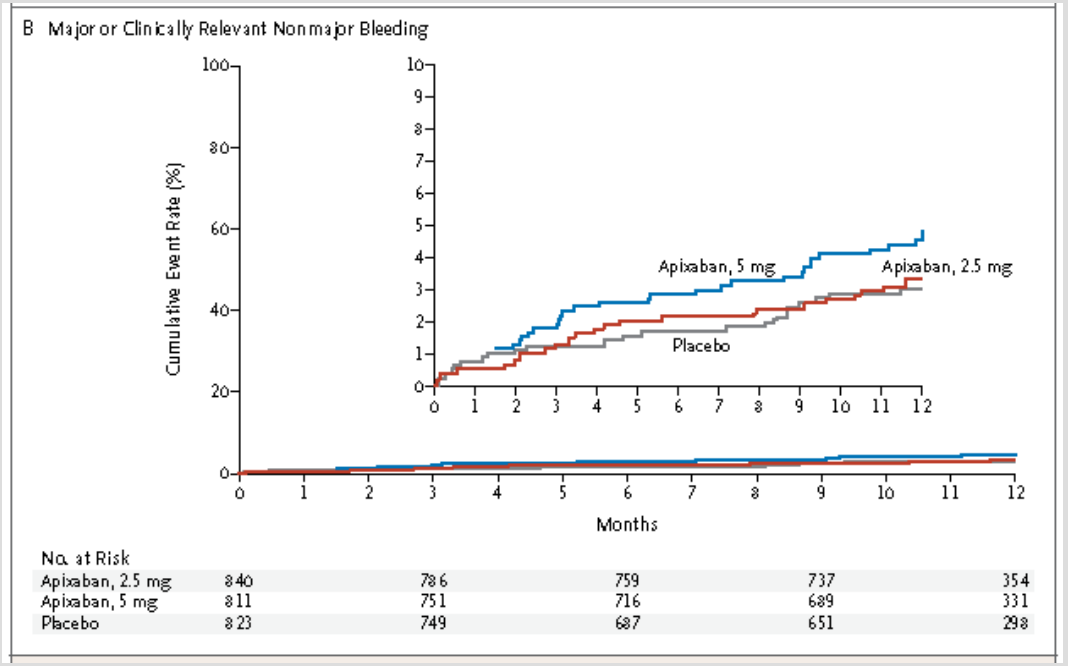
Rivaroxaban superior | Rivaroxaban non-inferior | Rivaroxaban inferior

P=0.003 for non-inferiority

HR Büller for the EINSTEIN Investigators. N Engl J Med 2012; published online March 26

AMPLIFY-EXT: two doses of apixaban

- 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



0.8% vs. 0.2% (2.5 mg) vs. 0.1% (5 mg)

G Agnelli for the AMPLIFY Investigators. N Engl J Med. 2012; Epub ahead of print