Ultrasound-Assisted Pharmacomechanical Thrombolysis: Emerging Data To Define Use In PE

Veith Symposium 2024

Assaf Graif MD

11/19/24

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Financial Disclosure

- Consultation fees from Boston Scientific, Penumbra

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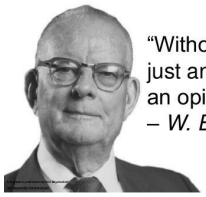
The Crux of it All



"Without data you're just another person with an opinion."
– *W. Edwards Deming*

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The Crux of it All

ULTIMA (2014)[1]	SEATTLE II (2015)[2]	OPTALYSE PE (2018)[3]	REAL-PE (2023)[4]	KNOCOUT PE (2024)[5]	HI-PEITHO[6]
• N=59 Acute intermediate-risk PE • Prospective RCT vs anticoagulation	• N=150 Acute submassive or massive PE • Prospective, multi-center, single-arm	• N=101 Acute intermediate risk PE • Prospective, randomized, multi-center, parallel-group	• N=2259 • Retrospective, comparative EHR study vs MT	• N=489 (prospective) Acute intermediate-risk PE • Multicenter registry	• N = up to 544 Acute intermediate-high risk PE • Prospective RCT vs AC • Standardized protocol
• Randomized • Superior reduction in RV/LV vs AC alone • 0% ICH / Major bleeding	• Significant RV/LV reduction • FDA Clearance in 2014 • 0% ICH • 0.7% GUSTO severe bleeding	• Sustained RV/LV reduction to 1 year • 3.6% ISTH major bleeding (overall)	• Lower 7-d major bleeding and ICH rate for EKOS vs large bore aspiration thrombectomy • Similar mortality, length of stay, 30-d readmission	• 1.6% ISTH major bleeding (72 h) • No intracerebral hemorrhagic events	• Enrolling now

1. Kucher N et al. Circulation 2014; 129: 479-486. 2 Piazza G, et al. JACC: Cardiovascular Interventions 2015; 8: 1382-92. 3. Tapson VF, et al. JACC Cardiovasc Interv. 2018;10(14):1427. doi:10.1016/j.jcin.2018.04.048. 4. Monteleone P, et al. JSCAI 2023; 5. Sterling KM, et al. Circ Cardiovasc Interv. 2024. doi: 10.1161/CIRCINTERVENTIONS.124.013948 6. Klok FA, et al. Am Heart J. 2022;254:43-52. doi:10.1016/j.ahj.2022.08.011

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Lysis Protocols

Trial	Regimen
PERFECT	Lysis at 0.5mg/hr/catheter for ~21-23 hours
ULTIMA	rTPA at 1 mg/h per USAT catheter. After 5 hours of treatment, the infusion rate of rtPA was reduced to 0.5 mg/h per catheter for 10 hours.
SEATTLE II	rTPA at 1 mg/h per catheter. 12 hours for 2 catheters and 24 hours for single catheter. Total of 24mg of rTPA.
OPTALYSE PE	Arm 1: 4 mg/catheter/2 h Arm 2: 4 mg/catheter/4 h Arm 3: 6 mg/catheter/6 h Arm 4: 12 mg/catheter/6 h (premature termination)
SUNSET sPE	USAT: 19 ± 7 mg over 14 ± 6 hours CDT: 18 ± 7 mg over 14 ± 5 hours
HI-PEITHO	2 mg bolus/catheter + 1 mg/hour/catheter for 7 hours (total of 9 or 18 mg)

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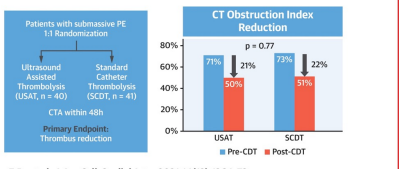
SUNSET sPE

CENTRAL ILLUSTRATION: Primary Endpoint of the Standard Versus Ultrasound-Assisted Catheter Thrombolysis for Submassive Pulmonary Embolism Trial



Avgerinos, E.D. et al. J Am Coll Cardiol Intv. 2021;14(12):1364-73.

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Where did it start?

Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism

Dissolution of Peripheral Arterial Thrombi by Ultrasound

ULTRASOUND ACCELERATES TRANSPORT OF RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR INTO CLOTS

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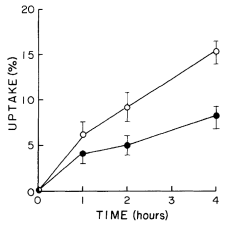
Not Just Mechanical



Francis, CW. et al. Ultrasound in Medicine and Biology 21.3 (1995): 419-424.

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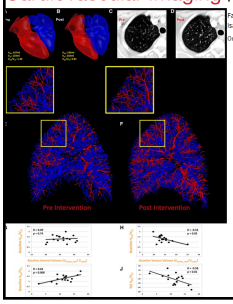
Circulation: Cardiovascular Imaging

Quantification and Significance of Pulmonary Vascular Volume in Predicting Response to Ultrasound-Facilitated, Catheter-Directed Fibrinolysis in Acute Pulmonary Embolism (SEATTLE-3D)



- The distal venous vascular volume and the degree of difference between distal arterial and venous volumes were related to baseline RV dilation, with the latter also predictive of the degree of RV decompression after therapy.
- These findings also suggest that in addition to proximal clot burden, processes involving the distal vasculature may play an important role in the impact of PE on the right heart.
- Aside from proximal clot reduction and vasodilatory effect of oxygen therapy, possible mechanisms for distal vascular reperfusion may include fibrinolysis of small vessel thromboembolic material

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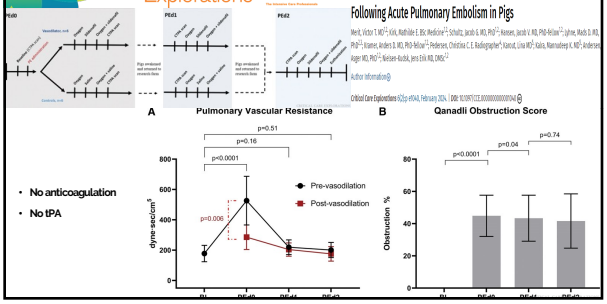
Critical Care Explorations

Changes in Pulmonary Vascular Resistance and Obstruction Score Following Acute Pulmonary Embolism in Pigs



- No anticoagulation
- No tPA

The Crux of All

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KNOCOUT PE Registry

Registry (Prospective Cohort N=489)

- Low total r-tPA dose (mean **18 mg**)
- Mean thrombolytic infusion duration **9.8 h** (in the US), 13.4 h (outside of US)
- RV/LV ratio reduced 24.6% post-procedure
- 1.6% Major bleeding within 72 hours
- No intracerebral hemorrhagic events
- 1% Mortality within 30 days
- Improvement in Quality of Life
  - PEmb reduction 41.1% by 3 months, 44.2% by 12 months
- **≤20mg r-tPA received by 69.5% of patients**
- **≤12mg r-tPA received by 31.0% of patients**

Stevens KM, et al. Circ Cardiovasc Interv. 2024. doi: 10.1161/CIRCINTERVENTIONS.123.013248

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Adverse Events Comparison

ISTH	GUSTO	TIMI	BARC
NON-CLINICALLY RELEVANT MINOR BLEEDING Minor bleed that does not meet the criteria for clinically relevant minor bleed	MILD Bleeding that does not meet criteria for either severe or moderate bleeding	MINIMAL Any clinically overt sign of hemorrhage (including imaging) that is associated with a 3 g/dl decrease in the Hb concentration or 9% decrease in the hematocrit	BARC 1 BARC 2
CLINICALLY RELEVANT MINOR BLEEDING A hospital admission for bleeding, or A physician guided medical or surgical treatment for bleeding, or A change in antithrombotic therapy	MODERATE Bleeding that requires blood transfusion but does not result in hemodynamic compromise	MINOR Observed blood loss: > 3 g/dl decrease in the Hb concentration or >10% decrease in the haematocrit	BARC 3A
MAJOR Fatal bleeding and/or Symptomatic bleeding in a critical area or organ and/or Bleeding causing a fall in Hb level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.	SEVERE Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention	MAJOR Intracranial hemorrhage or a > 5 g/dl decrease in the Hb concentration or a > 15% absolute decrease in the hematocrit	BARC 3B BARC 3C BARC 4 BARC 5

Blood Transfusion Recommendation

Clinical Review & Education

JAMA | Special Communication

Red Blood Cell Transfusion
2023 AABB International Guidelines

For hospitalized adult patients who are **hemodynamically stable**, the international panel recommends a restrictive transfusion strategy considering transfusion when the hemoglobin concentration is **less than 7 g/dL or 8 g/dL for those undergoing orthopedic surgery or those with preexisting cardiovascular disease**

Red Blood Cell Transfusion: 2023 AABB International Guidelines. JAMA. 2023 Nov 21Carson aet al.

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JSCAI
The official journal of the Society for Cardiovascular Angiography & Interventions

Original Research

Modern Treatment of Pulmonary Embolism (USCDT vs MT): Results From a Real-World, Big Data Analysis (REAL-PE)

Peter Monteleone, MD[a,*], Ryan Ahern, MD, MPH[b,c], Subhash Banerjee, MD[d], Kush R. Desai, MD[e], Daniella Kadian-Dodov, MD[f], Emily Webber, PhD[b], Sally Omidvar, MS, MSPH[b], Patrick Troy, MD[g], Sahil A. Parikh, MD[h]

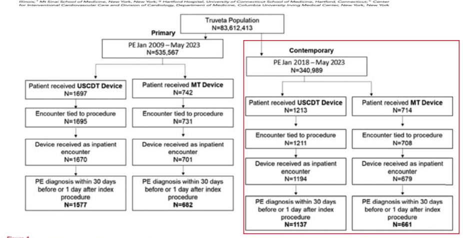

Figure 1.
Patient flowchart for inclusion in the primary and contemporary cohorts.

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REAL-PE

In contemporary cohort:

- Age ≥60 y — USCDT=57% and LBAT=64% (p=.004)
- Cancer — USCDT=15% and LBAT=21% (p=.002)
- Intracranial hemorrhage — USCDT=0.4% and LBAT=1.4% (p=.015)

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4 P. Monteleone et al. / Journal of the Society for Cardiovascular Angiography & Interventions 3 (2024) 101192

	Primary (2009-2023)			Contemporary (2018-2023)		
	p-value	USCDT	MT	p-value	USCDT	MT
Transfusion 7 days	<0.0001	30 (1.9%)	40 (5.9%)	<0.0001	22 (1.9%)	39 (5.9%)
Hgb decrease >2	<0.0001	842 (53.4%)	460 (67.4%)	<0.0001	580 (51.0%)	444 (67.2%)
Hgb decrease >5	<0.0001	233 (14.8%)	154 (22.6%)	<0.0001	154 (13.5%)	150 (22.7%)
Major Bleed Dx Code	0.137	180 (11.4%)	93 (13.6%)	0.0207	114 (10.0%)	90 (13.6%)
ISTH Major Bleed	0.0018	195 (12.4%)	118 (17.3%)	0.0002	125 (11.0%)	114 (17.2%)
BARC3B Major Bleed	0.019	186 (11.8%)	105 (15.4%)	0.0024	120 (10.6%)	102 (15.4%)

Central Illustration.
Assessed components of comparative bleeding incidence. χ^2 test *P* values provided. dx code, diagnostic code; Hgb, hemoglobin; transfusion 7 days, blood transfusion received within 7 days of the index procedure.

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Shameless Plug Warning!!!!

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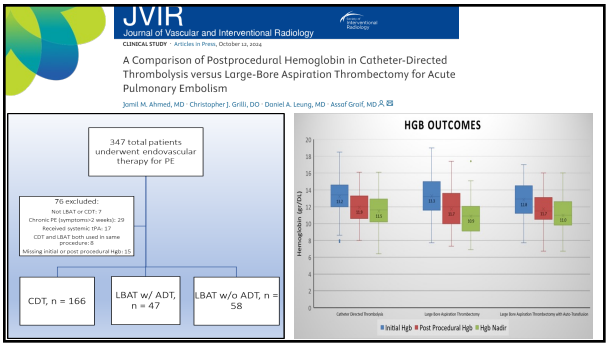

Table 4: Clinical Safety and Complications				
Variable	CDT (n = 166)	LBAT w/ ATD (n = 47)	LBAT w/o ATD (n = 58)	P
Received PRBC Transfusion after Procedure	4/166 (2.4)	4/47 (8.5)	3/58 (5.2)	0.2
Initial HGB (g/dl)				
Received PRBC	9.9±2.4	9.9±1.6	9.8±1.3	1
Did not receive HGB	13.3±1.9	13.1±2.1	13.5±2.3	0.7
GUSTO:				
Mild	6/166 (3.6)	7/47 (14.9)	7/58 (12.1)	0.01
Moderate	3/166 (1.8)	4/47 (8.5)	3/58 (5.2)	0.08
Major	2/166 (1.2)	0/47	0/58	0.5

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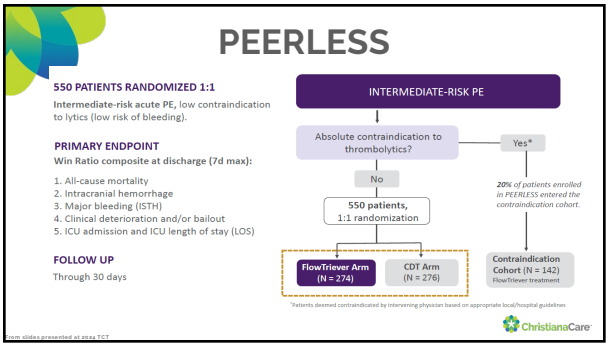

	CDT N = 276	FlowTriever N = 274	*P* value
Major bleeding (ISTH)	19 (6.9)	19 (6.9)	1.00
Adjudicated reasons for major bleeding			
• Fatal bleeding*	1 (0.4)	0 (0)	
• Symptomatic bleeding in a critical area or organ	2 (0.7)	2 (0.7)	
Intracranial hemorrhage†	1	2	
Hemarthrosis	1	0	
• Hgb drop ≥ 2 g/dL (1.24 mmol/L) and/or transfusion ≥ 2 units	16 (5.8)	17 (6.2)	
Access site source	10	8	
Transfusions administered with ≥ 2 units	8 (2.9)	1 (0.4)	
# units transfused	3.3 ± 1.8	2.0	
CRNM bleeding events‡	9 (3.3)	7 (2.6)	0.80
Minor bleeding events‡	1 (0.4)	6 (2.2)	0.07