Innovations in Treatment of Acute Pulmonary Embolism

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9/12/2021| Wisconsin Chapter ACC Annual Symposium

AdvocateAuroraHealth

Disclosures

- None

Introduction

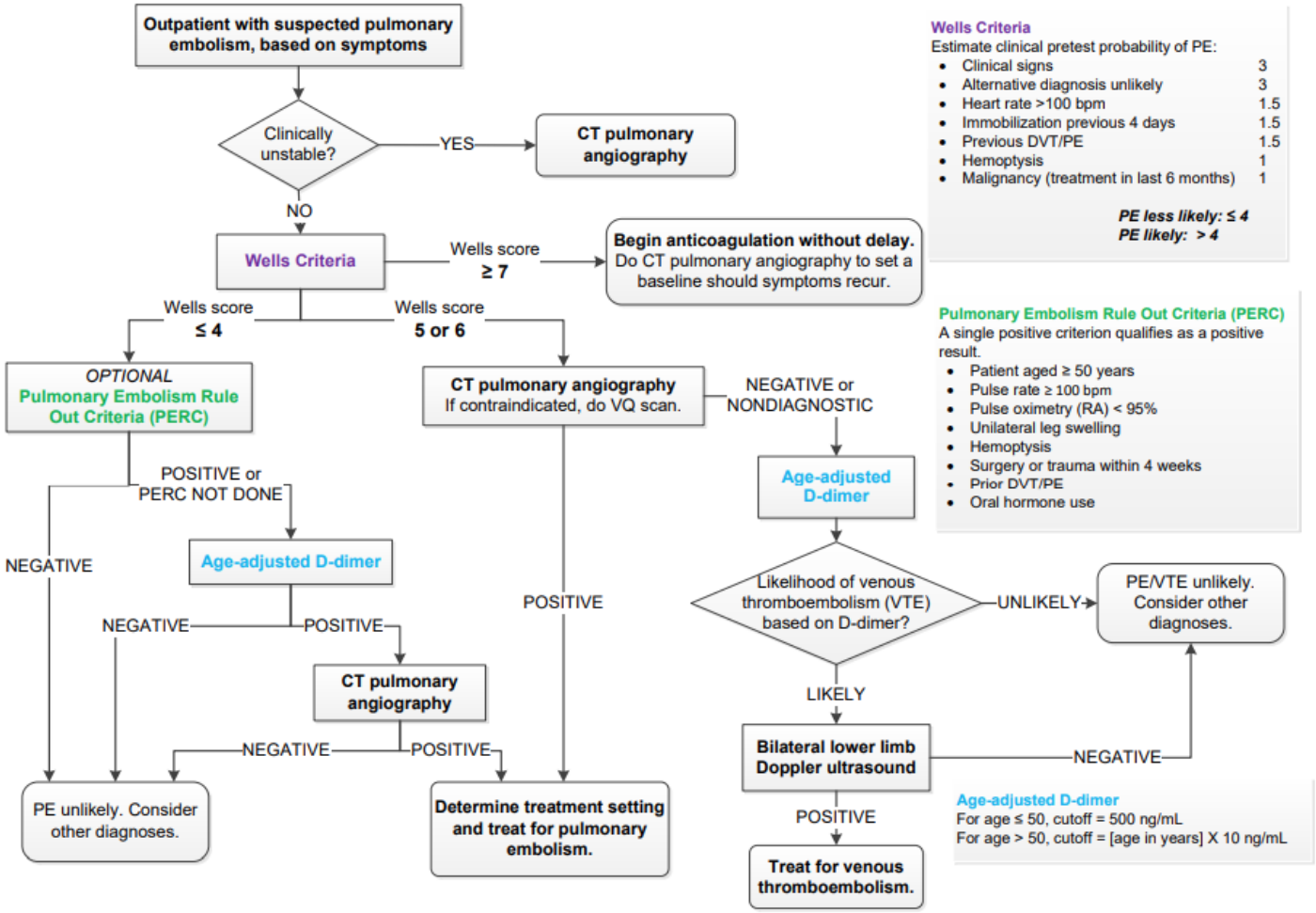
- **In US, PE is 3rd most common cause of cardiovascular death 60,000 to 100,000 deaths/yr [1].**
- **When there is clinical suspicion, PE should be confirmed with prompt imaging.**
- **Treatment has evolved with new catheter-based options**

Diagnosis

PE Evaluation and Diagnosis:

Non-pregnant Adults Without Cancer

This algorithm is based on ICSI 2013.



Risk stratification

- Age, comorbidities
- Vital signs: BP, HR, O_2 sats, resp rate
- Labs: Lactate, Troponin, NTproBNP
- Imaging for RV dysfunction: ECG, CTPA, echo
- Risk scores

PESI and sPESI

Parameter	Original version [226]	Simplified version [229]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic BP <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths per min	+20 points	–
Temperature <36°C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
Risk strata[a]	**Class I: ≤65 points** very low 30 day mortality risk (0–1.6%) **Class II: 66–85 points** low mortality risk (1.7–3.5%)	**0 points** 30 day mortality risk 1.0% (95% CI 0.0–2.1%)
	Class III: 86–105 points moderate mortality risk (3.2–7.1%) **Class IV: 106–125 points** high mortality risk (4.0–11.4%) **Class V: >125 points** very high mortality risk (10.0–24.5%)	**≥1 point(s)** 30 day mortality risk 10.9% (95% CI 8.5–13.2%)

Heavily weighted by pre-existing conditions

BOVA score

	0 points	1 point	2 points
Systolic BP	>100 mm Hg	--	90-100 mmHg
Elevated cardiac troponin*	No	--	Yes
RV dysfunction**	No	--	Yes
Heart rate, beats/min	<110	≥110	--

*Based on standard manufacturer assays and cutoff values.
**On TTE: Right to left ventricular (RV/LV) ratio >0.9, systolic pulmonary artery pressure (sPAP) >30, RV end diastolic diameter >30mm, RV dilation, or free wall hypokinesis. On CT: RV/LV ratio >1 based on short axis diameter measurements.

Bova Score	Stage	PE-related complications*	PE-related mortality
0–2	I (Low risk)	4.4%	3.1%
3–4	II (Intermediate risk)	18%	6.8%
>4	III (High risk)	42%	10%

*Defined as a composite including death from PE, hemodynamic collapse, or recurrent nonfatal PE. Hemodynamic collapse = systolic BP <90 mm Hg for at least 15 min or need for catecholamines, thrombolysis, endotracheal intubation, or CPR.

BOVA performs better than PESI score in predicting mortality and identifying patients that are likely to benefit from more aggressive treatment of PE

Indicators of risk	Mortality risk			
	Low risk = Nonmassive	Intermediate risk = Submassive		High risk = Massive
		Intermediate-low	Intermediate-high	
Hemodynamic Instability	–	–	–	+
PESI class III–V or sPESI ≥I or Bova≥3	–	+	+	+
RV dysfunction on TTE or CTPA	–	One or none	+	+
Elevated cardiac troponin	–		+	+

PERT

- **PERT approach to high- and intermediate-risk cases.**
- **Multidisciplinary team includes cardiology, critical care, cardiac surgery, hematology, vascular medicine, vascular surgery, radiology specialists**
- **Discuss complex cases and expedite treatment decisions**

Anticoagulation

- **Anticoagulation should be initiated as soon as PE is suspected.**
- **Low risk → DOAC preferred**
- **Submassive/Massive → start with parenteral, then transition to oral when stable**

Oxygenation and hemodynamic support

- Keep O2 sat >90%
- If refractory hypoxemia consider
  - R to L shunt
  - RV failure
- Promptly identify & treat acute RV failure

Treatment of right ventricular failure in acute PE

Strategy	Properties and use	Caveats
Volume optimization		
Cautious volume loading, saline, or Ringer's lactate, ⩽500 mL over 15–30 min	Consider in patients with normal–low central venous pressure (due, for example, to concomitant hypovolaemia)	Volume loading can over-distend the RV, worsen ventricular interdependence, and reduce CO [239]
Vasopressors and inotropes		
Norepinephrine, 0.2–1.0 μg/kg/min[a] [240]	Increases RV inotropy and systemic BP, promotes positive ventricular interactions, and restores coronary perfusion gradient	Excessive vasoconstriction may worsen tissue perfusion
Dobutamine, 2–20 μg/kg/min [241]	Increases RV inotropy, lowers filling pressures	May aggravate arterial hypotension if used alone, without a vasopressor; may trigger or aggravate arrhythmias
Mechanical circulatory support		
Veno–arterial ECMO/extracorporeal life support [251, 252, 258]	Rapid short-term support combined with oxygenator	Complications with use over longer periods (>5–10 days), including bleeding and infections; no clinical benefit unless combined with surgical embolectomy; requires an experienced team

Mechanical Circulatory Support

VA ECMO for shock

- **For hemodynamic stabilization to allow for thrombolysis, catheter therapies or surgical embolectomy**
- **Complete hemodynamic support, 5-6 L of output in conjunction with oxygenation and ventilation support.**
- **Bypasses the pulmonary circulation, reduces RV pre-load and distention.**

Reperfusion Treatment

- Systemic thrombolysis
- Catheter-based treatments
- Surgical embolectomy

Systemic thrombolysis

- Best results within 48H of symptom onset, but still effective up to 14 days
- Know contraindications for thrombolysis
- Standard treatment for massive PE
- rtPA 100mg over 2H
- Also shown efficacy in submassive PE
- 6-9% risk of major bleeding, 2-3% risk intracranial bleed

European Heart Journal (2015) **36**, 605–614
doi:10.1093/eurheartj/ehu218

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]

	All studies			Studies including[a] High-risk PE	Intermediate-risk PE	Low and intermediate-risk PE	Group difference
	OR (95% CI)	*P*-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P*-value
Mortality	0.59 (0.36 to 0.96)	0.034	0	0.48 (0.20 to 1.15)	0.42 (0.17 to 1.03)	0.96 (0.41 to 2.24)	0.36
PE mortality	0.29 (0.14 to 0.60)	<0.001	0	0.15 (0.03 to 0.78)	0.17 (0.05 to 0.67)	0.63 (0.20 to 1.97)	0.23
Death or treatment escalation	0.34 (0.22 to 0.52)	<0.001	0	0.18 (0.04 to 0.79)	0.37 (0.20 to 0.69)	0.35 (0.18 to 0.66)	0.67
PE recurrence	0.50 (0.27 to 0.94)	0.031	0	0.97 (0.31 to 2.98)	0.25 (0.06 to 1.03)	0.46 (0.17 to 1.21)	0.33

[a]Not exclusively.

	All studies			Alteplase	Tenecteplase	Other thrombolytics	Group difference
	OR (95% CI)	*P*-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P*-value
Major bleeding	2.91 (1.95 to 4.36)	<0.001	25	1.07 (0.43 to 2.62)	5.02 (2.72 to 9.26)	2.16 (1.03 to 4.54)	0.02
Fatal/intracranial haemorrhage	3.18 (1.25 to 8.11)	0.008	0	1.09 (0.27 to 4.40)	7.32 (1.64 to 32.63)	NA	0.07

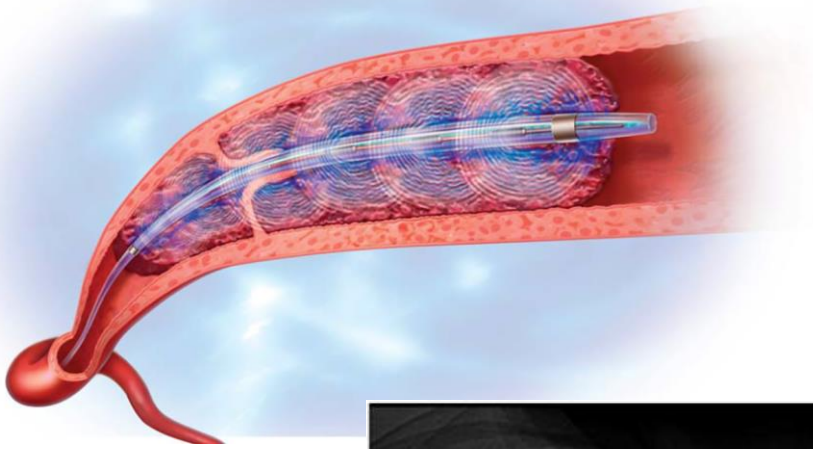
Catheter-directed treatments for acute pulmonary embolism

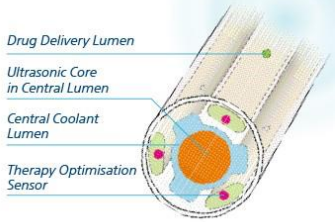
Catheter interventions with thrombolysis		Catheter interventions without thrombolysis	
Technique	Device examples	Technique	Device examples
Catheter-directed thrombolysis	UniFuse® (AngioDynamics, Latham, NY) Cragg-McNamara® (ev3 Endovascular, Plymouth, MN) 4—5 F infusion catheters, with 10—20 cm infusion length	Aspiration thrombectomy	Aspirex® 8 F or 10 F catheter (Straub Medical, Switzerland): rotational thrombectomy[a]
			Angiovac suction cannula® (AngioDynamics, Latham, NY): veno-venous bypass system, with 26 F access for inflow and 16—20 F access for outflow
			Indigo® Mechanical Thrombectomy System (Penumbra, Alameda, CA): 8 F vacuum-assisted aspiration with mechanical clot engagement
			Sheath with detachable haemostatic valve 8—9 F (Argon Medical Devices, Athens, TX), multi-purpose guide catheter (8—9 F), aspiration syringe (60 mL)
Ultrasound-assisted catheter-directed thrombolysis	EkoSonic 5.2® F 12 cm treatment zone device (EKOS, Bothell, WA)	Mechanical thrombectomy	Flowtriever® (Inari Medical, Irvine, CA): 20 F device with three self-expanding nitinol discs entrapping the thrombus with simultaneous aspiration
Rheolytic thrombectomy plus catheter-directed thrombolysis	AngioJet 6 F PE® thrombectomy with Power Pulse™ thrombolysis (Boston Scientific, Minneapolis, MN)[a]	Rheolytic thrombectomy	AngioJet 6 F PE® catheter (Boston Scientific, Minneapolis, MN)[a]
Combined techniques	For example, pigtail fragmentation (5 F) plus AngioJet 6 F PE® thrombectomy with Power Pulse™ thrombolysis	Thrombus fragmentation	Pigtail catheter (5—6 F) or peripheral balloon catheters (6—7 F, balloon diameter 5—10 mm)
		Combined techniques	Pigtail fragmentation (5 F) plus thrombectomy with Aspirex® 8/10 F

US-assisted catheter-directed thrombolysis

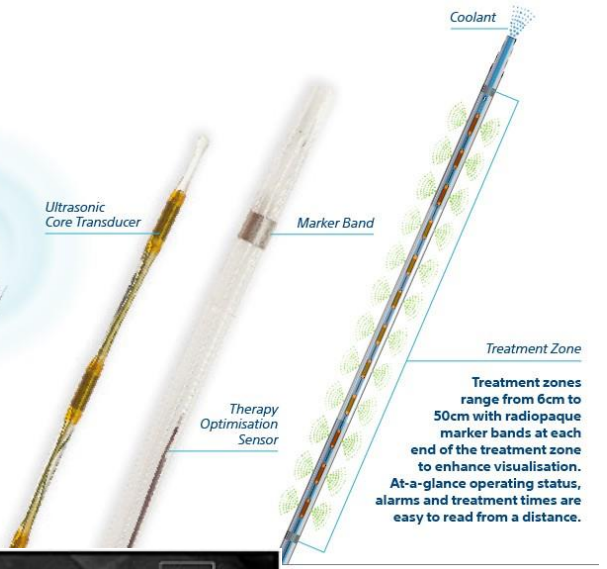
- **EKOS system uses US waves to enhance thrombolysis using low dose tPA**
- **In RCT 59 pts showed reduction in RV/LV ratio within 24 hrs with no increased risk of bleeding. Not powered for hard endpoints**
- **In ULTIMA, SEATTLE II & OPTALYSE-PE trials major bleeding 1-2%**

EkoSonic® Endovascular System

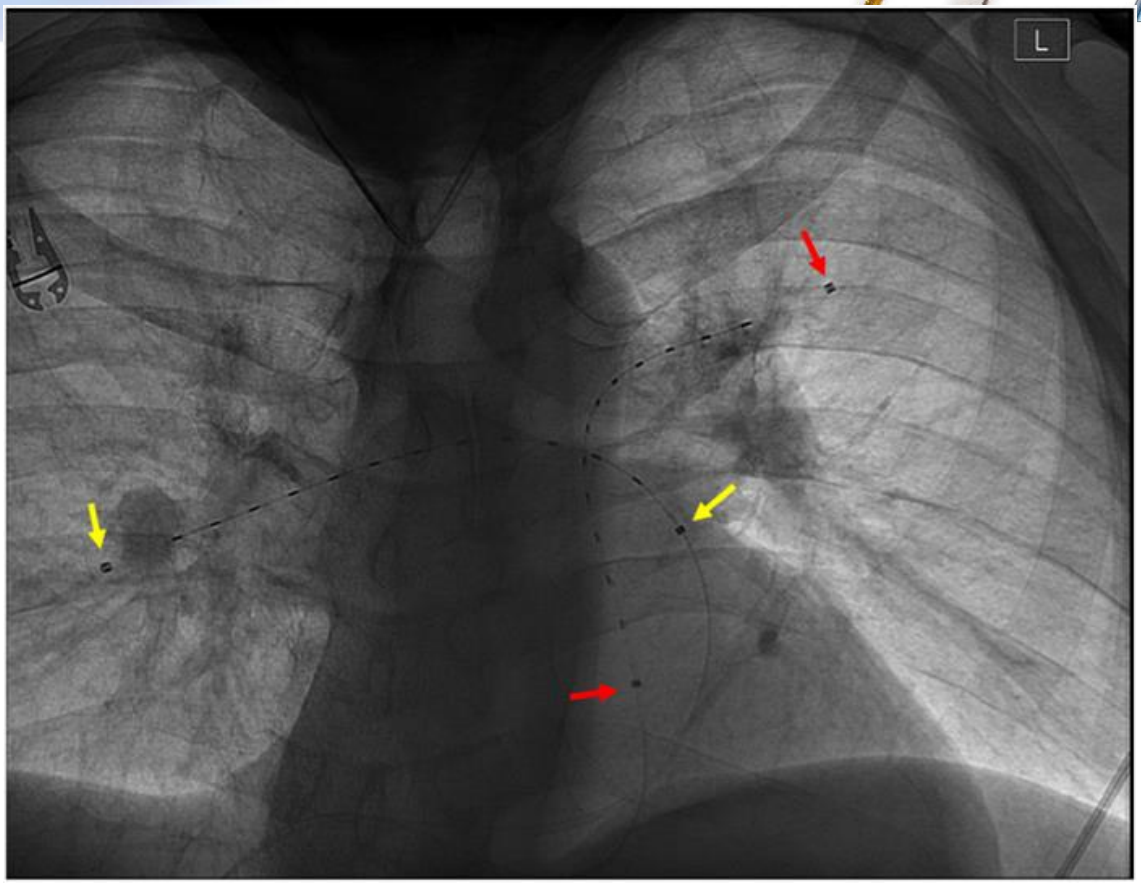




EKOS Infusion Catheter
Cross Section



Treatment zones range from 6cm to 50cm with radiopaque marker bands at each end of the treatment zone to enhance visualisation. At-a-glance operating status, alarms and treatment times are easy to read from a distance.

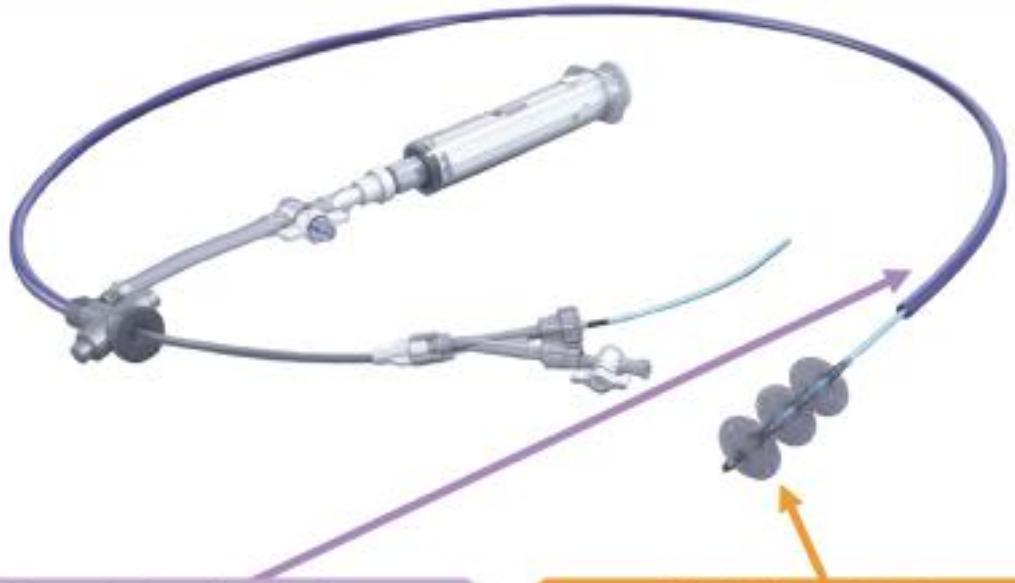


Catheter thrombectomy

Most used systems are:

- **Inari Flowtriever® (16,20,24 Fr)**
- **Penumbra Indigo® (4,6,8,12 Fr)**

FlowTriever System



Triever Aspiration Catheter

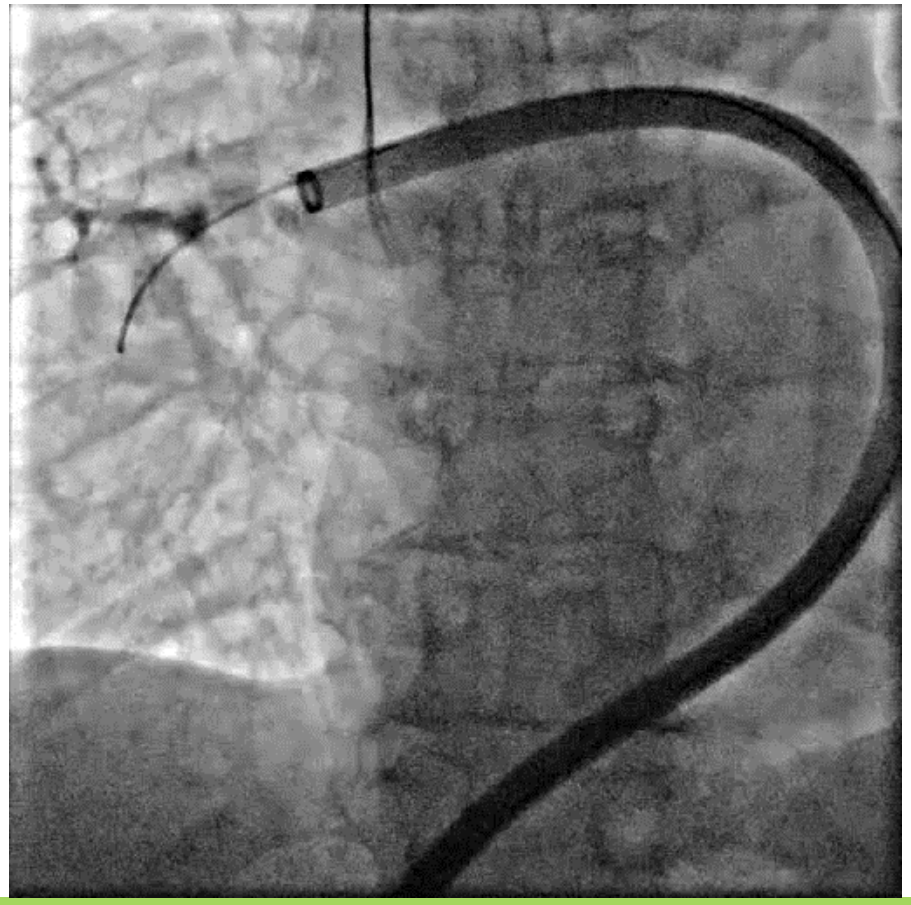
Available in 3 sizes
T16: 16 French lumen
T20: 20 French lumen
T24: 24 French lumen

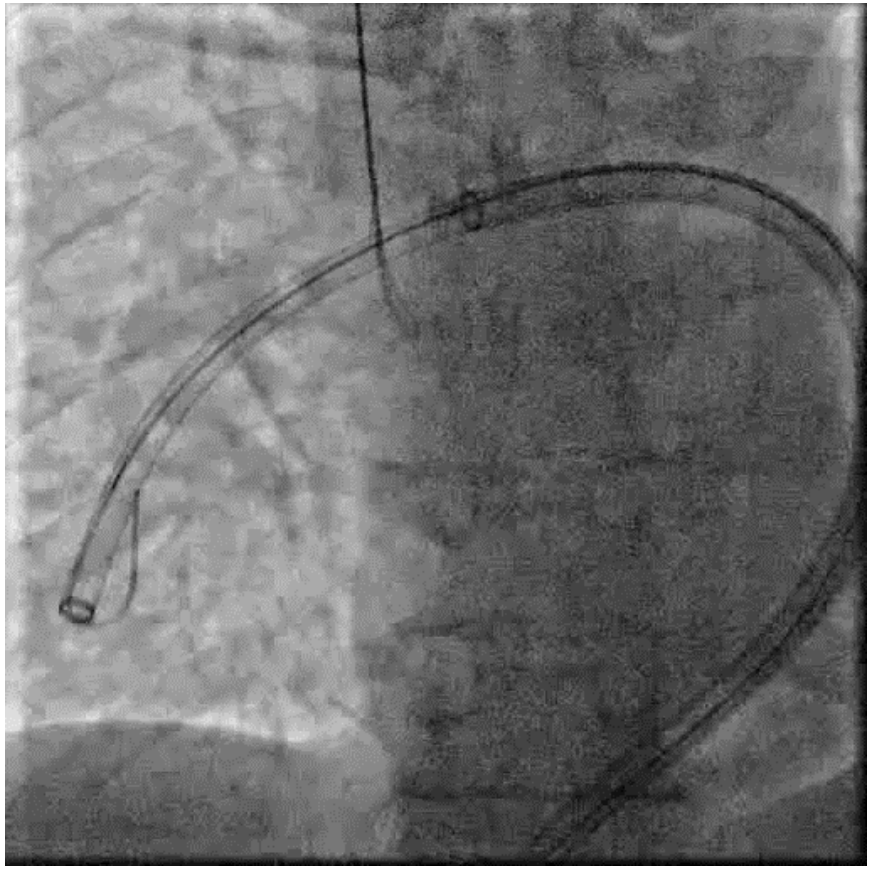
FlowTriever Catheter

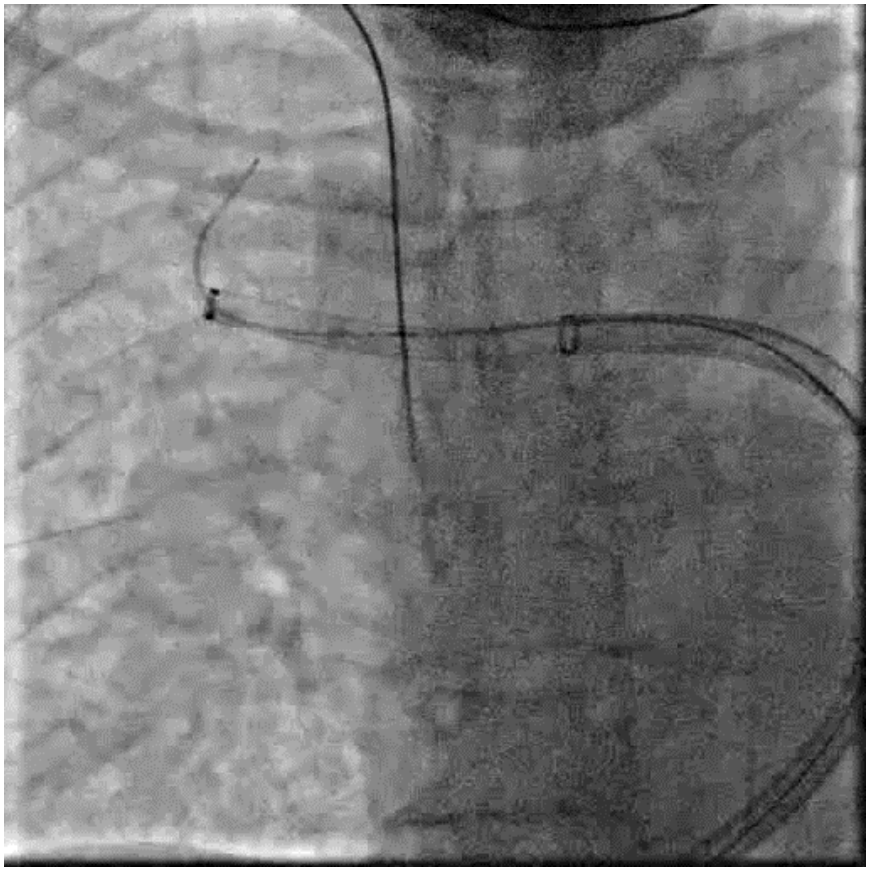
Available in 4 sizes
XL (19-25MM), L (15-18MM),
M (11-14MM), S (6-10MM)

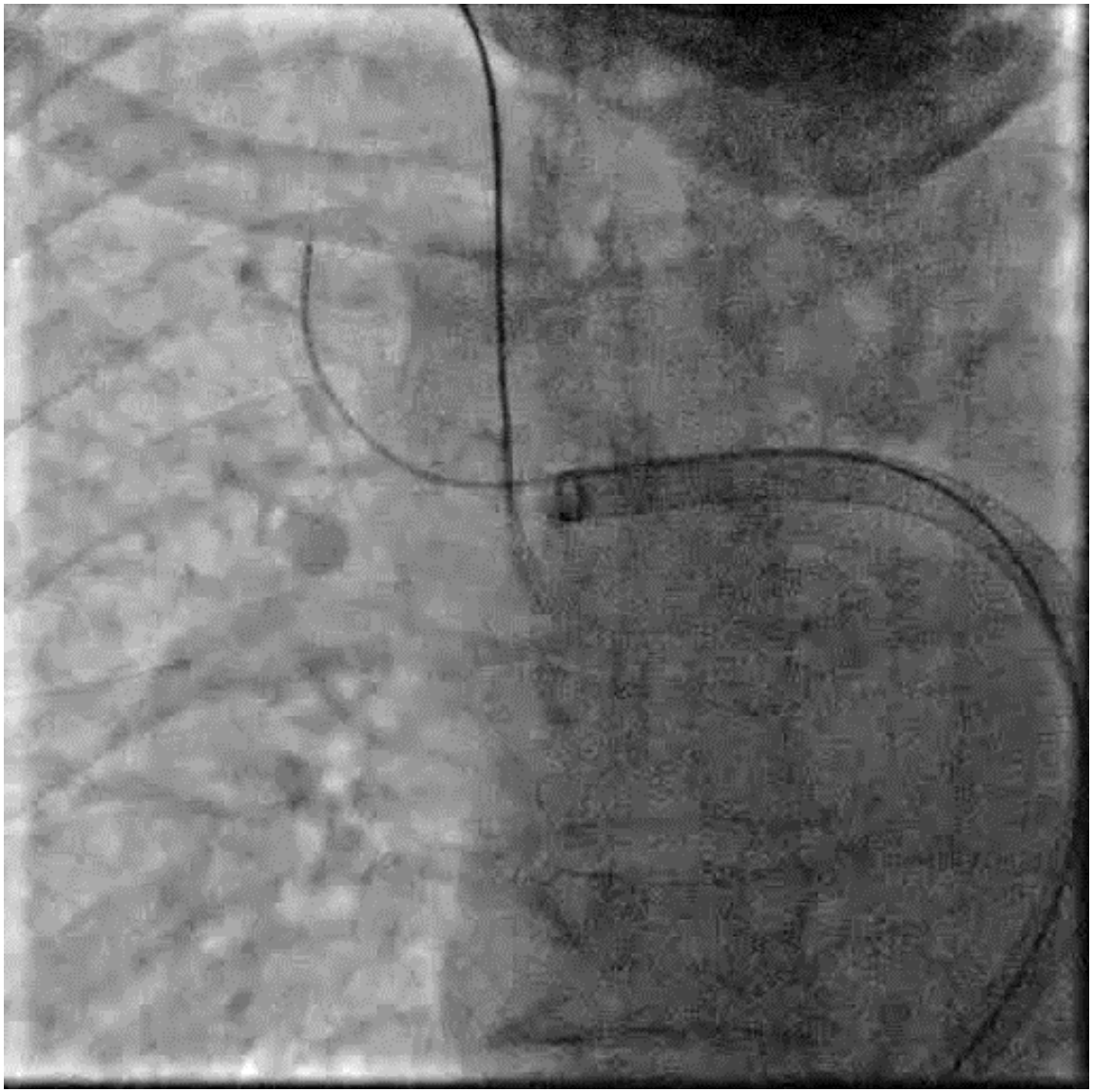
Case

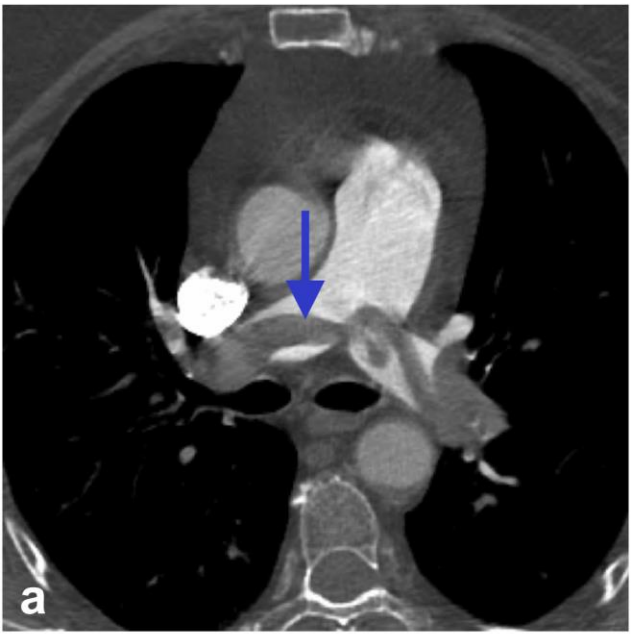
35yo F with h/o gastric bypass 7 days ago presenting with acute chest pain, diaphoresis, SOB 1 day. BP 94/60, HR 120, sPO2 90%. Bilat PE on CTPA, Troponin 2.1, Echo McConnell's sign







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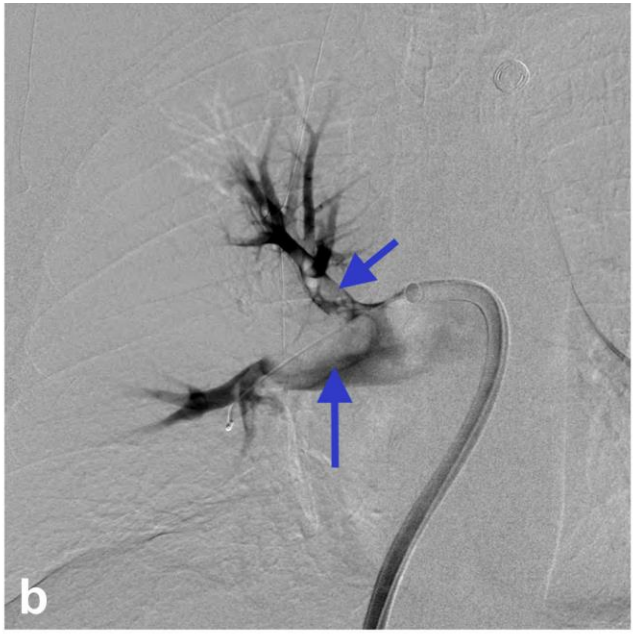
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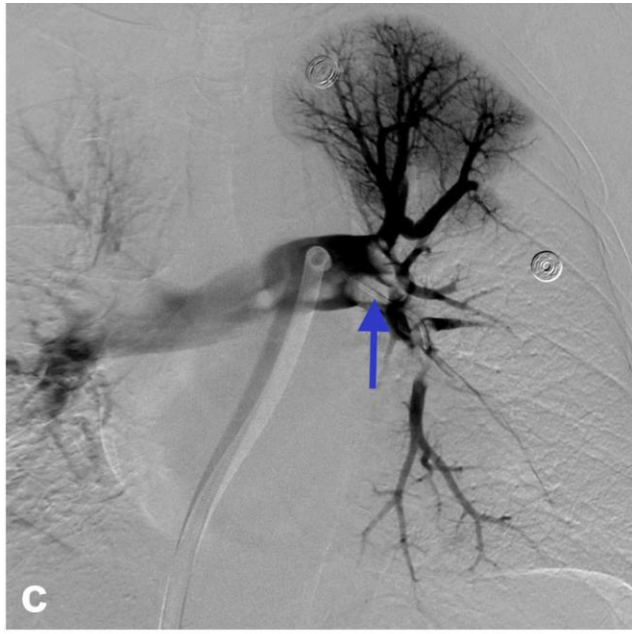
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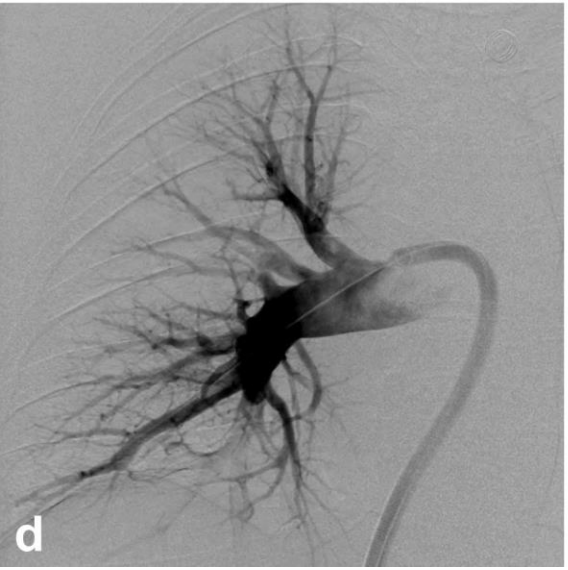
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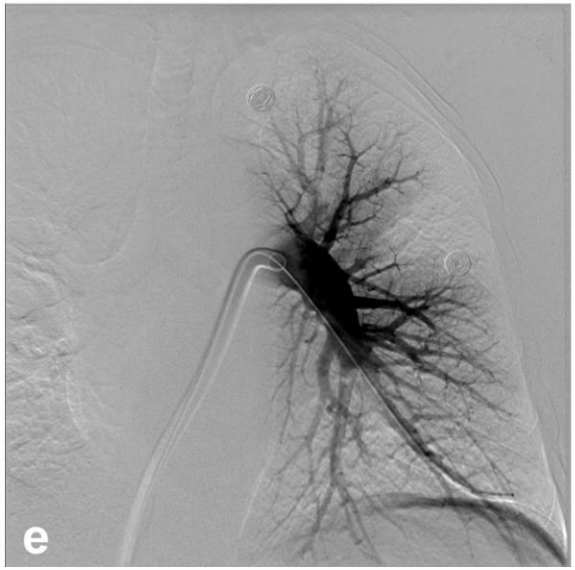
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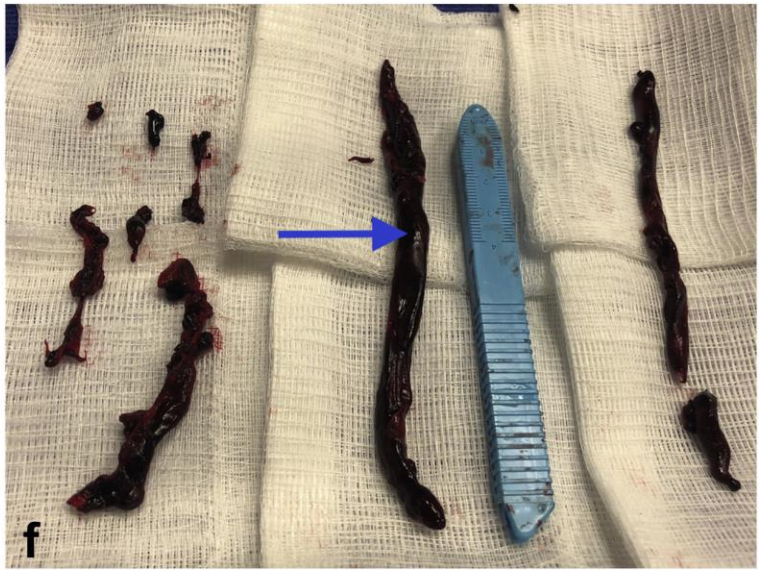
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Surgical embolectomy

- For high risk or intermediate-high risk PE.
- Combined with cardiopulmonary bypass without aortic cross-clamping or VA-ECMO
- Incision of both PA and removal/suction of clots
- NY state registry high risk PE surgical embolectomy vs systemic thrombolysis
  - Similar 30-day mortality 13% vs 15%
  - Recurrent PE and stroke higher in thrombolytic rx group

Recommendations for acute-phase treatment of high-risk pulmonary embolism[a]

Recommendations	Class[b]	Level[c]
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.	I	C
Systemic thrombolytic therapy is recommended for high-risk PE [282].	I	B
Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed[d] [281].	I	C
Percutaneous catheter-directed treatment should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed[d].	IIa	C
Norepinephrine and/or dobutamine should be considered in patients with high-risk PE.	IIa	C
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest[d] [252].	IIb	C

Recommendations for acute-phase treatment of intermediate- or low-risk pulmonary embolism

Reperfusion treatment

	Class[a]	Level[b]
Rescue thrombolytic therapy is recommended for patients with haemodynamic deterioration on anticoagulation treatment [282].	I	B
As an alternative to rescue thrombolytic therapy, surgical embolectomy[e] or percutaneous catheter-directed treatment[e] should be considered for patients with haemodynamic deterioration on anticoagulation treatment.	IIa	C
Routine use of primary systemic thrombolysis is not recommended in patients with intermediate- or low-risk PE[c,f] [179].	III	B

Recommendations for inferior vena cava filters

Recommendations	Class[a]	Level[b]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in cases of PE recurrence despite therapeutic anticoagulation.	IIa	C
Routine use of IVC filters is not recommended [302–304]	III	A

Summary: treatment strategy

<table>
<tr><th></th><th>Low risk</th><th colspan="2">Submassive</th><th>Massive</th></tr>
<tr><td>Presentation</td><td rowspan="2">• Normotensive
• Low risk per PESI class I & II or sPESI=0
• Bova 0-2 pts
• Normal biomarkers</td><td>• Low risk:
• PESI class III-IV or sPESI ≥1
• Bova 3-4</td><td>• High risk:
• PESI class V
• Bova >4</td><td rowspan="2">• Hypotension (systolic blood pressure <90 mmHg for ≥15 min, drop in systolic blood pressure of ≥40 mmHg or vasopressor)
• Thrombus in transit
• Syncope
• Cardiac arrest</td></tr>
<tr><td colspan="2">• Echo or CT evidence of RV strain
• Positive troponin
• Elevated BNP or NT-proBNP</td></tr>
<tr><td>Treatment</td><td>• Anticoagulation : Direct oral anticoagulants are preferred
• Candidates for early discharge</td><td colspan="3">• Anticoagulation: Consider unfractionated heparin over others if any of the therapies below are possible
• Catheter-directed therapy
• Surgical embolectomy
• Systemic thrombolytic
• High-risk PE and cardiogenic shock: Mechanical support to allow stability for thrombolysis, catheter-directed therapy, or surgical embolectomy</td></tr>
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Our Approach/algorithm

- **All PE: anticoagulation**
- **Low risk PE anticoag only, may use NOAC upfront**
- **For submassive or massive start with parenteral anticoag, get PERT team and transition to oral when more stable**
- **Submassive (Intermediate) low risk PE**
  - Anticoagulation only
- **Submassive (Intermediate) high risk PE**
  - Anticoagulation
  - Consider US-assisted catheter directed thrombolysis (if no CI)
  - Consider catheter embolectomy
- **Massive or High risk PE**
  - Systemic thrombolysis if no contraindication
  - If CI to thrombolysis: Surgical embolectomy vs catheter embolectomy
- **Escalate care if treatment fails**

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Thank you!

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PEITHO Trial
N Engl J Med 2014;370:1402-11.

- Double blind RCT of tenecteplase + heparin vs placebo + heparin.
- Hemodyn stable Acute PE within 14 days with RV dysfunction & elevated troponin
- 1006 patients randomized 1:1
- Death or hemodynamic decompensation at 7 days
  - tenecteplase group (2.6%) vs placebo group 5.6%
  - odds ratio, 0.44; (95% CI 0.23 to 0.87; P = 0.02).

In PEITHO the good, the bad and the ugly were equal

Table 3. Efficacy Outcomes.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12

Table 4. Safety Outcomes in the Intention-to-Treat Population.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003
Ischemic stroke	2 (0.4)	0		
Hemorrhagic stroke‡	10 (2.0)	1 (0.2)		
Serious adverse events between randomization and day 30	55 (10.9)	59 (11.8)	0.91 (0.62–1.34)	0.63

Contraindications for thrombolysis

Absolute contraindications to thrombolysis

- **Any prior ICH**
- **Known structural cerebrovascular lesion (e.g., arteriovenous malformation)**
- **Known malignant intracranial neoplasm (primary or metastatic)**
- **Ischemic stroke within 3 months except acute ischemic stroke within 3 hours**
- **Suspected aortic dissection**
- **Active bleeding or bleeding diathesis (except menses)**

Relative contraindications to thrombolysis

- **History of chronic, severe, poorly controlled hypertension**
- **Severe uncontrolled hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)**
- **Traumatic or prolonged (>10 min) cardiopulmonary resuscitation or major surgery (within <3 weeks)**
- **Recent (within 2 to 4 weeks) internal bleeding**
- **Non compressible vascular punctures**
- **For streptokinase/anistreplase: prior exposure (>5 days) or prior allergic reaction to these agents**
- **Pregnancy**
- **Active peptic ulcer**
- **History of prior ischemic stroke (>3 months), dementia, or known intracranial pathology not covered in absolute contraindications**
- **Current use of anticoagulants: the higher the INR, the higher the risk of bleeding; NOACs!!**