Respiratory Review of 2017: Pulmonary Vascular Disease

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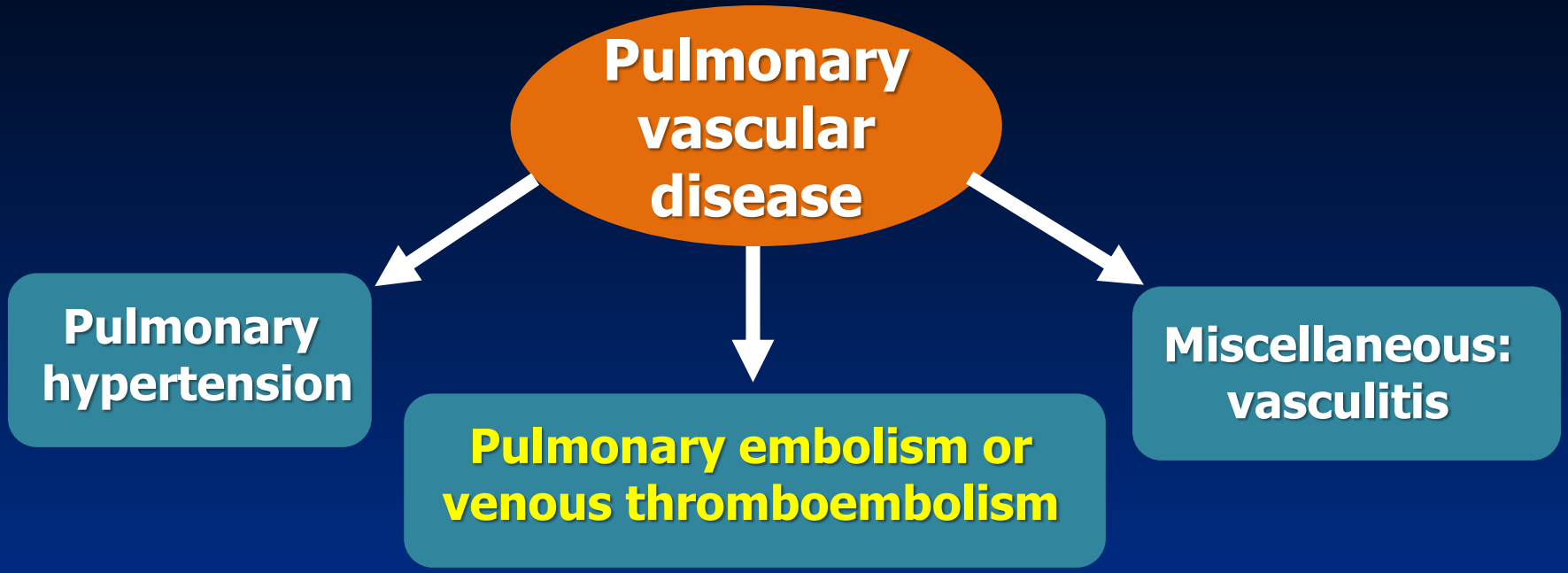
Introduction



- Journals, 2015-2016
  - AJRCCM, Thorax, ERJ, Chest
  - NEJM, Lancet, JAMA

Pulmonary embolism

- **Risk stratification**
  - European Society of Cardiology (ESC) 2014: *Becattini et al. ERJ 2016*
  - Right heart thrombi: *Koc et al. ERJ 2016; Barrios et al. ERJ 2016*
- **Treatment**
- **Cancer-associated VTE**

Risk stratification

Guideline → **Practicality?**

Clinical model	RV dysfunction	Clot burden
PESI sPESI	BNP/troponin Echo CT parameter	Obstruction index? DVT Central PE Right heart thrombi

- Normotensive PE patients for whom thrombolysis is beneficial
- Low-risk PE patients who can undergo early discharge or outpatient care

PESI and sPESI

Parameter	Pulmonary Embolism Severity Index	Simplified PESI
Age	Age in years	1 (if age >80)
Male	10	-
Cancer	30	1
Chronic heart failure	10	1
Chronic pulmonary disease	10	
Pulse rate ≥ 110/min	20	1
Systolic BP <100 mmHg	30	1
Respiratory rate >30/min	20	-
Body temperature <36° C	20	-
Altered mental status	60	-
SaO2 <90%	20	1
	Risk strata	
Low risk PE	Class I: ≤65 very low 30-d mortality risk (0–1.6%) Class II: 66–85 low mortality risk (1.7–3.5%)	0 points = 30-day mortality risk 1.0% (95% CI 0.0%–2.1%)
PESI High NPV for 30 d mortality	Class III: 86–105 moderate mortality risk (3.2–7.1%) Class IV: 106–125 high mortality risk (4.0–11.4%) Class V: >125 very high mortality risk (10.0–24.5%)	≥1 point(s) = 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

ESC guideline 2014

RV dilation on CT alone and combination of other prognostic markers (adverse outcome)

Predictors*	PPV (%)	NPV (%)	PLR	NLR	C-statistic
PESI*	24.8	92.7	2.8	0.7	0.648
NT-proBNP†	22.4	95.4	2.4	0.4	0.710
Troponin I‡	21.6	94.9	2.1	0.4	0.702
RVD-CT§	20.1	94.9	2.1	0.5	0.686
PESI* + NT-proBNP†	50.0	92.0	8.4	0.7	0.784
PESI* + troponin I‡	41.7	91.9	5.5	0.7	0.760
PESI* + RVD-CT§	43.1	92.3	6.5	0.7	0.754
PESI* + NT-proBNP† + troponin I‡	64.7	91.8	15.1	0.7	0.814
PESI* + NT-proBNP† + RVD-CT§	62.5	91.6	14.0	0.8	0.818
PESI* + troponin I‡ + RVD-CT§	60.7	91.5	11.8	0.7	0.786
PESI* + NT-proBNP† + troponin I‡ + RVD-CT§	71.4	91.5	20.8	0.8	0.835

- **Low PPV**
- **Unsatisfactory AUC**

Choi et al. Thromb Res 2014

Risk stratification of PE

European Society of Cardiology (ESC) 2014

Early mortality risk (In-hospital mortality)		Risk parameters and scores			
		Hypotension	PESI III-V or sPESI ≥ I	RV dysfunction on echo or CT	Blood cardiac biomarkers
High (>15%)		+	+	+	+
Intermediate (3-15%)	-high	-	+	Both positive	
	-low	-	+	Either one (or none) positive	
Low (<3%)		-	-	Both negative	

American Heart Association (AHA) 2011

Acute PE: mortality prediction by the 2014 ESC risk stratification model

Becattini et al. ERJ 2016;48:780

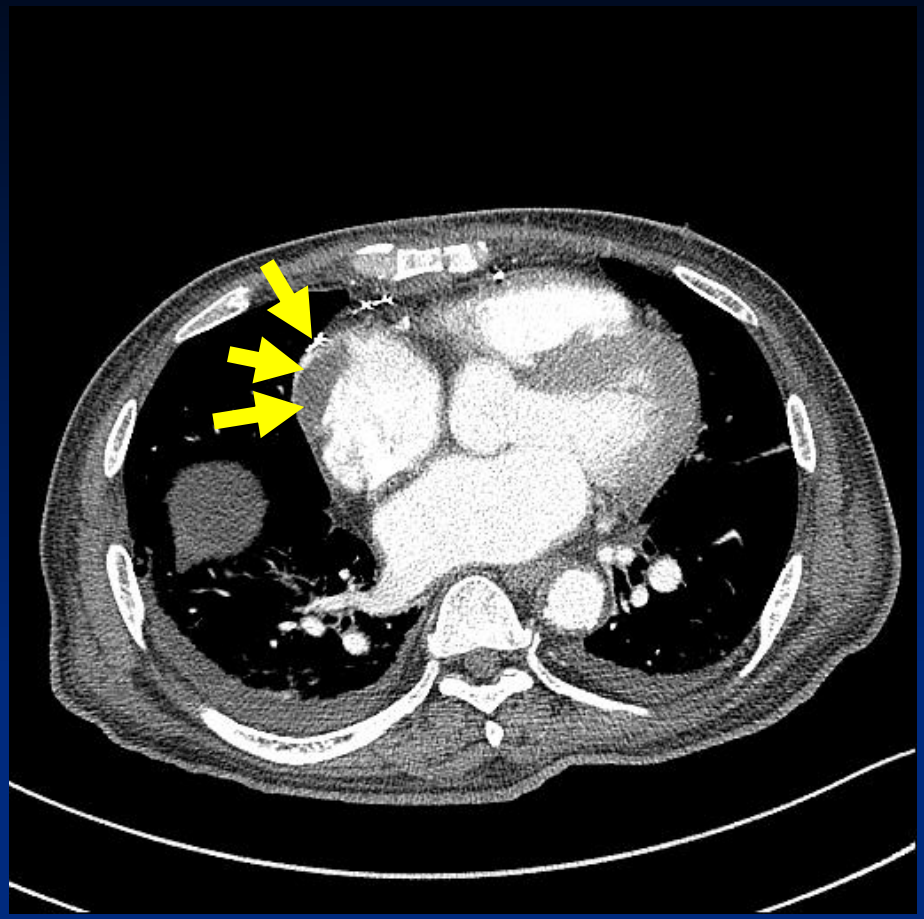
- 3 prospective cohorts

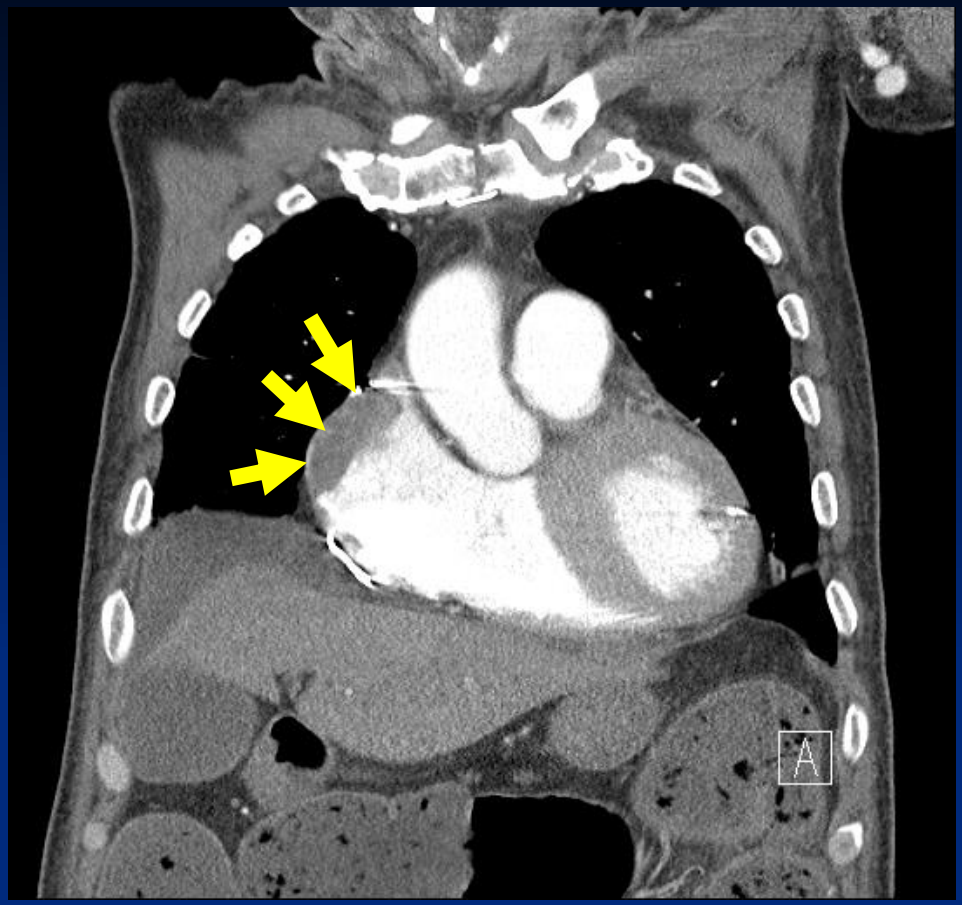
	ESC 2014		ESC 2008	
n=906	Death at 30 d	Death due to PE	Death at 30 d	Death due to PE
High 105 (12%)	23/105 (22, 14.0-29.8)	16/105 (15.2, 8.4-22.1)	23/105 (22, 14.0-29.8)	16/105 (15.2, 8.4-22.1)
Intermediate-high 272 (30%)	21/272 (7.7, 4.5-10.9)	13/272 (4.8, 2.2-7.3)	21/307* (6.8, 4.0-9.7)	13/307* (4.2, 2.0-6.5)
Intermediate-low 333 (37%)	20 /333 (6.0, 3.4-8.6)	7/333 (2.1, 0.6-3.6)	19/271** (7.0, 4.0-10.0)	8/271** (3.0, 0.9-5.0)
Low 196 (22%)	1/196 (0.5, 0-1.5)	1/196 (0.5, 0-1.5)	2/223 (0.9, 0-2.1)	0/223

C-statistic for death at 30 days and for death due to PE

	Death at 30 d	Death due to PE
2014 ESC model	0.71 (0.65-0.77)	0.75 (0.68-0.83)
2008 ESC model	0.71 (0.64-0.77)	0.76 (0.69-0.83)

Right heart thrombi





Right Heart Thrombi European Registry (RiTHER)

- Right heart thrombi on echo: 4% (ICOPER registry)
- Optimal therapy?
- Impact of RHT on mortality?
- 17 centers from 8 European countries

TABLE 2 Treatment and outcome according to the clinical characteristics of 138 patients with right heart thrombi

	All patients	HRPE	p-value (HRPE *versus* nHRPE)	nHRPE	IRPE	p-value (IRPE *versus* LRPE)	LRPE
Subjects	138	31		107	83		24
Thrombolysis	56 (41)	19 (61)	<0.01	37 (35)	32 (39)	0.17	5 (21)
Surgery or intervention	15 (10)	4 (13)	0.93	11 (10)	8 (10)	0.98	3 (12)
		8 (26)	0.03	59 (55)	43 (52)	0.20	16 (67)
30-day pulmonary embolism-related mortality	26 (19)	13 (42)	0.0002	13 (12)	13 (16)	0.038	0 (0)
30-day all-cause mortality	34 (25)	15 (48)	0.0005	19 (18)	17 (20)	0.29	2 (8)

Data are presented as n or n (%), unless otherwise stated. HRPE: high-risk pulmonary embolism; nHRPE: non-HRPE; IRPE: intermediate-risk pulmonary embolism; LRPE: low-risk pulmonary embolism.

RiHT shape S/O/P	81/44/13	22/7/2	0.22	59/37/11	47/26/10	0.21	12/11/1
RiHT mobility M/I	118/20	30/1	0.08	88/19	66/17	0.29	22/2
RiHT size ⩽5/>5 cm	98/40	20/11	0.37	78/29	60/23	0.99	18/6
RiHT protruding into PFO	14 (10)	3 (10)	0.81	11 (10)	9 (11)	0.98	2 (8)

Koc et al. ERJ 2016;47:869

TABLE 3 Univariable 30-day mortality predictors in patients with right heart thrombi

SI=HR/sBP	All-cause mortality		Pulmonary embolism-related mortality	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
All n=138				
sPESI score	2.56 (1.71–3.84)	<0.001	2.43 (1.58–3.73)	<0.0001
Shock index	5.82 (2.07–16.41)	0.001	8.96 (2.82–28.48)	0.0002
sBP <90 mmHg	4.89 (2.07–11.54)	<0.001	5.18 (2.01–13.39)	0.001
nHRPE n=107				
sPESI score	2.41 (1.42–4.07)	0.001	1.94 (1.11–3.40)	0.02
Shock index	29.8 (3.3–271.1)	0.003	83.99 (5.5–1295.7)	0.002

sPESI: simplified Pulmonary Embolism Severity Index; sBP: systolic blood pressure; nHRPE: non-high-risk pulmonary embolism.

- **In multivariate analysis, only sPESI predicted mortality; for nHRPE only, shock index predicted mortality.**
- **Right heart thrombi characteristics (size, mobility, shape) did not predict mortality.**

Koc et al. ERJ 2016;47:869

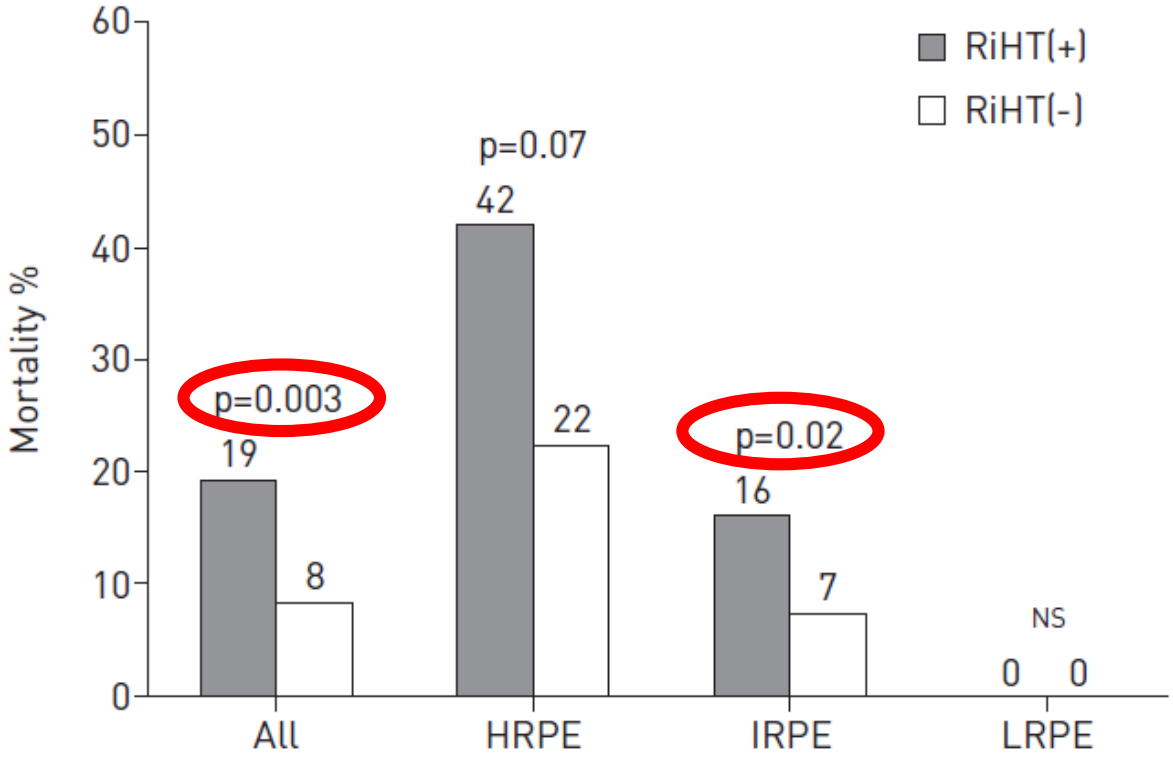


FIGURE 2 30-day pulmonary embolism-related mortality in 138 patients with right heart thrombi (RiHT(+)) and 276 propensity score-matched controls (RiHT(–)). HRPE: high-risk pulmonary embolism; IRPE: intermediate-risk pulmonary embolism; LRPE: low-risk pulmonary embolism.

Koc et al. ERJ 2016;47:869

Right heart thrombi in PE

- RIETE registry: prospectively enrolled VTE data
- PE, n=30254;
  2.6% (n=325/12441) of all PE patients with echo

- In multivariate analysis, association with RHT

	OR (95% CI)
Younger age, /year	1.01 (1.01–1.02)
Previous bleeding	2.56 (1.51–4.34)
Heart failure	2.06 (1.51–2.81)
Cancer	1.46 (1.11-1.91)
Syncope	1.83 (1.42-2.36)
SBP <100 mmHg	1.97 (1.48-2.63)
SaO2 <90%	1.58 (1.23-2.03)

Barrios et al. ERJ 2016;48:1377

TABLE 3 Factors associated with 30-day all-cause mortality in 12 441 patients with acute symptomatic pulmonary embolism

Risk factor	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age per year	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001
Cancer[#]	4.03 (3.26–4.99)	<0.001	4.03 (3.26–4.98)	<0.001
Recent major bleeding	1.82 (1.09–3.04)	0.02	1.73 (1.03–2.88)	0.04
Congestive heart failure	1.28 (0.96–1.70)	0.09		
Immobilisation[¶]	2.25 (1.80–2.83)	<0.001	2.34 (1.87–2.92)	<0.001
Syncope	0.93 (0.71–1.23)	0.63		
Systolic blood pressure <100 mmHg	2.14 (1.62–2.83)	<0.001	2.24 (1.71–2.93)	<0.001
Heart rate ⩾110 beats·min^{-1}	1.23 (0.97–1.58)	0.09	1.28 (1.01–1.63)	0.04
Arterial oxyhaemoglobin saturation <90%	1.20 (0.94–1.52)	0.14		
Right heart thrombi	2.46 (1.60–3.80)	<0.001	2.50 (1.62–3.84)	<0.001

[#]: active or under treatment in the last year; [¶]: immobilised patients defined as non-surgical patients who had been immobilised (*i.e.* total bed rest with bathroom privileges) for ⩾4 days in the month prior to pulmonary embolism diagnosis.

Barrios et al. ERJ 2016;48:1377

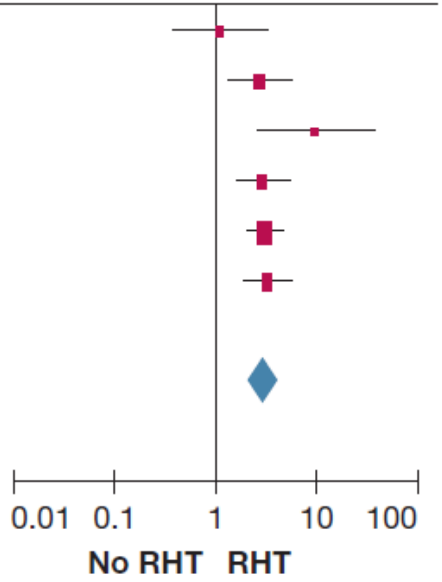
Prognostic significance of right heart thrombi in patients with acute symptomatic PE: a meta-analysis

- 4 retrospective and 2 prospective studies
- Short-term all-cause mortality

A

Study or Subgroup	RHT Events	RHT Total	No RHT Events	No RHT Total	Weight	OR M-H-Random-95% CI	Year
Casazza et al[10]	5	23	21	107	7.0%	1.14 (0.38-3.42)	1997
Torbicki et al[8]	10	45	106	1,115	14.4%	2.72 (1.31-5.65)	2003
Mollazadeh et al[24]	6	12	8	88	4.8%	10.00 (2.61-38.38)	2009
Kukla et al[23]	16	50	125	925	18.5%	3.01 (1.61-5.62)	2015
Barrios et al[25]	28	325	354	12,116	33.8%	3.13 (2.10-4.68)	2016
Koc et al[9]	34	138	25	276	21.5%	3.28 (1.87-5.77)	2016
Total (95% CI)		**593**		**14,627**	**100.0%**	**3.03 (2.24-4.11)**	
Total events	99		639				

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 6.28$, $df = 5$ ($P = .28$); $I^2 = 20\%$
Test for overall effect: $z = 7.13$ ($P < .00001$)

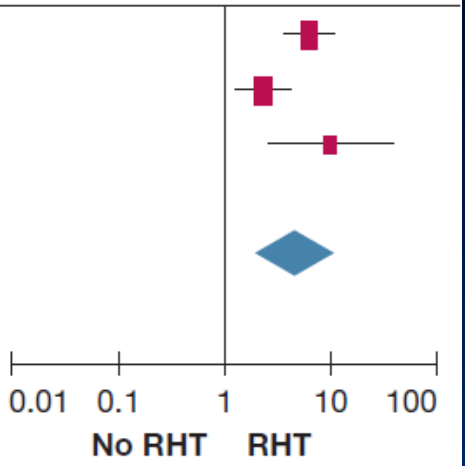


Barrios et al. Chest 2017;151:409

- **Short-term PE-related mortality**

Study or Subgroup	RHT Events	RHT Total	No RHT Events	No RHT Total	Weight	OR M-H, Random, 95% CI
Barrios et al[25]	17	325	105	12,116	39.8%	6.31 (3.74-10.67)
Koc et al[9]	26	138	25	276	38.3%	2.33 (1.29-4.21)
Mollazadeh et al[24]	6	12	8	88	21.9%	10.00 (2.61-38.38)
Total (95% CI)		**475**		**12,480**	**100.0%**	**4.77 (2.01-11.28)**
Total events	49		138			

Heterogeneity: $\tau^2 = 0.41$; $\chi^2 = 8.29$, $df = 2$ ($P = .02$); $I^2 = 76\%$
Test for overall effect: $z = 3.55$ ($P = .0004$)



- **Association between RHT and mortality: not strong**
  Mortality: linked to the hemodynamic status
  RHT→ additional benefit for risk stratification?

- **Systemic screening for RHT?**
  According to ESC 2014, positive PESI or sPESI (non-low risk PE)

- **Best treatment?**

Barrios et al. Chest 2017;151:409

Pulmonary embolism

- Risk stratification
- **Treatment**
  - Catheter directed thrombolysis (CDT): *Kuo et al. Chest 2015*
  - Pulmonary embolism response team (PERT): *Kabrhel et al. Chest 2016*
  - IVC filter (PREPIC2): *Mismetti et al. JAMA 2015*
- Cancer-associated VTE

PEITHO trial

- For normotensive PE with RV dysfunction + myocardial injury
- Tenecteplase + anticoagulation vs anticoagulation alone

Outcome	Tenecteplase (n=506)	Placebo (n=499)	OR (95% CI)	P-value
Primary outcome within 7 d	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
All cause mortality	6 (1.2)	9 (1.8)	0.65 (0.23-1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14-0.68)	0.002
Safety outcome within 7 d				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3-13.39)	<0.001
Stroke	12 (2.4)	1 (0.2)	12.10 (1.57-93.39)	0.003

- In patients with intermediate-risk PE, fibrinolytic therapy prevented hemodynamic decompensation but increased the risk of major bleeding and stroke.
- Reperfusion therapy with lower bleeding risk is needed.
- Conversion to catheter-directed therapy?

Meyer et al. NEJM 2014;370:1402

Catheter-directed thrombolysis (CDT)

- Thrombolysis is contraindicated or has failed
- Comorbidities or old age → cannot undergo embolectomy

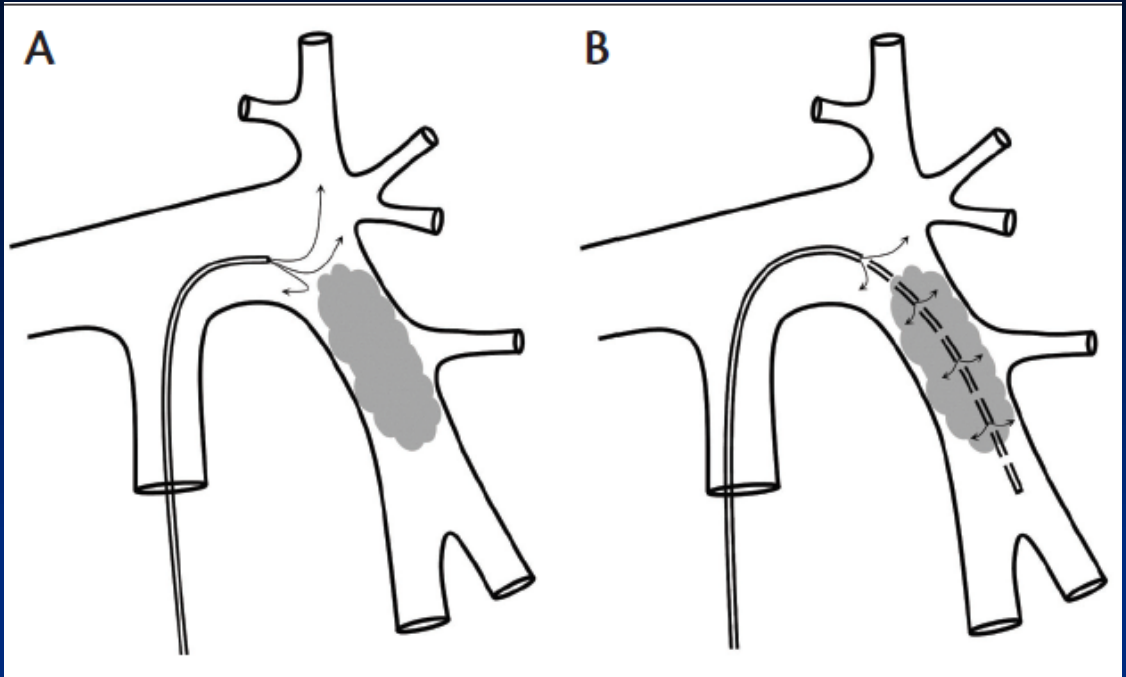


Figure 1. Infusion of a thrombolytic through a nonembedded catheter results in rapid dissipation of the drug through non-obstructed pathways (A). A multisidehole infusion catheter is embedded within an embolus in the left lower lobe, allowing thrombolytics to be infused directly into the clot (B).

CDT, cont.

- CDT with or without
  thrombus fragmentation, rheolytic, rotational, or suction thrombectomy (pharmacomechanical thrombolysis)

- Lower dose of drugs → lower incidence of bleeding
  (bolus 2-5 mg followed by 1 mg/h for 12-24 h)
  Higher cost and longer monitoring

- A meta-analysis
  - Success rate 87%
  - Minor and major complications: 7.9% and 2.4%, respectively

Engelberger RP, et al. Circulation 2011
Kuo WT, et al. J Vasc Interv Radiol 2009

PE response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT)

- Systemic thrombolysis→ 2-5% hemorrhagic stroke
- Catheter-directed thrombolysis (CDT) using pharmacomechanical methods and low-dose thrombolytic infusion
- A prospective multicenter registry data
- tPA 0.5-1.0 mg/h or urokinase 100,000 IU/h
- Success: massive PE, 24/28 (86%); submassive PE, 71/73 (97%)

Outcome	Value
Hospital stay, d	8.23±4.82
In-hospital death	6 (5.9)
>30-d mortality	1 (1.0)
IVC filter	65 (64.4)
Major bleeding within 30 d	0
ICH	0

Kuo et al. Chest 2015;148:667

Therapeutic decision-making

PE

Low risk → Anticoagulation alone: early discharge or OPD ?

Submassive

Massive

→ **Anticoagulation alone vs thrombolysis + anticoagulation**

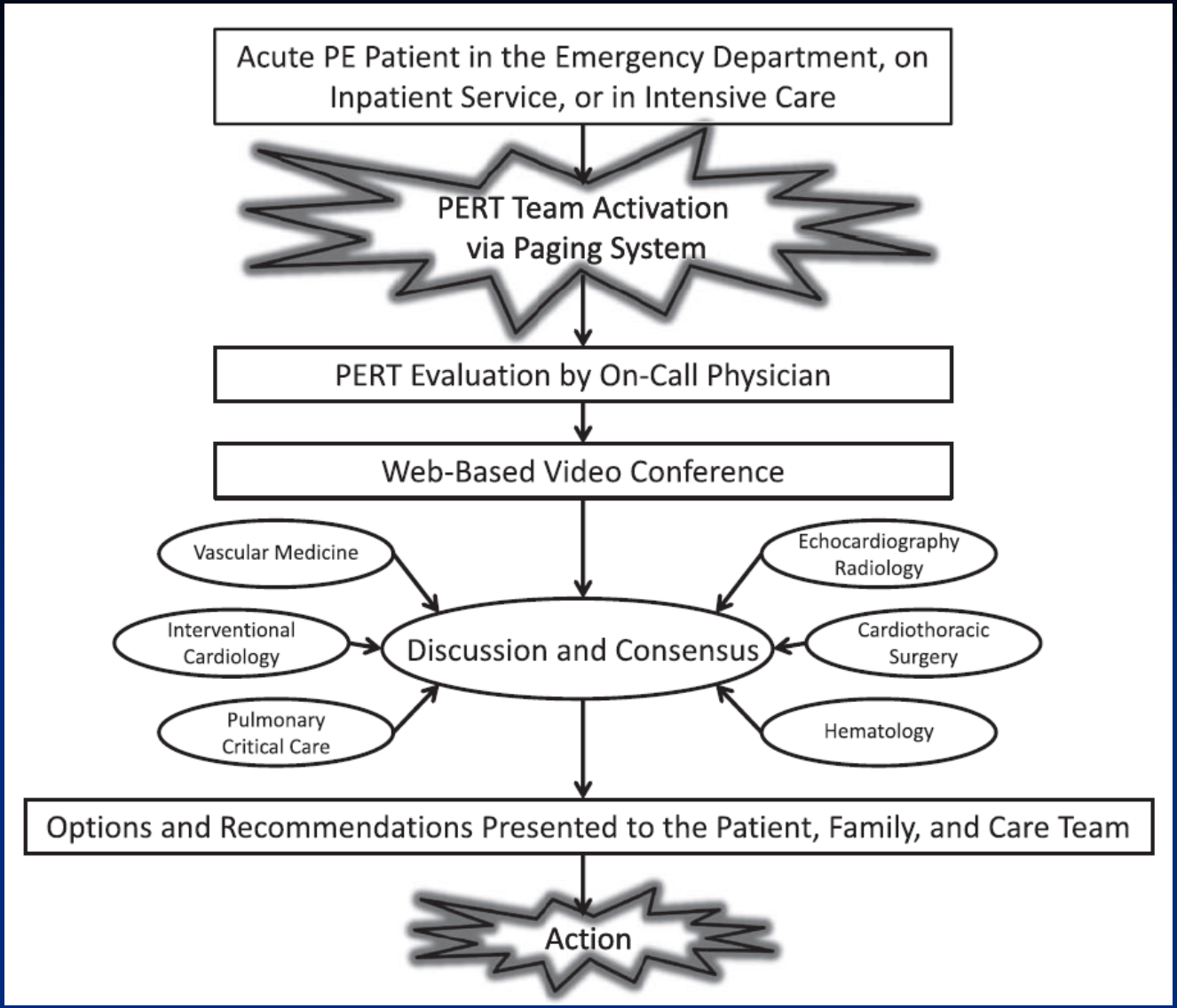
↓

Systemic thrombolysis
CDT
Surgical embolectomy

IVC filter
ECMO

?

Pulmonary Embolism Response Team (PERT)



Dudzinski and Piazza, Circulation 2016

Multidisciplinary pulmonary embolism response team

- To rapidly engage multiple specialists to deliver evidence -based and efficient care to patients with high-risk PE
- PERT activation n=394 over 30 mo
  Confirmed PE 314 (80%)
  Submassive PE 46% (n=143); massive PE 26% (n=80)
- Advanced treatment:
  CDT 28 (9%), systemic thrombolysis 14 (5%), embolectomy 8 (3%), suction thrombectomy 1 (0.3%)
- Thrombolysis or embolectomy, 23% of massive PE (EMPEROR 9%; ICOPER 13%)
- 30 day all cause mortality: 12%

Kabrhel et al. Chest 2016;150:384

Vena caval filters in the prevention of PE in patients with proximal DVT (PREPIC)

- A multicenter, randomized, open trial at 44 centers in France

Principal endpoints within the first 12 days after randomization

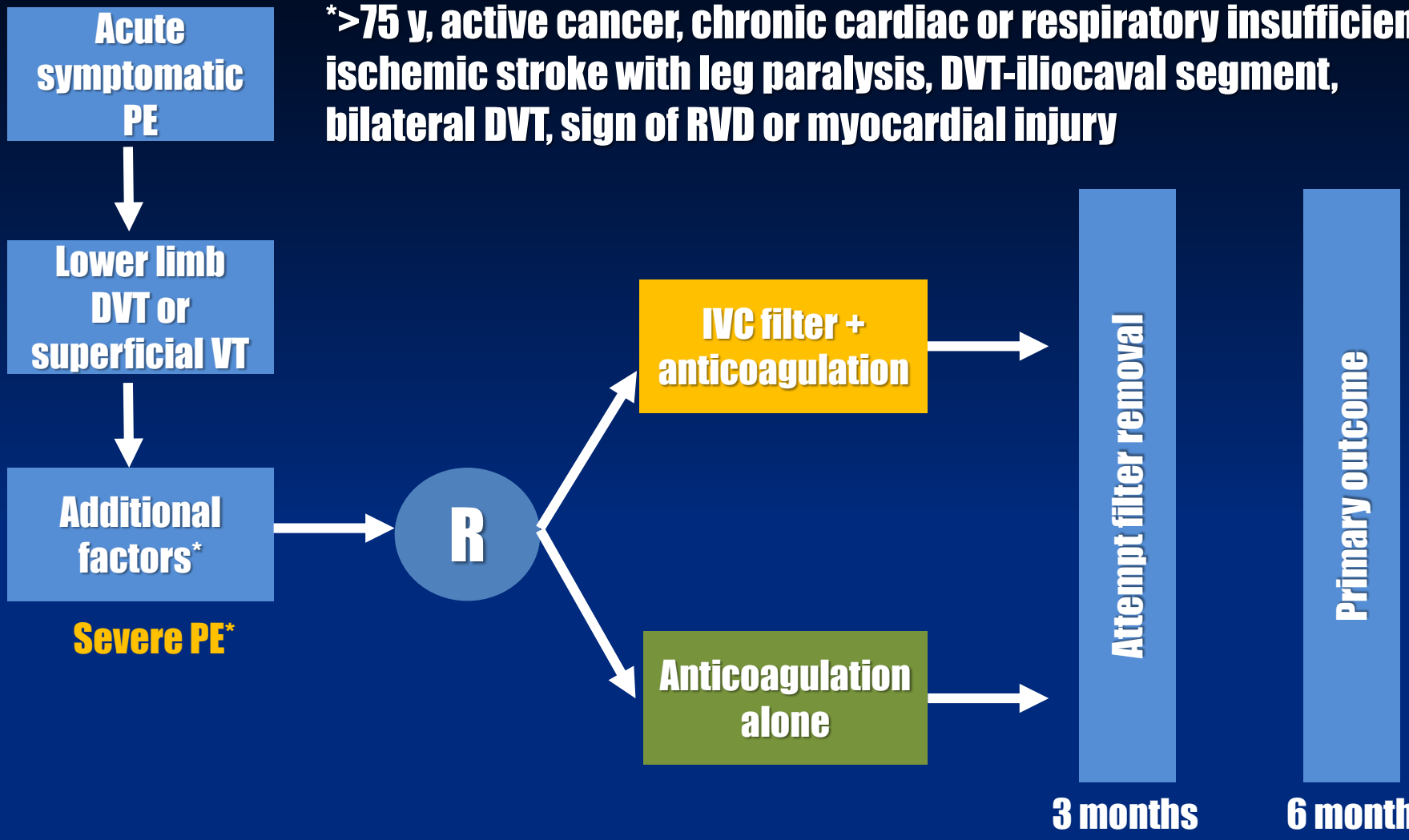
Event	Filter	No filter	OR	p-value
PE	2 (1.1)	9 (4.8)	0.22 (0.05-0.90)	0.03
Major bleeding	9 (4.5)	6 (3.0)	1.49 (0.53-4.20)	0.44
Death	5 (2.5)	5 (2.5)	0.99 (0.29-3.42)	0.99

Principal endpoints during the 2-year follow-up period

Event	Filter	No filter	OR	p-value
Symptomatic PE	6 (3.4)	12 (6.3)	0.50 (0.19-1.33)	0.16
Recurrent DVT	37 (20.8)	21 (11.6)	1.87 (1.10-3.20)	0.02
Major bleeding	17 (8.8)	22 (11.8)	0.77 (0.41-1.45)	0.41
Death	43 (21.6)	40 (20.1)	1.10 (0.72-1.70)	0.65

Decousus et al. NEJM 1998;338:409

Effect of a retrievable IVC filter plus anticoagulation vs anticoagulation alone on risk of recurrent PE (PREPIC2)



Mismetti et al. JAMA 2015;313;1627

Table 3. Clinical Outcomes For Patients With at Least 1 Event in the PREPIC2 Trial

Clinical Outcomes	Group, No. With Events (%)		Relative Risk, % (95% CI)	*P* Value[b]
	Filter (n = 200)[a]	Control (n = 199)		
At 3 Months				
Recurrent pulmonary embolism (primary efficacy outcome)[c]	6 (3.0)	3 (1.5)	2.00 (0.51-7.89)	.50
Fatal	6 (3.0)	2 (1.0)		
Nonfatal	0 (0.0)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	1 (0.5)	1.00 (0.06-15.9)	>.99
Recurrent venous thromboembolism	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.36
Major bleeding	8 (4.0)	10 (5.0)	0.80 (0.32-1.98)	.63
Death	15 (7.5)	12 (6.0)	1.25 (0.60-2.60)	.55
At 6 Months				
Recurrent pulmonary embolism[c]	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.54
Fatal	6 (3.0)	3 (1.5)		
Nonfatal	1 (0.5)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	2 (1.0)	0.50 (0.05-5.47)	>.99
Recurrent venous thromboembolism	8 (4.0)	6 (3.0)	1.33 (0.47-3.77)	.59
Major bleeding	13 (6.5)	15 (7.5)	0.87 (0.42-1.77)	.69
Death	21 (10.6)	15 (7.5)	1.40 (0.74-2.64)	.29

- **No evidence supporting the use of retrievable IVC filter in patients who can be treated with anticoagulation**
- **No insight into the outcome of patients with contraindication to anticoagulation**

Mismetti et al. JAMA 2015;313;1627

Pulmonary embolism

- Risk stratification
- Treatment
- Cancer-associated VTE
  - Evaluation for occult cancer: *Carrier et al. NEJM 2015*
  - LMWH (CATCH): *Lee et al. JAMA 2015*

Cancer-associated VTE

- Cancer patients: 4-fold greater risk of VTE
  Cancer patients receiving CTx: 6 fold

- VTE can be an early manifestation of cancer
  - Up to 10% of patients with unprovoked VTE
    vs 2.6% of patients with provoked events

Carson et al. NEJM 1992; Chew et al. Arch Intern Med 2006;
Sorensen et al. NEJM 2000;343:1846; Carrier et al. Ann Intern Med 2008

Risk of cancer after primary DVT or PE

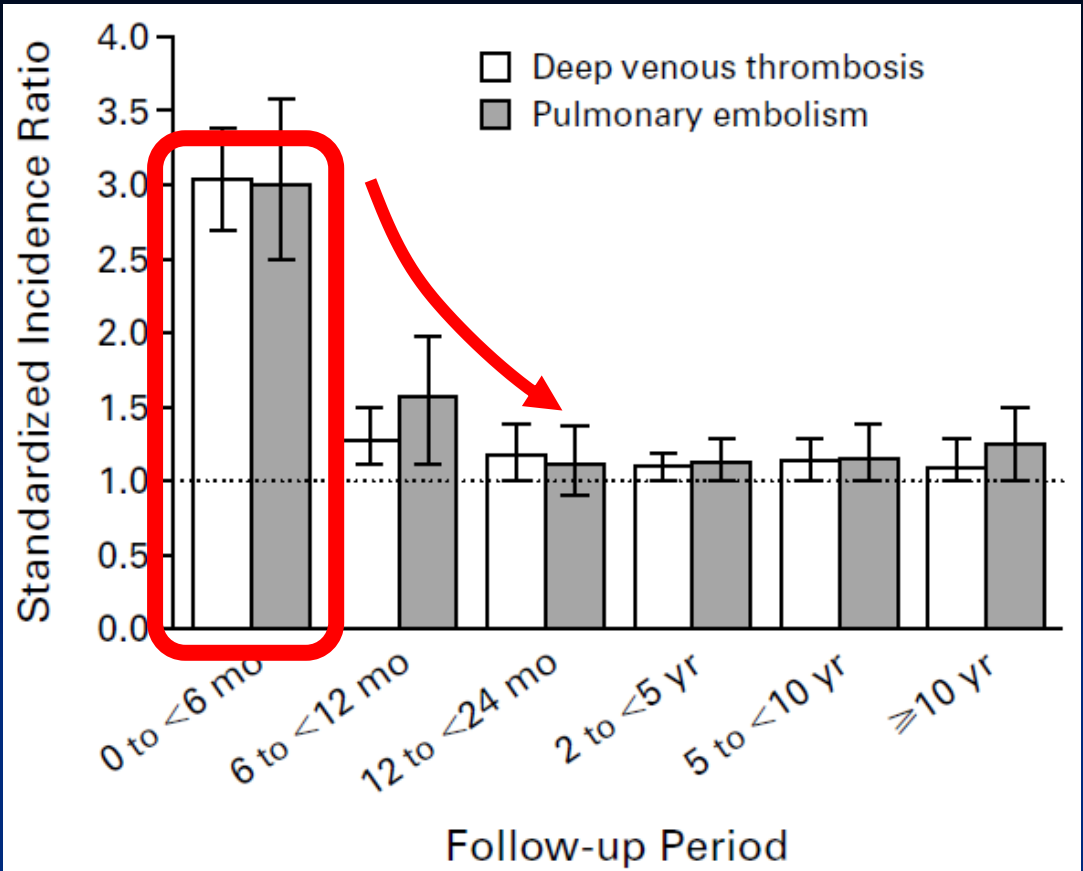


Figure 1. Risk of Cancer in Relation to the Length of the Follow-up Period in 26,653 Patients with Primary Deep Venous Thrombosis or Pulmonary Embolism.

- Danish National Registry
- 1977-1992
- Standardized incidence ratio=observed/expected cases

Sorensen et al. NEJM 1998;338:1169

Screening for Occult Malignancy in unprovoked VTE (SOME trial)

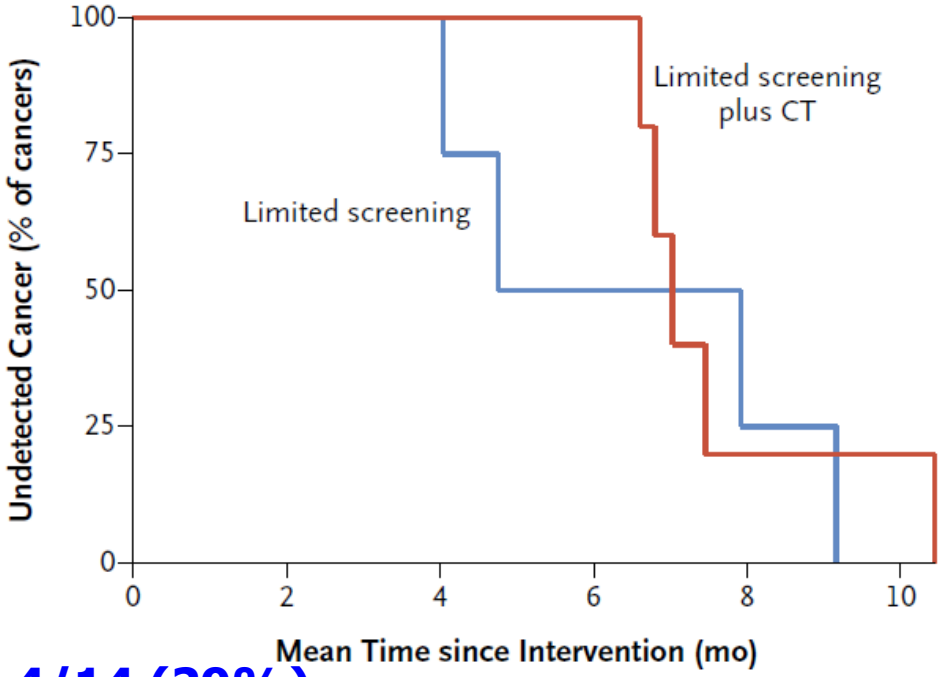
- Multicenter, open-label, randomized, controlled trial
- Limited screening (blood test, chest radiography, screening for breast, cervical, and prostate cancer) vs limited screening + CT (extensive screening)

- Comprehensive CT of abdomen and pelvis, including virtual colonoscopy and gastroscopy, biphasic enhanced CT of liver, parenchymal pancreatography, uniphasic enhanced CT of bladder

- New diagnosis of occult cancer: 33/854 (3.9%) for 1 y

- Occult cancer: 14/431 (3.2%) vs 19/423 (4.5%)
  Missed cancer: 4/14 (29%) vs 5/19 (26%)

Carrier et al. NEJM 2015;373:697



4/14 (29%)

No. at Risk						
Limited screening	4	4	4	2	1	0
Limited screening plus CT	5	5	5	5	1	1

5/19 (26%)

Figure 2. Kaplan–Meier Curves for Time to Detection of Missed Occult Cancer.

- **Inclusion of CT did not appear to detect more occult cancer, shorten the time to cancer diagnosis, or reduce cancer-related mortality**

Carrier et al. NEJM 2015;373:697

LMWH (dalteparin) vs VKA for cancer-associated VTE

- CLOT trial
- Dalteparin (200 IU/kg for 1 M followed by 150 IU/kg) alone vs dalteparin and VKA
- Recurrent VTE: HR 0.48
- No difference in major or any bleeding

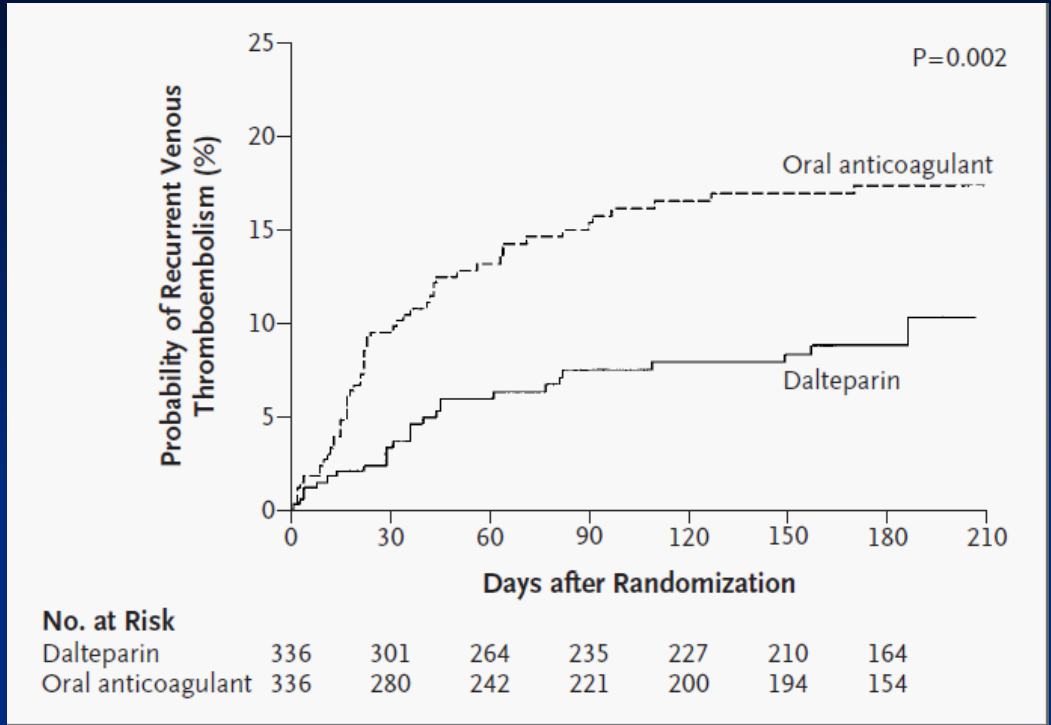


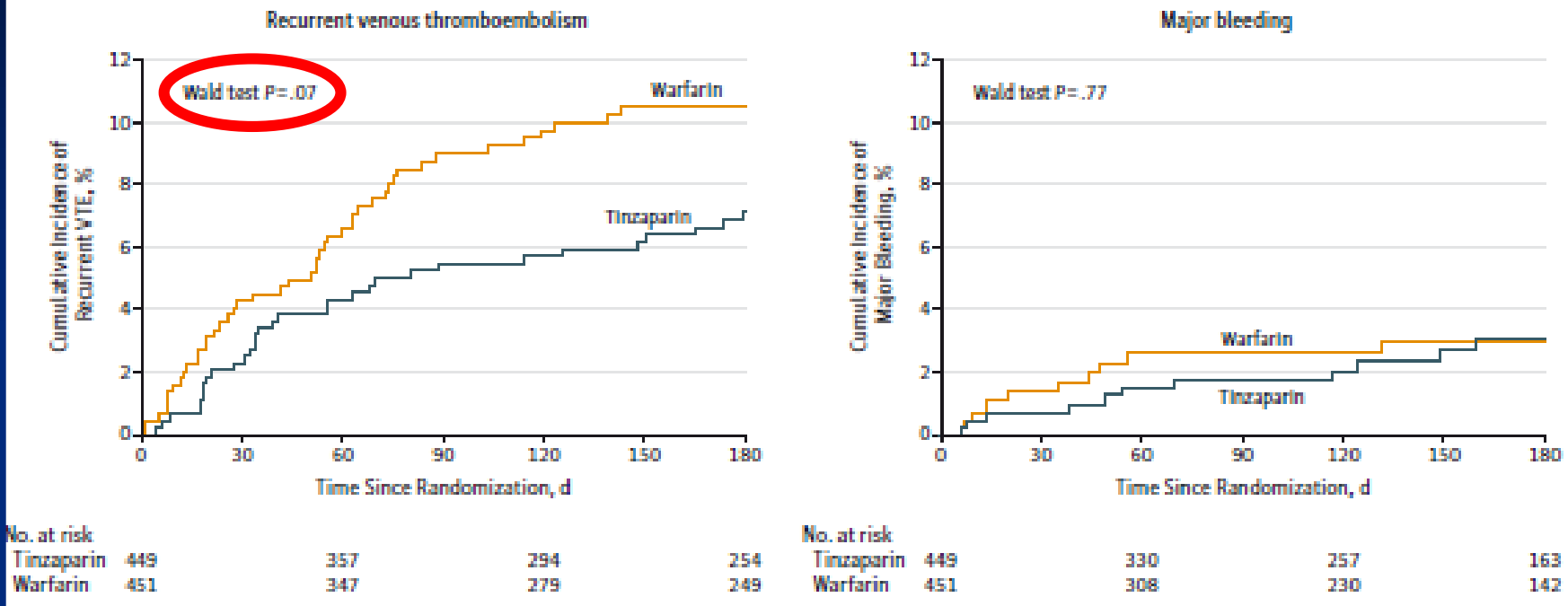
Figure 1. Kaplan–Meier Estimates of the Probability of Symptomatic Recurrent Venous Thromboembolism among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism.

Lee AYY et al. NEJM 2003;349:146

LMWH (tinzaparin) vs VKA for cancer-associated VTE

- Comparison of Acute Treatments in Cancer Hemostasis (CATCH)
- Phase 3, multinational , randomized, controlled, open-label trial
- Tinzaparin 175 IU/day once alone vs tinzaparin + VKA

Figure 2. Cumulative Incidence Among Patients With Active Cancer According to Treatment With Tinzaparin vs Warfarin



VTE indicates venous thromboembolism. Source: The left panel of Figure 2 was reproduced with permission from the American Society of Hematology.[24]

Lee AYY et al. JAMA 2015;314:677

Table 2. Primary and Secondary Efficacy and Safety Outcomes in the CATCH Trial

	No. (%)			
	Tinzaparin (n = 449)	Warfarin (n = 451)	HR (95% CI)	*P* Value
Primary Efficacy Outcome				
Recurrent VTE	31 (6.9)[a]	45 (10.0)	0.65 (0.41-1.03)	.07
Secondary Efficacy Outcomes				
Symptomatic DVT[b]	12 (2.7)	24 (5.3)	0.48 (0.24-0.96)	.04
Symptomatic nonfatal PE	3 (0.7)	2 (0.4)	NA	
Fatal PE[c]	17 (3.8)	17 (3.8)	0.96 (0.49-1.88)	.89
Incidental proximal DVT	0	1 (0.2)	NA	
Incidental PE	0	1 (0.2)	NA	
Recurrent VTE, per protocol, No./total patients (%)	29/351 (8.3)	39/307 (12.7)	0.62 (0.38-1.00)	.05
Safety Outcomes				
Major bleeding[d]	12 (2.7)	11 (2.4)		
Noncritical site	5 (1.1)	10 (2.2)	0.89 (0.40-1.99)	.77
Critical site	7 (1.6)	1 (0.2)		
Fatal bleeding[e]	0	0		
Clinically relevant nonmajor bleeding	49 (10.9)	69 (15.3)	0.58 (0.40-0.84)	.004
All bleeding	114 (25.4)	110 (24.4)	NA	
All-cause death	150 (33.4)	138 (30.6)		
Progression of cancer	105 (23.4)	93 (20.6)		
Fatal PE	17 (3.8)	19 (4.2)[f]	1.08 (0.85-1.36)	.54
Fatal bleeding[g]	3 (0.7)	3 (0.7)		
Other	25 (5.6)	23 (5.1)		

Lee AYY et al. JAMA 2015;314:677

- **Difference between CATCH and CLOT**
  Population of CATCH: patients with lower risk of VTE
  - lower incidence of metastatic disease, ECOG 2, anticancer treatment, previous history

Lee AYY et al. JAMA 2015;314:677

- **LMWH as long term anticoagulant in CAT**
  30% in MASTER registry

Imberti et al. Haematolgica 2008

- **DOAC vs LMWH in CAT?**
  DOAC = LMWH??

Posch et al. Thromb Res 2015

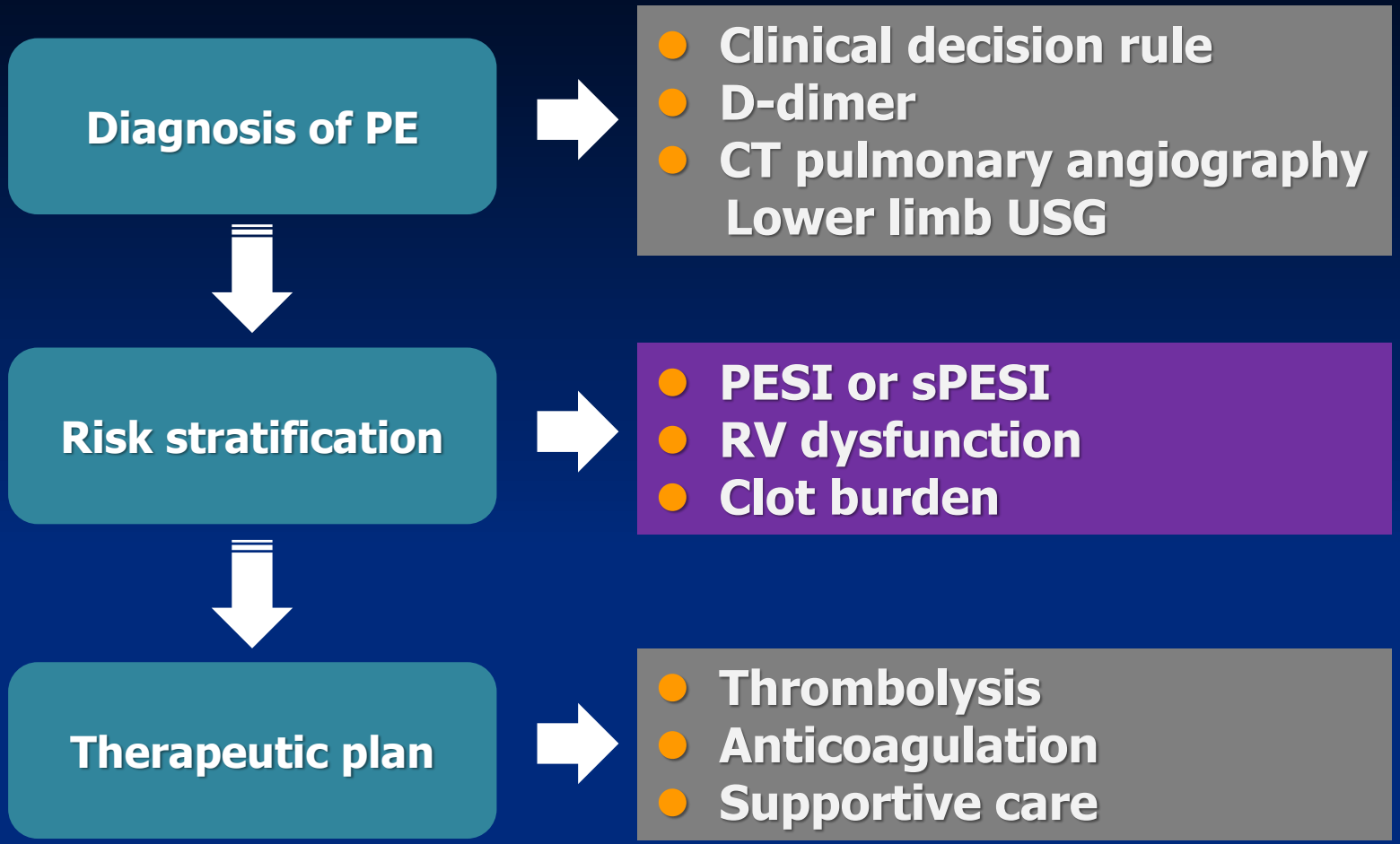
Summary

- ESC 2014 model→ limited role
  More effective risk stratification is needed for active use of reperfusion therapy
- RHT→ low incidence, higher mortality
  advanced therapy?
- CDT has an important role in the treatment of PE
  PERT is an emerging rapid response team

Summary, cont.

- Addition of IVC filter on anticoagulation is not beneficial
- Extensive work-up for occult cancer in patients with unprovoked VTE is not necessary
- In CAT, compared with warfarin, LMWH is associated with a lower rate of clinically relevant nonmajor bleeding and lower rate of PE recurrence

Approach to acute PE



Acute PE: mortality prediction by the 2014 ESC risk stratification model

- 3 prospective cohorts→ n=906

	ESC 2014		ESC 2008	
	Death at 30 d	Death due to PE	Death at 30 d	Death due to PE
High 105 (12%)	23/105 (22, 14.0-29.8)	16/105 (15.2, 8.4-22.1)	23/105 (22, 14.0-29.8)	16/105 (15.2, 8.4-22.1)
Intermediate-high 272 (30%)	21/272 (7.7, 4.5-10.9)	13/272 (4.8, 2.2-7.3)	21/307* (6.8, 4.0-9.7)	13/307* (4.2, 2.0-6.5)
Intermediate-low 333 (37%)	20 /333 (6.0, 3.4-8.6)	7/333 (2.1, 0.6-3.6)	19/271** (7.0, 4.0-10.0)	8/271** (3.0, 0.9-5.0)
Low 196 (22%)	1/196 (0.5, 0-1.5)	1/196 (0.5, 0-1.5)	2/223 (0.9, 0-2.1)	0/223

*RVD/troponin↑, both present; **either present.

Becattini et al. ERJ 2016;48:780

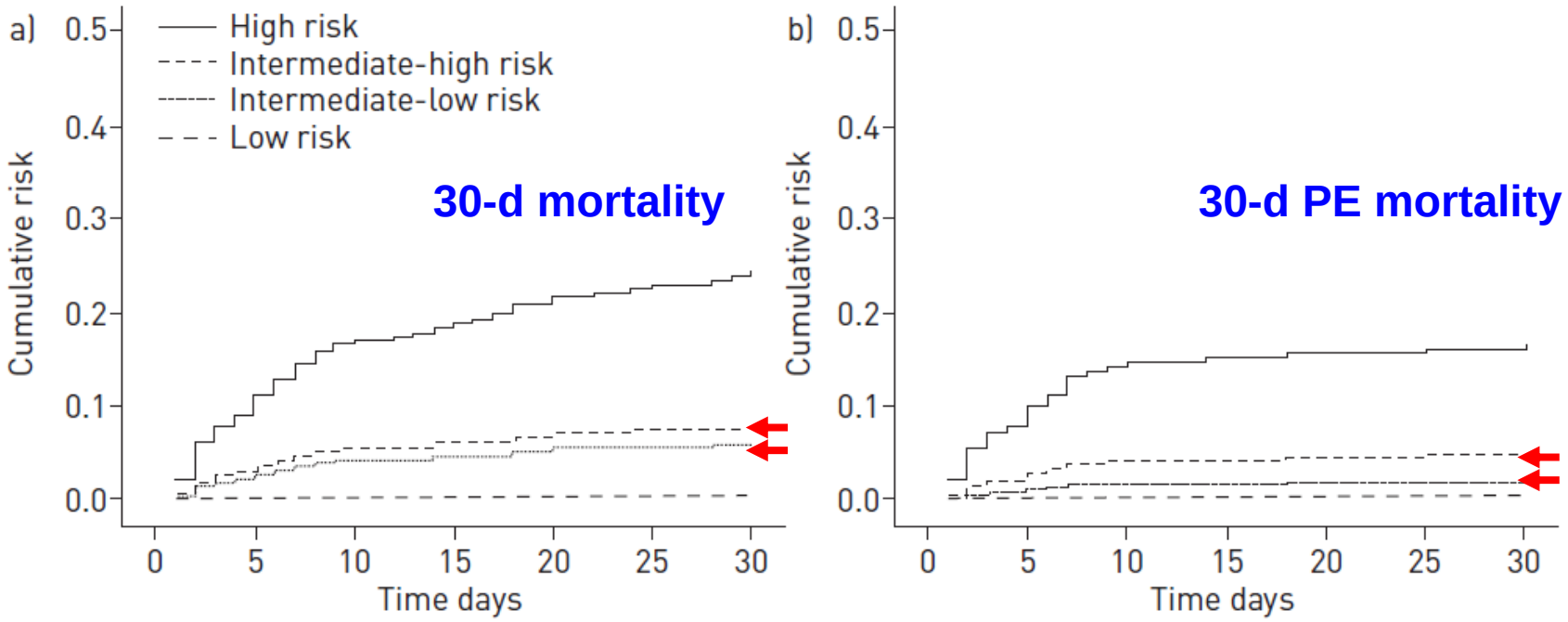


FIGURE 2 Risk of a) death at 30 days and b) death due to pulmonary embolism in patients belonging to different risk categories according to the 2014 European Society of Cardiology model.

C-statistic for death at 30 days and for death due to PE

	Death at 30 d	Death due to PE
2014 ESC model	0.71 (0.65-0.77)	0.75 (0.68-0.83)
2008 ESC model	0.71 (0.64-0.77)	0.76 (0.69-0.83)

Becattini et al. ERJ 2016;48:780

Prediction of early mortality in PE

Parameter	Cut-off value	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV, % (95% CI)	PPV, % (95% CI)	OR or HR	Study design
Echo		74 (61–84)	46 (27–66)	98 (96–99)	8 (6–10)	2.4 (1.3–4.3)	Meta-analysis
CTPA	RV/LV≥1	46 (51–56)	93 (89–96)	93 (54–64)	8 (5-14)	1.5 (0.7-3.4)	Meta-analysis
BNP	75-100 pg/mL	85 (64-95)	56 (50-62)	98 (94-99)	14 (9-21)	6.5 (2.0-2.1)	Meta-analysis
NT-proBNP	600 pg/mL	86 (69-95)	50 (46-54)	99 (97-100)	7 (5-19)	6.3 (2.2-18.3)	Prospective
Troponin I	Different	NR	NR	NR	NR	4.0 (2.2-7.2)	Meta-analysis
Troponin T	14 pg/mL	87 (71-95)	42 (38-47)	98 (95-99)	9 (6-12)	5.0 (1.7-14.4)	Prospective

ESC guideline 2014

TABLE 2 30-day clinical events after diagnosis and treatment for patients with acute symptomatic pulmonary embolism

	All patients	Presence of right heart thrombi	Absence of right heart thrombi	p-value
Patients n	12441	325	12116	
Primary outcome				
All-cause death	382 (3.1)	28 (8.6)	354 (2.9)	<0.001
Pulmonary embolism-related death	122 (1.0)	17 (5.2)	105 (0.9)	<0.001
Secondary outcomes				
Recurrent pulmonary embolism	93 (0.7)	6 (1.8)	87 (0.7%)	0.04
Major bleeding	440 (3.5)	15 (4.6)	425 (3.5%)	0.36

Data are presented as n (%), unless otherwise stated.

Barrios et al. ERJ 2016;48:1377

- **30-d all-cause mortality**

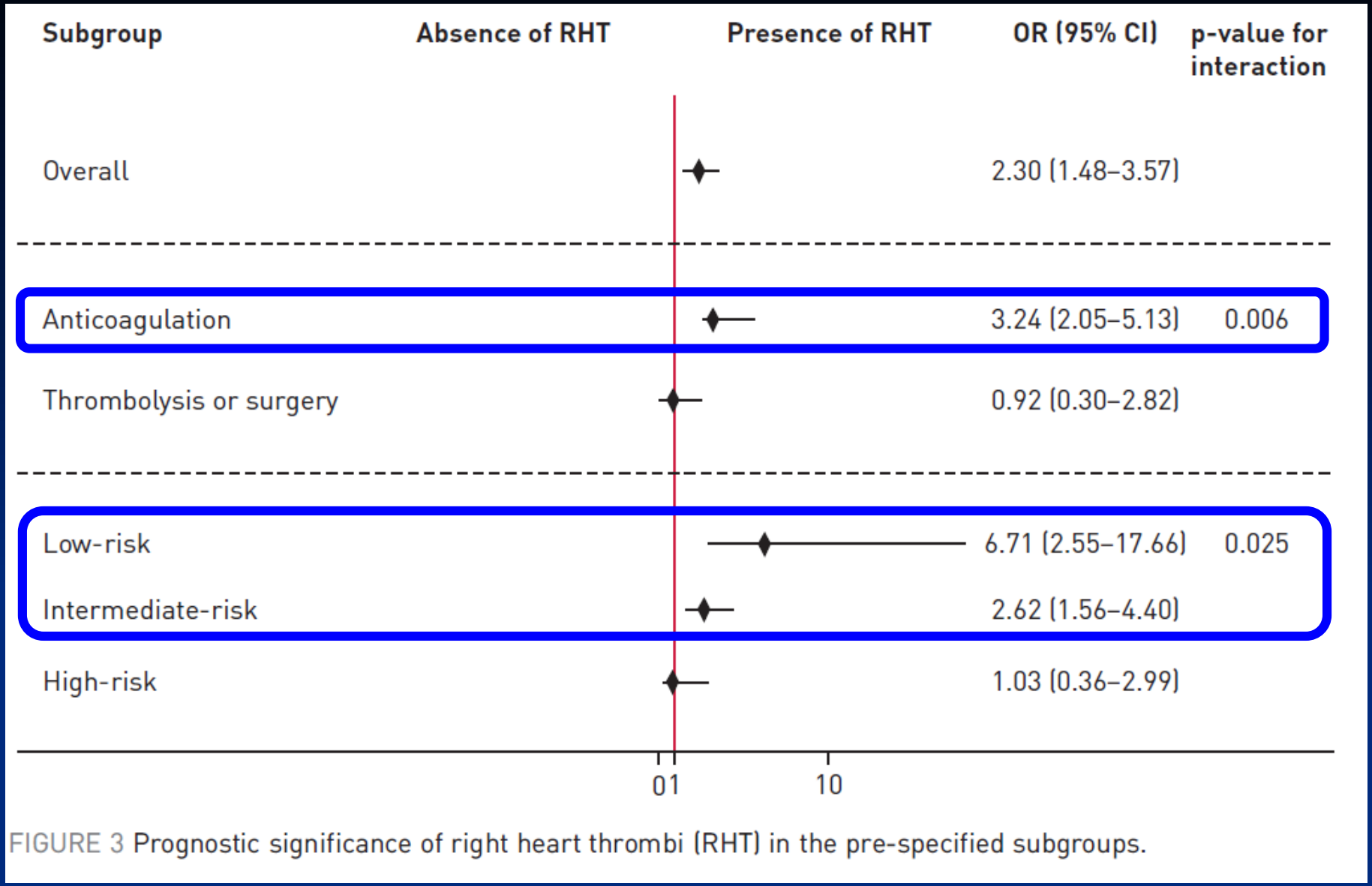
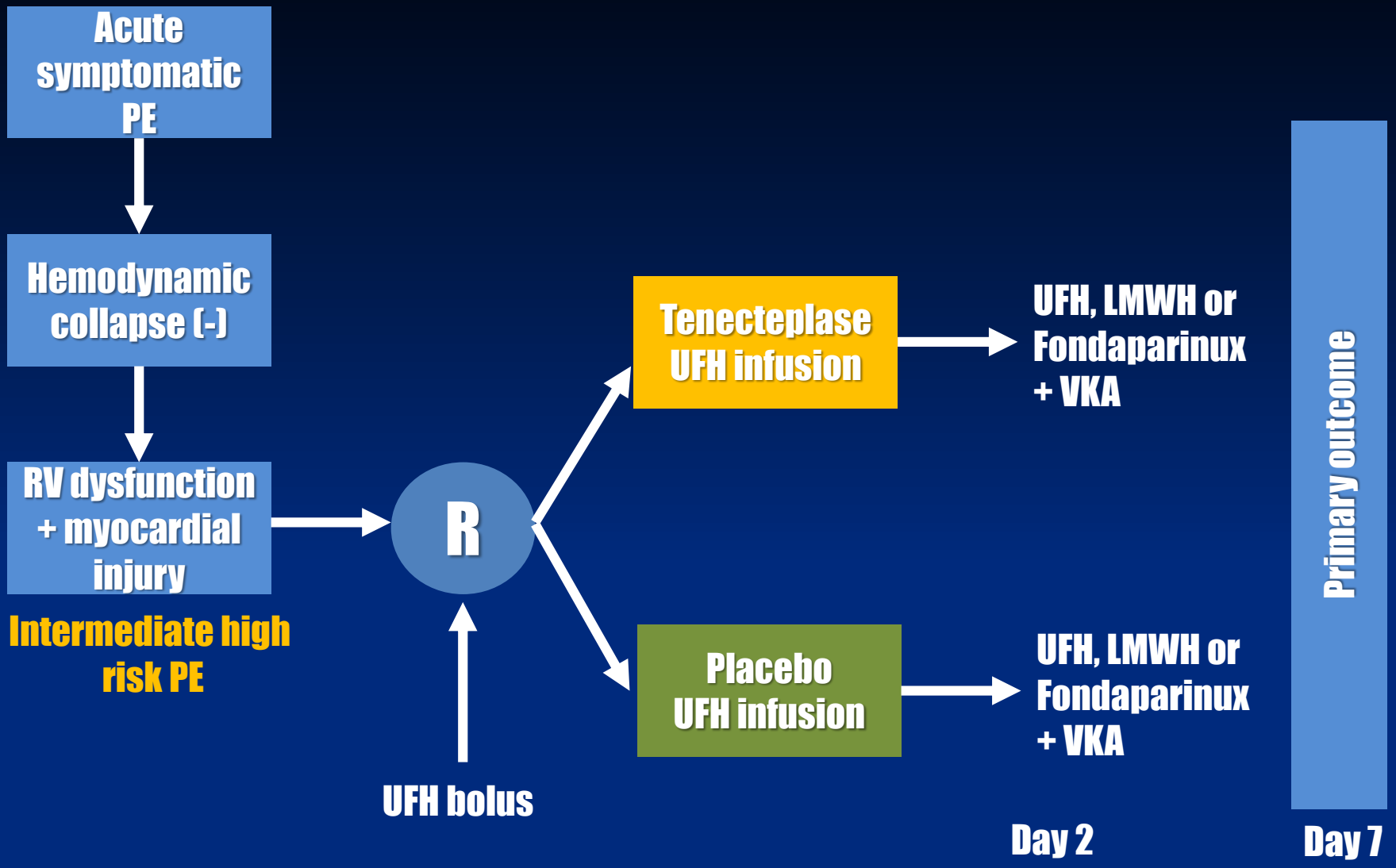


FIGURE 3 Prognostic significance of right heart thrombi (RHT) in the pre-specified subgroups.

Barrios et al. ERJ 2016;48:1377

PEITHO trial



Meyer et al. NEJM 2014;370:1402

Outcome of PEITHO study

Outcome	Tenecteplase (n=506)	Placebo (n=499)	OR (95% CI)	P-value
Primary outcome within 7 d	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
All cause mortality	6 (1.2)	9 (1.8)	0.65 (0.23-1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14-0.68)	0.002
Safety outcome within 7 d				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3-13.39)	<0.001
Stroke	12 (2.4)	1 (0.2)	12.10 (1.57-93.39)	0.003

- In patients with intermediate-risk PE, fibrinolytic therapy prevented hemodynamic decompensation but increased the risk of major bleeding and stroke.
- More complex risk stratification?
- Conversion to catheter-directed therapy?

Meyer et al. NEJM 2014;370:1402

Ultrasound-assisted CDT (USAT)

- US facilitates the delivery of drugs
  → reversible disaggregation of uncrosslinked fibrin fibers
  → increase thrombus penetration of drug

- A meta-analysis (20% massive PE)
  - All-cause mortality: 4.1%
  - Major bleeding: 2.3%
  - Minor bleeding: 10.9%

Figure 1 Tip of the ultrasound-assisted thrombolysis catheter, EkoSonic® Endovascular System (EKOS Corporation; Bothell, WA, USA). The catheter is composed of a 5.2-Fr multi-sidehole drug infusion catheter (treatment zone marker delineated with an arrow head) and a microsonic core wire containing the ultrasound elements (marked with small arrows). During ultrasound-assisted thrombolysis, the multi-element ultrasound core wire is placed inside the infusion catheter.

Engelberger et al. Eur Heart J 2014
Mostafa A, et al. Int J Cardiol 2016

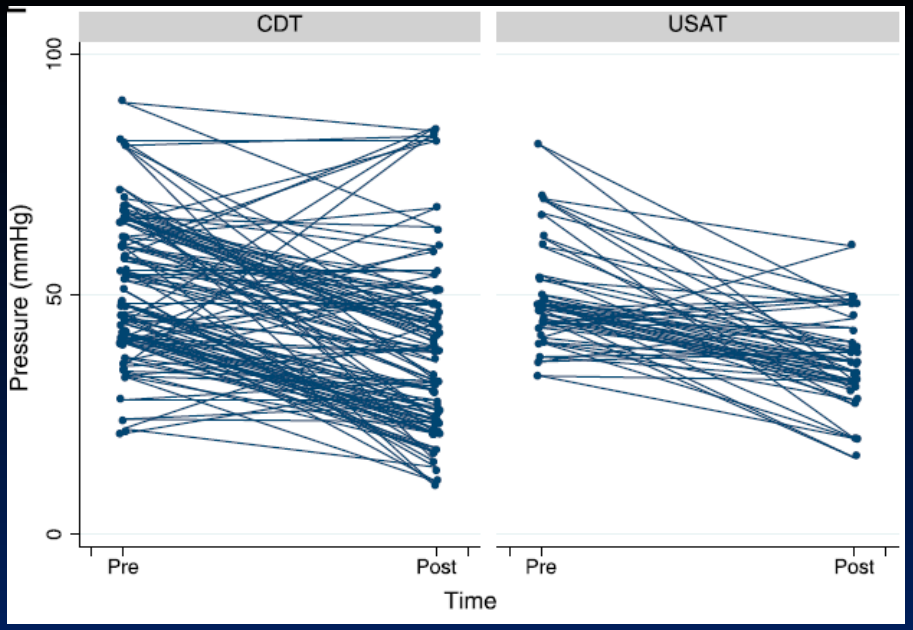


TABLE 3] USAT vs Standard CDT

Available Pressure Data	USAT	Standard CDT	*P* Value
PA pressure at baseline, mm Hg	49.83 ± 11.14 (n = 29)	51.79 ± 15.26 (n = 63)	.697
PA pressure post-CDT, mm Hg	36.07 ± 9.62 (n = 29)	37.77 ± 18.01 (n = 63)	.897
Pressure change post-CDT, mm Hg	−13.76 ± 11.20 (n = 29)	−14.02 ± 16.39 (n = 63)	.900
Available tPA data			
tPA dose, mg	30.27 ± 9.07 (n = 36)	25.63 ± 11.71 (n = 40)	.055
Infusion time,[a] h	23.19 ± 8.09 (n = 36)	20.76 ± 11.51 (n = 27)	.103

Data are presented as mean ± SD. No significant difference was identified between these groups. PA = pulmonary artery; tPA = tissue plasminogen activator; USAT = ultrasound-assisted thrombolysis. See Table 2 legend for expansion of other abbreviation.

[a]Data from overnight infusions.

Kuo et al. Chest 2015;148:667

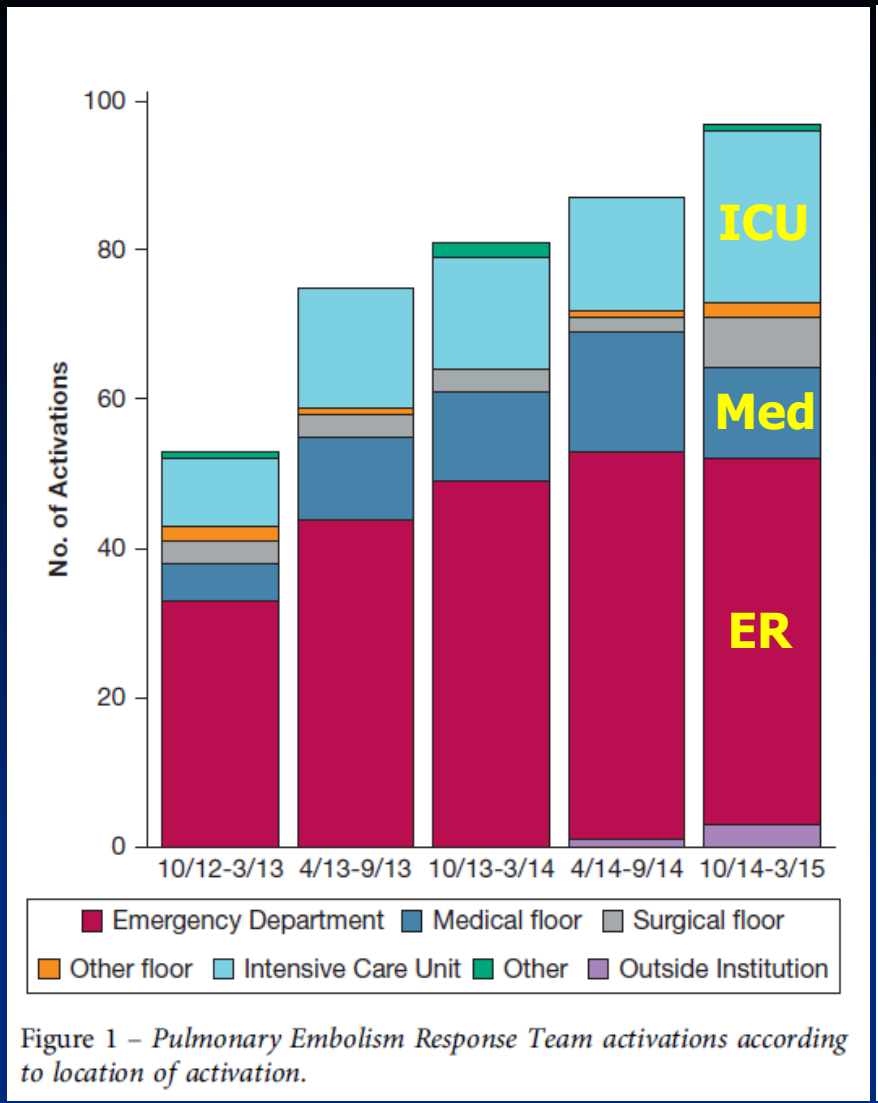


Figure 1 – *Pulmonary Embolism Response Team activations according to location of activation.*

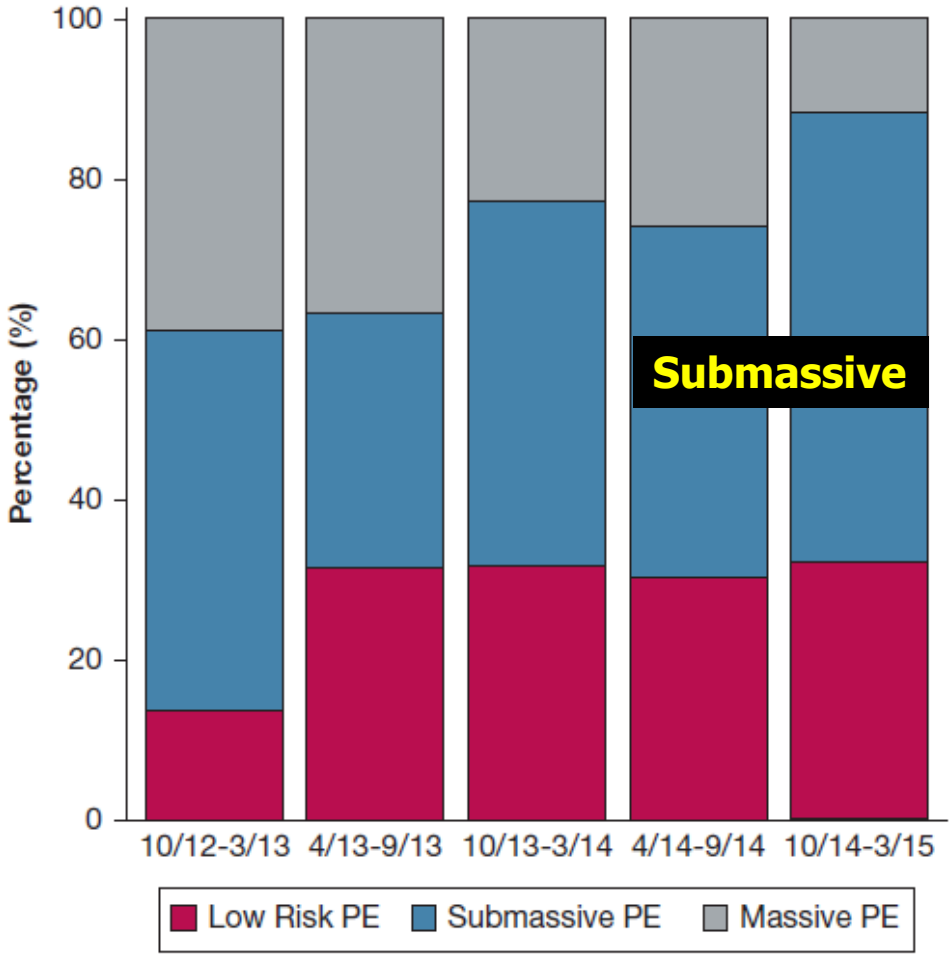


Figure 2 – *PE severity category among patients with confirmed PE. PE = pulmonary embolism.*

- **National PERT consortium over 40 institutions in US**

Kabrhel et al. Chest 2016;150:384

Eight-year follow-up of patients with permanent vena cava filters in the prevention of PE

Characteristics	Filter n=200	No filter n=200	HR	P-value
Symptomatic PE	9 (6.2)	24 (15.1)	0.37 (0.17-0.79)	0.008
Symptomatic recurrent DVT	57 (35.7)	41 (27.5)	1.52 (1.02-2.27)	0.042
Symptomatic VTE	58 (36.4)	55 (35.4)	1.12 (0.78-1.62)	0.54
PTS	109 (70.3)	107 (69.7)	0.87 (0.66-1.13)	0.30
Death	98 (48.1)	103 (51.0)	0.97 (0.74-1.28)	0.83
Major bleeding	26 (15.4)	31 (18.5)	0.84 (0.50-1.42)	0.52

PREPIC Study Group, Circulation 2005

Cancer-associated VTE

- **Cancer patients: 4-fold greater risk of VTE**
  Cancer patients receiving CTx: 6 fold
- **Death from PE in cancer patients < 1%**
- **Higher mortality after adjusted for stage**
  → more aggressive cancer biology
- **Cancer at the same time as or within 1 y after VTE**
  → advanced stage, poor prognosis
- **Up to 10% of patients with unprovoked VTE**
  vs 2.6% of patients with provoked events

Carson et al. NEJM 1992; Chew et al. Arch Intern Med 2006;
Sorensen et al. NEJM 2000;343:1846; Carrier et al. Ann Intern Med 2008

Risk factors predictive of occult cancer detection in patients with unprovoked VTE

- A total of 33 (3.9%) out of the 854 included patients received a new diagnosis of cancer at 1-year follow-up

- Age ≥ 60 years (HR, 3.11; 95% CI, 1.41-6.89)
  previous provoked VTE (HR, 3.20; 95% CI, 1.19-8.62)
  current smoker status (HR, 2.80; 95% CI, 1.24-6.33)
  were associated with occult cancer detection
- Combined effect of 3 characteristics: 3.33 (95% CI 1.73-4.92)

Risk	Age <60				Age ≥ 60			
	No VTE		Prior provoked VTE		No VTE		Prior provoked VTE	
	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker
2-y	0.2	0.6	0.7	1.8	0.6	1.8	2.0	5.5
5-y	1.8	5.0	5.7	15.2	5.6	14.8	16.8	40.2

Ihaddadene et al. Blood 2016;127:2035

Development of a risk prediction score for occult cancer in patients with VTE

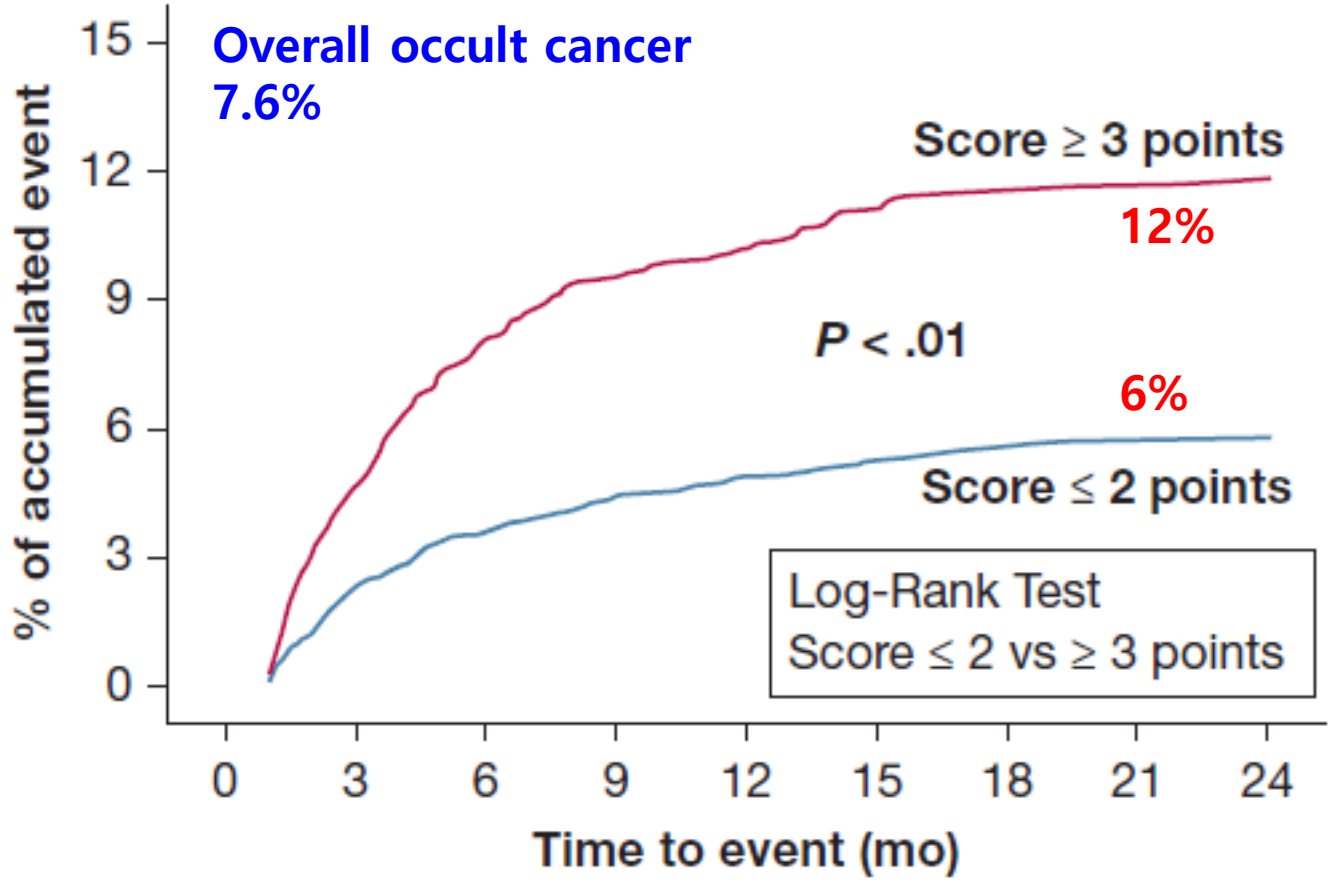
- A nested case-control study, RIETE registry
- 30 d~24 m after VTE

TABLE 2] Multivariable Analysis and Score to Identify Patients With Increased Risk for Occult Cancer

Variable	β Coefficient	OR	95% Confidence Limits		*P* Value	Points
			Lower	Upper		
Male sex	0.378	1.46	1.19	1.79	< .001	+1
Age > 70 y	0.642	1.90	1.55	2.33	< .001	+2
Underlying conditions						
Chronic lung disease	0.338	1.40	1.07	1.84	.015	+1
Anemia	0.539	1.71	1.38	2.13	< .001	+2
Platelet count ≥ 350 × 10^6/mm^3	0.334	1.40	1.03	1.90	.034	+1
Risk factors for VTE						
Postoperative status	−0.722	0.49	0.32	0.73	< .001	−2
Prior VTE	−0.392	0.68	0.51	0.89	.006	−1

Hosmer-Lemeshow test: $\chi^2 = 4.33$, degree of freedom = 8; $P = .826$; C-statistic = 0.64 (95% CI, 0.61-0.66). List of variables included in the multivariable regression analysis: age > 70 y, BMI, chronic lung disease, platelet count ≥ 350,000 × 1,000/mm, anemia, recent surgery, hormone therapy, unprovoked VTE, varicose veins, and prior VTE. Anemia was defined as hemoglobin levels < 12 g/dL in women and < 13 g/dL in men.

Jara-Palomares et al. Chest 2017:151:564



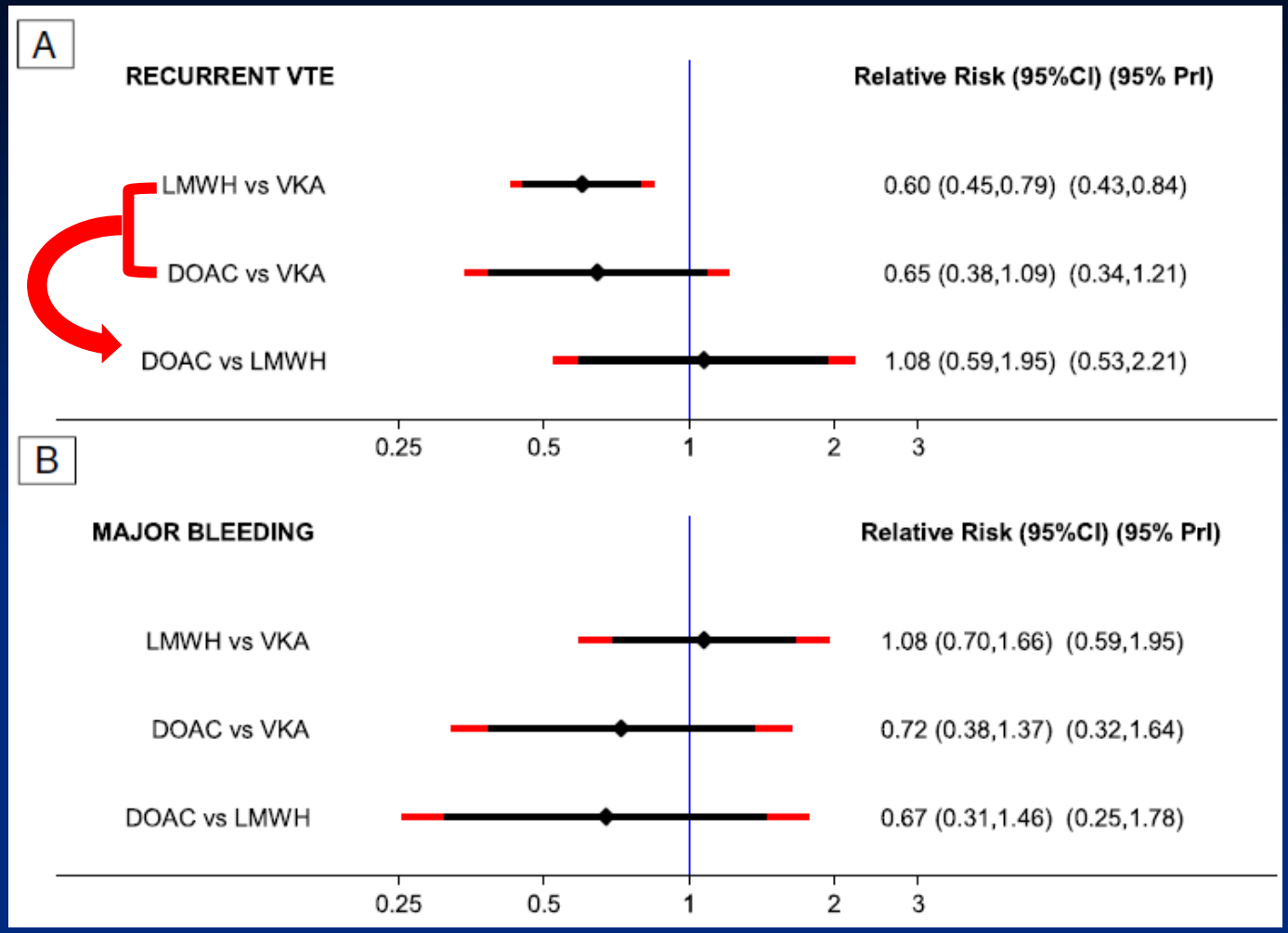
Score (No. at risk)								
≤ 2 points (n = 4,150)	4,053	4,001	3,967	3,947	3,933	3,919	3,911	3,909
≥ 3 points (n = 1,714)	1,634	1,575	1,551	1,539	1,524	1,516	1,514	1,511

Figure 2 – *Cumulative incidence of occult cancer over 2 years taking into account score (≤ 2 vs ≥ 3 points) (time-to-event data).*

Jara-Palomares et al. Chest 2017:151:564

LMWH vs DOAC in CAT?

- Network meta-analysis



Posch et al. Thromb Res 2015