Acute massive and submassive pulmonary embolism

Understanding the unmet need for advanced therapy in PE

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Objectives: 1) Understand the pathogenesis of pulmonary embolism 2) When to intervene with catheter directed thrombolysis vs. IV thrombolysis 3) New treatment options for pulmonary emboli

I have no financial disclosures.

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]

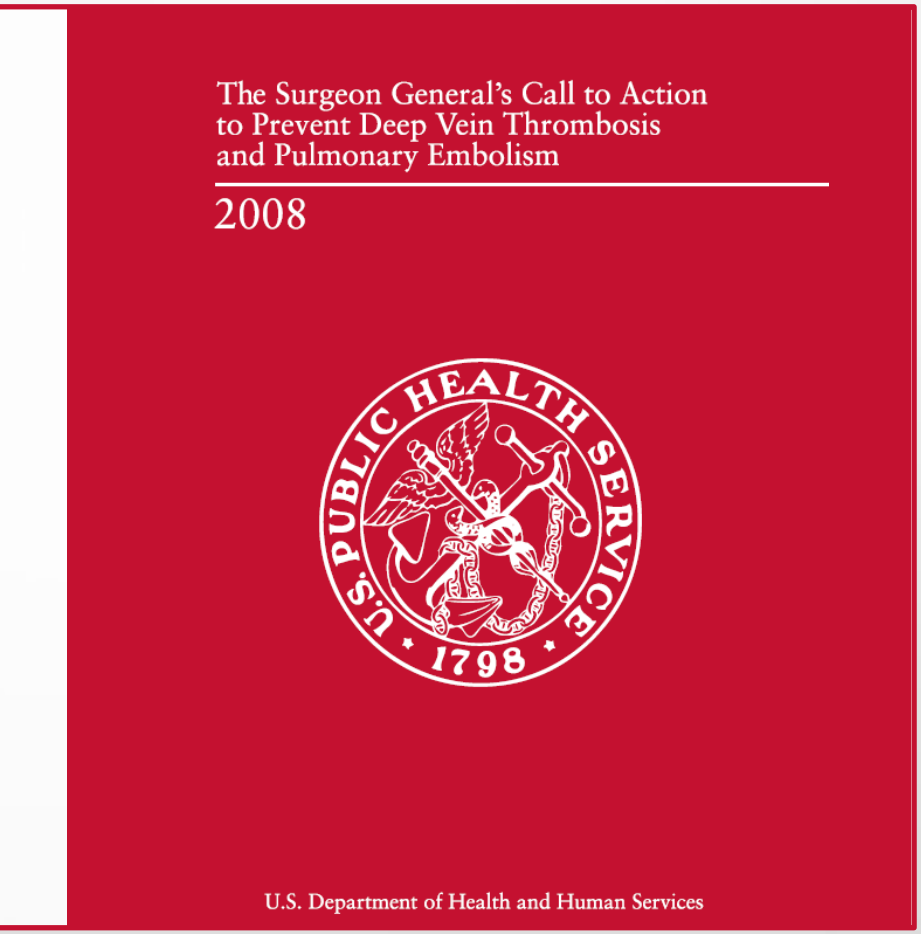
Venous thromboembolism[3]

- 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

High incidence

- 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.

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

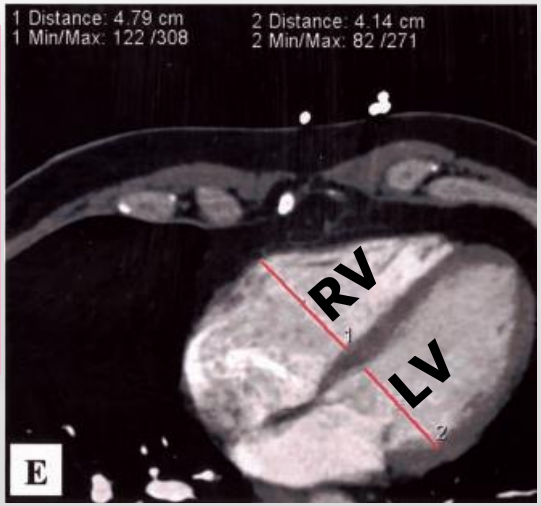
PE risk stratification

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

Why treat intermediate risk PE patients aggressively?

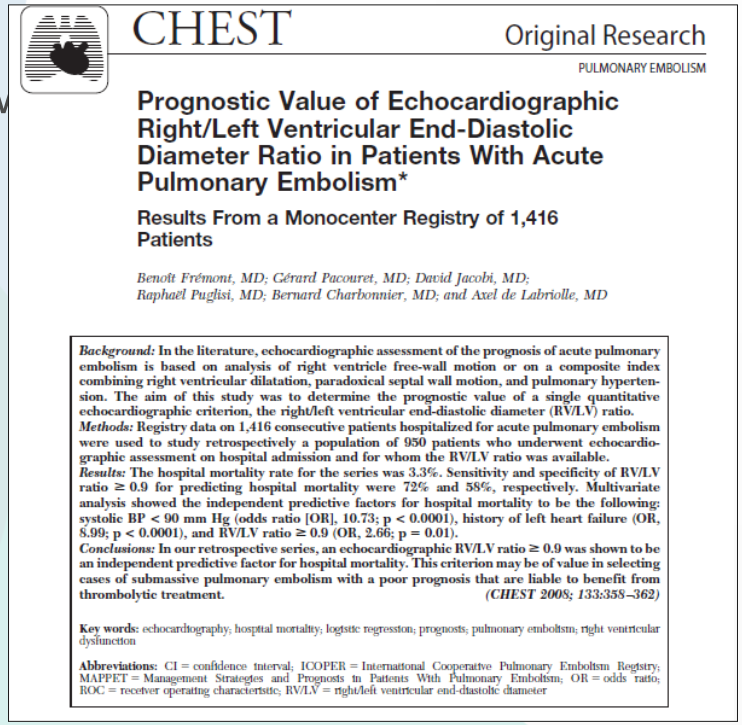
- Various studies report presence of right ventricular dysfunction (RVD) as a predictor of poor clinical outcomes

1. Mortality
2. Adverse events
3. VTE recurrence

Adverse outcomes associated with RVD – 3x higher mortality if RV/LV ≥

- 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

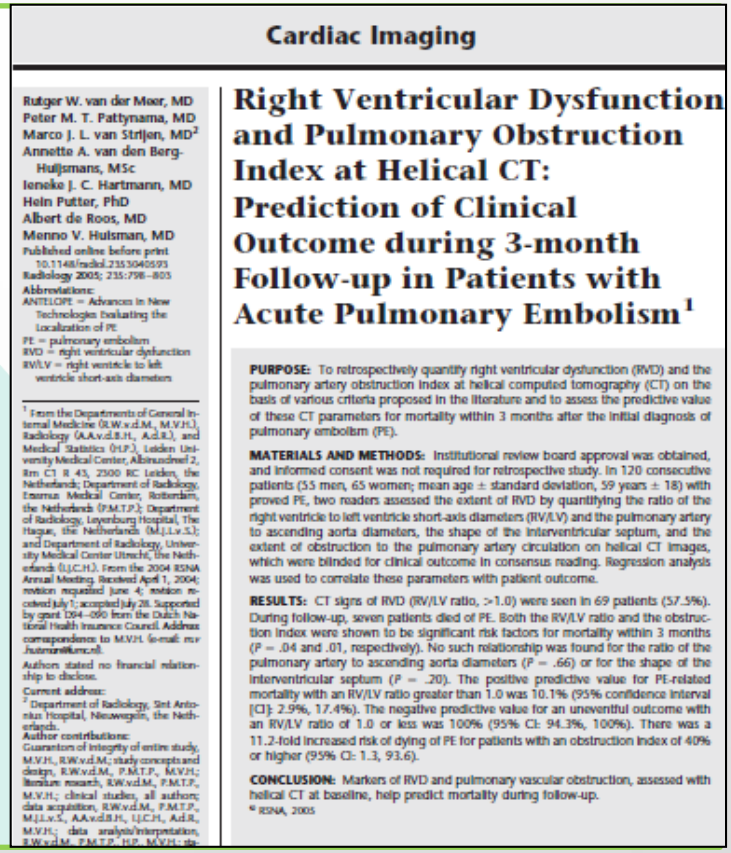
Abbreviations: CI = confidence interval; ICOPER = International Cooperative Pulmonary Embolism Registry; MAPPET = Management Strategies and Prognosis in Patients With Pulmonary Embolism; OR = odds ratio; ROC = receiver operating characteristic; RV/LV = right/left ventricular end-diastolic diameter

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 risk

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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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.

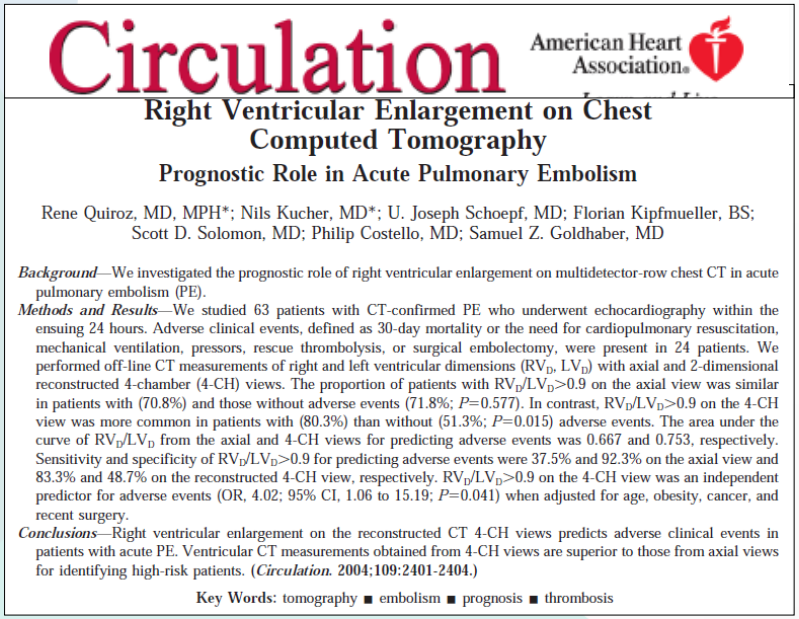
© RSNA, 2005

Van der Meer RW et al. Right ventricular 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

- Patients with RVD defined as RV/LV >0.9 have a greater chance of adverse events within 30 days

- Retrospective analysis of 63 patients with chest CT
- **Adverse event rate at 30 days:**
  - **80.3%** if RV/LV ratio > 0.9
  - **51.3%** if RV/LV ratio ≤ 0.9



Circulation

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Right Ventricular Enlargement on Chest Computed Tomography

Prognostic Role in Acute Pulmonary Embolism

Rene Quiroz, MD, MPH*; Nils Kucher, MD*; U. Joseph Schoepf, MD; Florian Kipfmueller, BS; Scott D. Solomon, MD; Philip Costello, MD; Samuel Z. Goldhaber, MD

Background—We investigated the prognostic role of right ventricular enlargement on multidetector-row chest CT in acute pulmonary embolism (PE).

Methods and Results—We studied 63 patients with CT-confirmed PE who underwent echocardiography within the ensuing 24 hours. Adverse clinical events, defined as 30-day mortality or the need for cardiopulmonary resuscitation, mechanical ventilation, pressors, rescue thrombolysis, or surgical embolectomy, were present in 24 patients. We performed off-line CT measurements of right and left ventricular dimensions (RV_D, LV_D) with axial and 2-dimensional reconstructed 4-chamber (4-CH) views. The proportion of patients with $RV_D/LV_D>0.9$ on the axial view was similar in patients with (70.8%) and those without adverse events (71.8%; $P=0.577$). In contrast, $RV_D/LV_D>0.9$ on the 4-CH view was more common in patients with (80.3%) than without (51.3%; $P=0.015$) adverse events. The area under the curve of RV_D/LV_D from the axial and 4-CH views for predicting adverse events was 0.667 and 0.753, respectively. Sensitivity and specificity of $RV_D/LV_D>0.9$ for predicting adverse events were 37.5% and 92.3% on the axial view and 83.3% and 48.7% on the reconstructed 4-CH view, respectively. $RV_D/LV_D>0.9$ on the 4-CH view was an independent predictor for adverse events (OR, 4.02; 95% CI, 1.06 to 15.19; $P=0.041$) when adjusted for age, obesity, cancer, and recent surgery.

Conclusions—Right ventricular enlargement on the reconstructed CT 4-CH views predicts adverse clinical events in patients with acute PE. Ventricular CT measurements obtained from 4-CH views are superior to those from axial views for identifying high-risk patients. (*Circulation.* **2004;109:2401-2404.**)

Key Words: tomography ■ embolism ■ prognosis ■ thrombosis

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

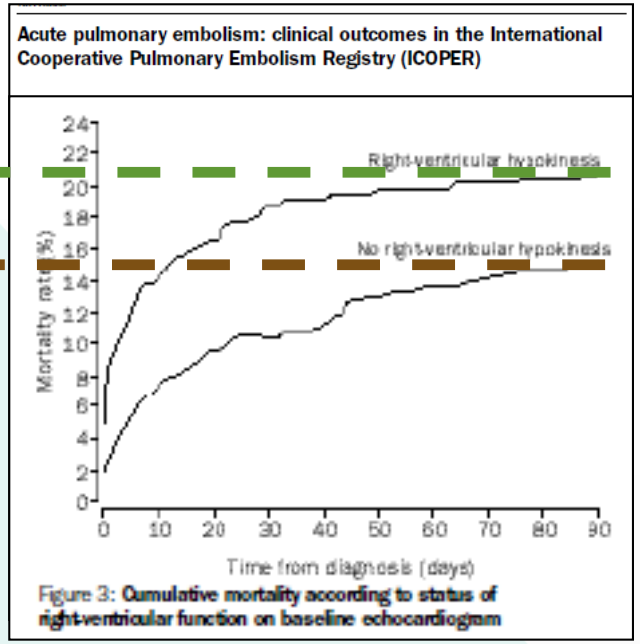
Adverse outcomes associated with RVD

- Presence of RV hypokinesis associated with 57% 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 – 8x 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**

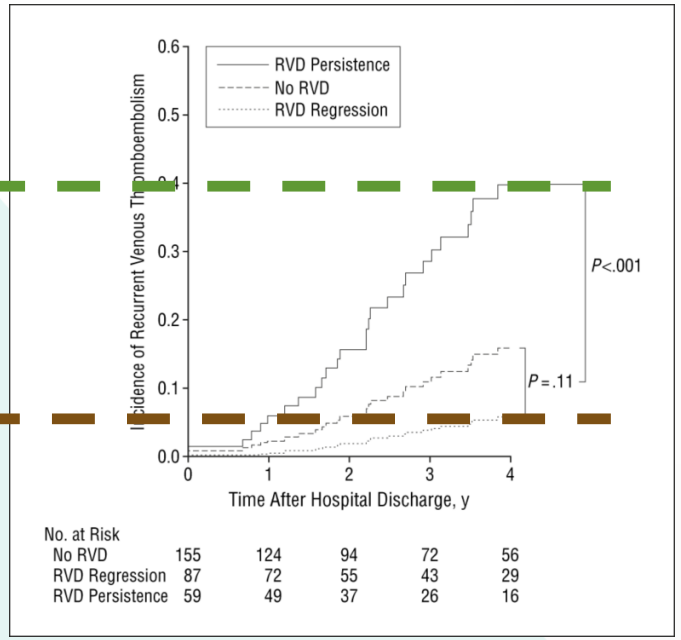


Figure: Cumulative incidence of recurrent venuous thromboembolism. RVD indicated right ventricular dysfunction.

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

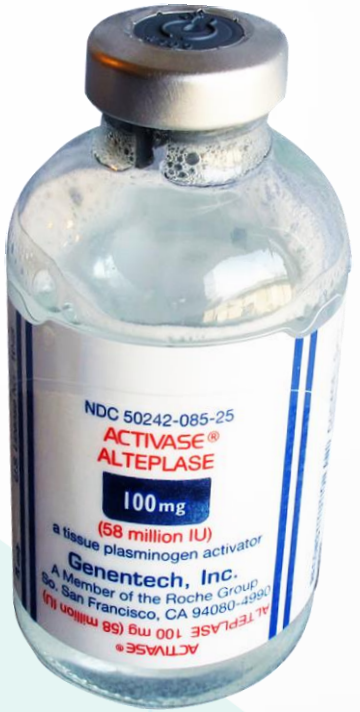
Rationale for thrombolysis in acute PE

- 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

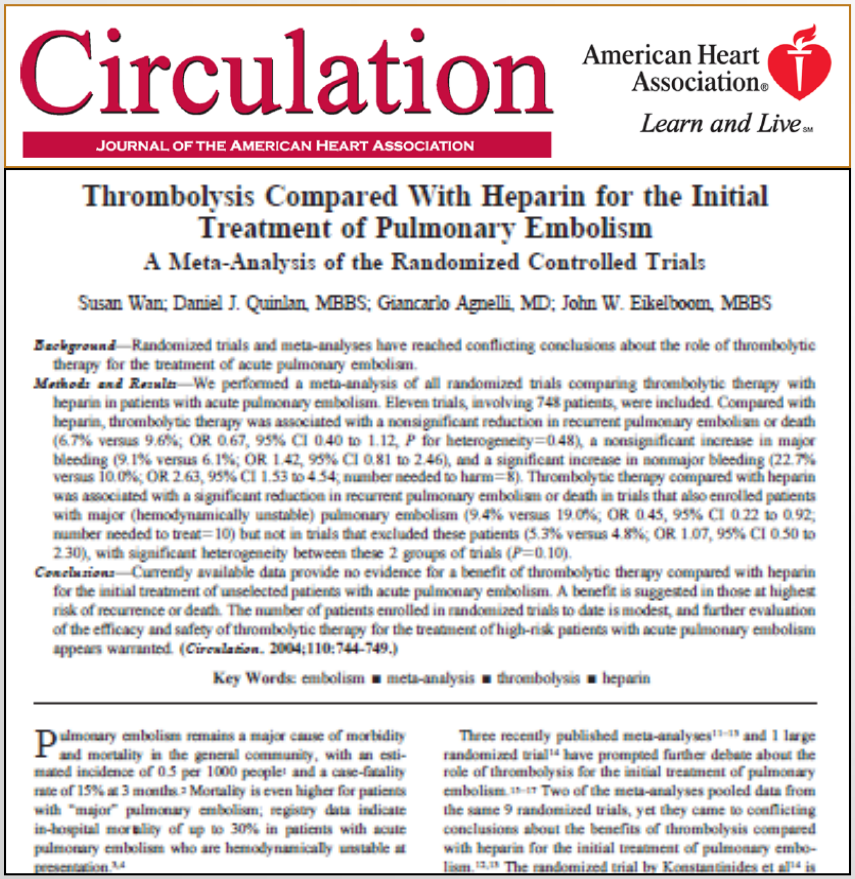
Piazza G and Goldhaber SZ. Finbrinolysis for acute pulmonary embolism. Vascular Medicine 2010 15(5):419-428

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

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

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.

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**

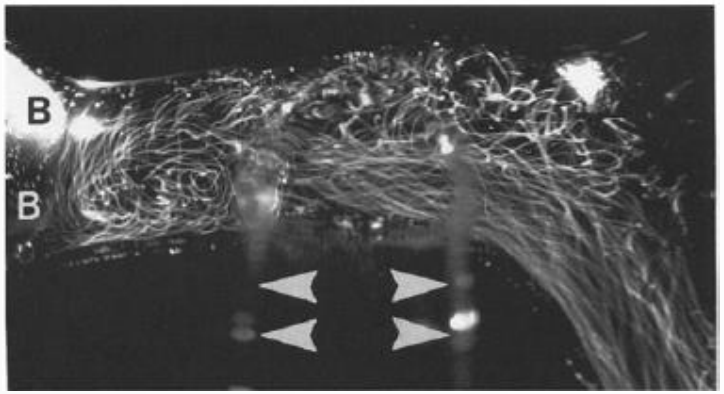
Meyer G et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014 Apr 10;370(15):1402-11

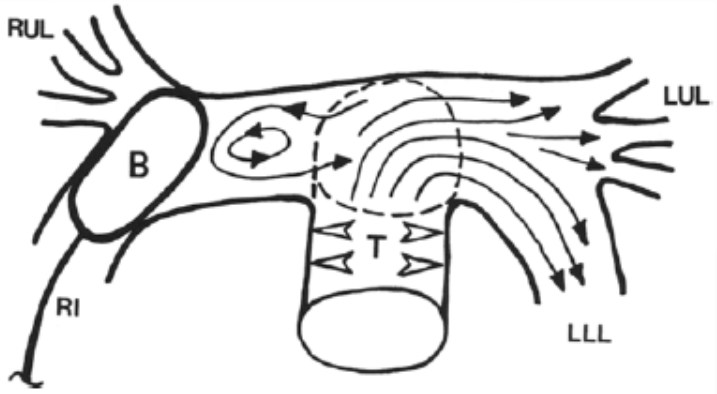
Adoption of IV thrombolysis hampered by elevated risk of severe bleeds

- 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
3. Kucher, N et al. Massive PE. Circulation 2006;113:577-82

IV thrombolysis—limited drug delivery to thrombus





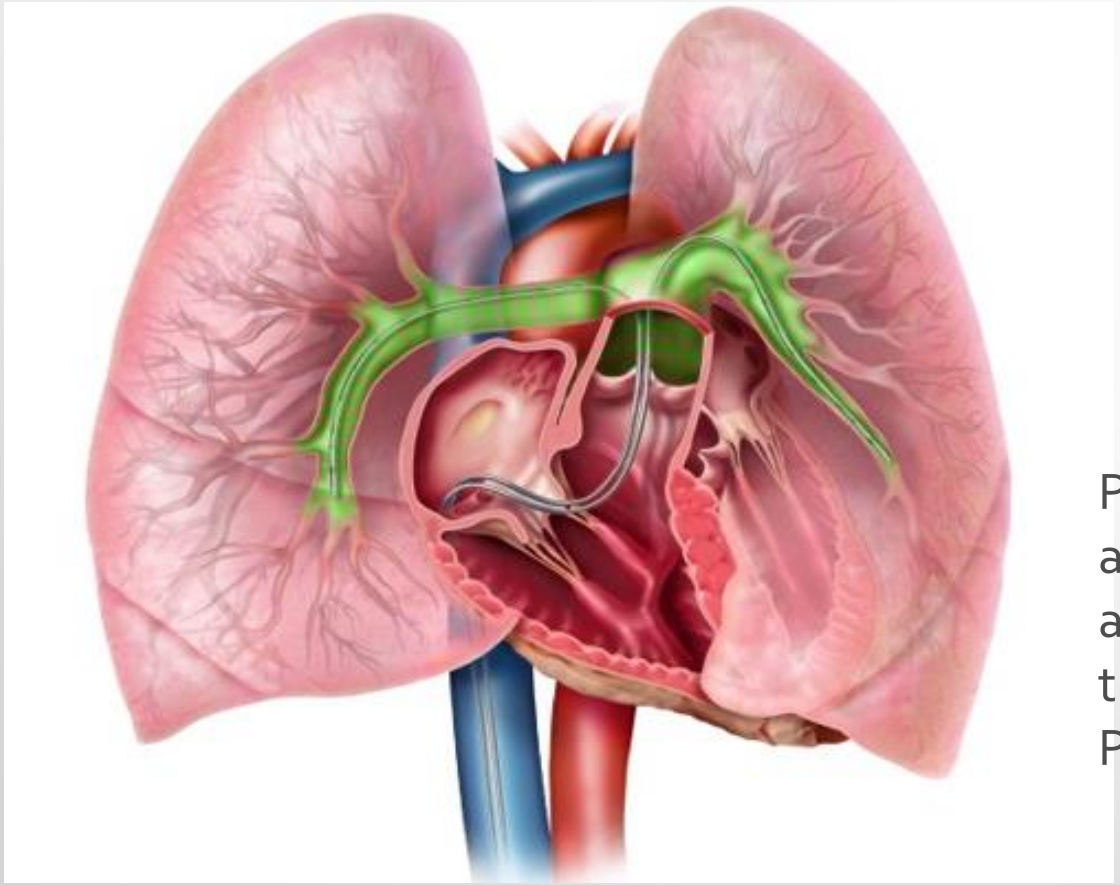
In vitro model of obstruction in the right main Pulmonary Artery
High-speed photo of systemically injected glass beads demonstrates how a vortex forms proximal to the obstruction and alters systemic drug delivery away from target embolus

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-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

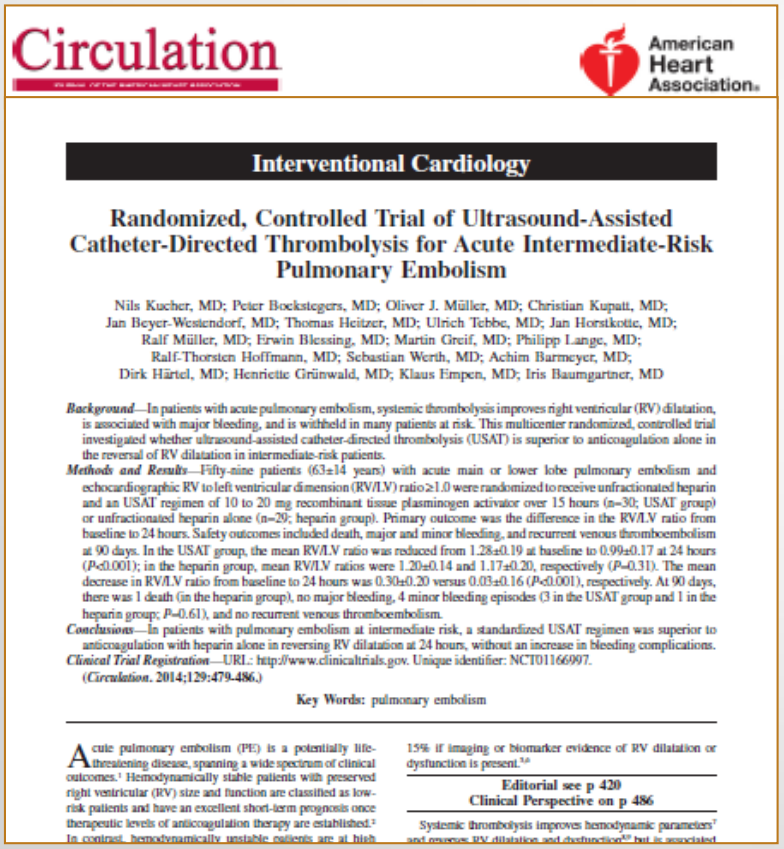


Placement in the left and right pulmonary arteries for the treatment of bilateral PE

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

- ULTIMA trial
- SEATTLE II trial
- Meta-analysis of historical published data
- Recent single-center studies

ULTIMA study compared 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.[3,6]

Editorial see p 420
Clinical Perspective on p 486

Systemic thrombolysis improves hemodynamic parameters[7] and reverses RV dilatation and dysfunction[8,9] 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

RCT compared EKOS® to heparin for the treatment of intermediate risk PE

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

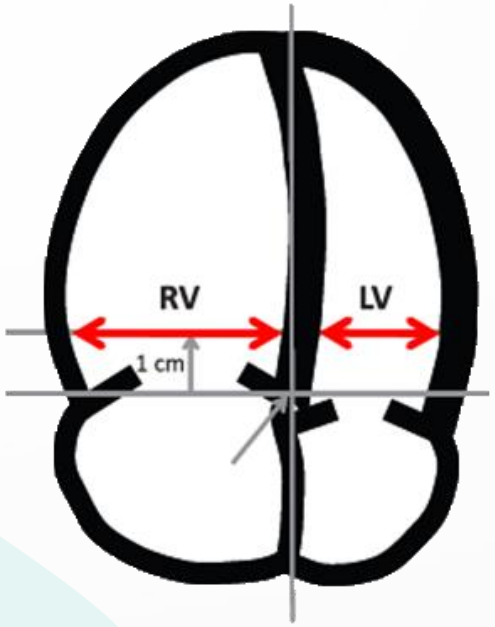
Unfractionated heparin

- 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

ULTIMA Trial
Measuring RV/LV Ratio

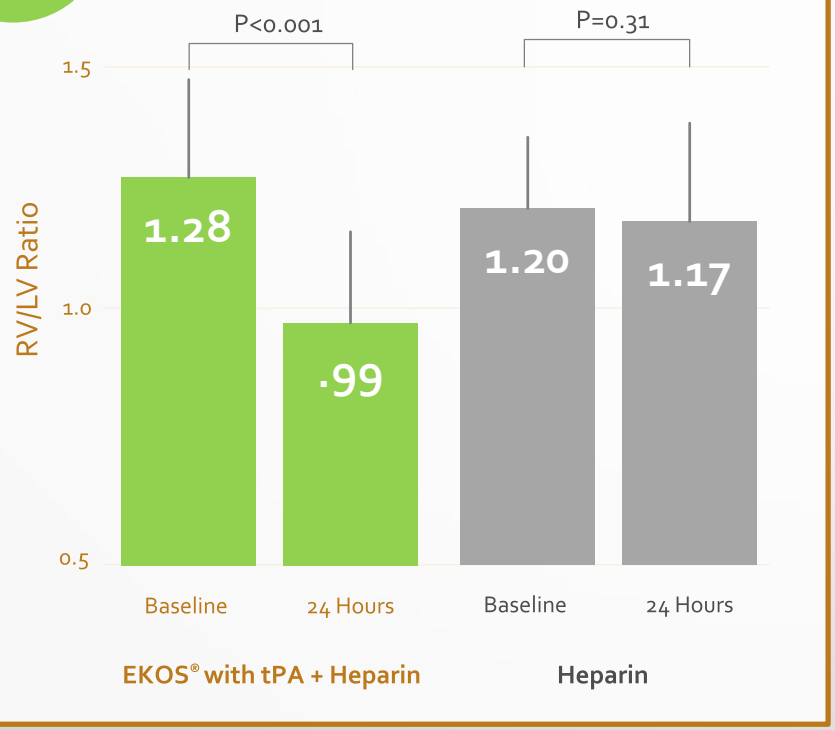
- Apical 4-Chamber view
- End diastolic image
- Center line through interventricular septum
- Obtain tricuspid annular line
- Obtain subannular line 1cm above annular line
- Obtain RV and LV dimensions using endocardial borders



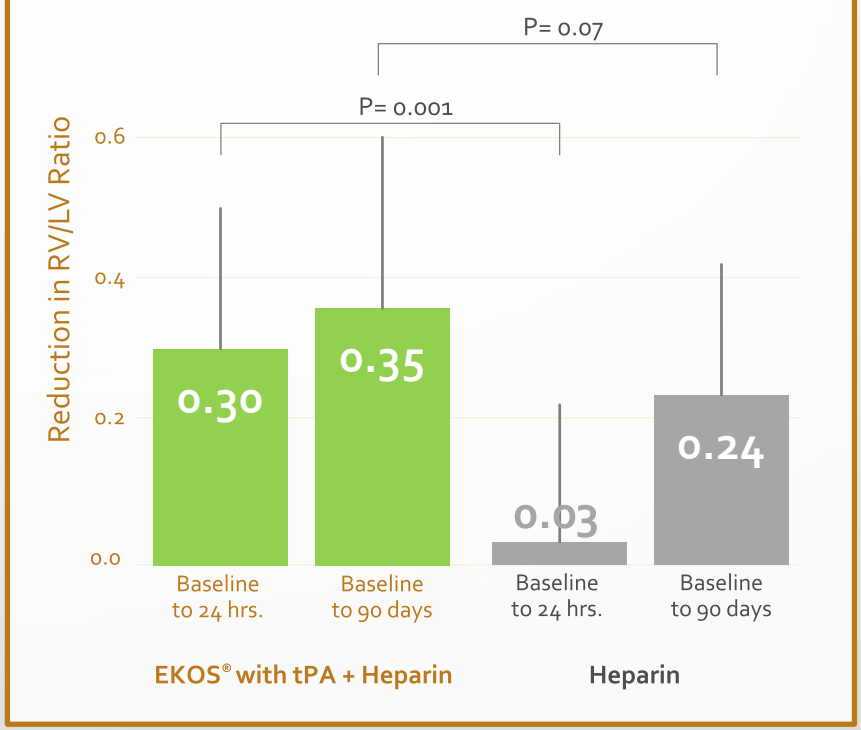
Kucher N et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479-486

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

RV/LV RATIO SIGNIFICANTLY IMPROVED AT 24 HOURS



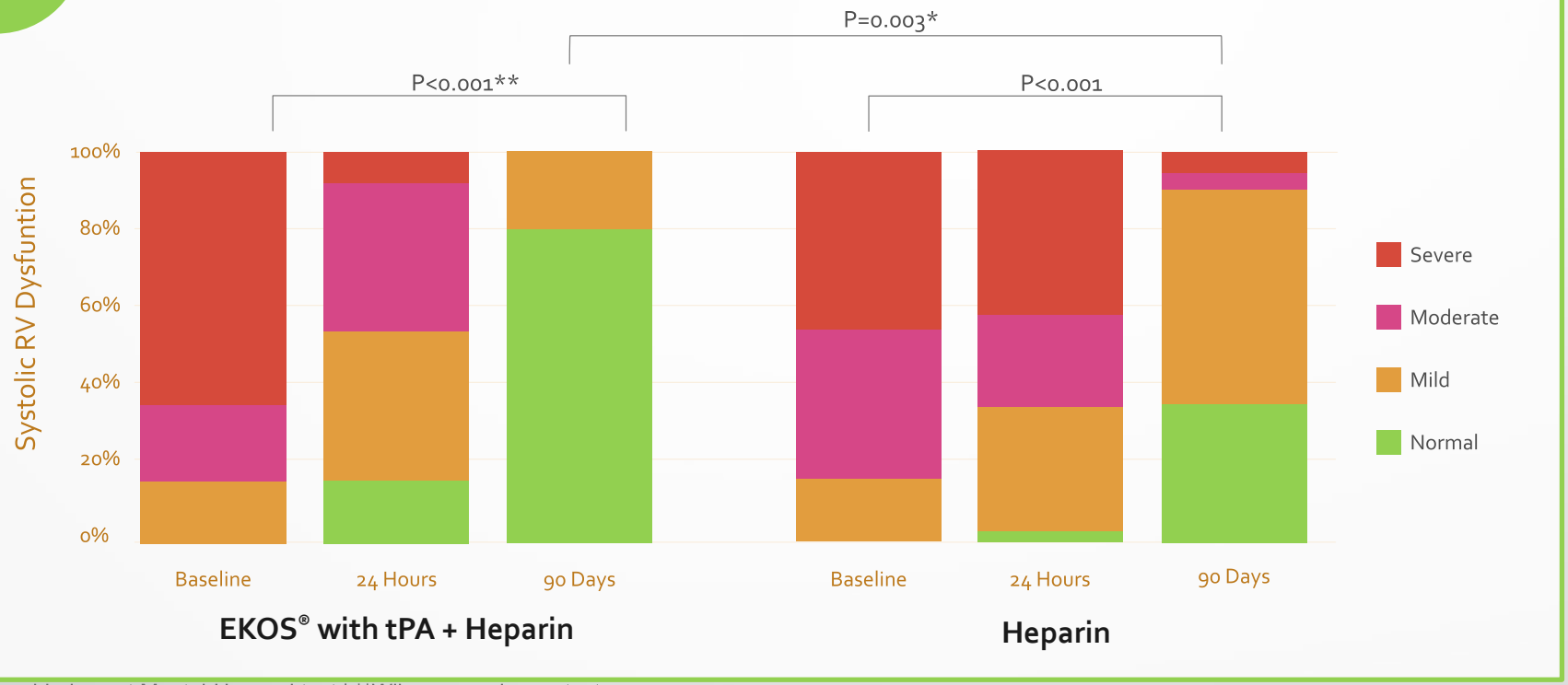
REDUCTION IN RV/LV RATIO SIGNIFICANTLY GREATER AT 24 HOURS AND IMPROVED AT 90 DAYS



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 with EKOS® with tPA + Heparin than Heparin alone

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.

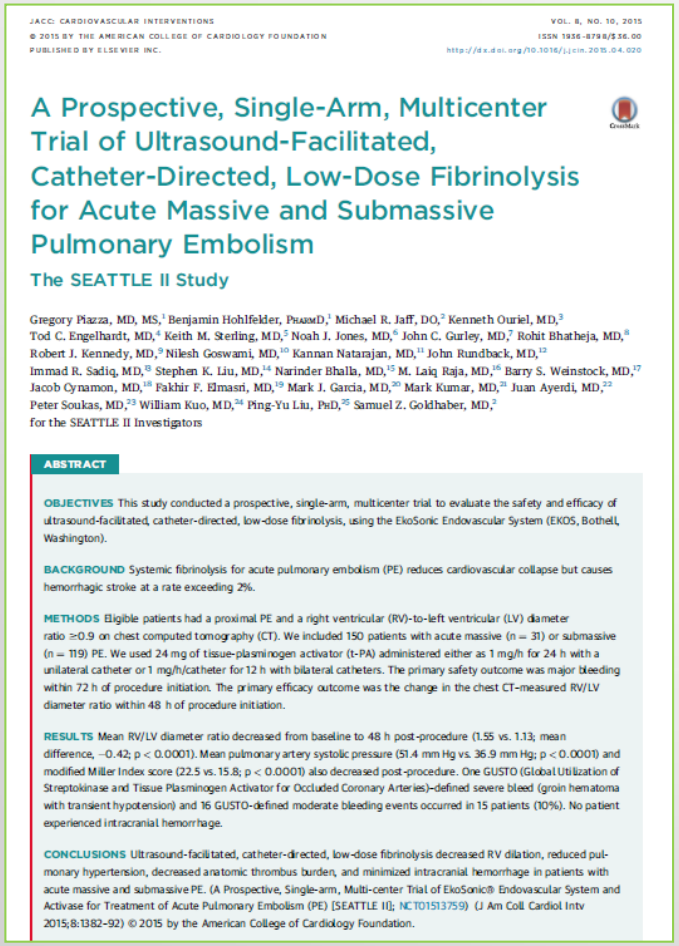
ULTIMA study

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



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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, MD,[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.

The SEATTLE II Study

Endpoints

- Primary Efficacy
  - Change in core lab-measured RV/LV ratio from baseline to 48 hours as assessed by chest CT
- Secondary Efficacy
  - Change in invasively measured PA systolic pressure from baseline to device removal and as estimated on 48-hour echocardiogram
- Primary Safety
  - Adjudicated major bleeding within 72 hours of the start of the procedure

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.

The SEATTLE II Study

Patient characteristics and treatment details

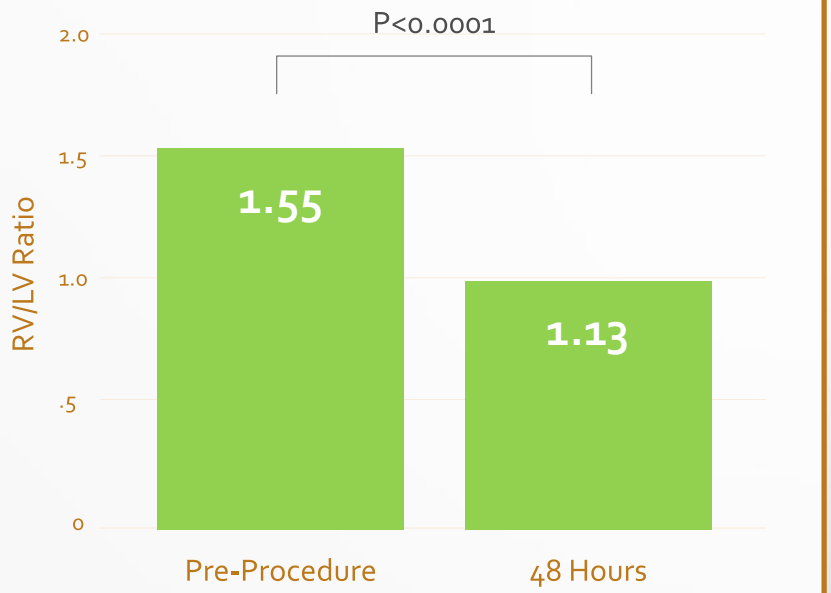
	N	%
Total enrollment	150*	100%
Massive/Submassive PE	31/119	21%/79%
History of previous DVT	30	20%
History of previous PE	15	10%
Concomitant use of antiplatelet agents	51	34%
Unilateral/Bilateral PE	20/130	13%/87%
Total rtPA dose	**23.7 ± 2.9 mg**	

* Denotes 1 patient died prior to treatment

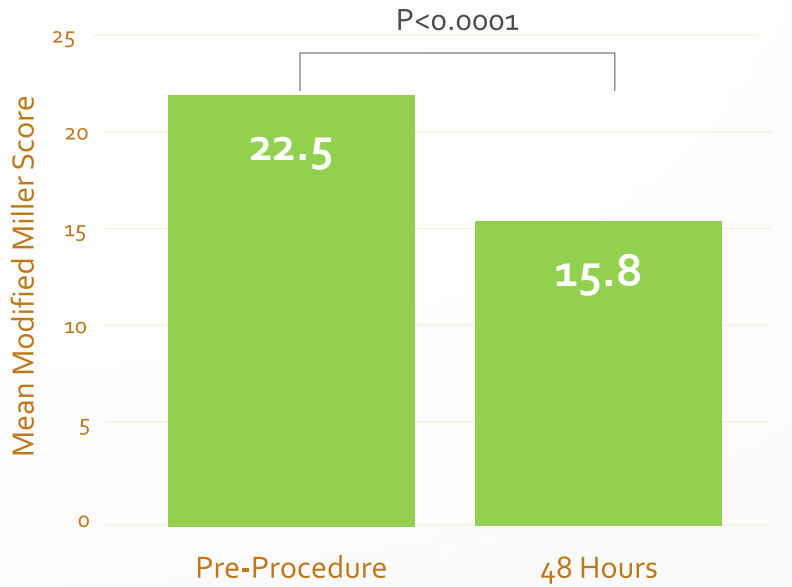
Piazza G et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. The SEATTLE II Study. J Amer Coll Cardiol: Cardiovasc Interventions 2015; 8(10):1382-1392.

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

25% DECREASE IN RV/LV OVER 48 HOURS



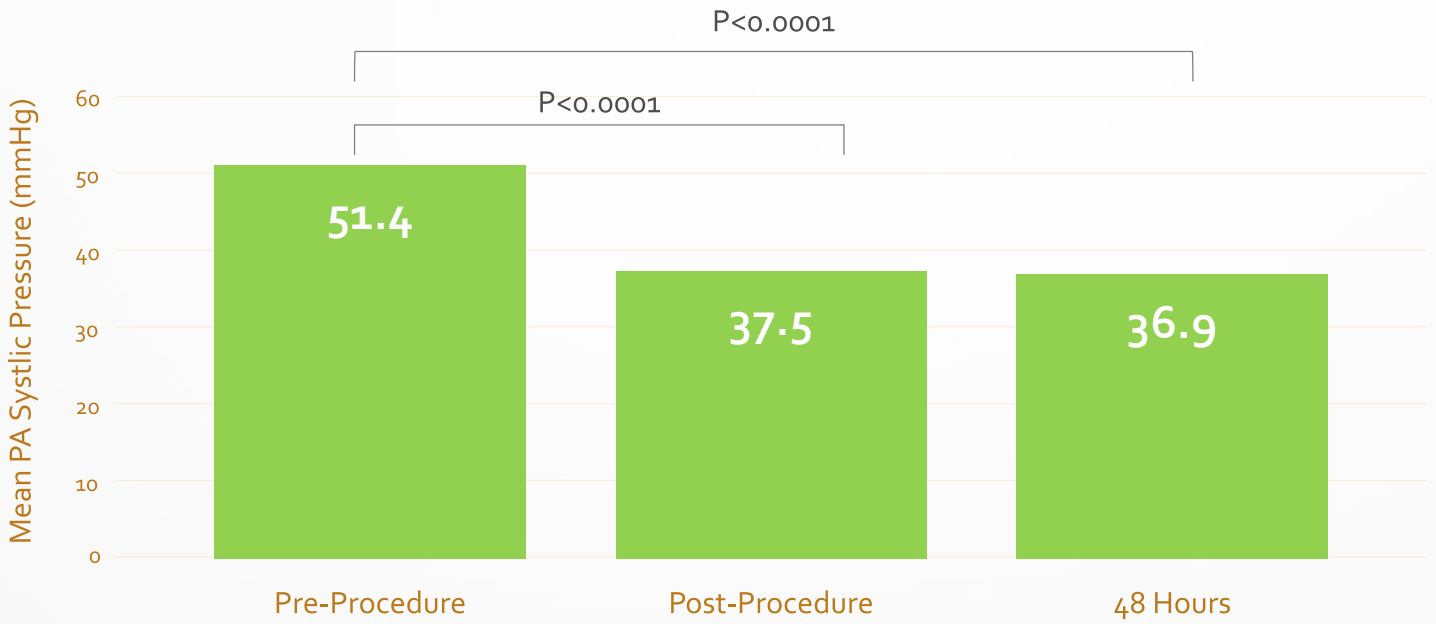
RAPIDLY RELIEVED PULMONARY ARTERY OBSTRUCTION



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



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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.

Early study showed safer and more effective lysis with EKOS® than CDT

- Single center retrospective comparative study
- 25 patients with massive pulmonary embolism (PE) were treated with either EKOS® or catheter directed thrombolysis (CDT) without ultrasound.
- 11 patients received EKOS® therapy for 15 PE lesions
- 14 patients received CDT therapy for 18 PE lesions

	EKOS® (n=11)	CDT (n=14)	P value
Complete thrombolysis	100%	50%	0.01
Thrombolytic dose (tPA, mg)	17.2 ± 2.36	25.43 ± 5.27	0.03
Bleeding complications	0%	21.4%	0.02

Lin et al. Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. Vascular. 2009 Nov-Dec;17 Suppl 3:S137-47

Single center experience showed CTA evidence of RVD resolution with EKOS®

- Single center retrospective single arm study
- 24 patients with high risk (n=5) or intermediate risk (n=19) PE treated with EKOS®
- Mean rtPA dose was 33.5±15.5 mg over 19.7 hours

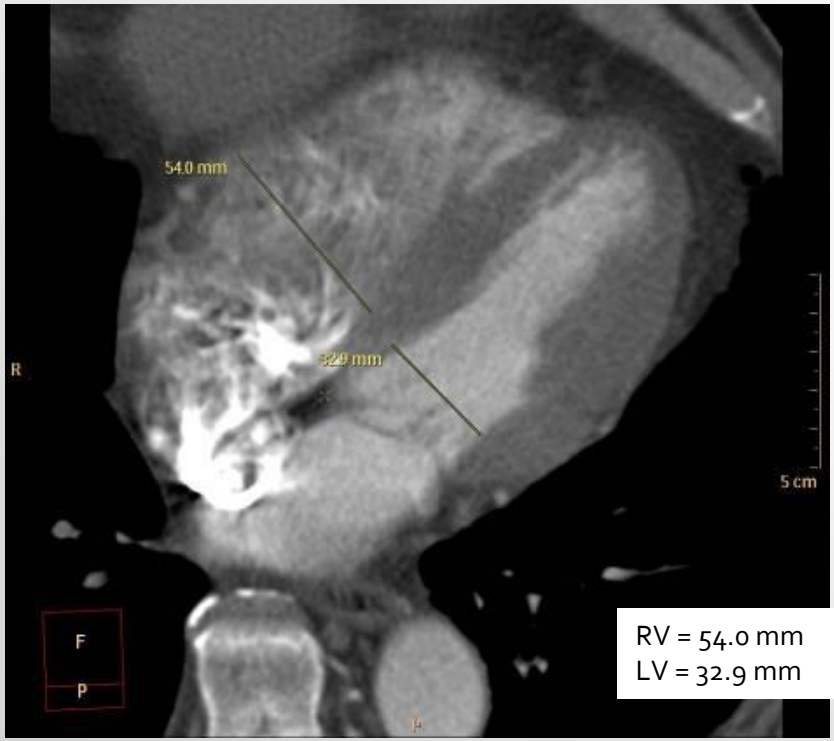
	Pre-EKOS®	Post-EKOS®	P-Value
RV/LV ratio	1.33 ± 0.24	1.00 ± 0.13	<0.001
Modified Miller Score	17.8 ± 5.3	8.7 ± 5.1	<0.001

- No deaths or systemic bleeding complications, including intracranial hemorrhage; 4 access site bleeds requiring transfusion

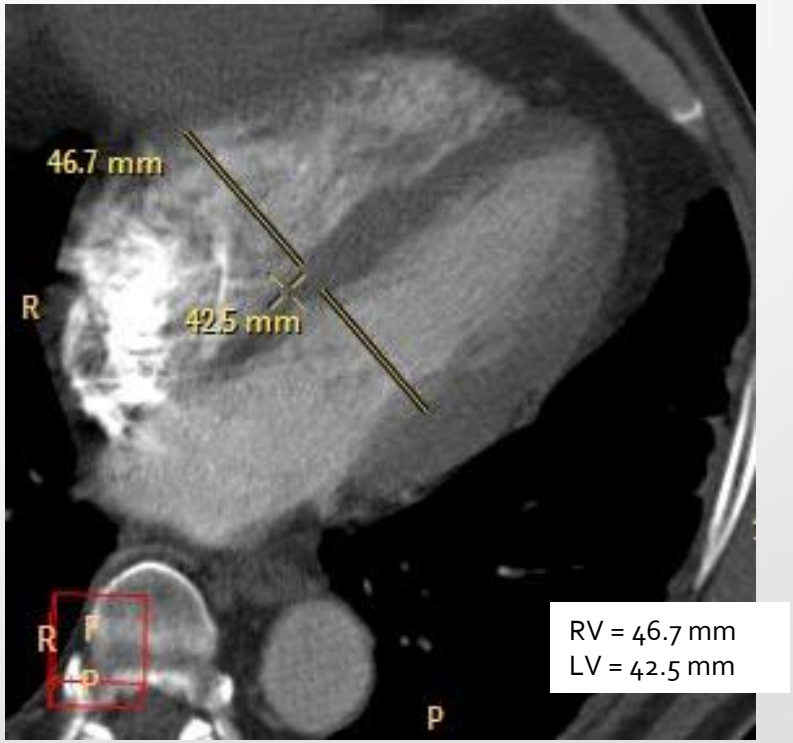
Engelhardt TC et al. Catheter-directed ultrasound-accelerated thrombolysis for the treatment of acute pulmonary embolism. Thromb Res. 2011; Aug;128(2):149-54.

Single center experience showed CTA evidence of RVD resolution

Case Study 1



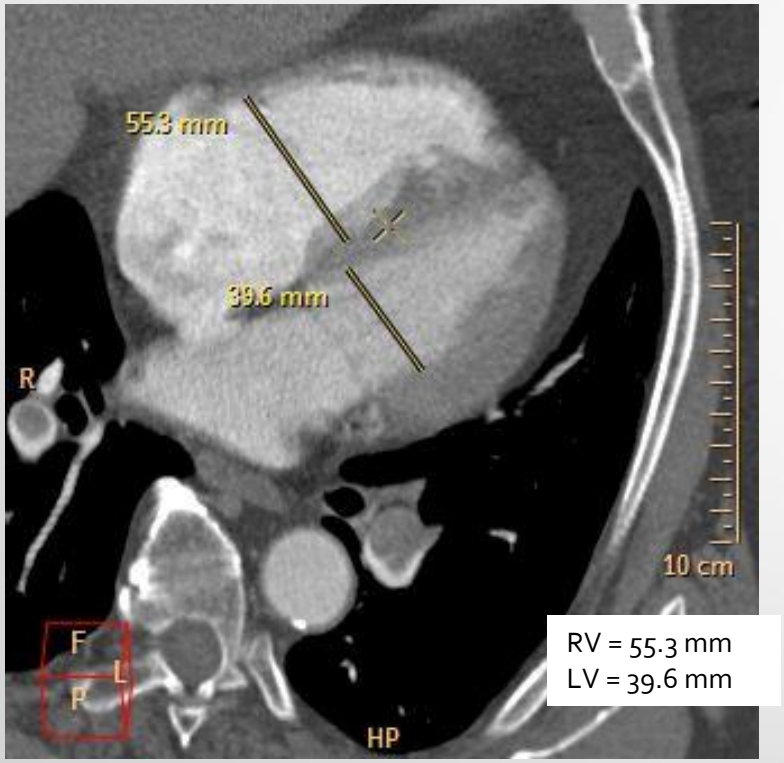
Pre-treatment:
RV/LV = 1.64



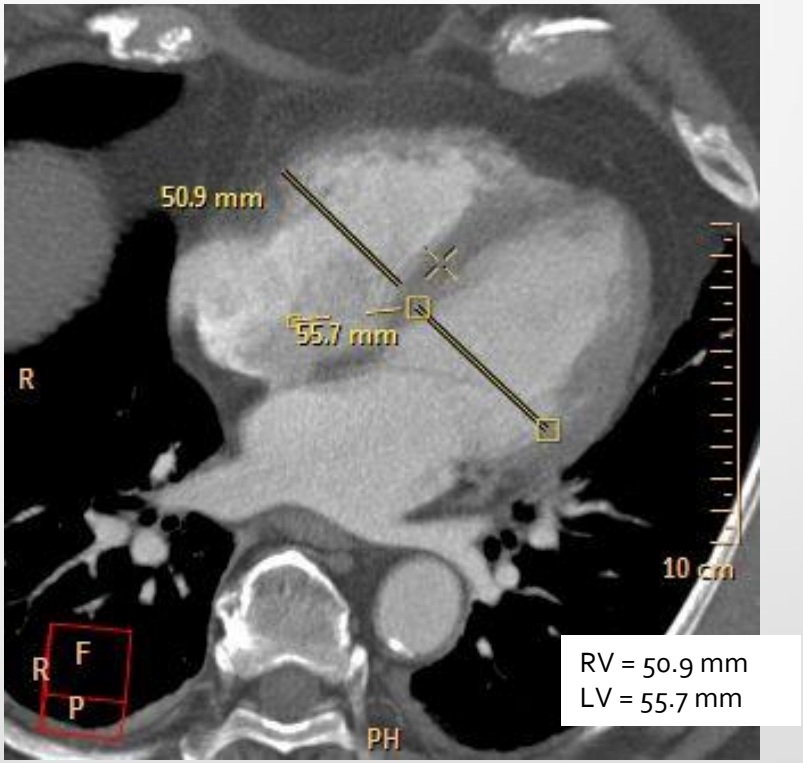
Post-treatment
RV/LV = 1.10

Single-center experience showed CTA evidence of RVD resolution

Case Study 2



Pre-treatment
RV/LV = 1.40



Post-treatment
RV/LV = 0.91

Largest US single-center EKOS® registry reported minimal risk of adverse events

- Single-center retrospective observational study
- 60 consecutive patients with either massive or submassive PE
- No intracranial hemorrhage, one intra-abdominal hemorrhage leading to hypovolemic shock and death, and one puncture site hematoma

Treatment details	
Bilateral PE Unilateral PE	N=53 (88%) N=7 (12%)
Massive PE Submassive PE	N=12 (20%) N=48 (80%)
Thrombus clearance: - Complete (>90%) - Near complete (50-90%) - Partial (<50%)	 N=33 (57%) N=24 (41%) N=1 (2%)
Total rtPA dose Total infusion time	35.1±1.1 mg 19.6±6.0 hrs.

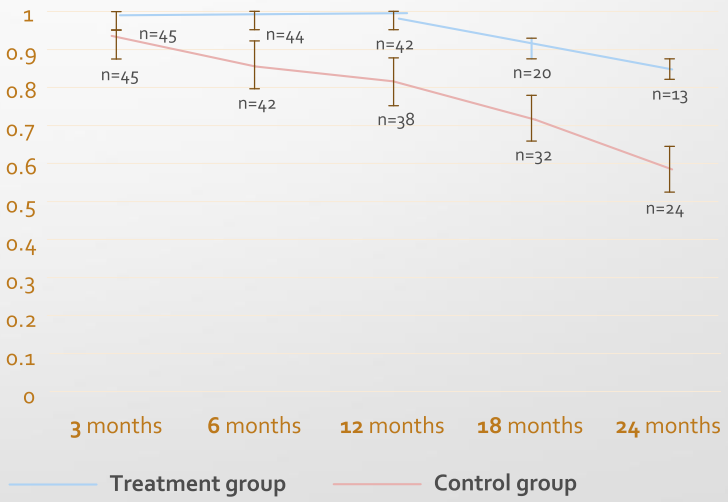
Outcomes	
Survival to discharge ICU stay (median) Hospital stay (median)	N=57 (95%) 1 day 9 days
90-day survival: - Overall - Submassive PE - Massive PE	 N=56 (93%) N=47 (98%) N=9 (75%)
Adverse events: - Major bleeding - Minor bleeding - Cardiopulmonary arrest - Acute renal injury - Recurrent PE	 N=1 (1.7%) N=1 (1.7%) N=1 (1.7%) N=1 (1.7%) N=0 (0%)

Kennedy RJ et al. Thrombus Resolution and Hemodynamic Recovery Using Ultrasound-accelerated Thrombolysis in Acute Pulmonary Embolism. J Vasc Interv Radiol 2013;24:841-848.

EKOS® PE treatment showed shorter length of stay, more favorable long-term mortality compared to anti-coagulation alone

- Single-center retrospective study to evaluate safety and efficacy of EKOS® therapy
- n=45
- Comparison to separate control group (n=45) of intermediate to high-risk PE patients treated with systemic heparin or anticoagulation alone
- Average LoS: EKOS® treated = **3.2 days** versus AC = **6.7 days**

- 24-month survival rates favored EKOS® treated patients



Nykamp M et al. Safety and efficacy of ultrasound-accelerated catheter-directed lytic therapy in acute pulmonary embolism with and without hemdynamic instability. J Vasc Surg: Venous and Lymphatic Disord 2015; 3(5) 251-257.

Single-center study showed significant reduction in PA pressure, RV/LV ratio using EKOS®

- Single-center study of 45 consecutive acute submassive PE patients (30 retrospective, 15 prospective)
- SEATTLE II protocol used and described
- Results
  - Decrease in average PA pressure from 49.8 mmHg to 31.1 mmHg (p<.0001)
  - Decrease in average RV:LV ratio from 1.59 to 0.93 (p<.0001)
  - 0 deaths, 0 re-admissions for PE in 30-day follow up
  - 4 minor bleeds at access sites, 2 major bleeds (1 pt. 3 days post-lysis; 1 pt. from a previous puncture site)

EKOS® treatment is a safe and effective method to treat submassive PE to reduce acute pulmonary hypertension and RVD

Bagla S et al. Ultrasound-Accelerated Catheter-Directed Thrombolysis for Acute Submassive Pulmonary Embolism. J Vasc Interv Radiol 2015; 26(7): 1001-1006.

Summary—1 OF 2

- RV dysfunction in PE patients predicts poor outcomes
  - Mortality
  - Adverse events
  - VTE recurrence
- Anticoagulant therapy does not actively resolve the existing thrombus
- IV thrombolysis is not used broadly
  - Clinical data show improvement in hemodynamics,
  - but it carries an elevated risk of severe bleeding, including ICH
- Use of EKOS® enhances thrombolytic therapy by an intra-catheter ultrasound technology, which
  - Loosens the fibrin structure
  - Increases drug penetration into the fibrin matrix
  - Ultimately reduces drug dose, treatment time and risk of complications

Bagla S et al. Ultrasound-Accelerated Catheter-Directed Thrombolysis for Acute Submassive Pulmonary Embolism. J Vasc Interv Radiol 2015; 26(7): 1001-1006.

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Summary—2 OF 2

- Clinical data establish the evidence for EKOS® in massive and submassive (intermediate risk) PE
  - ULTIMA—prospective, randomized, controlled, multicenter trial
  - SEATTLE II—prospective, 1-arm, multicenter trial
  - Single-center studies
- Consistent EKOS® results among the various published studies
  - Restoration of hemodynamics as evidenced by a reduced RV/LV ratio and decreased PA pressure
  - Resolution of pulmonary artery obstruction
  - Favorable outcomes with low dose thrombolysis (20-24 mg tPA based on the clinical trials)
  - No reports of intracranial hemorrhage in published clinical studies

Bagla S et al. Ultrasound-Accelerated Catheter-Directed Thrombolysis for Acute Submassive Pulmonary Embolism. J Vasc Interv Radiol 2015; 26(7): 1001-1006.

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Questions?