Insights Into the Management of Acute Pulmonary Embolism

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Interventional Cardiology & Endovascular Medicine

Disclosers

NONE

Pulmonary Embolism (PE)

Annual incidence

- United States: 69 per 100,000/year[1]
- Over 600,000 cases annually[2]
  - 1–2 PE episodes per 1000 people, up to 10 per 1000 in the elderly population[3-6]

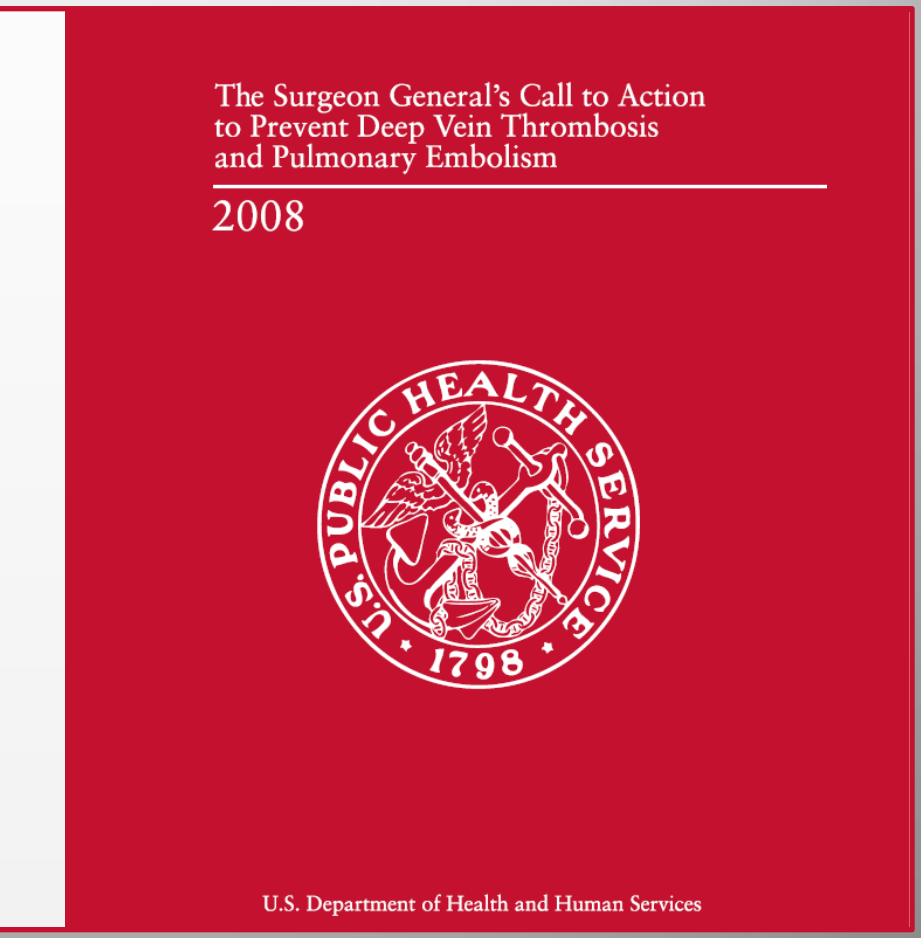
Venous thromboembolism[3]

- PE commonly originates from lower limb deep vein thrombosis (DVT)
- 79% of patients presenting with PE have evidence of DVT
- PE occurs in up to 50% of patients with proximal DVT

1. Silverstein MD et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism. Arch intern Med 1998;158:585-93.
2. Wood KE et al. Major pulmonary embolism: review of a pathphysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002;121:877-905.
3. Tapson VF. Acute pulmonary embolism. N Engl J Med 2008;358(10):1037-1052.
4. Geering et al. CMAJ 2012; 184(3):305-310
5. Chunilal et al. JAMA 2003;290:2849–58
6. Siccama et al. Ageing Res Rev 2011;10:304–13

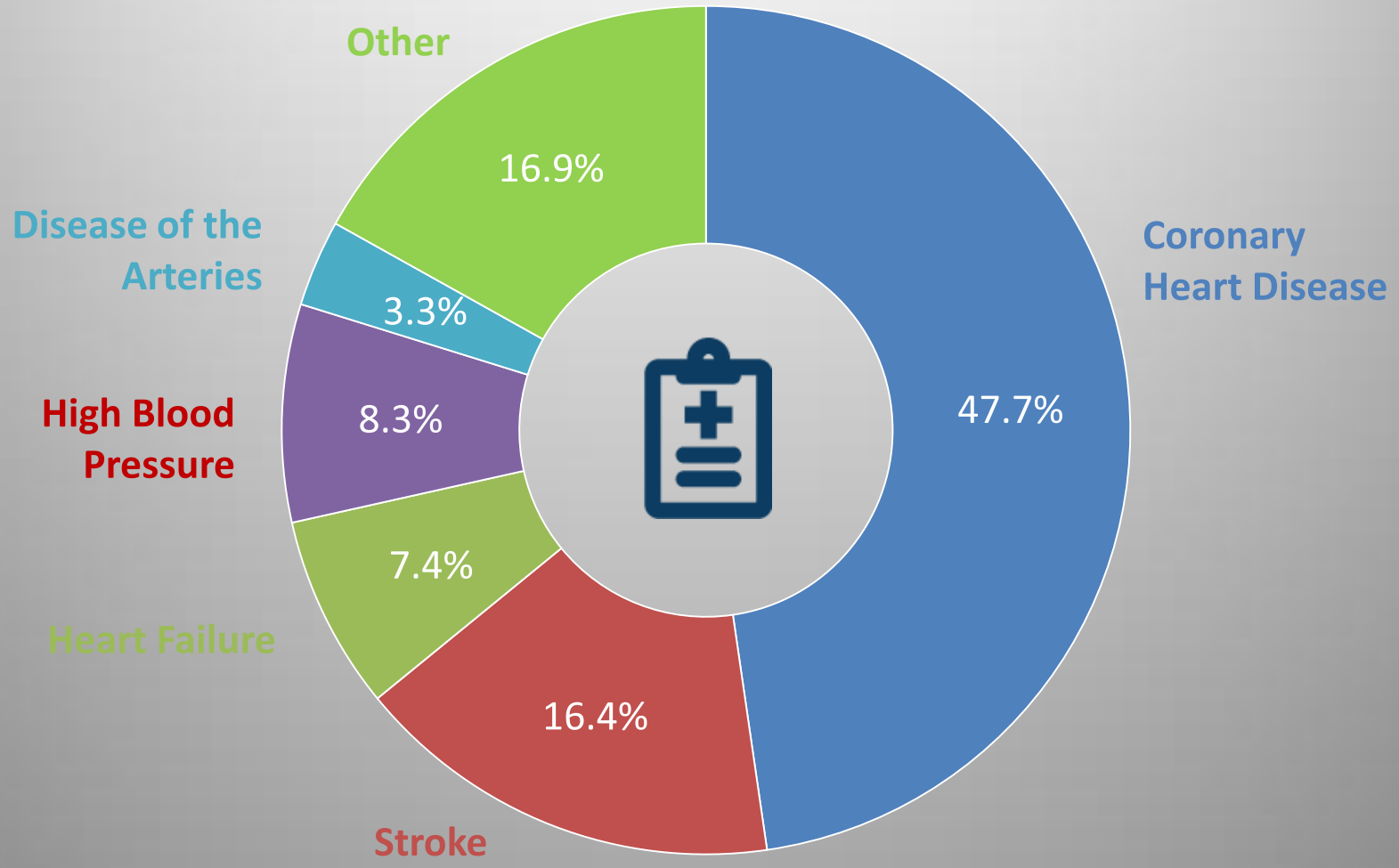
PE Mortality

- 100,000–180,000 PE-related deaths annually in the US
- PE is the most preventable cause of death among hospitalized patients



The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. US Department of Health and Human Services report, 2008.

AHA 2015 Statistics:
PE is the 3rd cause of CV death



Mozaffarian D et al. Heart Disease and Stroke Statistics – 2015 Update: A report from the American Heart Association. Circulation 2015; 131: e29-e322

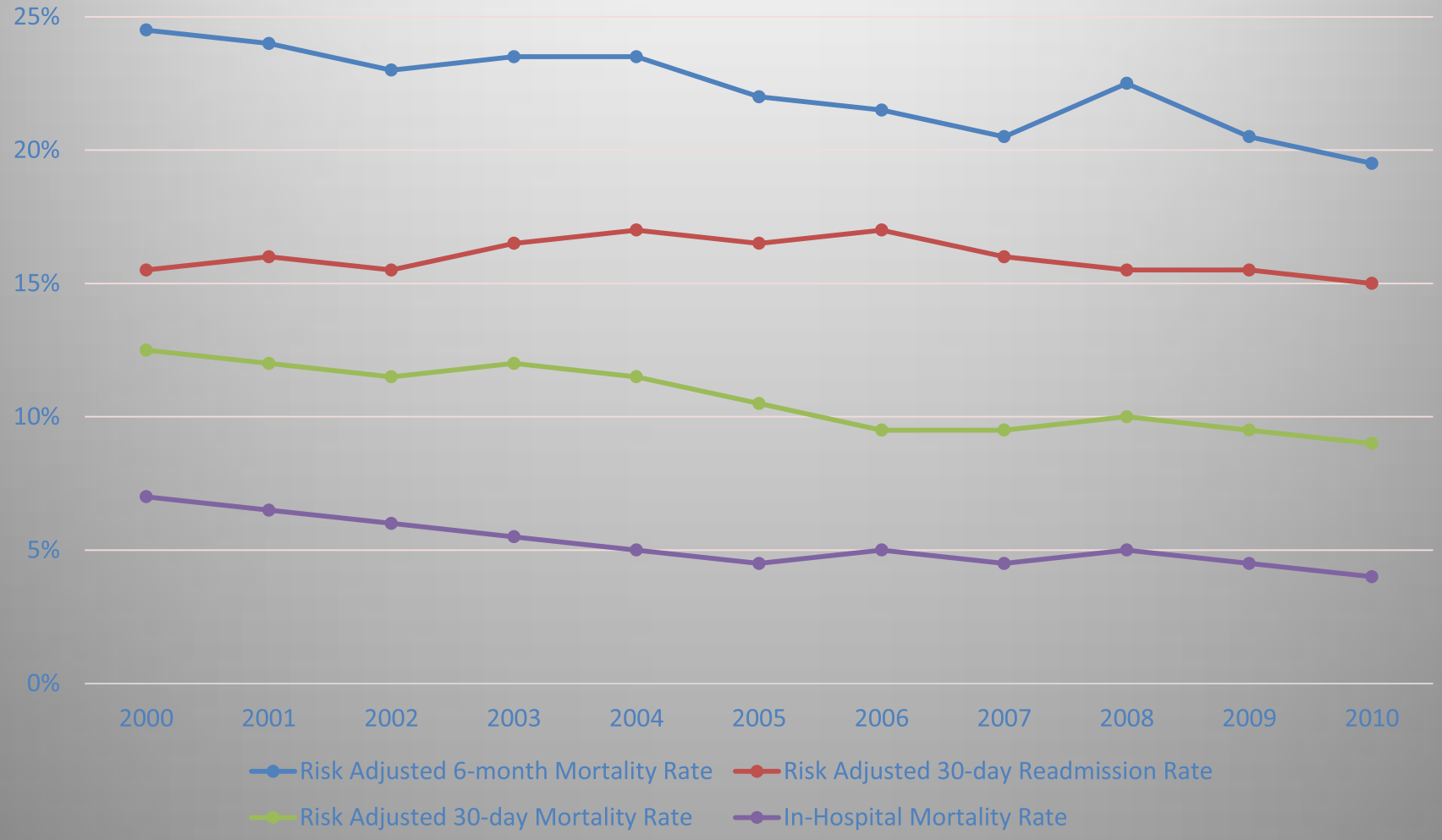
PE: A silent and fatal epidemic

Most patients who die from PE are not diagnosed at pre-mortem, and are not even suspected pre-mortem[1]

Study	Autopsies	PE present	PE suspected pre-mortem
Rubenstein[2]	1,276	44	14 (32%)
Stein[3]	404	59	6 (30%)
Lau[4]	11,044	116	27 (23%)
Morganthaler[5]	2,427	92	45 (49%)
Pulido[6]	1,032	231	42 (18%)

1. Tapson V. Emerging Management Options for PE: What the Vascular Specialist Must Know. VEITHsymposium 2012
2.Rubenstein I et al. Fatal pulmonary emboli in hospitalized patients: an autopsy study. Arch Intern Med. 1988 Jun;148(6):1425-6
3.Stein PD and Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest 1995 Oct.;108(4):978-81
4.Lau G. Pulmonary thromboembolism is not uncommon—results and implications of a five-year study of 116 necropsies. Ann Acad Med Singapore. 1995 May;24(3):356-65
5.Morganthaler TI et al. Clinical characteristics of fatal pulmonary embolism in a referral hospital. Mayo Clin Proc 1995;70:417-24
6.Pulido T et al. Pulmonary embolism as a cause of death in patients with heart disease. Chest. 2006 May;129(5):1282-7.

High PE mortality
High re-admission rates



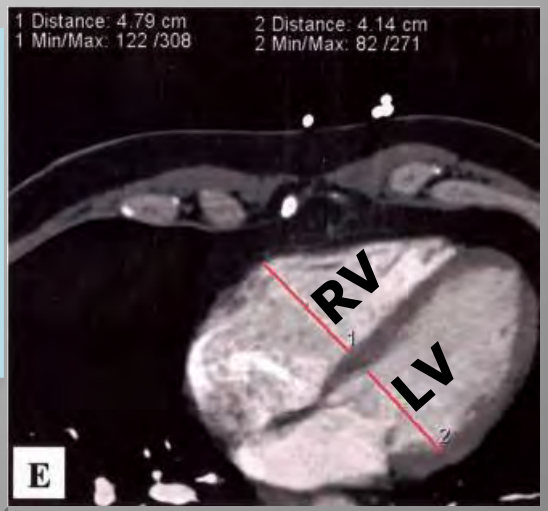
PE risk stratification

Patient risk stratification (per AHA Scientific Statement 2011)

Massive PE	Submassive PE	Minor/Nonmassive PE
High risk	**Moderate/intermediate risk**	**Low risk**
• Sustained hypotension (systolic BP <90 mmHg for ≥ 15 min) • Inotropic support • Pulselessness • Persistent profound bradycardia (HR <40 bpm with signs or symptoms of shock)	• Systemically normotensive (systolic BP ≥90 mmHg) • **RV dysfunction** • Myocardial necrosis	• Systemically normotensive (systolic BP ≥90 mmHg) • No RV dysfunction • No myocardial necrosis

RV dysfunction

- RV/LV ratio > 0.9 or RV systolic dysfunction on echo
- RV/LV ratio > 0.9 on CT
- Elevation of BNP (>90 pg/mL)
- Elevation of NTpro-BNP (>500 pg/mL)
- ECG changes
  - New complete or incomplete RBBB
  - Anteroseptal ST elevation or depression
  - Anteroseptal T-wave inversion

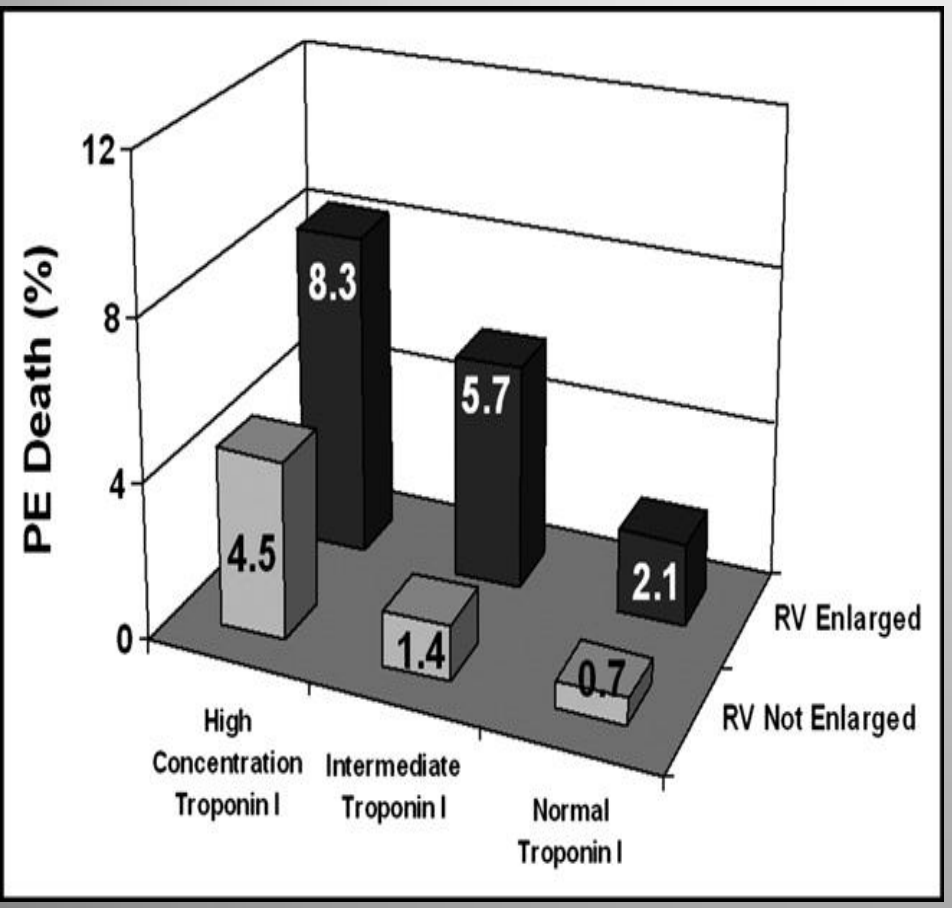


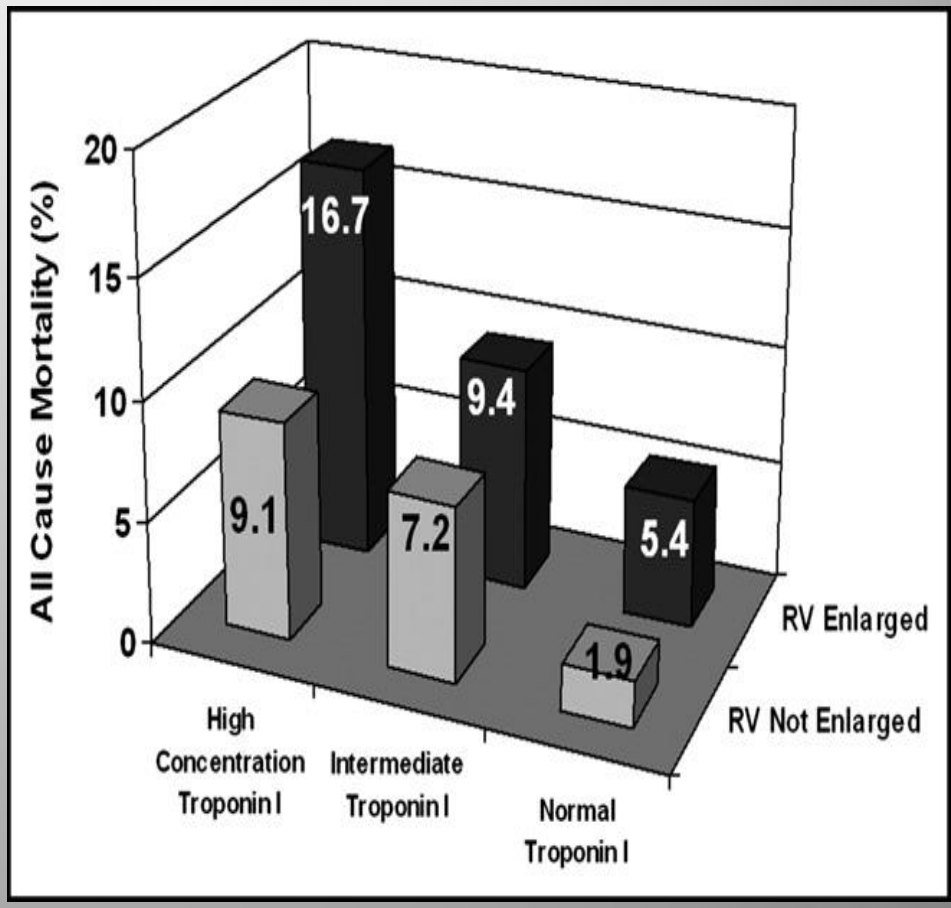
Jaff et al. Circulation 2011;123(16):1788-1830

Jaff M et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123(16):1788-1830

Quiroz R et. al. Right ventricular enlargement on chest computed tomography. Circulation. 2004;109:2401-2404

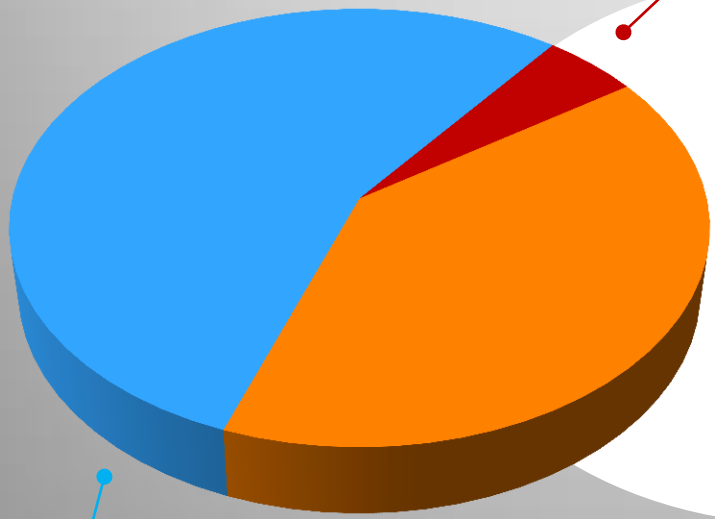
RV Dysfunction/ Tn Elevation Combo in PE: Prognosis (n=1,273)





Stein et al. Am J Cardiol 2010; 106: 558-563

PE patient population profile



MASSIVE PE
[High risk]
5% PE population
58%[1] **mortality** @ 3 months

SUBMASSIVE PE
[Moderate/Intermediate risk]
40% PE population
2-3%[2,3] **mortality** to
21%[1] **mortality** @ 3 months

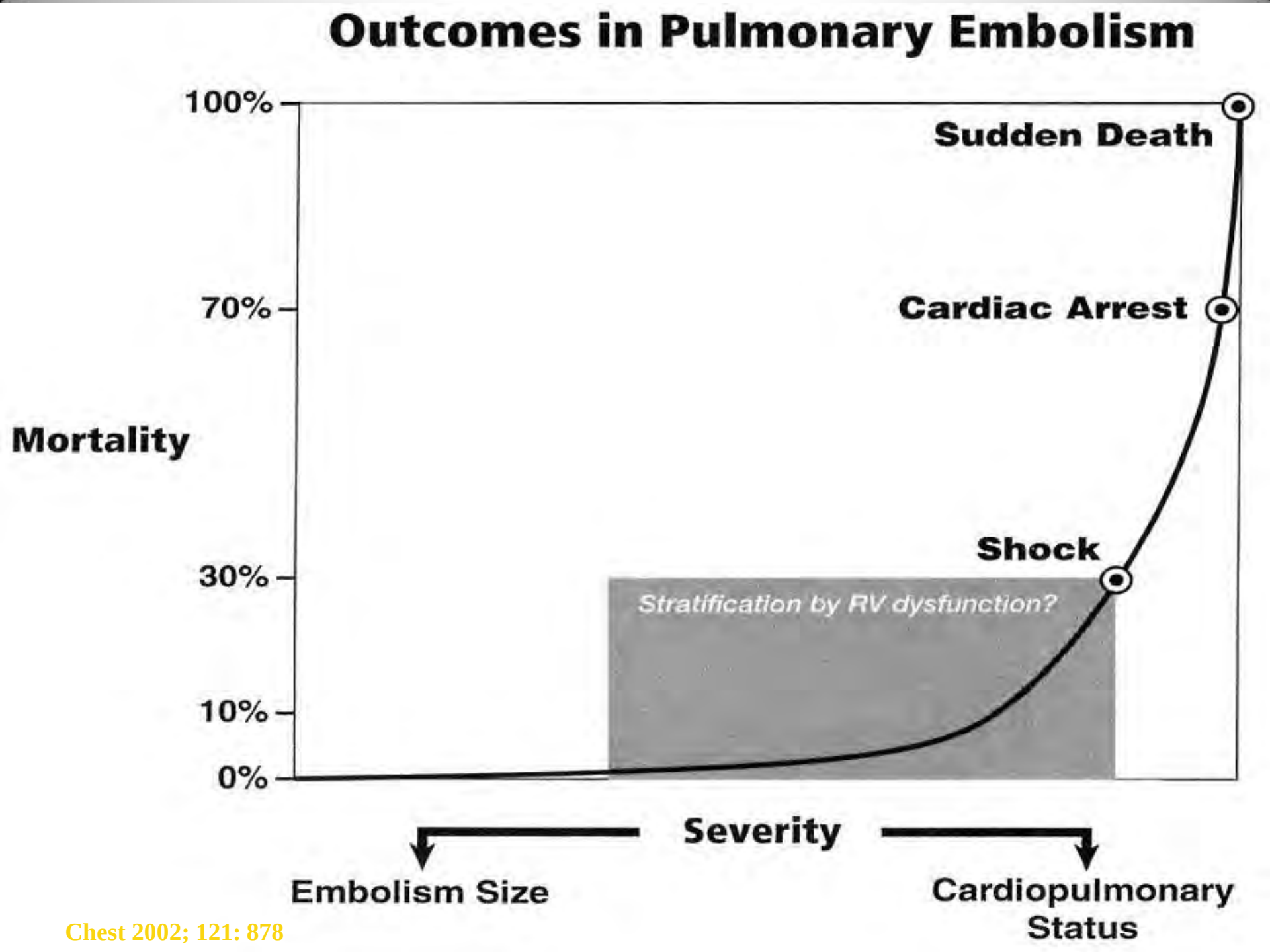
MINOR PE
[Low risk]
55% PE population
Good prognosis
Low mortality rate

1.Goldhaber SZ et al. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386-1389

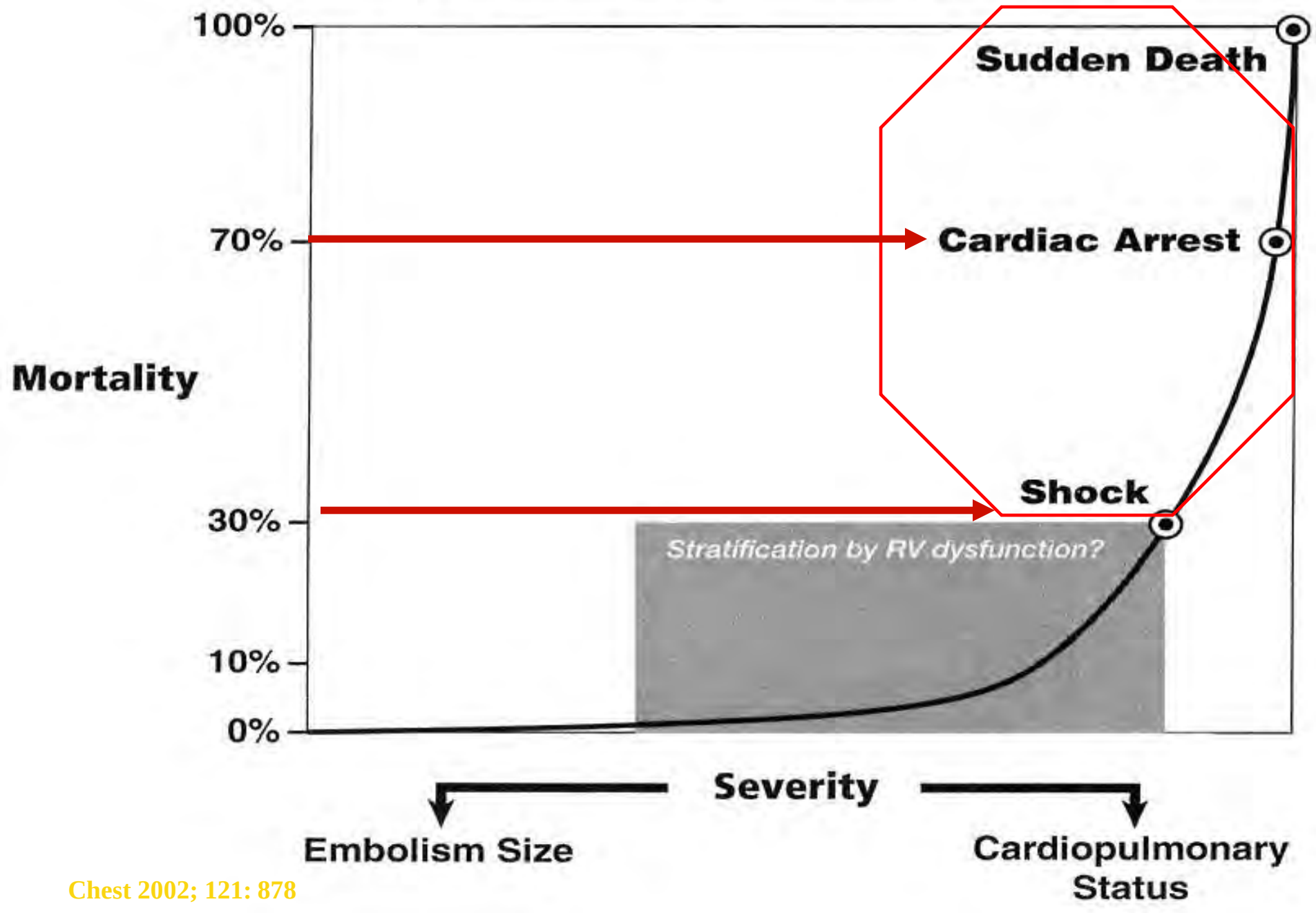
2.Meyer G et al. Fibrinolysis for Patients with Intermediate Risk Pulmonary Embolism. New Engl J Med 2014; 370: 1402-11

3.Casazza F et al. Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry (IPER). Thrombosis Research 2012; 130:847-852

Registry. *Lancet* 1999;353:1386-1389

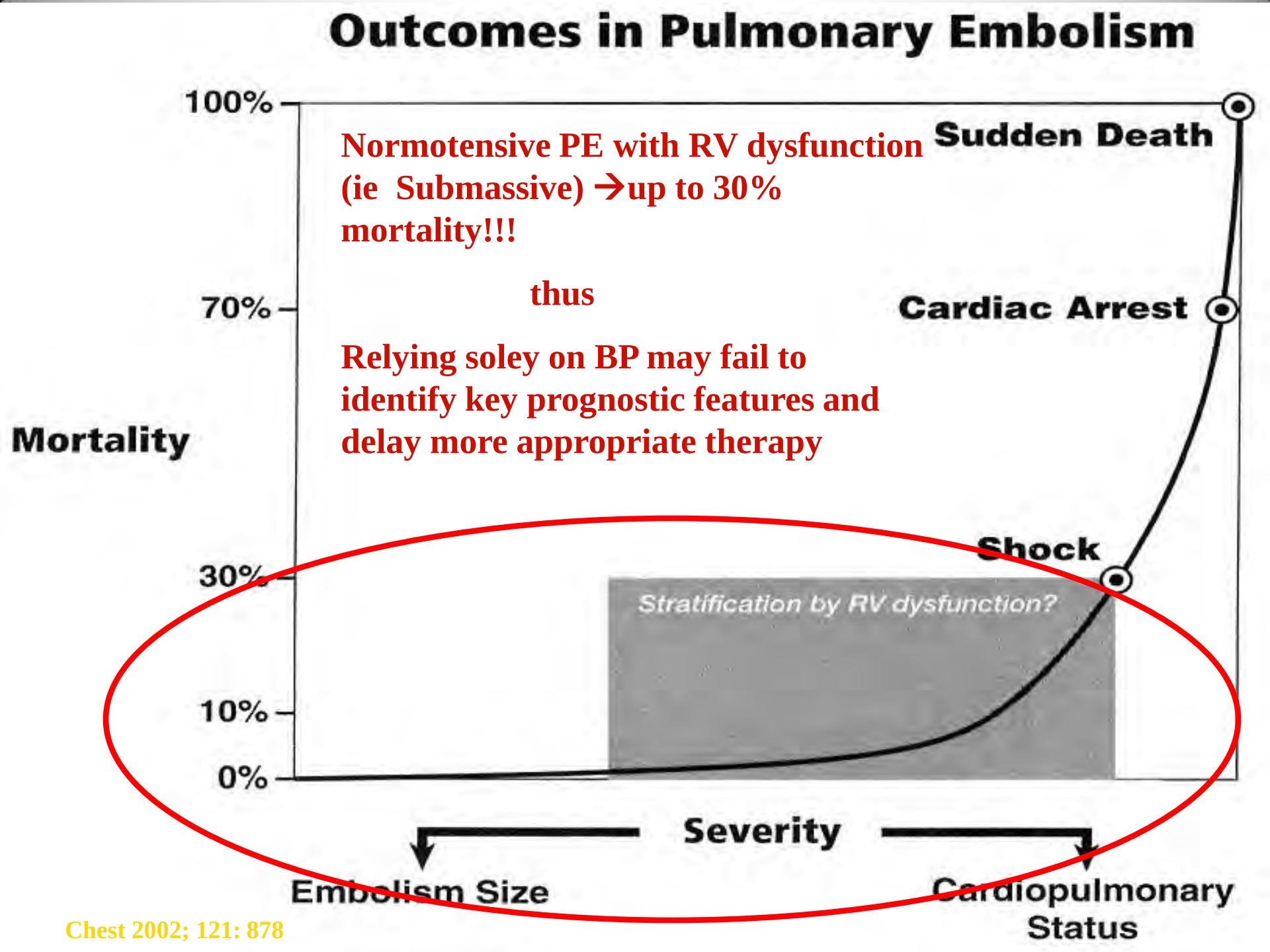

Outcomes in Pulmonary Embolism
100%
70%
30%
10%
0%
Mortality
Sudden Death
Cardiac Arrest
Shock
Stratification by RV dysfunction?
Severity
Embolism Size
Cardiopulmonary Status
Chest 2002; 121: 878

Outcomes in Pulmonary Embolism



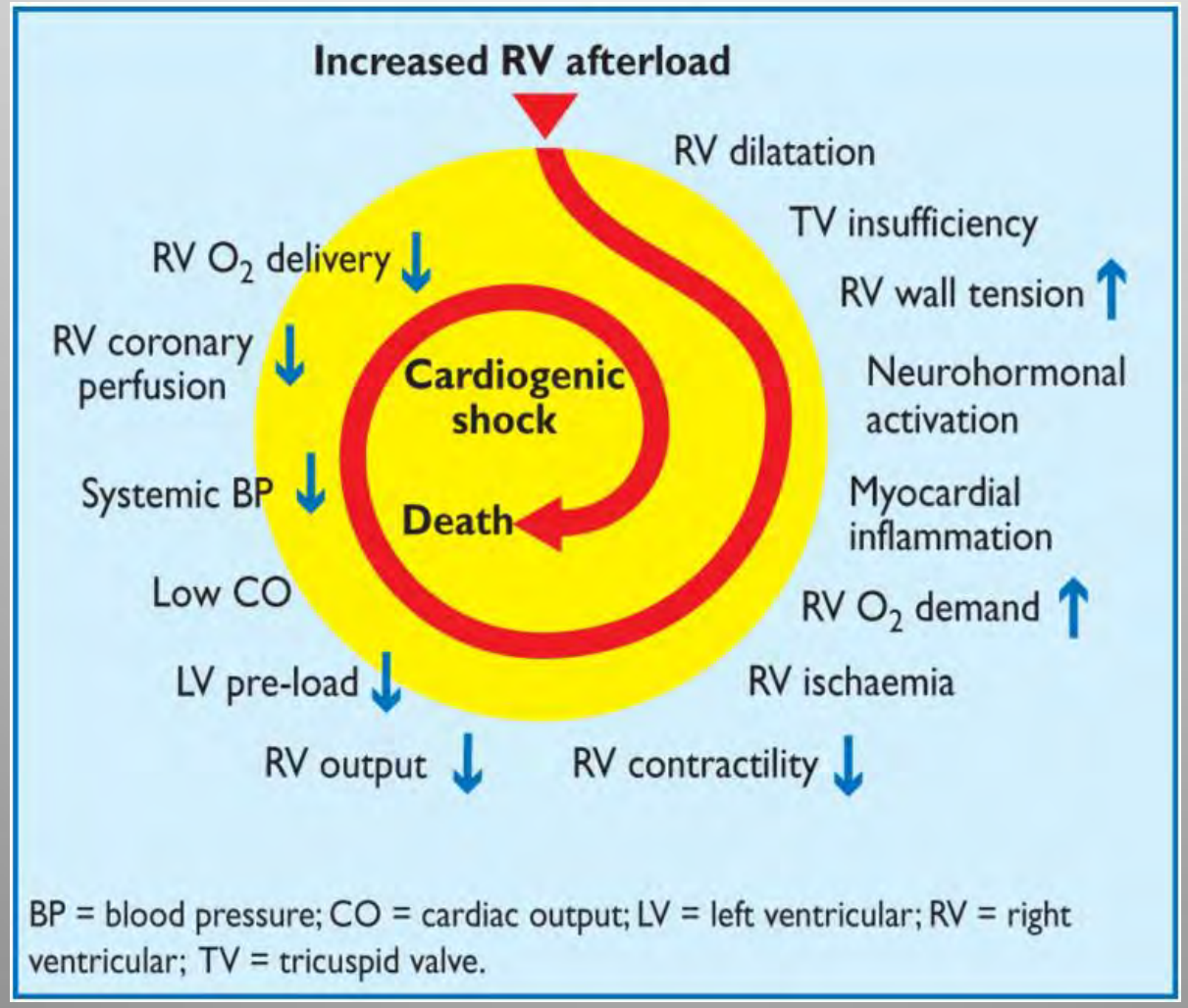
Chest 2002; 121: 878

Outcomes in Pulmonary Embolism



Chest 2002; 121: 878

Why submassive PE patients are at risk:
Hemodynamic collapse in acute PE



BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.

Konstantinides SV et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. European Heart Journal 2014. 35: 3033-3080.

Why treat intermediate risk PE patients aggressively?

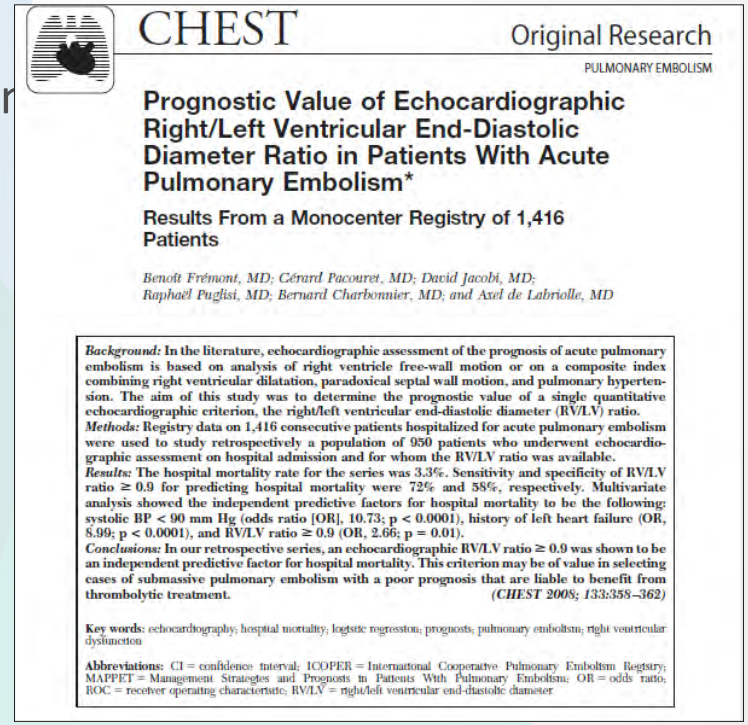
- Various studies report presence of right ventricular dysfunction (RVD) as a predictor of poor clinical outcomes

1. Mortality
2. Adverse events
3. VTE recurrence

Adverse outcomes associated with RVD

3x higher *in-hospital* mortality

- Echocardiographic RV/LV ratio ≥ 0.9 shown to be independent predictive factor of hospital mortality
  - Registry of 1,416 patients
  - **Mortality rate:**
    - 1.9% if RV/LV ratio < 0.9
    - 6.6% if RV/LV ratio ≥ 0.9



CHEST Original Research

PULMONARY EMBOLISM

Prognostic Value of Echocardiographic Right/Left Ventricular End-Diastolic Diameter Ratio in Patients With Acute Pulmonary Embolism*

Results From a Monocenter Registry of 1,416 Patients

Benoît Frémont, MD; Gérard Pacouret, MD; David Jacobi, MD; Raphaël Puglisi, MD; Bernard Charbonnier, MD; and Axel de Labriolle, MD

Background: In the literature, echocardiographic assessment of the prognosis of acute pulmonary embolism is based on analysis of right ventricle free-wall motion or on a composite index combining right ventricular dilatation, paradoxical septal wall motion, and pulmonary hypertension. The aim of this study was to determine the prognostic value of a single quantitative echocardiographic criterion, the right/left ventricular end-diastolic diameter (RV/LV) ratio.
Methods: Registry data on 1,416 consecutive patients hospitalized for acute pulmonary embolism were used to study retrospectively a population of 950 patients who underwent echocardiographic assessment on hospital admission and for whom the RV/LV ratio was available.
Results: The hospital mortality rate for the series was 3.3%. Sensitivity and specificity of RV/LV ratio ≥ 0.9 for predicting hospital mortality were 72% and 58%, respectively. Multivariate analysis showed the independent predictive factors for hospital mortality to be the following: systolic BP < 90 mm Hg (odds ratio [OR], 10.73; $p < 0.0001$), history of left heart failure (OR, 8.99; $p < 0.0001$), and RV/LV ratio ≥ 0.9 (OR, 2.66; $p = 0.01$).
Conclusions: In our retrospective series, an echocardiographic RV/LV ratio ≥ 0.9 was shown to be an independent predictive factor for hospital mortality. This criterion may be of value in selecting cases of submassive pulmonary embolism with a poor prognosis that are liable to benefit from thrombolytic treatment. ***(CHEST 2008; 133:358–362)***

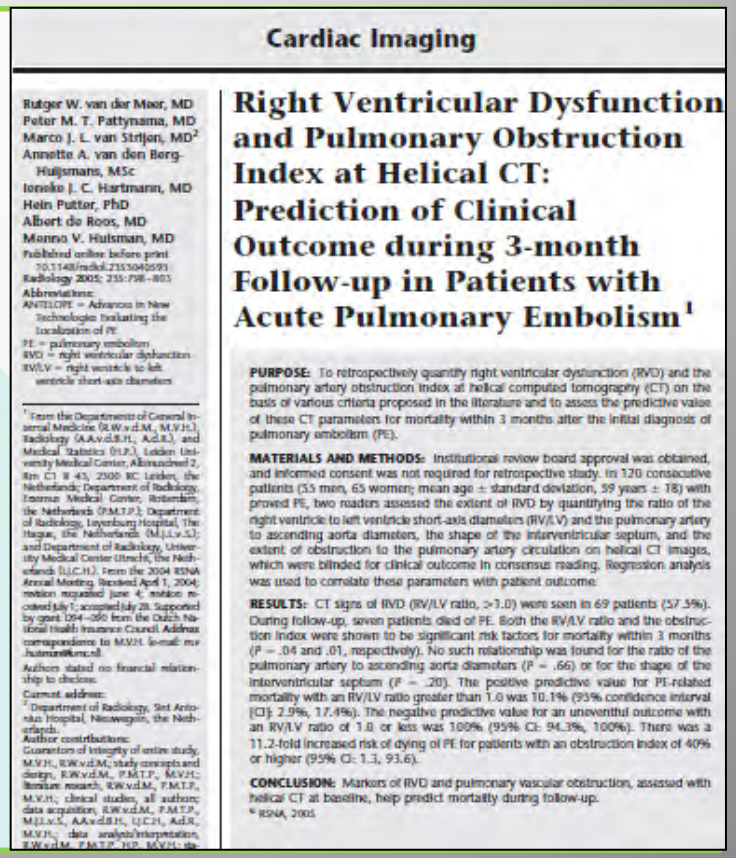
Key words: echocardiography; hospital mortality; logistic regression; prognosis; pulmonary embolism; right ventricular dysfunction

Abbreviations: CI = confidence interval; ICOPER = International Cooperative Pulmonary Embolism Registry; MAPPET = Management Strategies and Prognosis in Patients With Pulmonary Embolism; OR = odds ratio; ROC = receiver operating characteristic; RV/LV = right/left ventricular end-diastolic diameter

Fremont B et al. Prognostic value of echocardiographic right/left ventricular end-diastolic diameter ratio in patients with acute pulmonary embolism. CHEST 2008;133:358-362

Adverse outcomes associated with RVD
Increased *mortality at 3 months*

- PE-related mortality risk increases with stepwise increase in RV/LV Ratio
  - Retrospective analysis of 120 patients with hemodynamically stable PE based on chest CT
  - **PE-related mortality at 3 months:**
    - **17%** if RV/LV ≥ 1.5
    - **8%** if 1.0 ≤ RV/LV < 1.5
    - **0%** if RV/LV < 1.0



Cardiac Imaging

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Published online before print 10.1148/radiol.2353040593
Radiology 2005; 235:798–803

Abbreviations:
ANTELOPE = Advances in New Technologies Evaluating the Localization of PE
PE = pulmonary embolism
RVD = right ventricular dysfunction
RV/LV = right ventricle to left ventricle short-axis diameters

Right Ventricular Dysfunction and Pulmonary Obstruction Index at Helical CT: Prediction of Clinical Outcome during 3-month Follow-up in Patients with Acute Pulmonary Embolism[1]

PURPOSE: To retrospectively quantify right ventricular dysfunction (RVD) and the pulmonary artery obstruction index at helical computed tomography (CT) on the basis of various criteria proposed in the literature and to assess the predictive value of these CT parameters for mortality within 3 months after the initial diagnosis of pulmonary embolism (PE).

MATERIALS AND METHODS: Institutional review board approval was obtained, and informed consent was not required for retrospective study. In 120 consecutive patients (55 men, 65 women; mean age ± standard deviation, 59 years ± 18) with proved PE, two readers assessed the extent of RVD by quantifying the ratio of the right ventricle to left ventricle short-axis diameters (RV/LV) and the pulmonary artery to ascending aorta diameters, the shape of the interventricular septum, and the extent of obstruction to the pulmonary artery circulation on helical CT images, which were blinded for clinical outcome in consensus reading. Regression analysis was used to correlate these parameters with patient outcome.

RESULTS: CT signs of RVD (RV/LV ratio, >1.0) were seen in 69 patients (57.5%). During follow-up, seven patients died of PE. Both the RV/LV ratio and the obstruction index were shown to be significant risk factors for mortality within 3 months ($P = .04$ and .01, respectively). No such relationship was found for the ratio of the pulmonary artery to ascending aorta diameters ($P = .66$) or for the shape of the interventricular septum ($P = .20$). The positive predictive value for PE-related mortality with an RV/LV ratio greater than 1.0 was 10.1% (95% confidence interval [CI]: 2.9%, 17.4%). The negative predictive value for an uneventful outcome with an RV/LV ratio of 1.0 or less was 100% (95% CI: 94.3%, 100%). There was a 11.2-fold increased risk of dying of PE for patients with an obstruction index of 40% or higher (95% CI: 1.3, 93.6).

CONCLUSION: Markers of RVD and pulmonary vascular obstruction, assessed with helical CT at baseline, help predict mortality during follow-up.

© RSNA, 2005

Van der Meer RW et al. Right ventribular dysfunction and pulmonary obstruction index at helical CT: prediction of clinical outcome during 3-month follow-up in patients with acute pulmonary embolism. Radiology 2005; 235:798-803.

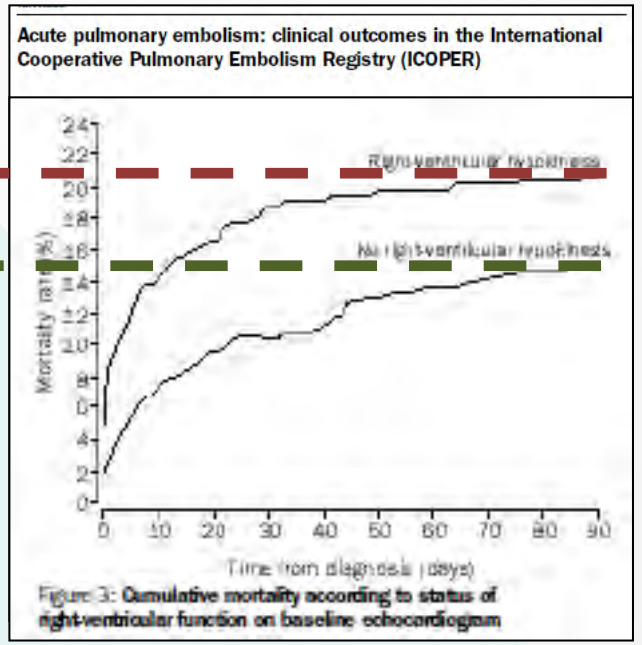
Adverse outcomes associated with RVD

- Presence of RV hypokinesis associated with increase in mortality rate at 3 months
  - Prospective study of 2,454 consecutive PE patients at 52 hospitals in 7 countries

Mortality rate at 3 months

21% with **hypokinesis**

15% with no **hypokinesis**



Goldhaber, SZ et al, Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER), Lancet 1999; 353: 1386-89.

Adverse outcomes with unresolved RVD

8 x incidence of *recurrent VTE*

- PE patients with RVD unresolved exhibit 8x increased incidence of recurrent VTE compared to those with RVD resolved at discharge
  - Retrospective analysis of 301 patients with first episode PE with mean f/u at 3.1 years

Incidence of VTE at 4 years

0.4 if RVD **unresolved**

0.05 if RVD **resolved**

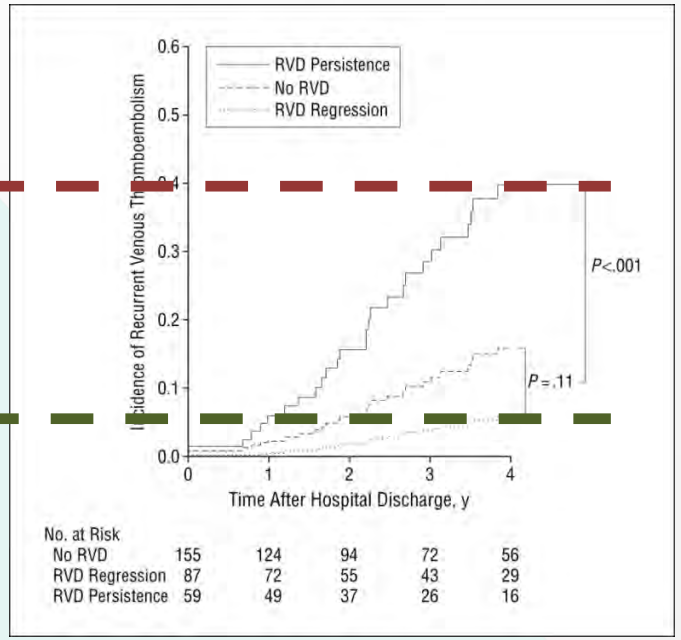


Figure: Cumulative incidence of recurrent venuous thromboembolism. RVD indicated right ventricular dysfunction.

Grifoni S et al. Association of Persistent Right Ventricular Dysfunction at Hospital Discharge After Acute Pulmonary Embolism with Recurrent Thromboembolic Events. Arch Intern Med 2006; 166:2151-2156

Standard PE therapy

- Anticoagulation (ac)—Heparin
  - AC therapy prevents further clot growth
  - Studies[1,2,3] found
    - LMWH as effective as UFH in reducing recurrent PE
    - LMWH carries reduced bleeding risk compared to UFH
- Standard Of Care: usually UFH or LMWH, followed by oral warfarin
  - However, AC therapy relies on endogenous tPA to dissolve occluding clot[4]
    - a process that typically occurs over several weeks or months
    - endogenous fibrinolysis may often be incomplete at the end

1. Simonneau G et al. A comparison of low-molecular weight heparin with unfractionated heparin for acute pulmonary embolism. N Engl J Med 1997;337(10):663-669.
2. Buller HR et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med 2003;349(18): 1695-1702.
3. Meyer G et al. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. Thromb Heamost 1995;74(6):1432-1435

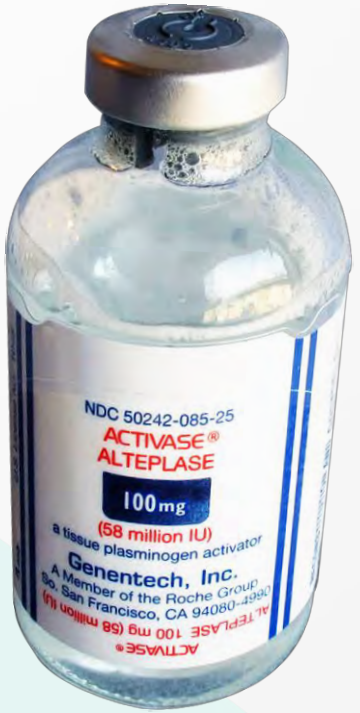
Rationale for thrombolysis in acute PE

- Reduce Thrombus Burden (not achievable by AC alone)
  - Reverse RV afterload/failure toward prevention of hemodynamic collapse
  - Improve pulmonary reperfusion/capillary blood flow/gas exchange
  - Restore systemic arterial perfusion pressure
  - Decrease the risk of developing chronic pulmonary hypertension

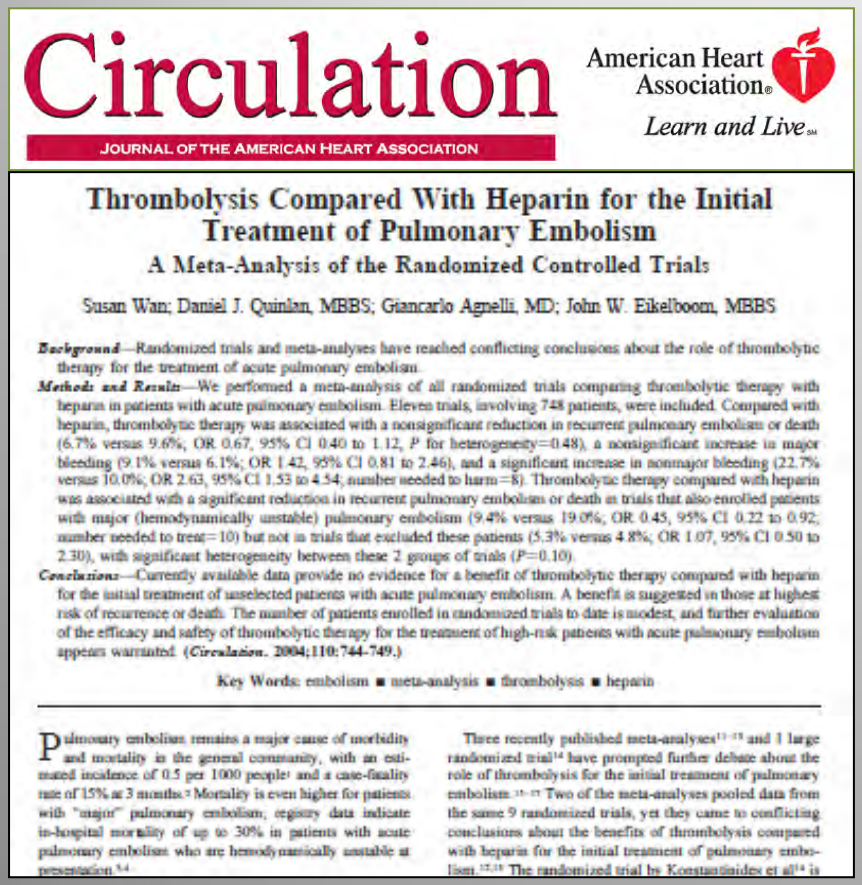
Piazza G and Goldhaber SZ. Finbrinolysis for acute pulmonary embolism. Vascular Medicine 2010 15(5):419-428

IV thrombolysis with tPA

- 100 mg tPA infused over 2 hours
- Indicated for management of acute **massive** PE in adults
  - For the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs
  - For the lysis of pulmonary emboli accompanied by unstable hemodynamics, e.g., failure to maintain blood pressure without supportive measures



Meta-analysis suggests reduced risk of recurrent PE or death from thrombolysis compared with heparin



Circulation

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Thrombolysis Compared With Heparin for the Initial Treatment of Pulmonary Embolism

A Meta-Analysis of the Randomized Controlled Trials

Susan Wan; Daniel J. Quinlan, MBBS; Giancarlo Agnelli, MD; John W. Eikelboom, MBBS

Background—Randomized trials and meta-analyses have reached conflicting conclusions about the role of thrombolytic therapy for the treatment of acute pulmonary embolism.

Methods and Results—We performed a meta-analysis of all randomized trials comparing thrombolytic therapy with heparin in patients with acute pulmonary embolism. Eleven trials, involving 748 patients, were included. Compared with heparin, thrombolytic therapy was associated with a nonsignificant reduction in recurrent pulmonary embolism or death (6.7% versus 9.6%; OR 0.67, 95% CI 0.40 to 1.12, *P* for heterogeneity=0.48), a nonsignificant increase in major bleeding (9.1% versus 6.1%; OR 1.42, 95% CI 0.81 to 2.46), and a significant increase in nonmajor bleeding (22.7% versus 10.0%; OR 2.63, 95% CI 1.53 to 4.54; number needed to harm=8). Thrombolytic therapy compared with heparin was associated with a significant reduction in recurrent pulmonary embolism or death in trials that also enrolled patients with major (hemodynamically unstable) pulmonary embolism (9.4% versus 19.0%; OR 0.45, 95% CI 0.22 to 0.92; number needed to treat=10) but not in trials that excluded these patients (5.3% versus 4.8%; OR 1.07, 95% CI 0.50 to 2.30), with significant heterogeneity between these 2 groups of trials (*P*=0.10).

Conclusions—Currently available data provide no evidence for a benefit of thrombolytic therapy compared with heparin for the initial treatment of unselected patients with acute pulmonary embolism. A benefit is suggested in those at highest risk of recurrence or death. The number of patients enrolled in randomized trials to date is modest, and further evaluation of the efficacy and safety of thrombolytic therapy for the treatment of high-risk patients with acute pulmonary embolism appears warranted. (*Circulation*. 2004;110:744-749.)

Key Words: embolism ■ meta-analysis ■ thrombolysis ■ heparin

Pulmonary embolism remains a major cause of morbidity and mortality in the general community, with an estimated incidence of 0.5 per 1000 people[1] and a case-fatality rate of 15% at 3 months.[2] Mortality is even higher for patients with "major" pulmonary embolism; registry data indicate in-hospital mortality of up to 30% in patients with acute pulmonary embolism who are hemodynamically unstable at presentation.[3,4]

Three recently published meta-analyses[11–13] and 1 large randomized trial[14] have prompted further debate about the role of thrombolysis for the initial treatment of pulmonary embolism.[11–17] Two of the meta-analyses pooled data from the same 9 randomized trials, yet they came to conflicting conclusions about the benefits of thrombolysis compared with heparin for the initial treatment of pulmonary embolism.[12,13] The randomized trial by Konstantinides et al[14] is

- Meta analysis of randomized clinical trials for PE comparing thrombolytic therapy with heparin
- Total of 11 trials, 748 patients included
- Data from trials that included massive PE

	Trials That Included Patients with Major PE		
Outcome	**Thrombolysis n/N(%)**	**Heparin n/N(%)**	**OR (95% CI)**
Recurrent PE or death	12/128 (9.4)	24/126 (19.0)	0.45 (0.22–0.92)
Recurrent PE	5/128 (3.9)	9/126 (7.1)	0.61 (0.23–1.62)
Death	8/128 (6.2)	16/126 (12.7)	0.47 (0.20–1.10)
Major bleeding	28/128 (21.9)	15/126 (11.9)	1.98 (1.00–3.92)

PE Indicated Pulmonary embolism

Wan S et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism. Circulation. 2004 Aug. 10;110(6):744-9.

Meta-analysis suggested thrombolysis was associated with lower mortality for intermediate-risk PE, recurrent PE

Major bleeding was also significantly increased, but not for patients 65 years and younger

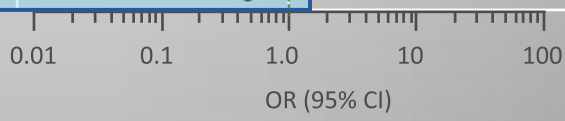
Outcome of Interest (No. of Studies Reporting)	No. of Events/No. of Patients, Absolute Event Rate (%)		No. Needed to Treat or harm	*P* Value
	Thrombolytic Group	Anticoagulant Group		
All-cause mortality (16)	23/1061 (2.17)	41/1054 (3.89)	NNT = 59	.01
Major bleeding (16)[a]	98/1061 (9.24)	36/1054 (3.42)	NNH = 18	<.001
ICH (15)	15/1024 (1.46)	2/1019 (.19)	NNH = 78	.002
Recurrent PE (15)	12/1024 (1.17)	31/1019 (3.04)	NNT = 54	.003
Age > 65 y				
All-cause mortality (5)	14/673 (2.08)	24/658 (3.65)	NNT = 64	.07
Major bleeding (5) [a]	87/673 (12.93)	27/658 (4.10)	NNH = 11	<.001
Age ≤ 65 y				
All-cause mortality (11)	9/388 (2.32)	17/396 (4.29)	NNT = 51	.09
Major bleeding (11) [a]	11/388 (2.84)	9/396 (2.27)	NNH = 176	.89
Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT = 65	.03
Major bleeding (8) [a]	67/866 (7.74)	20/889 (2.25)	NNH = 18	<.001

Chatterjee S et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: a Meta-analysis. JAMA 2014; 311(23):2414-2421.

Lysis in submassive PE

Mortality meta-analysis

	Thrombolytics		Anticoagulants					
Source	**# of Events**	**# of Patients**	**# of Events**	**# of Patients**	**OR (95% CI)**	**Favors Thrombolytics**	**Favors Anticoagulants**	**Weight, %**
Goldhaber et al,[2] 1993	0	46	2	55	0.16 (0.01-2.57)			5.3
Konstantinides et al,[3] 2002	4	118	3	138	1.58 (0.35-7.09)			18.4
TIPES,[29] 2010	0	28	1	30	0.14 (0.00-7.31)			2.7
Fasullo et al,[11] 2011	0	37	6	35	0.11 (0.02-0.58)			15.1
MOPETT,[10] 2012	1	61	3	60	0.35 (0.05-2.57)			10.5
ULTIMA,[30] 2013	0	30	1	29	0.13 (0.00-6.59)			2.7
TOPCOAT,[9] 2014	1	40	1	43	1.08 (0.07-17.53)			5.3
PEITHO,[8] 2014	6	506	9	499	.66 (0.24-1.82)			40.0
Total	**12**	**866**	**26**	**889**	**.48 (0.25-0.92)**			**100.0**

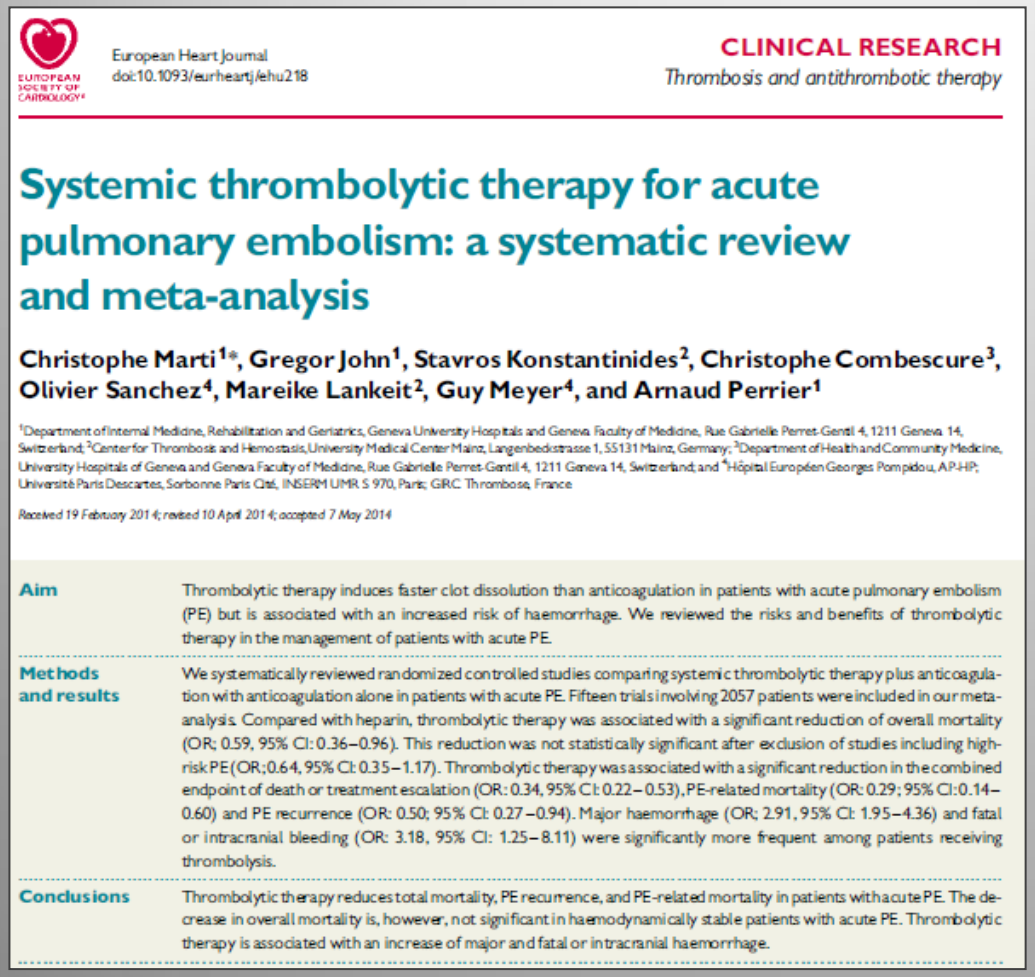


Heterogeneity: $\chi^2_7 = 7.63$; $P = .37$; $I^2 = 8\%$
Overall effect: $z = 2.22$; $P = .03$

Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT = 65	.03
Major bleeding (8)[a]	67/866 (7.74)	20/889 (2.25)	NNH = 18	<.001

Chatterjee S et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: a Meta-analysis. JAMA 2014; 311(23):2414-2421.

Review and meta-analysis on systemic thrombolysis for PE weighed risks and benefits



European Heart Journal
doi:10.1093/eurheartj/ehu218

CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis

Christophe Marti[1]*, Gregor John[1], Stavros Konstantinides[2], Christophe Combescure[3], Olivier Sanchez[4], Mareike Lankeit[2], Guy Meyer[4], and Arnaud Perrier[1]

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Received 19 February 2014; revised 10 April 2014; accepted 7 May 2014

Aim Thrombolytic therapy induces faster clot dissolution than anticoagulation in patients with acute pulmonary embolism (PE) but is associated with an increased risk of haemorrhage. We reviewed the risks and benefits of thrombolytic therapy in the management of patients with acute PE.

Methods and results We systematically reviewed randomized controlled studies comparing systemic thrombolytic therapy plus anticoagulation with anticoagulation alone in patients with acute PE. Fifteen trials involving 2057 patients were included in our meta-analysis. Compared with heparin, thrombolytic therapy was associated with a significant reduction of overall mortality (OR; 0.59, 95% CI: 0.36–0.96). This reduction was not statistically significant after exclusion of studies including high-risk PE (OR; 0.64, 95% CI: 0.35–1.17). Thrombolytic therapy was associated with a significant reduction in the combined endpoint of death or treatment escalation (OR: 0.34, 95% CI: 0.22–0.53), PE-related mortality (OR: 0.29; 95% CI: 0.14–0.60) and PE recurrence (OR: 0.50; 95% CI: 0.27–0.94). Major haemorrhage (OR; 2.91, 95% CI: 1.95–4.36) and fatal or intracranial bleeding (OR: 3.18, 95% CI: 1.25–8.11) were significantly more frequent among patients receiving thrombolysis.

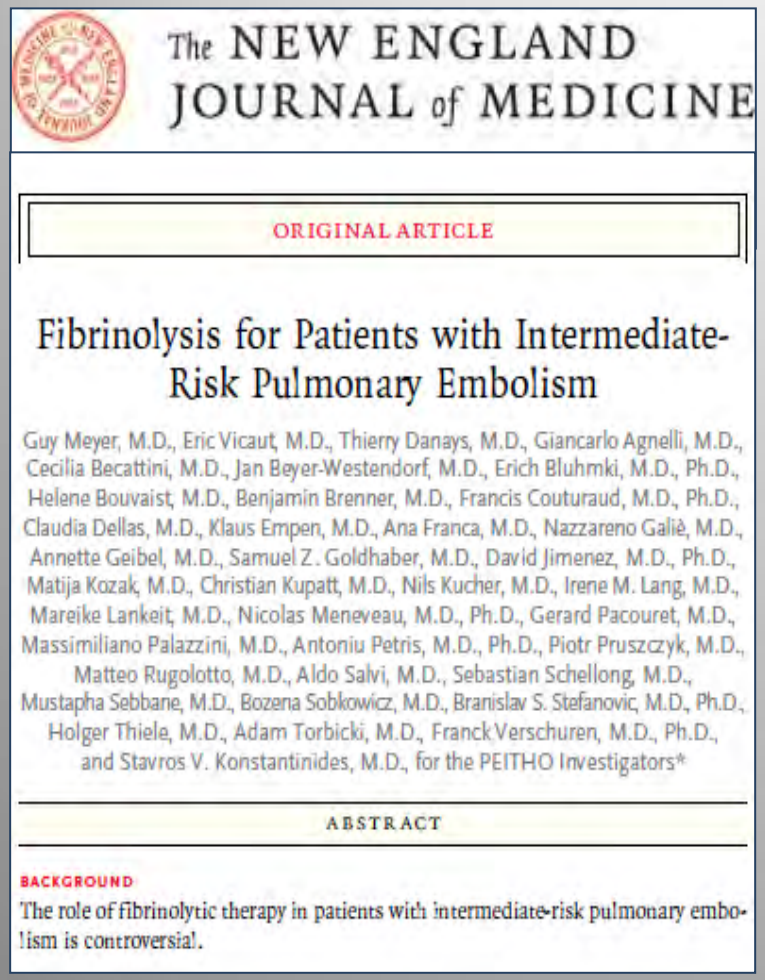
Conclusions Thrombolytic therapy reduces total mortality, PE recurrence, and PE-related mortality in patients with acute PE. The decrease in overall mortality is, however, not significant in haemodynamically stable patients with acute PE. Thrombolytic therapy is associated with an increase of major and fatal or intracranial haemorrhage.

For acute PE patients, thrombolytic therapy

- Reduced total mortality, PE recurrence, and PE-related mortality
- Decrease in overall mortality not significant in intermediate-risk PE patients
- Associated with an increase in major, fatal or ICH

Marti C et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2014; 36: 605-614.

RCT examined benefit of IV thrombolysis in intermediate-risk PE



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., Ana Franca, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kupatt, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Mareike Lankeit, M.D., Nicolas Meneveau, M.D., Ph.D., Gerard Pacouret, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pruszczyk, M.D., Matteo Rugolotto, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Thiele, M.D., Adam Torbicki, M.D., Franck Verschuren, M.D., Ph.D., and Stavros V. Konstantinides, M.D., for the PEITHO Investigators*

ABSTRACT

BACKGROUND

The role of fibrinolytic therapy in patients with intermediate-risk pulmonary embolism is controversial.

PEITHO Trial

Primary Objective

- Investigate clinical benefits (efficacy) of thrombolysis with tenecteplase over placebo in **normotensive patients with acute intermediate-risk PE** (both treatment arms receive standard heparin anticoagulation)

Secondary Objective

- To assess the safety of tenecteplase in patients with intermediate-risk PE

Meyer G et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014 Apr 10;370(15):1402-11

IV thrombolysis reduced the risk of hemodynamic collapse

	Tenecteplase (n=506)	Placebo (n=499)	P value
All cause mortality within 7 days	6 (1.2%)	9 (1.8%)	0.42
Hemodynamic collapse within 7 days	8 (1.6%)	25 (5.0%)	0.002
– Need for CPR – Hypotension/BP drop – Catecholamines needed	1 8 3	5 18 14	

Meyer G et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014 Apr 10;370(15):1402-11

But the benefit of lysis came at the cost of major bleeds (including ICH)

	Tenecteplase (n=506)	Placebo (n=499)	P value
Bleeding by day 7			
Major extracranial bleeding	32 (6.3%)	6 (1.2%)	<0.001
Major bleeding as defined by ISTH	58 (11.5%)	12 (2.4%)	
All Strokes by day 7	**12 (2.4%)**	**1 (0.2%)**	
Hemorrhagic	10	1	0.003
Ischemic	2	0	
Serious adverse events (SAE) by day 30	**55 (10.9%)**	**59 (11.8%)**	**0.63**

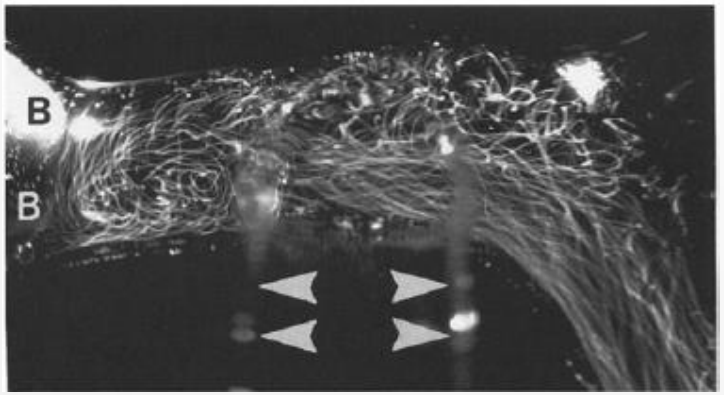
Meyer G et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014 Apr 10;370(15):1402-11

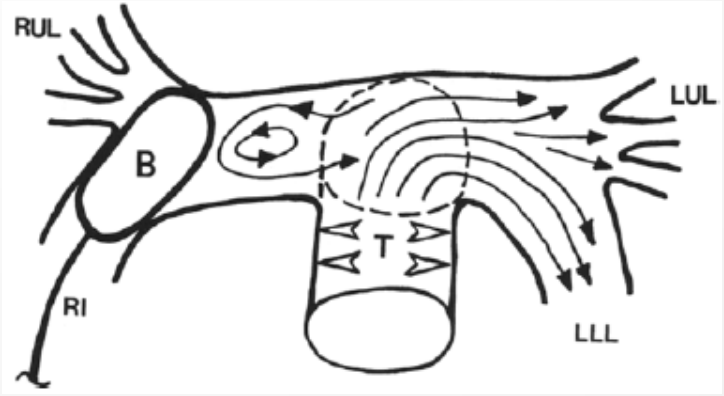
Adoption of IV thrombolysis hampered by elevated risk of severe bleeds

- In randomized trials, systemic PE thrombolysis is associated with a 11.5% risk of major bleeding and a 6.3% risk of intracranial hemorrhage[1]
- In clinical practice, systemic PE thrombolysis is associated with a 19.2% risk of major bleeding and a 5% risk of intracranial hemorrhage[2]
- In clinical practice, systemic thrombolysis is withheld in up to two thirds of patients with high-risk (massive) PE[3]

1. Meyer G et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370: 1402-11.
2. Fiumara, K et al. Predictors of Major Hemorrhage Following Fibrinolysis for Acute PE. Am J Cardiol 2006;97:127-9

IV thrombolysis—limited drug delivery to thrombus





In vitro model of obstruction in the right main Pulmonary Artery
High-speed photo of systemically injected glass beads demonstrates how a vortex forms proximal to the obstruction and alters systemic drug delivery away from target embolus

Schmitz-Rode T et al. Simulated flow pattern in massive pulmonary embolism: significance for selective intrapulmonary thrombolysis. Cardiovasc Intervent Radiol 1998; 21: 199-204.

Catheter Techniques: "Pharmaco-mechanical" Therapy

Mechanical Fragmentation

Hydrodynamic (AngioJet®)

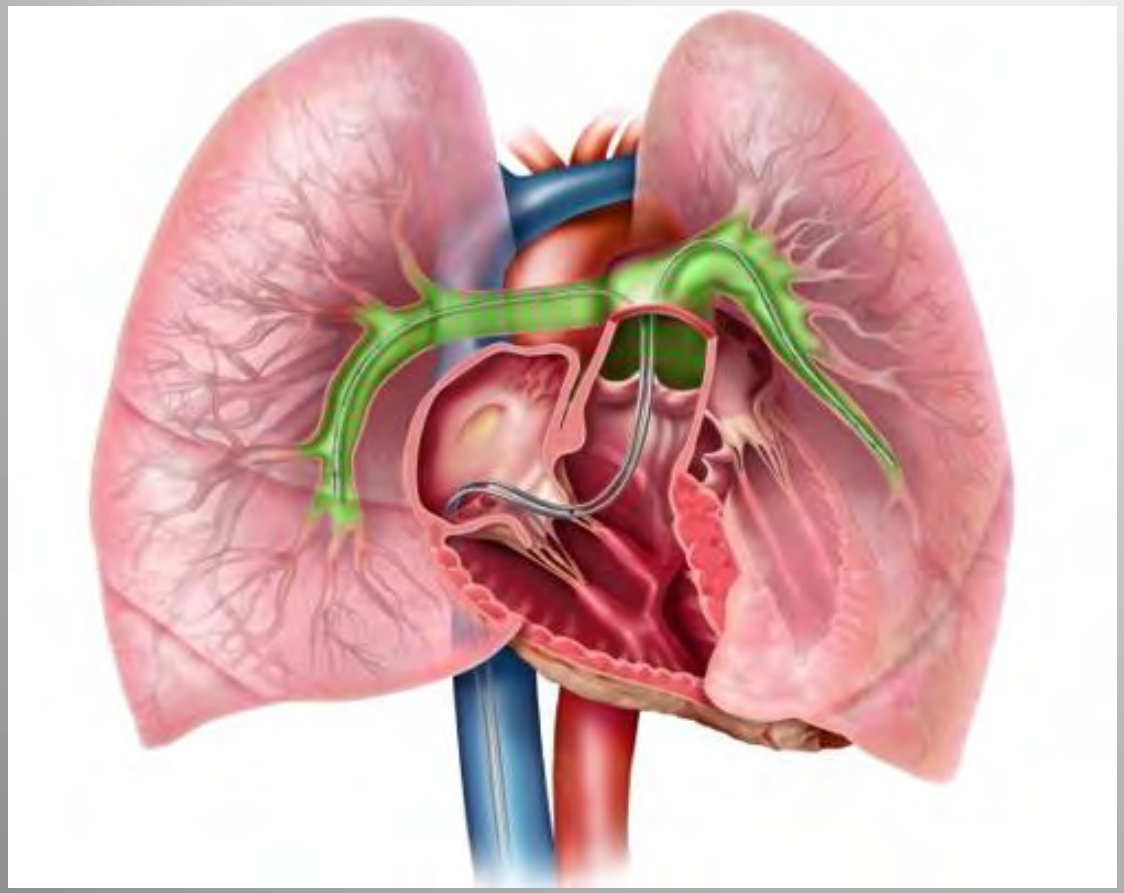
Ultrasound-Accelerated Fibrinolysis (EKOS®)

Suction Embolectomy (AngioVac®)

Catheter-based thrombolysis

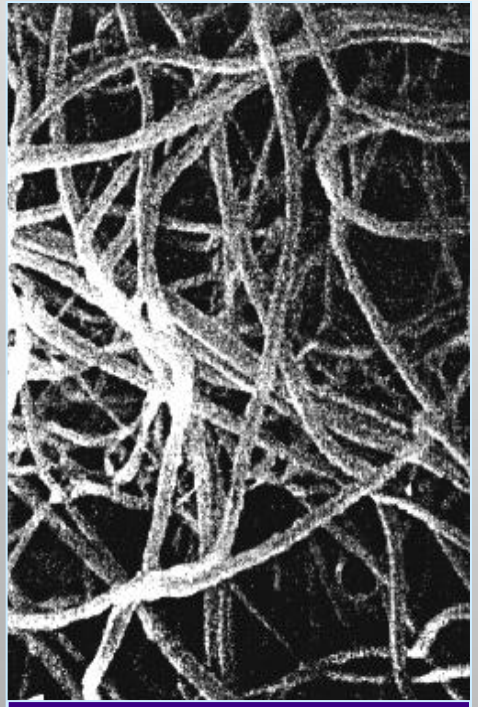
- Local administration of lytic agent
- Higher local drug concentration results in more rapid and complete thrombolysis
- Even distribution results in faster treatment of thrombus

EkoSonic® Endovascular System

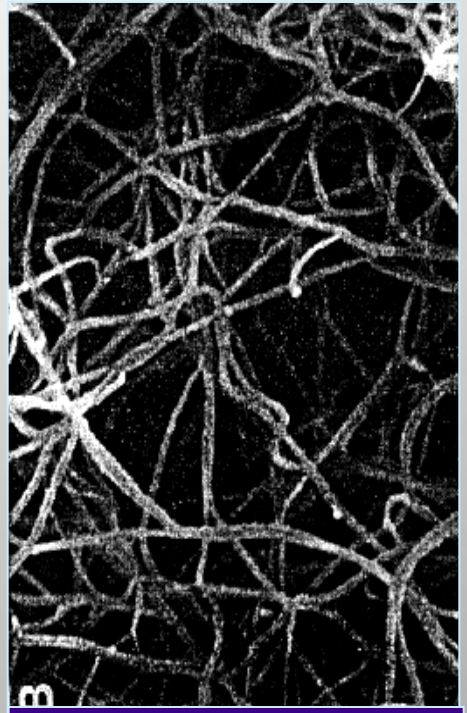


Placement in the left and right pulmonary arteries for the treatment of bilateral PE

Ultrasound Accelerated Thrombolysis



Fibrin without Ultrasound



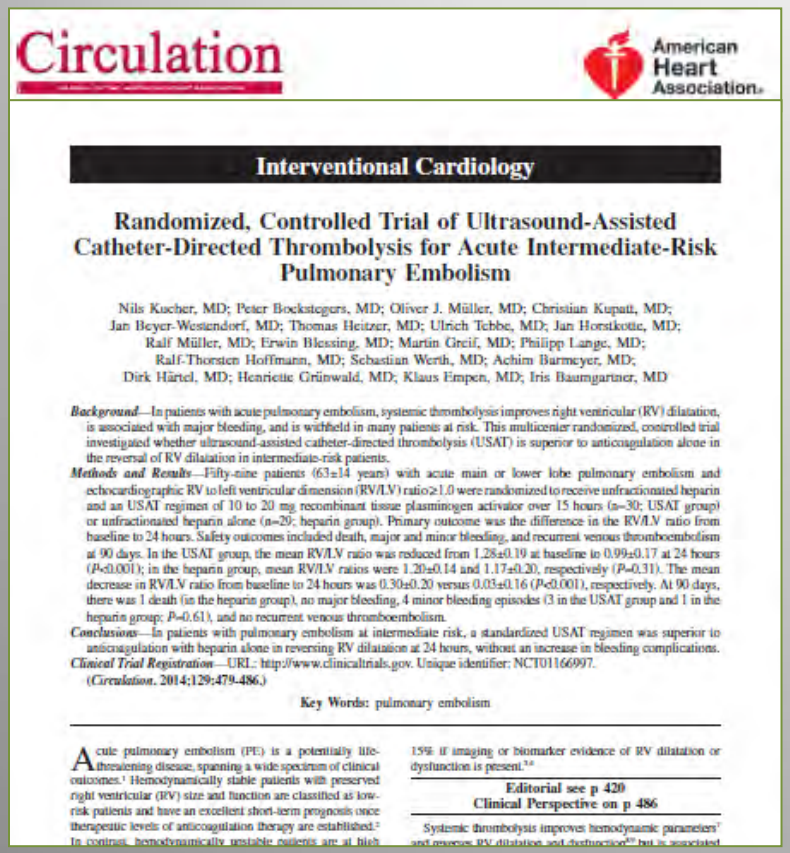
Fibrin With Ultrasound

The premise: Low-power ultrasound energy loosens fibrin strands, increases thrombus surface area, enhances lytic penetration, speeding thrombolysis, and facilitates reduction in fibrinolytic drug dose.

Review of the clinical evidence for EKOS® for the treatment of PE

- ULTIMA trial
- SEATTLE II trial
- Meta-analysis of historical published data

ULTIMA study
Comparing EKOS® to heparin in intermediate risk PE therapy



Circulation

American Heart Association.

Interventional Cardiology

Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism

Nils Kucher, MD; Peter Boekstegers, MD; Oliver J. Müller, MD; Christian Kupatt, MD; Jan Beyer-Westendorf, MD; Thomas Heitzer, MD; Ulrich Tebbe, MD; Jan Horstkotte, MD; Ralf Müller, MD; Erwin Blessing, MD; Martin Greif, MD; Philipp Lange, MD; Ralf-Thorsten Hoffmann, MD; Sebastian Werth, MD; Achim Barmeyer, MD; Dirk Härtel, MD; Henriette Grünwald, MD; Klaus Empen, MD; Iris Baumgartner, MD

Background—In patients with acute pulmonary embolism, systemic thrombolysis improves right ventricular (RV) dilatation, is associated with major bleeding, and is withheld in many patients at risk. This multicenter randomized, controlled trial investigated whether ultrasound-assisted catheter-directed thrombolysis (USAT) is superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk patients.

Methods and Results—Fifty-nine patients (63±14 years) with acute main or lower lobe pulmonary embolism and echocardiographic RV to left ventricular dimension (RV/LV) ratio≥1.0 were randomized to receive unfractionated heparin and an USAT regimen of 10 to 20 mg recombinant tissue plasminogen activator over 15 hours (n=30; USAT group) or unfractionated heparin alone (n=29; heparin group). Primary outcome was the difference in the RV/LV ratio from baseline to 24 hours. Safety outcomes included death, major and minor bleeding, and recurrent venous thromboembolism at 90 days. In the USAT group, the mean RV/LV ratio was reduced from 1.28±0.19 at baseline to 0.99±0.17 at 24 hours (P<0.001); in the heparin group, mean RV/LV ratios were 1.20±0.14 and 1.17±0.20, respectively (P=0.31). The mean decrease in RV/LV ratio from baseline to 24 hours was 0.30±0.20 versus 0.03±0.16 (P<0.001), respectively. At 90 days, there was 1 death (in the heparin group), no major bleeding, 4 minor bleeding episodes (3 in the USAT group and 1 in the heparin group; P=0.61), and no recurrent venous thromboembolism.

Conclusions—In patients with pulmonary embolism at intermediate risk, a standardized USAT regimen was superior to anticoagulation with heparin alone in reversing RV dilatation at 24 hours, without an increase in bleeding complications.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01166997.

(*Circulation*. 2014;129:479-486.)

Key Words: pulmonary embolism

Acute pulmonary embolism (PE) is a potentially life-threatening disease, spanning a wide spectrum of clinical outcomes.[1] Hemodynamically stable patients with preserved right ventricular (RV) size and function are classified as low-risk patients and have an excellent short-term prognosis once therapeutic levels of anticoagulation therapy are established.[2] In contrast, hemodynamically unstable patients are at high 15% if imaging or biomarker evidence of RV dilatation or dysfunction is present.[3,4]

Editorial see p 420
Clinical Perspective on p 486

Systemic thrombolysis improves hemodynamic parameters[5] and reverses RV dilatation and dysfunction[6–9] but is associated

The first RCT for an advanced catheter-based modality

Primary Objective

- Determine whether fixed low-dose catheter-directed ultrasound accelerated thrombolysis is superior to heparin alone in reversal of RV dilatation in submassive/intermediate risk PE

Kucher N et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479-486

ULTIMA study

Comparing EKOS® to heparin in intermediate risk PE therapy

Patients: Acute PE with RV/LV ≥ 1.0

Randomization

30 Patients

Unfractionated heparin + Ultrasound-assisted CDT using EKOS®

Infusion Protocol

- rtPA 1mg/h; saline coolant 35ml/h
- Patients monitored in the intermediate or ICU
- After five hours, rtPA reduced to 0.5 mg/h
- At 15(+/-) hours, rtPA infusion, saline coolant and ultrasound discontinued
- EkoSonic® devices removed in the intermediate or ICU

29 Patients

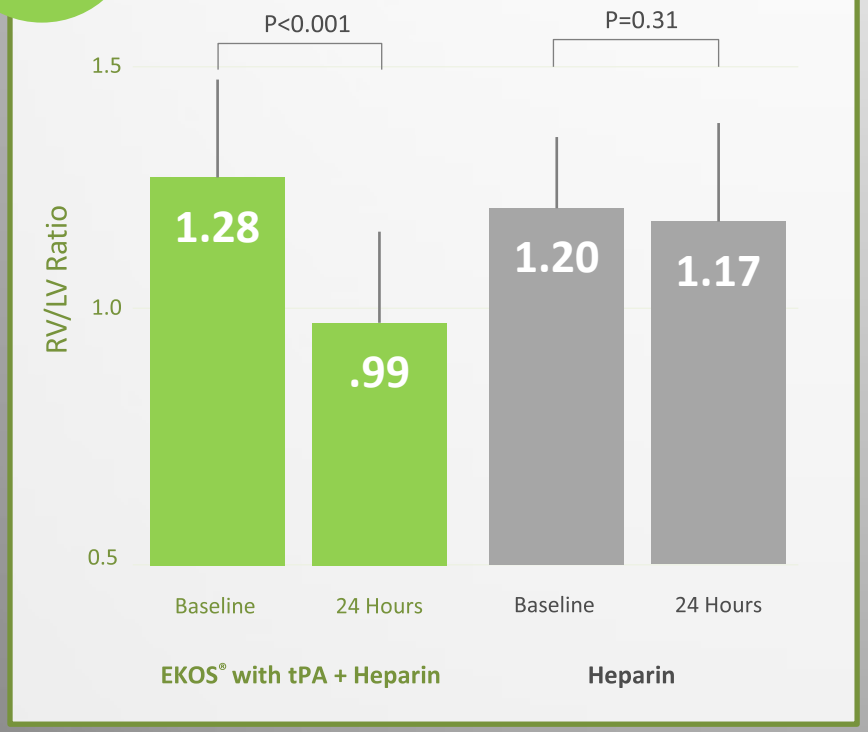
Unfractionated heparin

- IV bolus: 80 IU/kg
- Infusion: 18 IU/kg/hour

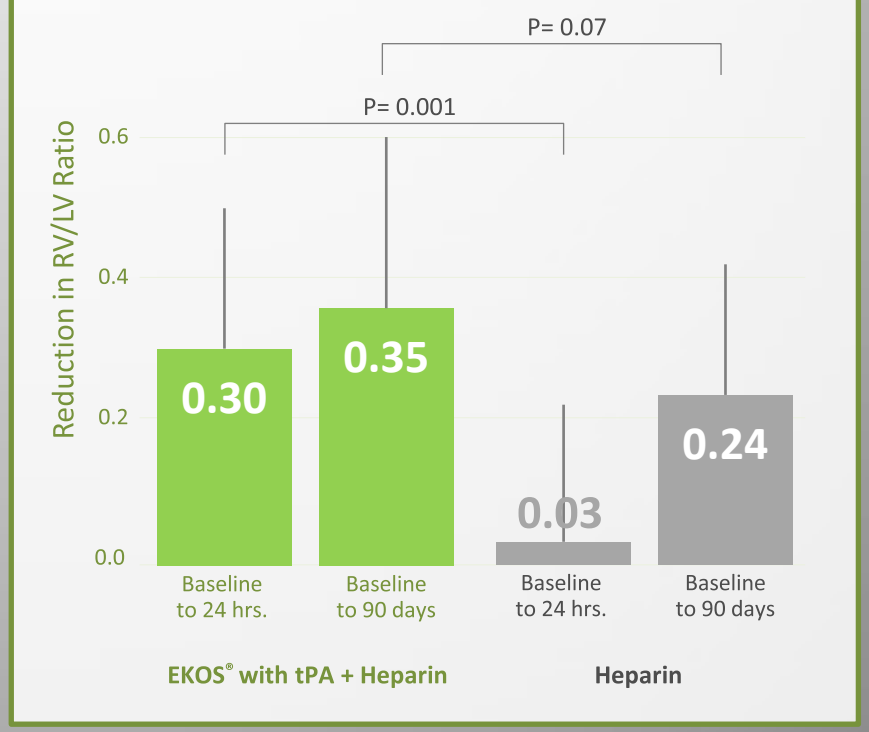
Kucher N et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479-486

Greater RVD reduction with EKOS® with tPA + heparin than with heparin alone

RV/LV RATIO SIGNIFICANTLY IMPROVED AT 24 HOURS



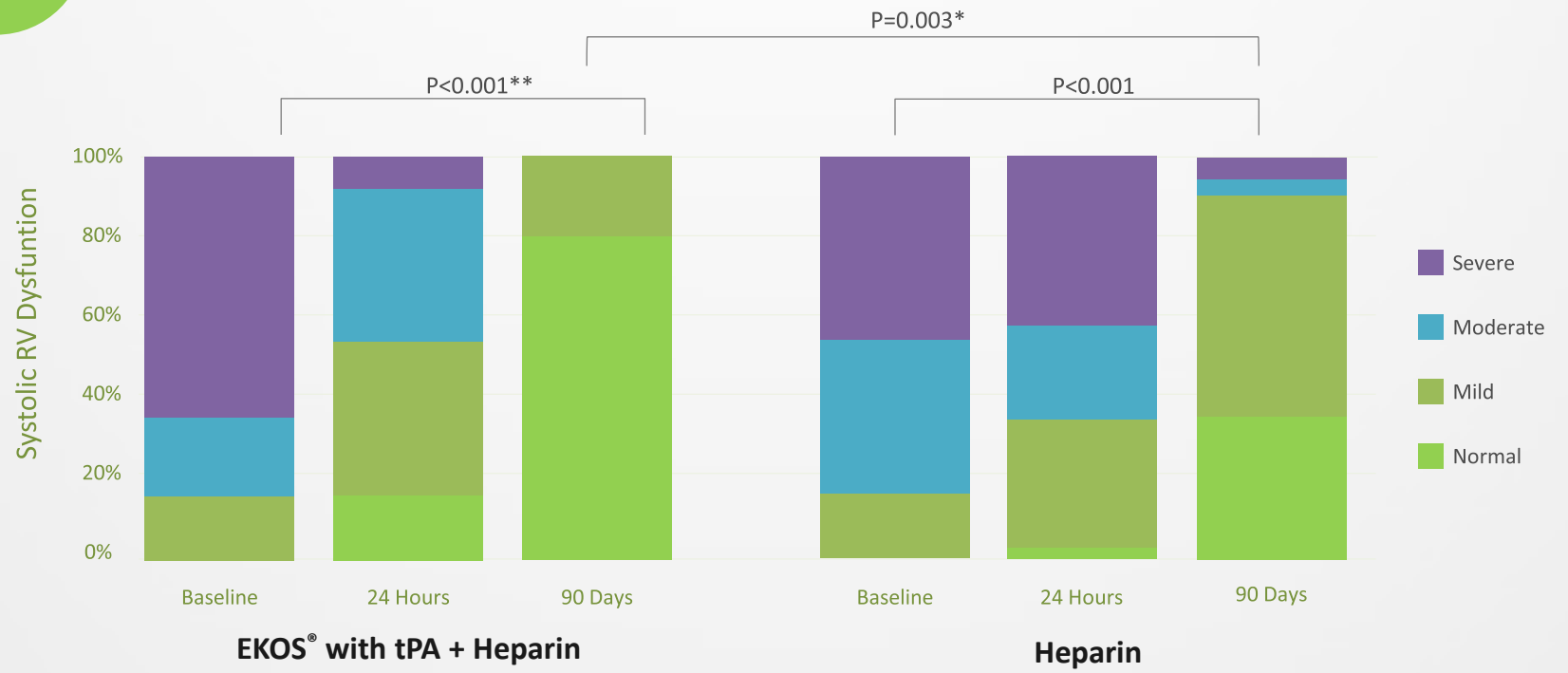
REDUCTION IN RV/LV RATIO SIGNIFICANTLY GREATER AT 24 HOURS AND IMPROVED AT 90 DAYS



Kucher N et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479-486

More improved echo findings from EKOS® with tPA + heparin than heparin alone

SYSTOLIC RV DYSFUNCTION SIGNIFICANTLY IMPROVED



*Two-sided exact Mantel-Haenzel test | **Wilcoxon rank sum test

Kucher N et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479-486

No statistical difference in safety Outcomes

No Deaths Or Significant Bleeding Complications

Clinical outcomes at 90 days	EKOS® with tPA + Heparin N= 30		Heparin N= 29		P-Value
Death	0	0%	1*	0%	0.49
Recurrent venous thromboembolism	0	0%	0	0%	1.00
Major bleeding	0	0%	0	0%	1.00
Minor bleeding	3**	10%	1	3%***	0.61

*Rehospitalization and death from advanced pancreatic cancer

**Two patients with transient mild hemoptysis without medical intervention, one patient with groin hematoma requiring manual compression

***One patient with transient bleeding following endoscopic removal of colon polyp

Kucher N et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism.

ULTIMA study

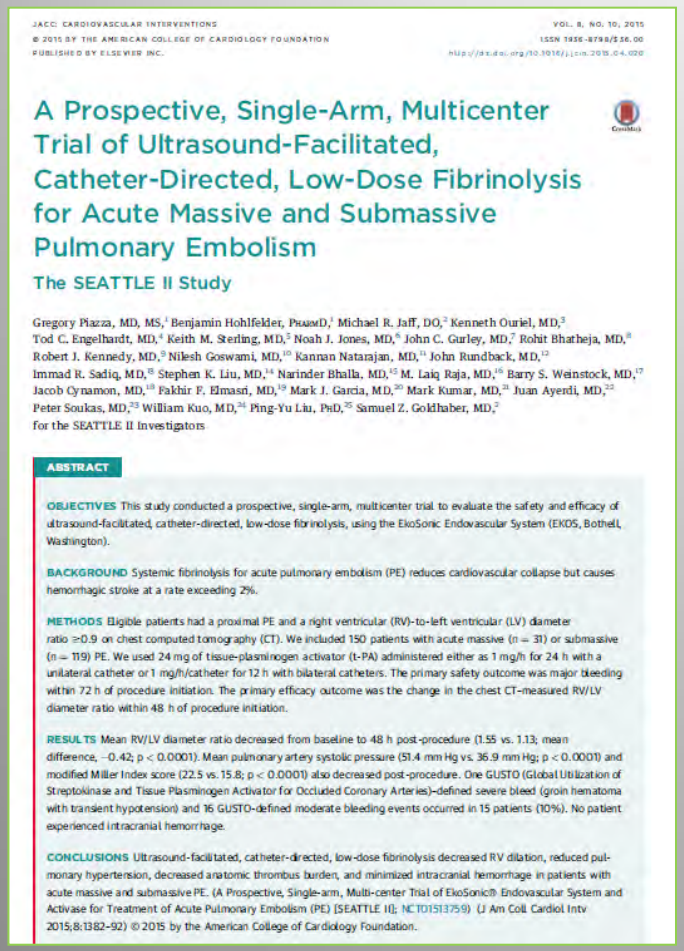
CONCLUSION

ULTIMA confirmed that a fixed-dose, ultrasound-assisted catheter-directed thrombolysis EKOS® regimen was superior to anticoagulation alone in improving RV dysfunction at 24 hours without an increase in bleeding complications.

Kucher N et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479-486

SEATTLE II Study

Examined EKOS® benefit in a clinical trial setting in the US



JACC: CARDIOVASCULAR INTERVENTIONS
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.
VOL. 8, NO. 10, 2015
ISSN 1936-8798/$36.00
http://dx.doi.org/10.1016/j.jcin.2015.04.020

A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism

The SEATTLE II Study

Gregory Piazza, MD, MS,[1] Benjamin Hohlfelder, PharmD,[1] Michael R. Jaff, DO,[2] Kenneth Ouriel, MD,[3] Tod C. Engelhardt, MD,[4] Keith M. Sterling, MD,[5] Noah J. Jones, MD,[6] John C. Gurley, MD,[7] Rohit Bhatheja, MD,[8] Robert J. Kennedy, MD,[9] Nilesh Goswami, MD,[10] Kannan Natarajan, MD,[11] John Rundback, MD,[12] Immad R. Sadiq, MD,[13] Stephen K. Liu, MD,[14] Narinder Bhalla, MD,[15] M. Laiq Raja, MD,[16] Barry S. Weinstock, MD,[17] Jacob Cynamon, MD,[18] Fakhir F. Elmasri, MD,[19] Mark J. Garcia, M.D.,[20] Mark Kumar, MD,[21] Juan Ayerdi, MD,[22] Peter Soukas, MD,[23] William Kuo, MD,[24] Ping-Yu Liu, PhD,[25] Samuel Z. Goldhaber, MD,[2]
for the SEATTLE II Investigators

ABSTRACT

OBJECTIVES This study conducted a prospective, single-arm, multicenter trial to evaluate the safety and efficacy of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis, using the EkoSonic Endovascular System (EKOS, Bothell, Washington).

BACKGROUND Systemic fibrinolysis for acute pulmonary embolism (PE) reduces cardiovascular collapse but causes hemorrhagic stroke at a rate exceeding 2%.

METHODS Eligible patients had a proximal PE and a right ventricular (RV)-to-left ventricular (LV) diameter ratio ≥0.9 on chest computed tomography (CT). We included 150 patients with acute massive ($n = 31$) or submassive ($n = 119$) PE. We used 24 mg of tissue-plasminogen activator (t-PA) administered either as 1 mg/h for 24 h with a unilateral catheter or 1 mg/h/catheter for 12 h with bilateral catheters. The primary safety outcome was major bleeding within 72 h of procedure initiation. The primary efficacy outcome was the change in the chest CT–measured RV/LV diameter ratio within 48 h of procedure initiation.

RESULTS Mean RV/LV diameter ratio decreased from baseline to 48 h post-procedure (1.55 vs. 1.13; mean difference, −0.42; $p < 0.0001$). Mean pulmonary artery systolic pressure (51.4 mm Hg vs. 36.9 mm Hg; $p < 0.0001$) and modified Miller Index score (22.5 vs. 15.8; $p < 0.0001$) also decreased post-procedure. One GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries)–defined severe bleed (groin hematoma with transient hypotension) and 16 GUSTO-defined moderate bleeding events occurred in 15 patients (10%). No patient experienced intracranial hemorrhage.

CONCLUSIONS Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis decreased RV dilation, reduced pulmonary hypertension, decreased anatomic thrombus burden, and minimized intracranial hemorrhage in patients with acute massive and submassive PE. (A Prospective, Single-arm, Multi-center Trial of EkoSonic® Endovascular System and Activase for Treatment of Acute Pulmonary Embolism (PE) [SEATTLE II]; NCT01513759) (J Am Coll Cardiol Intv 2015;8:1382–92) © 2015 by the American College of Cardiology Foundation.

Evaluate ultrasound-facilitated fibrinolysis using EKOS® for massive and submassive PE (n=150; 22 centers):

- Efficacy – as measured by reduction in RV/LV ratio
- Safety – as measured by major bleeding within 72 hours

Ultrasound-facilitated fibrinolysis using EKOS®

- If unilateral PE: tPA 1 mg/hr using one device for 24 hours
- If bilateral PE: tPA 1 mg/hr per device (using two simultaneously) for 12 hours

Follow up at 48 +/- 6 hours

- CT measurement of RV/LV ratio
- Echocardiogram to estimate PA systolic pressure

Piazza G et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. The SEATTLE II Study. J Amer Coll Cardiol: Cardiovasc Interventions 2015; 8(10):1382-1392.

SEATTLE II Study

Patient characteristics and treatment details

	N	%
Total enrollment	150*	100%
Massive/Submassive PE	31/119	21%/79%
History of previous DVT	30	20%
History of previous PE	15	10%
Concomitant use of antiplatelet agents	51	34%
Unilateral/Bilateral PE	20/130	13%/87%
Total rtPA dose	**23.7 ± 2.9 mg**	

* Denotes 1 patient died prior to treatment

Piazza G et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. The SEATTLE II Study. J Amer Coll Cardiol: Cardiovasc Interventions 2015; 8(10):1382-1392.

Reduced RV/LV ratio and Modified Miller Score at 48 hours post-EKOS®

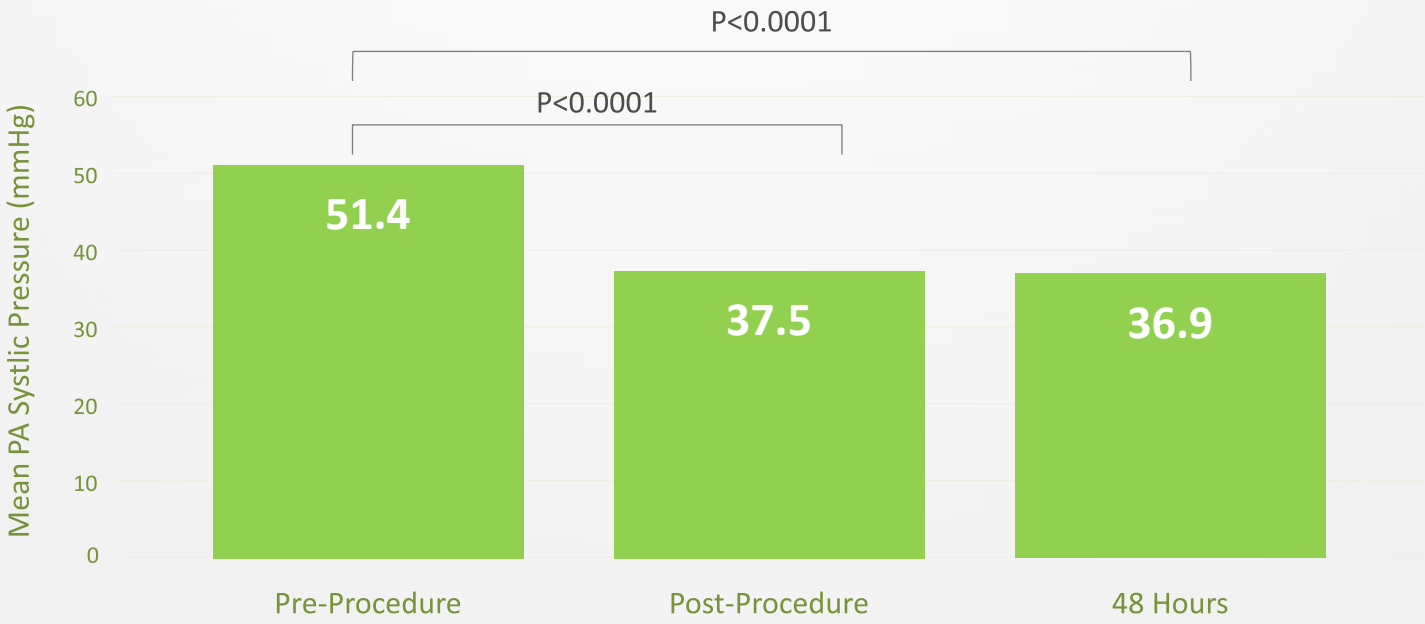
25% DECREASE IN RV/LV OVER 48 HOURS

RAPIDLY RELIEVED PULMONARY ARTERY OBSTRUCTION

Piazza G et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. The SEATTLE II Study. J Amer Coll Cardiol: Cardiovasc Interventions 2015; 8(10):1382-1392.

Reduced pulmonary artery pressure immediately post-procedure

REDUCED PULMONARY HYPERTENSION



Piazza G et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. The SEATTLE II Study. J Amer Coll Cardiol: Cardiovasc Interventions 2015; 8(10):1382-1392.

Zero cases of intracranial hemorrhage reported in the study

Clinical outcomes*	N = 150
Mean length of stay ± SD, days	8.8 ± 5
In-hospital death, n (%)	3 (2)
30-day mortality**, n (%)	4 (2.7)
Serious adverse events due to device, n (%)	2 (1.3)
Serious adverse events due to t-PA, n (%)	2 (1.3)
IVC filter placed, n (%)	24 (16)
Major bleeding within 30 days**, n (%) GUSTO moderate** GUSTO severe**	17 (11.4) 16 (10.7) 1 (0.7)
Intracranial hemorrhage, n (%)	0 (0)

*All death, serious adverse and bleeding events were adjudicated by an independent safety monitor
**N = 149 (1 patient lost to follow-up)

Piazza G et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. The SEATTLE II Study. J Amer Coll Cardiol: Cardiovasc Interventions 2015; 8(10):1382-1392.

Zero cases of intracranial hemorrhage reported in the study

Minimized Risk of Intracranial hemorrhage

Study	Intracranial hemorrhage (Fibrinolysis Group)
ICOPER Goldhaber SZ, et al. 1999	9/304 (3%)
PEITHO Meyer G, et al. 2014	10/506 (2%)
SEATTLE II Piazza G, et al. 2015	0/150 (0%)

Piazza G et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. The SEATTLE II Study. J Amer Coll Cardiol: Cardiovasc Interventions 2015; 8(10):1382-1392.

SEATTLE II study

CONCLUSION

Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute PE improves RV function and decreases pulmonary hypertension and angiographic obstruction. By minimizing the risk of intracranial bleed, it represents a potential "game-changer" in the treatment of high-risk PE patients

Piazza G et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. The SEATTLE II Study. J Amer Coll Cardiol: Cardiovasc Interventions 2015; 8(10):1382-1392.

Metanalysis showed consistent recovery of hemodynamics among patients treated using EKOS®

Summary of published studies on ultrasound-assisted thrombolysis for acute pulmonary embolism

First author and year of publication	No. of patients	Patients with high-risk PE	Total rt-PA dose (mg)	Total thrombolysis duration (h)	RV/LV ratio		Mean pulmonary artery pressure (mmHg)	
					Before	After	Before	After
Chamsuddin *et al.* (2008)[26]	10	NA	21.8	24.8 ± 8.4	NA	NA	NA	NA
Lin *et al.* (2009)[25]	11	2 (18)	17.2 ± 2.4	17.4 ± 5.2	NA	NA	NA	NA
Engelhardt *et al.* (2011)[29]	24	5 (21)	33.5 ± 15.5	19.7 ± 8.1	1.33 ± 0.24[d]	1.0 ± 0.13[d]	NA	NA
Quintana *et al.* (2013)[28]	10	2 (20)	18 (7-28)[g]	20.8 (12-49)[g]	NA	NA	NA	NA
Kennedy *et al.* (2103)[21]	60	12 (20)	35.1 ± 11.1	19.6 ± 6.0	NA	NA	27 ± 9	20 ± 6
Engelberger *et al.* (2013)[21]	52	14 (27)	21.0 ± 5.7	15.2 ± 1.7	1.42 ± 0.21[j]	1.06 ± 0.23[j]	37 ± 9	25 ± 8
Kucher *et al.* (2013)[30]	30	0 (0)	20.8 ± 3.0	15.0 ± 1.0	1.28 ± 0.19[j]	.99 ± 0.17[j]	20 ± 9	24 ± 7
Total [l]	197	35 (18)	26.9[m]	17.8[m]	1.36 ± 0.21	1.03 ± 0.20	31.1 ± 9.0	22.7 ± 6.9

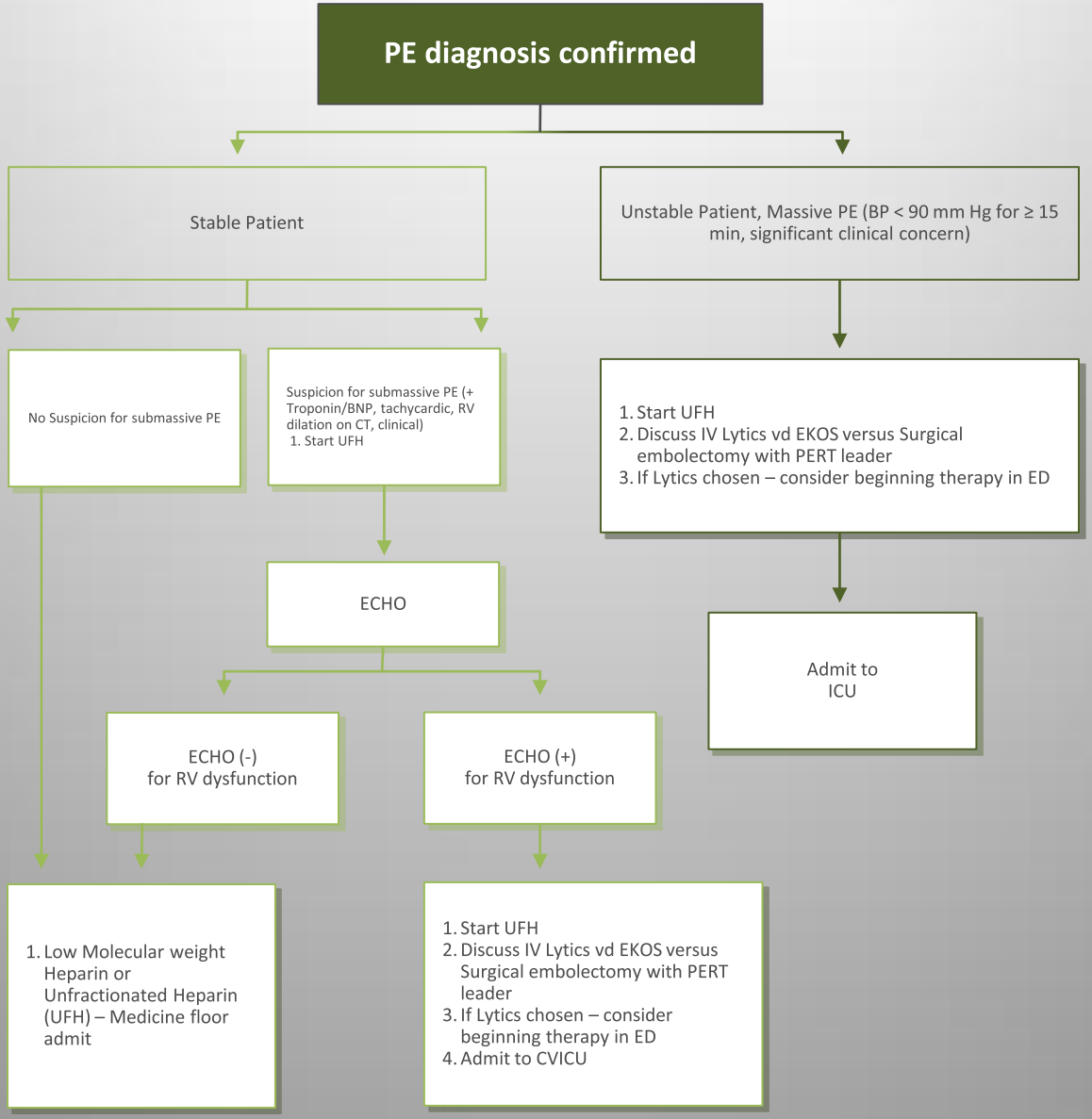
Engelberger RP et al. Ultrasound-assisted thrombolysis for acute pulmonary embolism: a systematic review. Eur Heart J. 2014 Mar;35(12):758-64

Metaanalysis demonstrated a favorable safety profile among patients treated using EKOS®

Summary of published studies on ultrasound-assisted thrombolysis for acute pulmonary embolism

First author and year of publication	No. of patients	Patients with high-risk PE	Total rt-PA dose (mg)	Total thrombolysis duration (h)	Bleeding Complications		Mortality at 3 months
					Minor	Major	
Chamsuddin *et al.* (2008)[26]	10	NA	21.8	24.8 ± 8.4	2 (20)	0 (0)[a]	0 (0)
Lin *et al.* (2009)[25]	11	2 (18)	17.2 ± 2.4	17.4 ± 5.2	0 (0)	0 (0)[c]	1 (9)
Engelhardt *et al.* (2011)[29]	24	5 (21)	33.5 ± 15.5	19.7 ± 8.1	2 (8)	4 (17)[f]	0 (0)
Quintana *et al.* (2013)[28]	10	2 (20)	18 (7-28)[g]	20.8 (12-49)[g]	2 (20)	0 (0)[i]	0 (0)
Kennedy *et al.* (2103)[21]	60	12 (20)	35.1 ± 11.1	19.6 ± 6.0	1 (2)	1 (2)[a]	4 (7)
Engelberger *et al.* (2013)[21]	52	14 (27)	21.0 ± 5.7	15.2 ± 1.7	11 (21)	1 (4)[k]	2 (4)
Kucher *et al.* (2013)[30]	30	0 (0)	20.8 ± 3.0	15.0 ± 1.0	3 (10)	0 (0)[k]	0 (0)
Total [l]	197	35 (18)	26.9[m]	17.8[m]	21 (10.7)	7 (3.6)	7 (3.6)

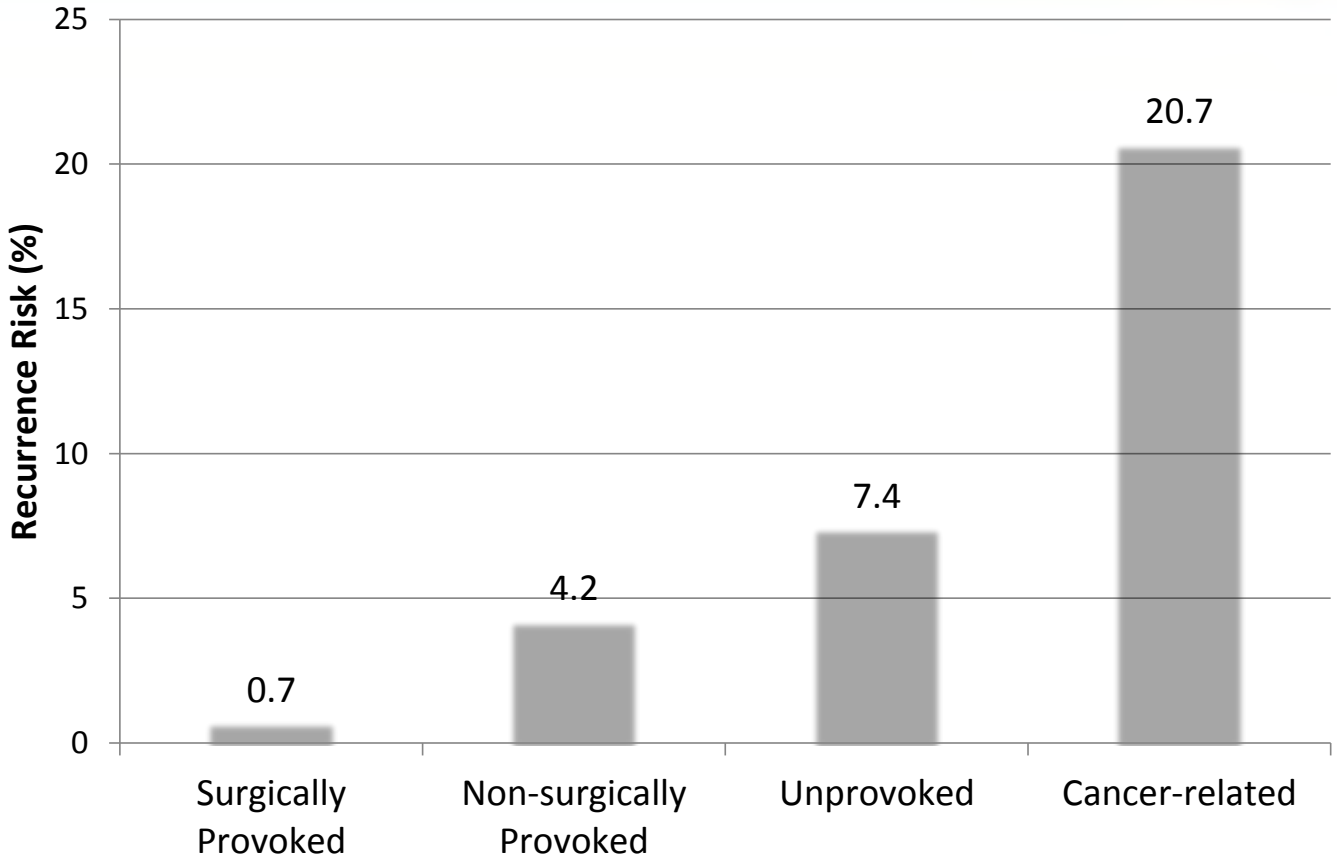
Engelberger RP et al. Ultrasound-assisted thrombolysis for acute pulmonary embolism: a systematic review. Eur Heart J. 2014 Mar;35(12):758-64



Bloomer TL et al. Acute Pulmonary Embolism Network and Multidisciplinary Response Team Approach to Treatment. Crit Pathways in Cardiol 2015; 14: 90-96

VTE Recurrence Risk
Provoked vs Unprovoked

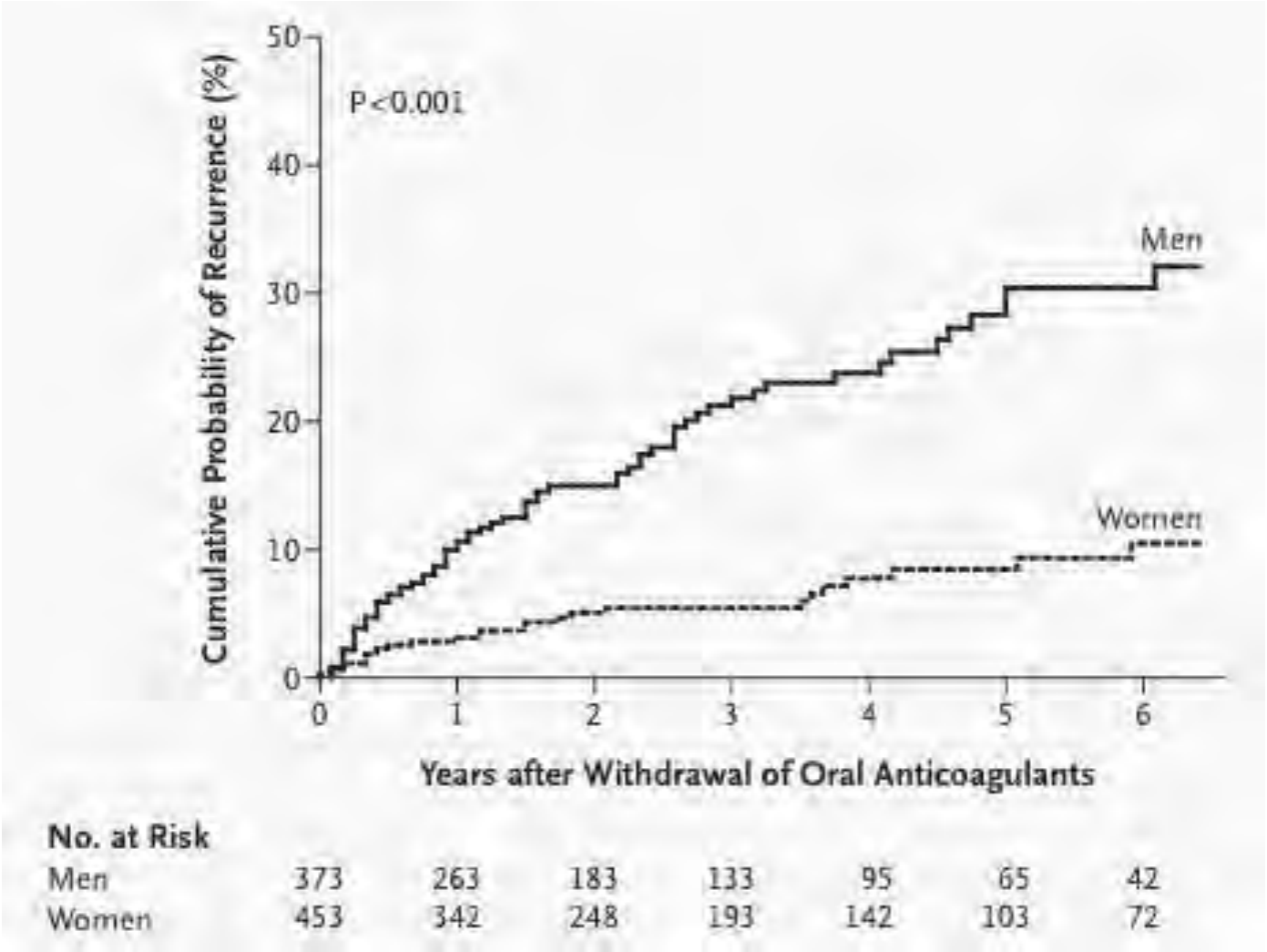
University of Michigan
Samuel and Jean Frankel
Cardiovascular Center



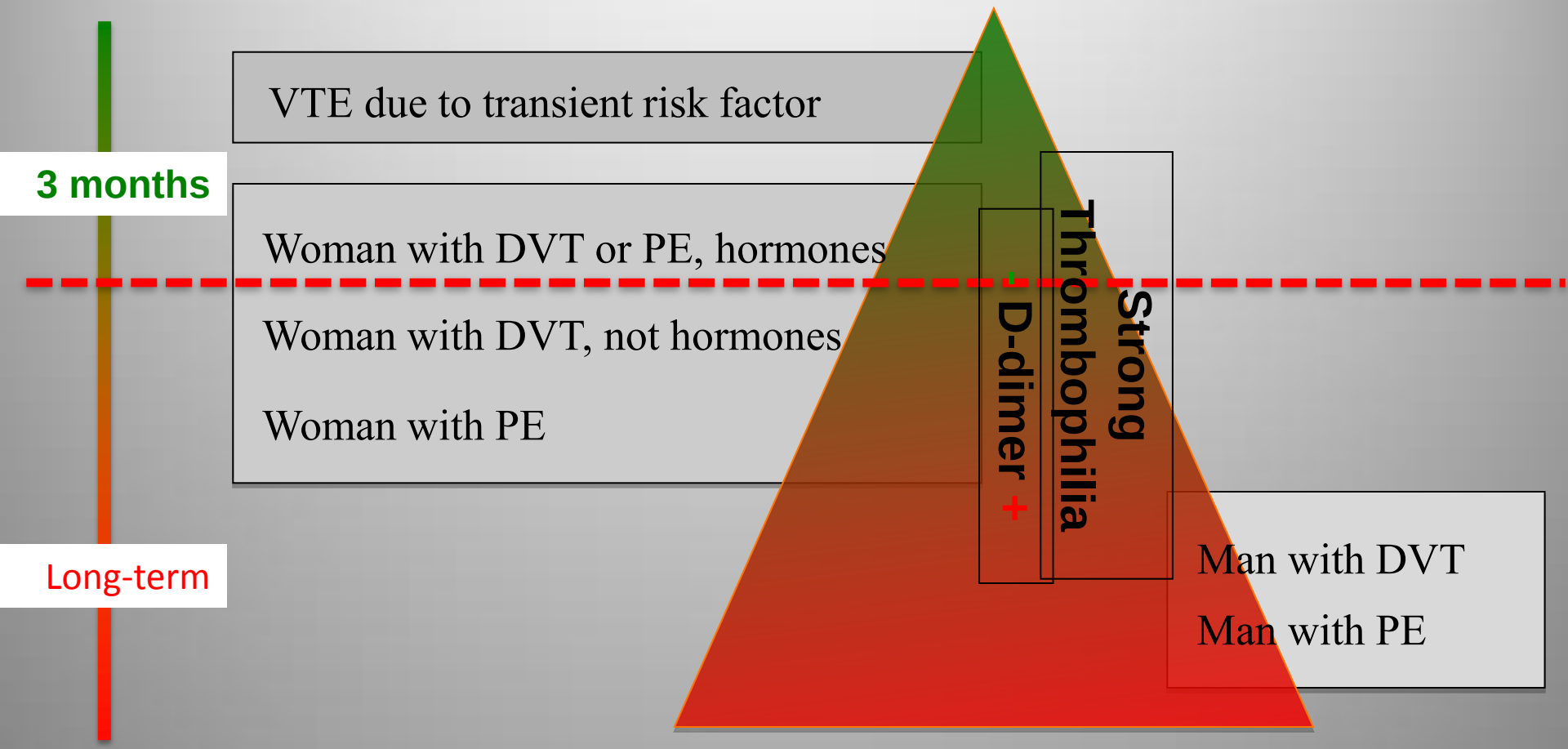
Arch Int Med 2010;170:1710-1716
Blood 2002; 100:3484-8

VTE Recurrence Risk - Gender

Gender



How Long to take AC ?



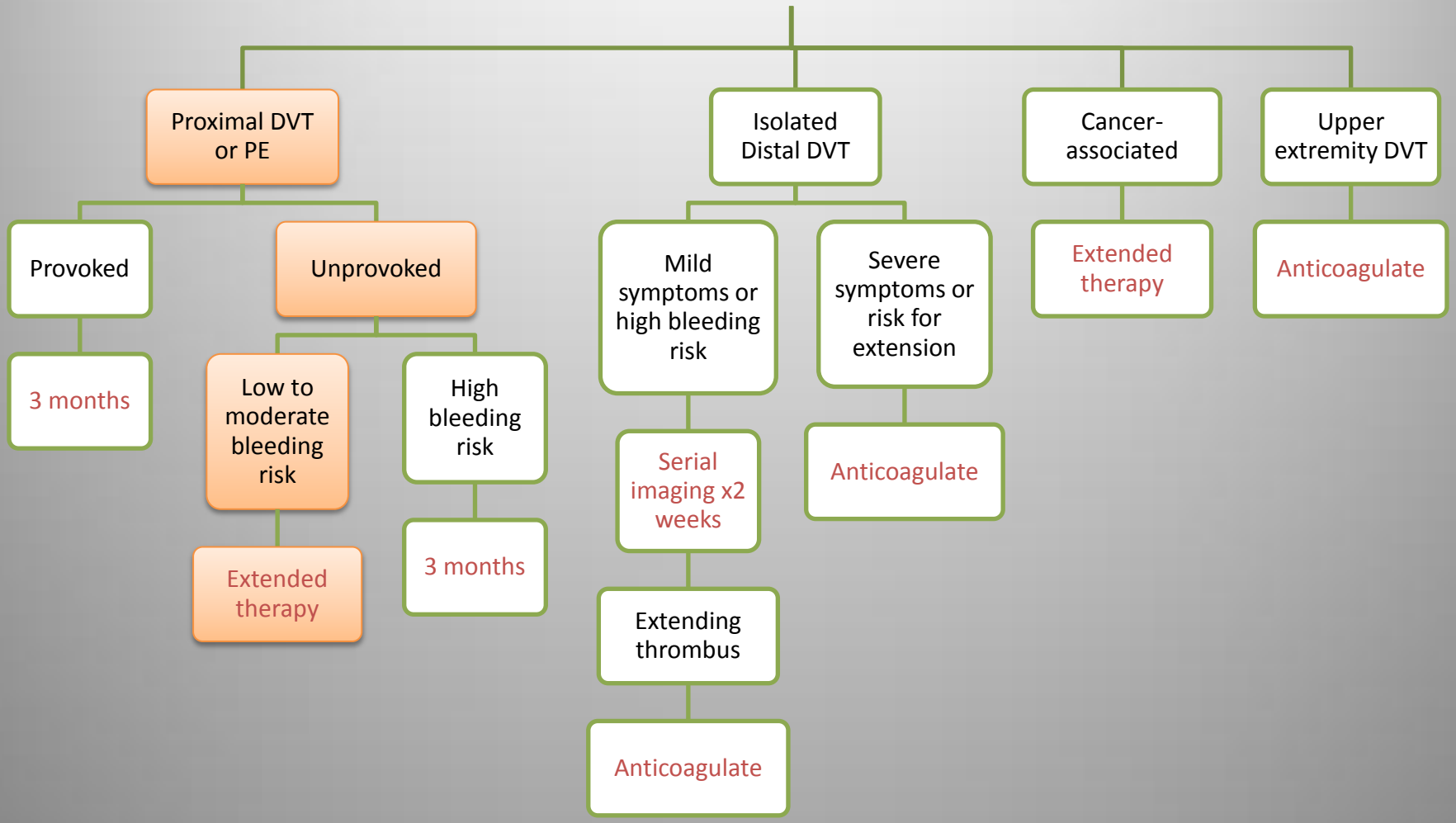
<u>Other risk factors for recurrence</u>: Obesity?; age?

<u>Other considerations</u>: Bleeding, fluctuating INRs, lifestyle impact, pt preference

Antithrombotic Therapy for VTE

CHEST Guidelines 2016

Duration of Therapy



Conclusions

- Pulmonary embolism carries high morbidity and mortality.
- Quick recognition of massive PE allows for application of rapid effective treatment to prevent complications and reduce mortality.
- RV dysfunction on echo/CT and the presence of a DVT are a “high risk” groups within the submassive category

Conclusions

- To date, thrombolysis of any kind has yet to prove mortality benefit in submassive PE in RCT.
- Ultrasound accelerated thrombolysis appear to have less bleeding risks with improvement in hemodynamic parameters
- Ultrasound accelerated thrombolysis uses less lytic, *may* reduce mortality, and thus may have a role in the "high risk" submassive PE patients

Thank You

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