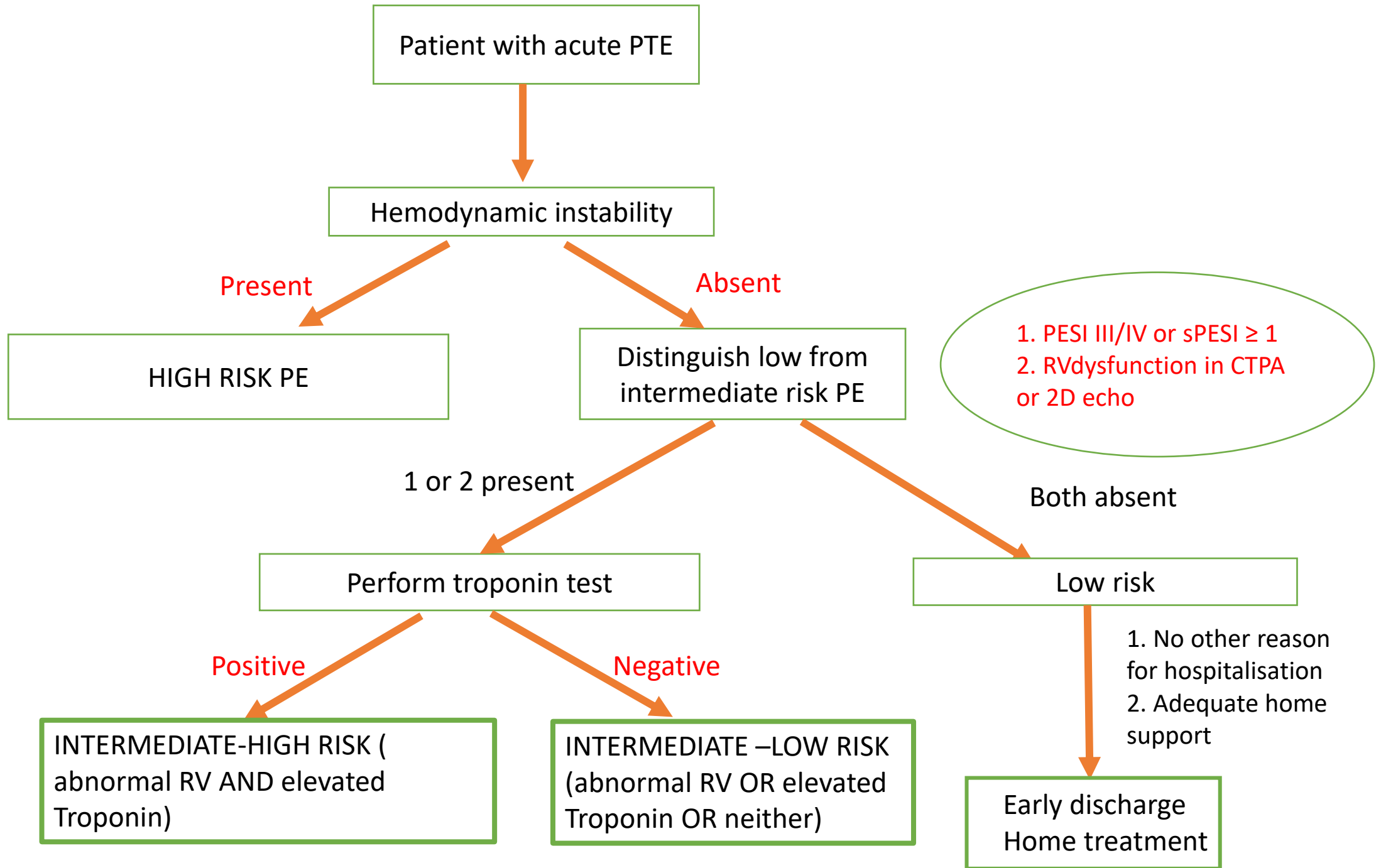


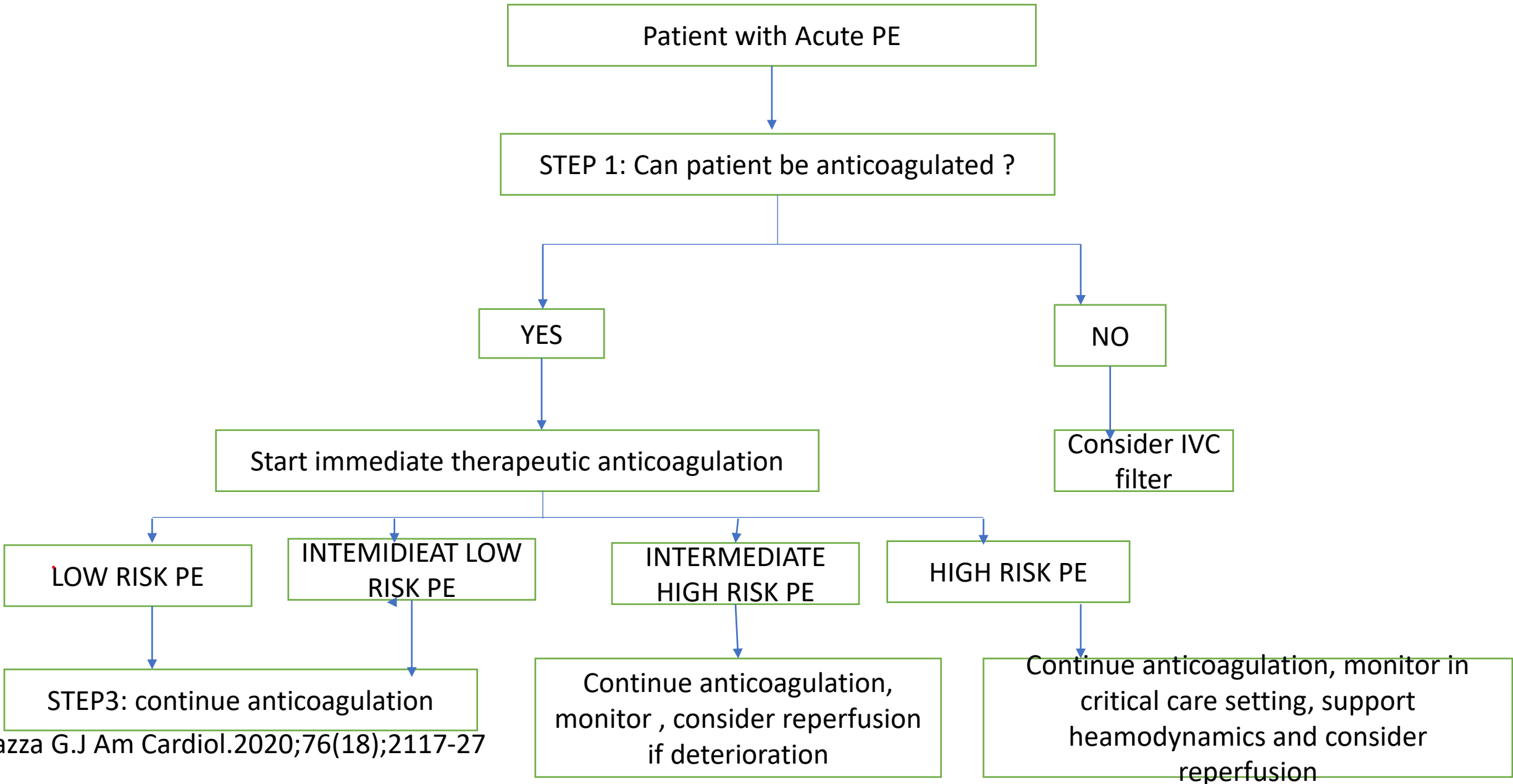
**MANAGEMENT OF INTERMEDIATE
RISK PULMONARY EMBOLISM**

OUTLINE

- Severity classification of pulmonary embolism
- Systemic thrombolysis
- Catheter based therapy
- Oral anticoagulants
- Duration of anticoagulation
- IVC filter
- Subsegmental and incidental pulmonary embolism

- American Heart Association (AHA) and the European Society of Cardiology (ESC)
- **Massive (AHA) or high risk (ESC):** Hypotension (SBP<90 mm Hg, a drop of >40 mm Hg for at least 15 minutes or need for vasopressor support)
 - ≈5% of hospitalized patients with PE
 - Mortality of ≈30% within 1 month.
- **Submassive (AHA) or intermediate risk (ESC):** RV strain without hypotension (RV/left ventricular [LV] ratio >0.9) or increase in cardiac biomarkers
 - 30-55% of hospitalized patients
 - Mortality 2-3% over period of 7 to 30 days
- **Low risk (ESC and AHA)-**Do not meet criteria for submassive (AHA) or intermediate-risk (ESC) PE.
 - 40% to 60% of hospitalized patients
 - Mortality of ≈1% within 1 month





Management of Intermediate-Risk PE

- Anticoagulation
- Systemic Fibrinolysis
- Catheter based intervention
- Surgical pulmonary embolectomy
- Mechanical circulatory supports

- PIETHO Trail
- RTC
- 1006 patients
- Intermediate-Risk PE
- Tenectapase + heparin vs placebo + heparin
- Exclusion- onset of symptoms more than 15days and hemodynamic decompensation

- Primary outcome: Death or haemodynamic decompensation within 7 days
- Secondary outcomes: Mortality at 7 days and 30 days

- Death or haemodynamic decompensation within 7 days – Significantly lower in thrombolysis group.2.6% vs. 5.6% in placebo group
- Major extracranial bleeding – Significantly higher in thrombolysis group 6.3% vs. 1.2%
- Haemorrhagic stroke – Significantly higher in thrombolysis group 2% vs 0.2%
- >75 years had a non-significant increase in the rate of major extra-cranial bleeding compared with patients who were ≤ 75 years 11.1% vs. 4.1%
- Secondary outcomes: Mortality at 7 days and 30 days – No significant difference

Meyer, Guy et al. “Fibrinolysis for patients with intermediate-risk pulmonary embolism.” *The New England journal of medicine* vol. 370,15 (2014): 1402-11



Research

Original Investigation

Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage

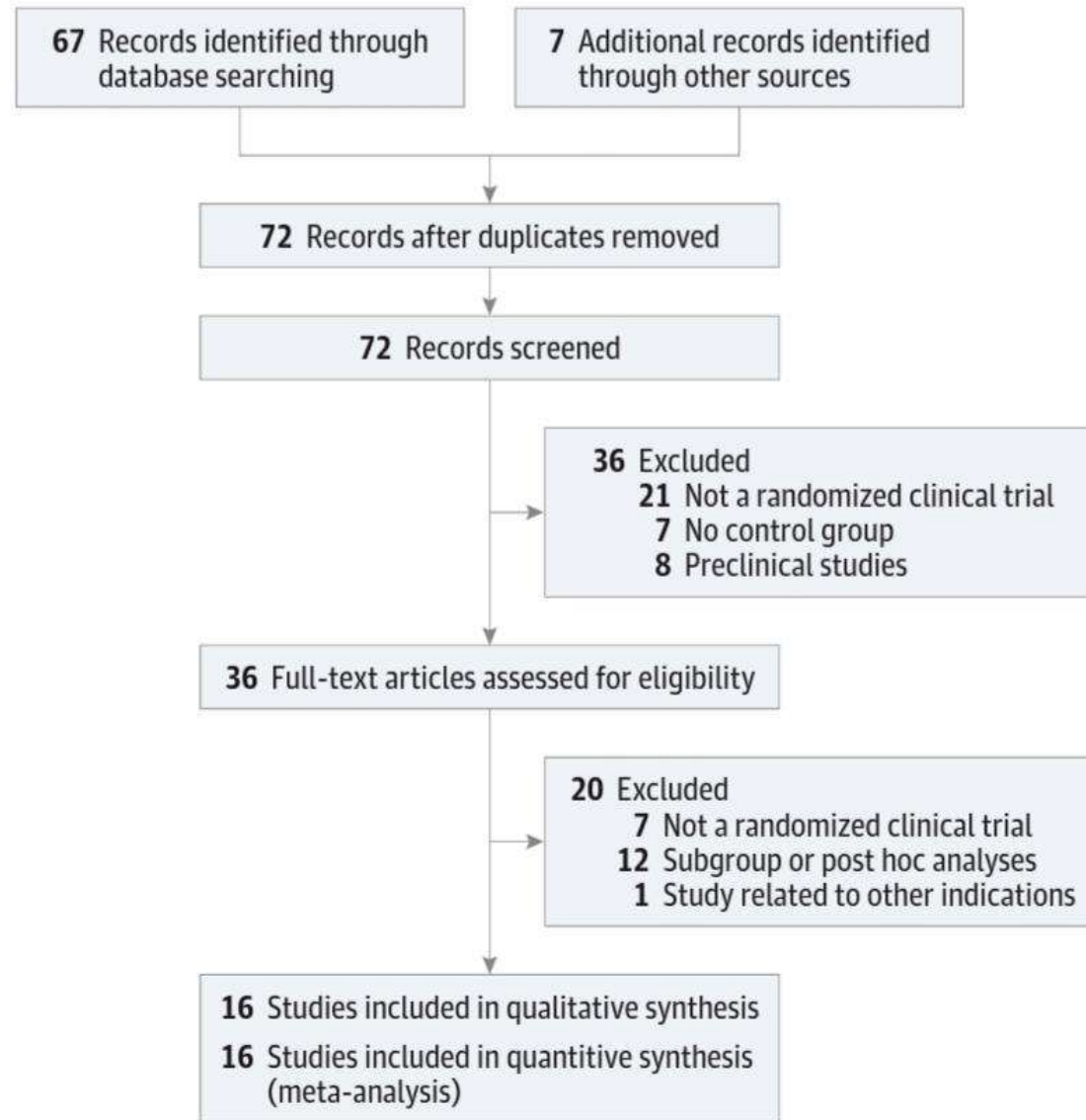
A Meta-analysis

Saurav Chatterjee, MD; Anasua Chakraborty, MD; Ido Weinberg, MD; Mitul Kadakia, MD; Robert L. Wilensky, MD; Partha Sardar, MD; Dharam J. Kumbhani, MD, SM, MRCP; Debabrata Mukherjee, MD, MS; Michael R. Jaff, DO; Jay Giri, MD, MPH

- Aim -To determine mortality benefits and bleeding risks associated with thrombolytic therapy compared with anticoagulation in acute pulmonary embolism, including the subset of hemodynamically stable patients with right ventricular dysfunction (intermediate-risk pulmonary embolism).

Chatterjee, Saurav et al. “Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis.” *JAMA* vol. 311,23 (2014): 2414-21.

• STUDY	• OUTCOMES	• RESULTS
<ul style="list-style-type: none"> • Meta analysis • 16 studies included 	<ul style="list-style-type: none"> • The primary outcomes - all-cause mortality and major bleeding. • Secondary outcomes - risk of recurrent embolism and intracranial hemorrhage (ICH). 	<ul style="list-style-type: none"> • Use of thrombolytics was associated with lower all-cause mortality (2.17% vs 3.89% with anticoagulant) • Greater risks of major bleeding 9.24% vs 3.42% • ICH 1.46% vs 0.19% • Major bleeding was not significantly increased in patients 65 years and younger (OR, 1.25) • Thrombolysis was associated with a lower risk of recurrent pulmonary embolism 1.17% vs 3.04%. • In intermediate-risk pulmonary embolism trials, thrombolysis was associated with lower mortality (OR, 0.48; and more major bleeding events (OR, 3.1).



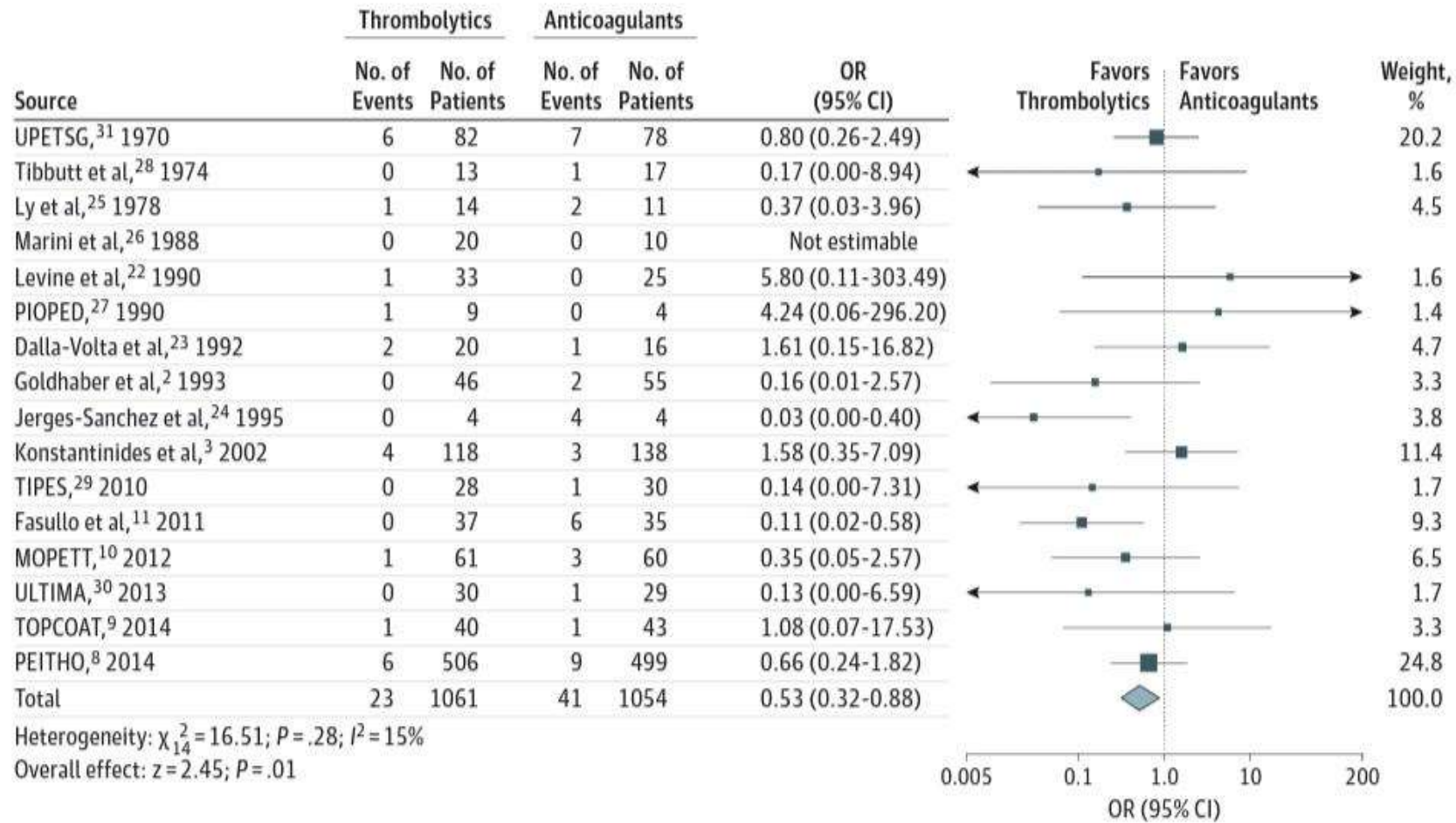
Chatterjee, Saurav et al. “Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis.” *JAMA* vol. 311,23 (2014): 2414-21.

Table 2. Absolute Risk Metrics of Outcomes of Major Interest

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 (0.19)	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, Saurav et al. “Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis.” *JAMA* vol. 311,23 (2014): 2414-21.

Figure 2. Odds of Mortality in Patients With Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation



Chatterjee, Saurav et al. “Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis.” *JAMA* vol. 311,23 (2014): 2414-21.

- MOPETT TRAIL
- RTC
- 121 patients with moderate PE
- Thrombolysis group [TG], n = 61 patients) or anticoagulation alone (control group [CG], n = 60
- tPA(50mg) >50kg /0.5mg/kg if <50kg
- Inclusion: signs and symptoms suggestive of PE, with confirmatory imaging (CT or V/Q)moderate PE
- Exclusion: onset of symptoms >10 days, >8 hours since start of parenteral anticoagulation, BP<95 or ≥200/100, contraindication to thrombolysis

- Primary outcome: development of pulmonary hypertension (pulmonary artery systolic pressure ≥ 40mmHg) as assessed by ECHO at 28 months

- Primary outcome: development of pulmonary hypertension
 16% in treatment group vs. 57% in control group
 mean PASP at 28 months 28 vs. 43 mmHg
- Secondary outcomes:
- composite endpoint of pulmonary hypertension and recurrent PE at 28 months
 16% in treatment group vs. 63% in control group,
 P<0.001
 - Recurrent PE-0% vs. 5%,
 - Mortality-1.6% vs. 5%
 - Total mortality + recurrent PE
 1.6% vs. 10%
 - Bleeding 0% vs. 0%

Sharifi, Mohsen et al. "Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial)." *The American journal of cardiology* vol. 111,2 (2013): 273-7.

<ul style="list-style-type: none"> • ULTIMA • Randomized, Controlled Trial • Intermediate-risk patients • 59 patients • Ultrasound-Assisted Catheter-Directed Thrombolysis • USAT(10-20mg rt PA) + HEPARIN vs HEPARIN 	<ul style="list-style-type: none"> • Primary outcome - the difference in the RV/LV ratio from baseline to 24 hours. • Safety outcomes -death, major and minor bleeding, and recurrent venous thromboembolism at 90 days 	<ul style="list-style-type: none"> • Mean decrease in RV/LV ratio from baseline to 24 hours - 0.30 ± 0.20 versus 0.03 ± 0.16 • No major bleeding • 4 minor bleeding episodes (3 in the USAT group and 1 in the heparin group; $P=0.61$), • No recurrent venous thromboembolism.
		<p>Standardized USAT regimen was superior to anticoagulation with heparin alone in reversing RV dilatation at 24 hours, without an increase in bleeding complications.</p>



Efficacy and Safety of Low Dose Recombinant Tissue-Type Plasminogen Activator for the Treatment of Acute Pulmonary Thromboembolism

A Randomized, Multicenter, Controlled Trial

*Chen Wang, MD, PhD, FCCP; Zhenguo Zhai, MD, PhD; Yuanhua Yang, MD; Qi Wu, MD; Zhaozhong Cheng, MD; Lirong Liang, MD, PhD; Huaping Dai, MD; Kewu Huang, MD; Weixuan Lu, MD; Zhonghe Zhang, MD; Xiansheng Cheng, MD; Ying H. Shen, MD, PhD; for the China Venous Thromboembolism (VTE) Study Group**

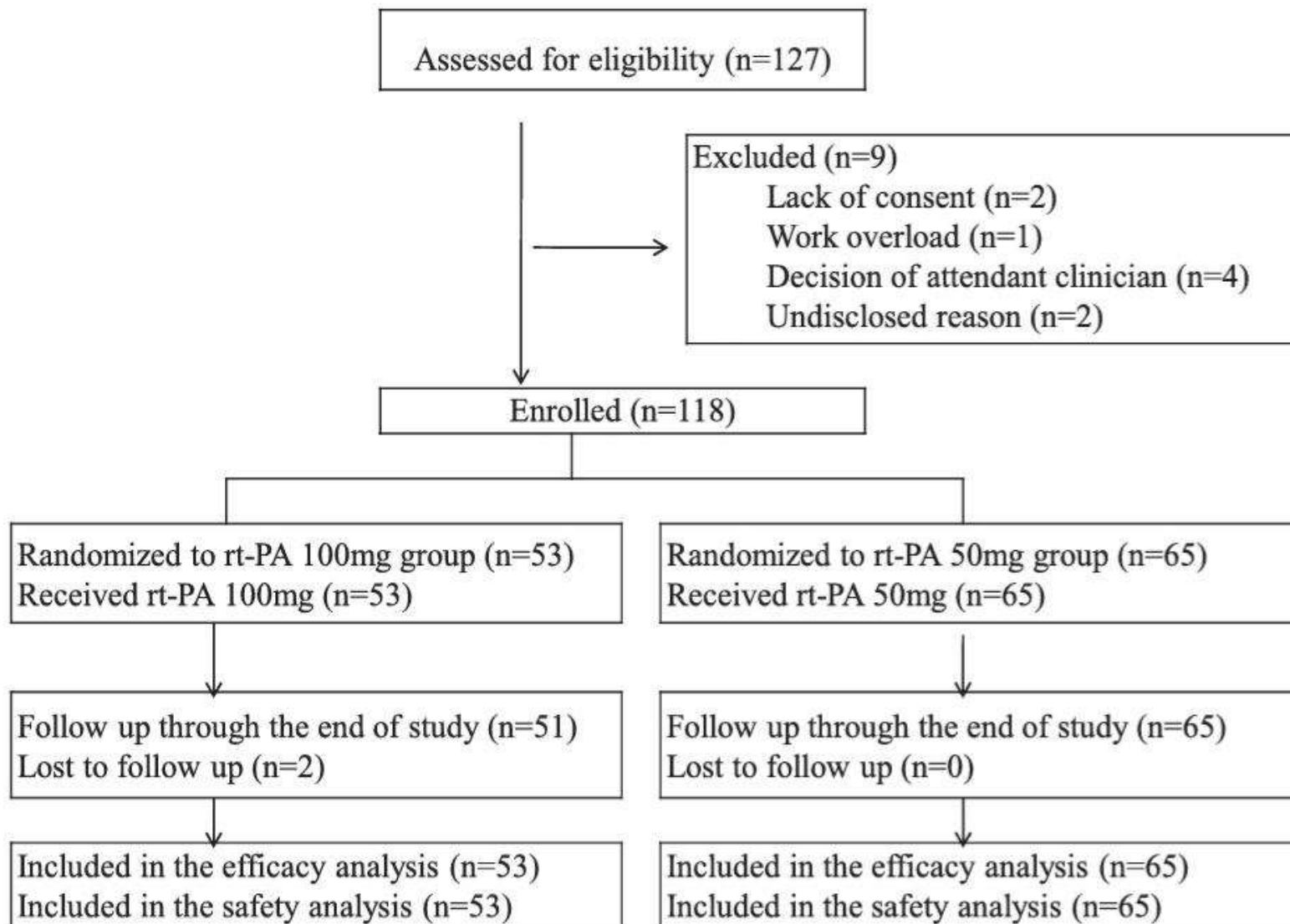
AIM- To compare the efficacy and safety of a 50 mg/2 h rt-PA regimen with a 100 mg/2 h rt-PA regimen in patients with acute PTE.

Wang, Chen et al. "Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial." *Chest* vol. 137,2 (2010): 254-62.

- A prospective, randomized, multicenter trial
- 118 patients with acute PTE and either hemodynamic instability or massive pulmonary artery obstruction were randomly assigned to receive a treatment regimen of **either rt-PA at 50 mg/2 h (n = 65) or 100 mg/2 h (n = 53)**.

- The efficacy-determined by improvements of right ventricular dysfunctions (RVDs) on echocardiograms, lung perfusion defects on ventilation perfusion lung scans, and pulmonary artery obstructions on CT angiograms.
- The adverse events, including death, bleeding, and PTE recurrence.

- Progressive improvements in RVD in both groups
- Three (6%) patients in the rt-PA 100 mg/2 h group and one (2%) in the rt-PA 50 mg/2 h group died as the result of either PTE or bleeding.
- The 50 mg/2 h rt-PA regimen resulted in less bleeding tendency than the 100 mg/2 h regimen (3% vs 10%), especially in patients with a body weight < 65 kg (14.8% vs 41.2%)
- No fatal recurrent PTE was found in either group.



Patient enrollment, randomization and follow up

Wang, Chen et al. "Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial." *Chest* vol. 137,2 (2010): 254-62.

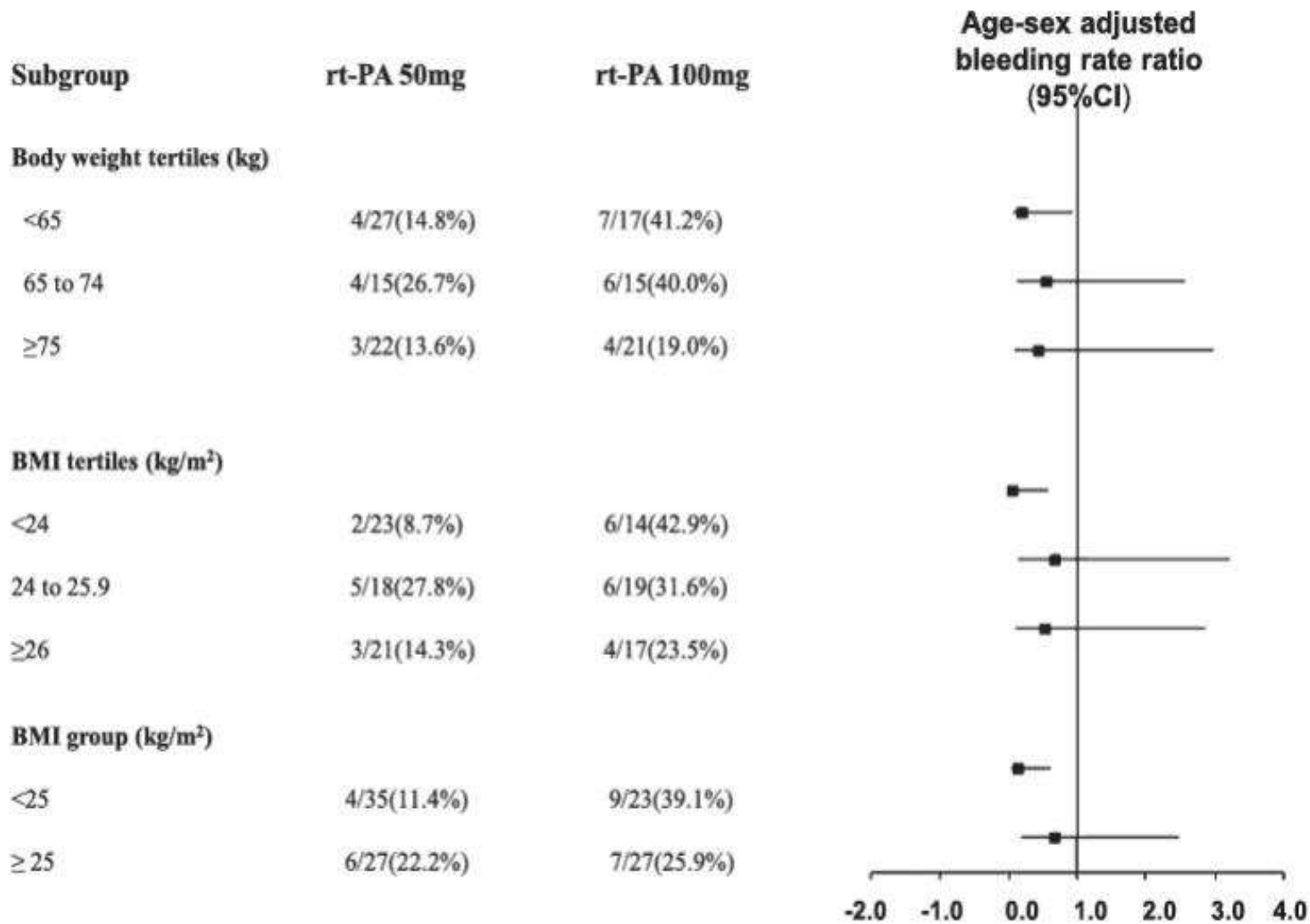


FIGURE 3. Comparisons of total bleeding complications between two treatments for PTE in patients with different body weights and BMI subgroups. See Figures 1 and 2 legends for expansion of other abbreviations.

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

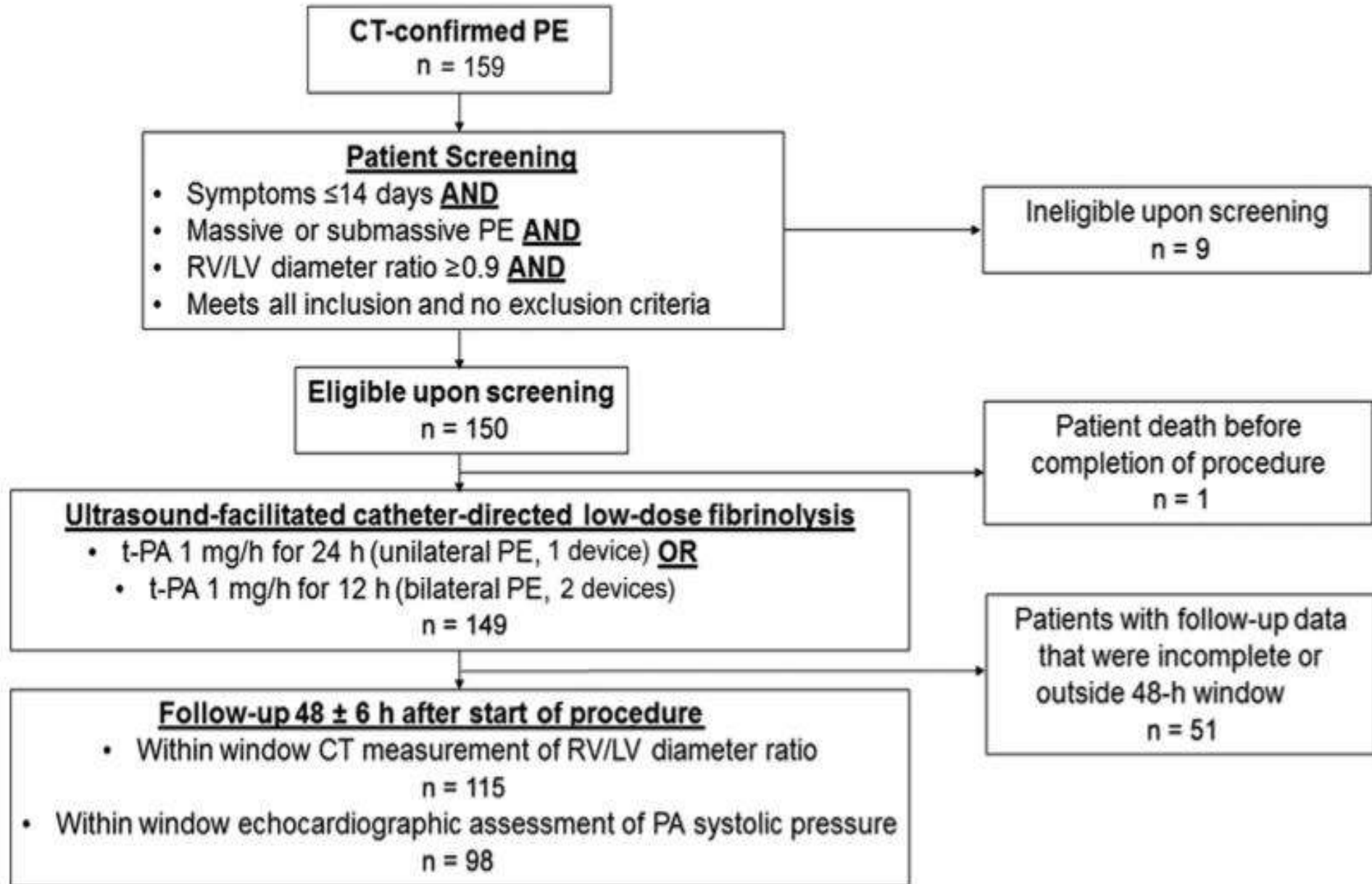
The SEATTLE II Study



Aim-evaluate the safety and efficacy of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis, using the EkoSonic Endovascular System (EKOS, Bothell, Washington).

<ul style="list-style-type: none"> • SEATTLE II Study • Prospective, single-arm, multicenter trial • acute massive (n = 31) or submassive (n = 119) PE • Eligibility -proximal PE and a right ventricular (RV)-to-left ventricular (LV) diameter ratio ≥ 0.9 on chest computed tomography (CT). 	<ul style="list-style-type: none"> • Intervention-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. • Primary safety outcome -major bleeding within 72 h of procedure initiation. • The primary efficacy outcome - the change in the chest CT-measured RV/LV diameter ratio within 48 h of procedure initiation. 	<ul style="list-style-type: none"> • Mean RV/LV diameter ratio decreased from baseline to 48 h post-procedure (1.55 vs. 1.13) • Mean pulmonary artery systolic pressure (51.4 mm Hg vs. 36.9 mm Hg;) • Modified Miller Index score (22.5 vs. 15.8; decreased post-procedure • Moderate bleeding events occurred in 15 patients (10%). • No ICH intracranial haemorrhage
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Piazza, Gregory 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." *JACC. Cardiovascular interventions* vol. 8,10 (2015): 1382-1392.



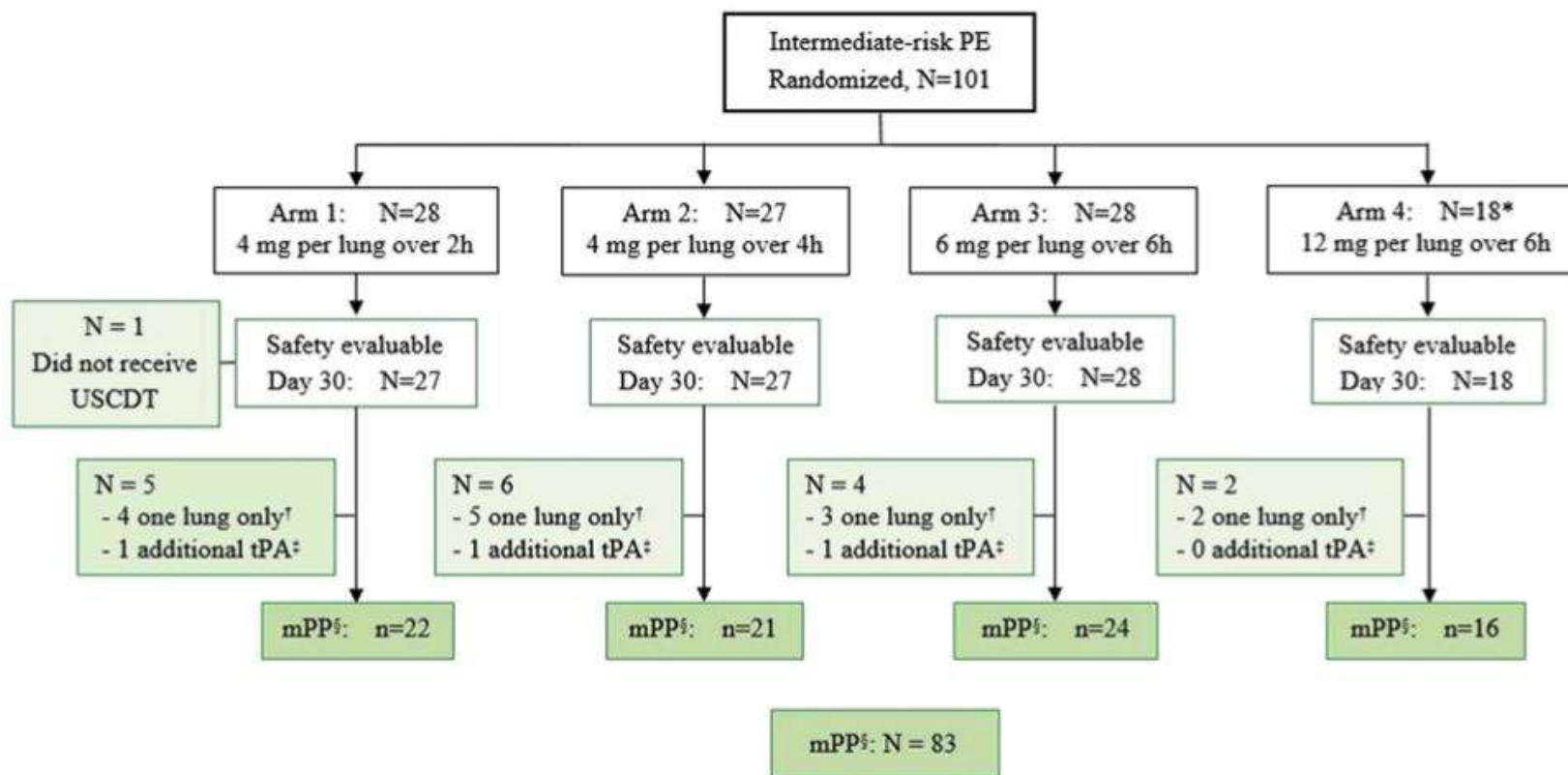
- OPTALYSE PE Trail
- Randomized trial
- AIM- lowest optimal tPA dose and delivery duration by USCDT
- 101 patients
- Hemodynamically stable adults with acute intermediate-risk pulmonary embolism
- Patients received treatment with 1 of 4 USCDT regimens.
- The tPA dose ranged from 4 to 12 mg per lung and infusion duration from 2 to 6h.

- The primary efficacy end point – reduction in RV /LV ratio by CT /2D ECHO
- Secondary endpoint-embolic burden by refined modified Miller score, measured on CTPA 48 hours after initiation of USCDT.

- Decrease in RA/LV ratio was same in all 4 groups (improved by 25%)
- Four patients experienced major bleeding(4%). 2 intracranial hemorrhage event
- Treatment with USCDT using a shorter delivery duration and lower-dose tPA -associated with improved RV function and reduction in clot burden.

Tapson, Victor F et al. “A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism: The OPTALYSE PE Trial.” *JACC. Cardiovascular interventions* vol. 11,14 (2018): 1401-1410.

FIGURE 1 Patient Flow and Evolution From ITT to mPP



Tapson, Victor F et al. "A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism: The OPTALYSE PE Trial." *JACC. Cardiovascular interventions* vol. 11,14 (2018): 1401-1410. doi:10.1016/j.jcin.2018.04.008

- FLARE Study
- Prospective, Single-Arm, Multicenter Trial
- Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism
- 106 patients
- Aim-evaluate the safety and effectiveness of percutaneous mechanical thrombectomy using the FlowTrievers System (Inari Medical, Irvine, California)

- Primary effectiveness end point—core laboratory—assessed change in RV/LV ratio.
- The primary safety endpoint – comprised device-related death, major bleeding, treatment-related clinical deterioration, pulmonary vascular injury, or cardiac injury within 48h of thrombectomy.

- Mean procedural time-94min
- Mean ICU stay 1.5 days
- 43 patients (41.3%) did not require any ICU stay
- At 48h post procedure, average RV/LV ratio reduction-0.38(25.1%).
- 3.8% experienced 6 major adverse events, with 1 patient (1.0%) major bleeding
- No ICH

Tu, Thomas et al. “A Prospective, Single-Arm, Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism: The FLARE Study.” *JACC. Cardiovascular interventions* vol. 12,9 (2019): 859-869.



American Journal of Interventional Radiology



Vascular Interventions *Technical Innovation*

Safety of the Inari FlowTrievers device for mechanical thrombectomy in patients with acute submassive and massive pulmonary embolism and contraindication to thrombolysis

Michael Markovitz¹, Nicholas Lambert¹, Lowell Dawson¹, Glenn Hoots²

Aim- evaluates the safety of percutaneous mechanical thrombectomy with the Inari FlowTrievers System (Inari Medical, Irvine, California) for the treatment of acute massive/submassive pulmonary embolism (PE) specifically in therapeutically anticoagulated patients with contraindication to thrombolysis

A single-center retrospective chart review on patients with contraindication to thrombolysis and massive/submassive PE who underwent FlowTrier thrombectomy

- Primary outcomes - procedure or device-related complications within 30 days of discharge.
- Secondary outcomes - technical and clinical success defined by improvement in mean pulmonary artery pressure (PAP), oxygen saturation, and heart rate.

- 13 patients
- technical success achieved in all cases.
- Zero major or minor adverse events, technical complications, delayed procedure-related complications, or deaths within 30 days of hospital discharge occurred.
- Mean PAP decreased significantly by 19.1% (32.5 ± 13.3 mmHg to 26.3 ± 12.4 mmHg; $P = 0.0074$, 95% confidence interval (CI) 2.0–10.5 mmHg).
- Oxygen saturation improved post-procedure (increased $3.9 \pm 3.8\%$; $p = 0.0032$, 95% CI 1.66.1%) as did heart rate (decreased 22.2 ± 17.0 bpm; $P < 0.001$, 95% CI 11.9–32.4

<ul style="list-style-type: none"> • EXTRACT-PE • Prospective, Multicenter Trial • Evaluate the Safety and Efficacy of the Indigo Aspiration System in Acute Pulmonary Embolism • 119 patient acute submassive PE 	<ul style="list-style-type: none"> • Primary efficacy endpoint-change in RV/LV ratio from base line to 48 hours post-procedure on CTPA • Primary safety endpoint-a composite of 48 hours major adverse events: device related death, major bleeding ,and device-related serious adverse events 	<ul style="list-style-type: none"> • Median device insertion to removal time 37.0 min. • Two(1.7%) patients received intraprocedural thrombolytics. • Mean RV/LV ratio reduction from base line to 48h post-procedure 0.43. • Two (1.7%) patients experienced 3 major adverse events. • Rates of cardiac injury, pulmonary vascular injury, clinical deterioration , major bleeding, and device-related death at 48h - 0%,1.7%,1.7%,1.7%,and 0.8%,respectively.
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Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT)

Initial Results From a Prospective Multicenter Registry

William T. Kuo, MD, FCCP; Arjun Banerjee, BS; Paul S. Kim, MD; Frank J. DeMarco Jr, MD, FCCP; Jason R. Levy, MD; Francis R. Facchini, MD; Kamil Unver, MBiomedE, MBA; Matthew J. Bertini, MD; Akhilesh K. Sista, MD; Michael J. Hall, MD; Jarrett K. Rosenberg, PhD; and Miguel A. De Gregorio, MD, PhD

Kuo, William T et al. “Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial Results From a Prospective Multicenter Registry.” *Chest* vol. 148,3 (2015): 667-673.

- Aim-safety and effectiveness of catheter-directed therapy (CDT) as an alternative treatment of acute PE.
- Population -101 patients -acute massive (n-28) or submassive PE(n-73)
- Catheter-Directed Therapy-immediate catheter-directed mechanical or pharmacomechanical thrombectomy using defined modern CDT techniques, including low-profile catheters (10F), catheter-directed fragmentation of PE, intraclotlytic injection (if drug was given), and aspiration and / CDT with tPA or Urokinase

Kuo, William T et al. "Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial Results From a Prospective Multicenter Registry." *Chest* vol. 148,3 (2015): 667-673.

- Clinical success - defined as meeting all three end points: stabilization of hemodynamics; improvement in pulmonary hypertension, right-sided heart strain, or both; and survival to hospital discharge.
- Clinical success - 24 of 28 patients with massive PE (85.7%; 95% CI, 67.3%-96.0%) and 71 of 73 patients with submassive PE (97.3%; 95% CI, 90.5%-99.7%).
- Four of six deaths - due to massive PE, and two due to submassive PE

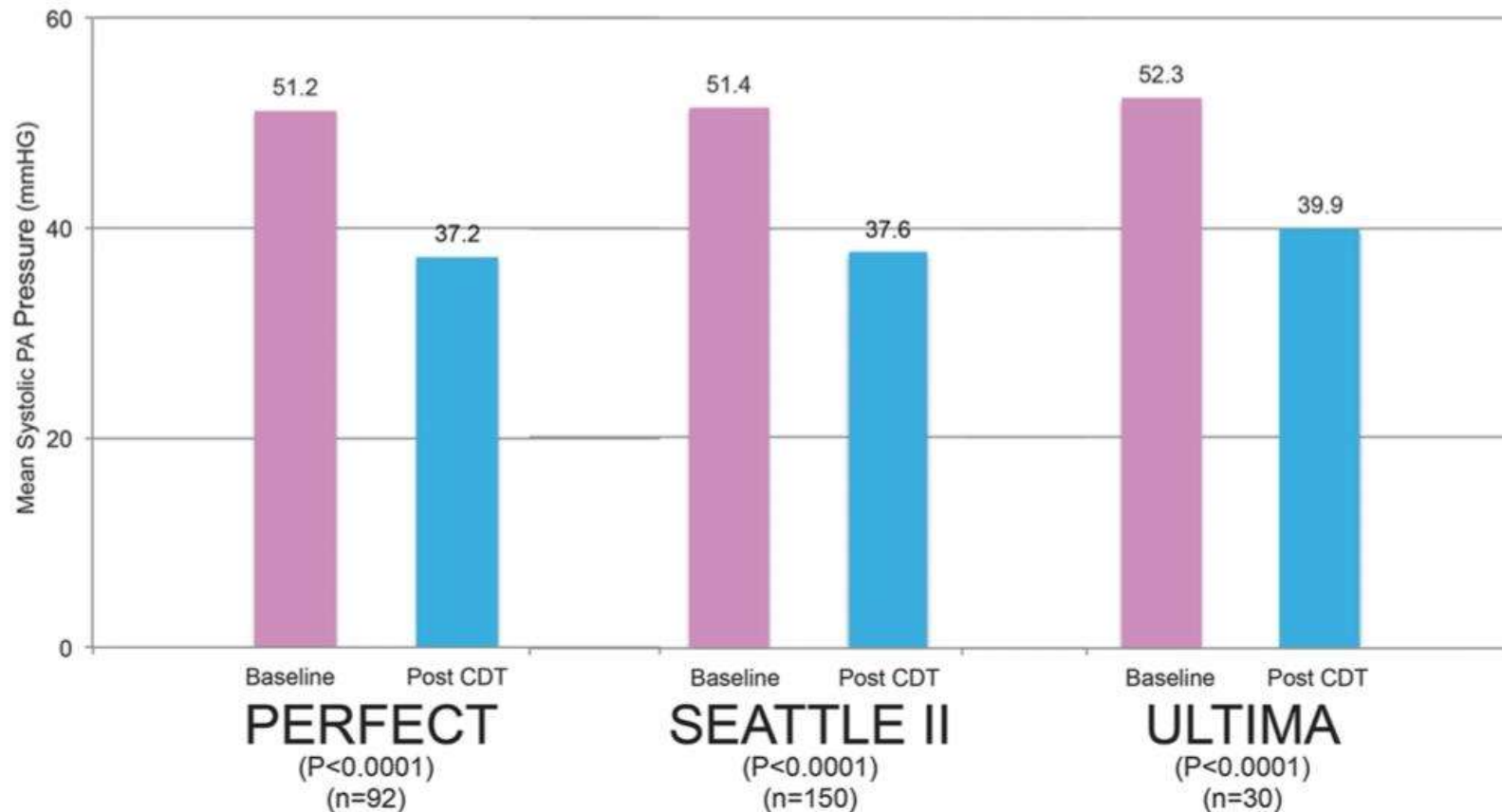
Kuo, William T et al. "Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial Results From a Prospective Multicenter Registry." *Chest* vol. 148,3 (2015): 667-673.

- Mean pulmonary artery pressure improved from 51.17 ± 14.06 to 37.23 ± 15.81 mm Hg
- Follow-up echo, 57 of 64 (81%) showed improvement in right-sided heart strain.
- No major procedure-related complications, major hemorrhages, or hemorrhagic strokes.
- No advantage in patients treated with USAT vs standard CDT
- CDT may be performed effectively without the added cost associated with USAT infusion catheters.

Kuo, William T et al. "Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial Results From a Prospective Multicenter Registry." *Chest* vol. 148,3 (2015): 667-673.

Safety Outcomes after CDT	Values
Hospital stay, d	8.23 ± 4.82
In-hospital death .	6 (5.9)
30-d mortality	1 (1.0)
IVC filter placed	65 (64.4)
Major bleeding within 30 d	0
Intracranial hemorrhage	0

Kuo, William T et al. “Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial Results From a Prospective Multicenter Registry.” *Chest* vol. 148,3 (2015): 667-673.





Kuo, William T et al. "Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial Results From a Prospective Multicenter Registry." *Chest* vol. 148,3 (2015): 667-673.




Original Article

VASCULAR
MEDICINE

Outcomes of catheter-directed versus systemic thrombolysis for the treatment of pulmonary embolism: A real-world analysis of national administrative claims

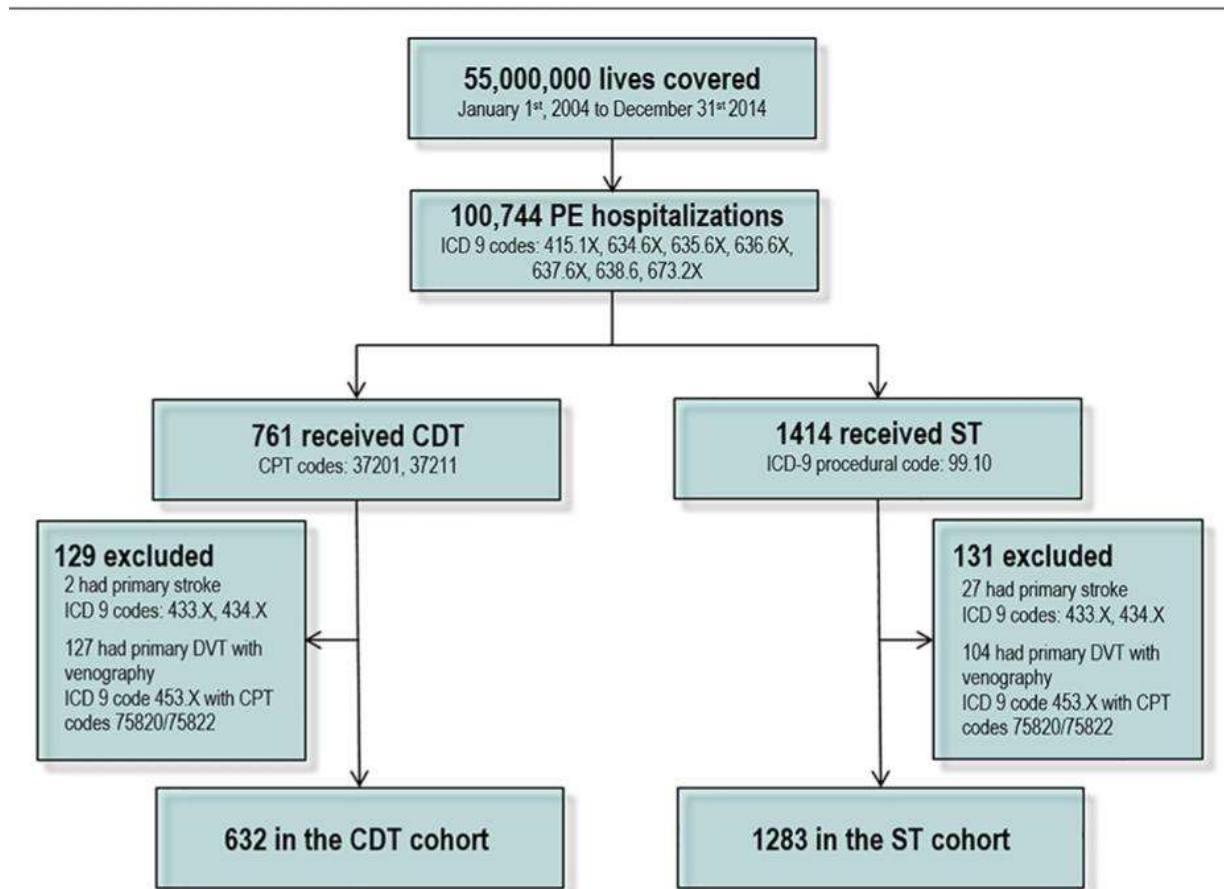
Bram J Geller^{1,2} , Srinath Adusumalli^{3,4,5}, Steven C Pugliese⁶, Sameed Ahmed M Khatana^{3,4,5}, Ashwin Nathan^{3,4,5}, Ido Weinberg⁷ , Michael R Jaff⁸, Taisei Kobayashi^{3,4}, Jeremy A Mazurek³, Sameer Khandhar³, Lin Yang^{4,5}, Peter W Groeneveld^{4,5} and Jay S Giri^{3,4}

Vascular Medicine
2020, Vol. 25(4) 334–340
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Geller et al. Outcomes of catheter-directed versus systemic thrombolysis for the treatment of pulmonary embolism: A real-world analysis of national administrative claims, *Vascular Medicine* 2020, Vol. 25(4) 334 – 340

- Retrospective analysis
- Study population-all patients hospitalized with a PE between January 1, 2004 and December 31, 2014 by searching the database for hospitalization claims with a PE ICD-9-CM code
- 623 in CDT and 1283 high risk features patients in ST group
- Primary outcome - intracranial hemorrhage during the index hospitalization, in-hospital bleeding, and in-hospital mortality
- Secondary endpoints -30-day mortality and 1-year mortality. These were assessed by using the Social Security Death

Geller et al. Outcomes of catheter-directed versus systemic thrombolysis for the treatment of pulmonary embolism: A real-world analysis of national administrative claims, *Vascular Medicine* 2020, Vol. 25(4) 334 –340



Geller et al. Outcomes of catheter-directed versus systemic thrombolysis for the treatment of pulmonary embolism: A real-world analysis of national administrative claims, *Vascular Medicine* 2020, Vol. 25(4) 334–340

- CDT was associated with 1) similar ICH rates, 2) increased all-cause bleeding, and 3) lower short and intermediate-term mortality when compared with ST
- the results should not be extrapolated to patients with a lower risk of mortality
- large-scale randomized clinical trials with appropriate comparator arms is needed

Geller et al. Outcomes of catheter-directed versus systemic thrombolysis for the treatment of pulmonary embolism: A real-world analysis of national administrative claims, *Vascular Medicine* 2020, Vol. 25(4) 334 –340

Early switch to oral anticoagulation in patients with acute intermediate-risk pulmonary embolism (PEITHO-2): a multinational, multicentre, single-arm, phase 4 trial

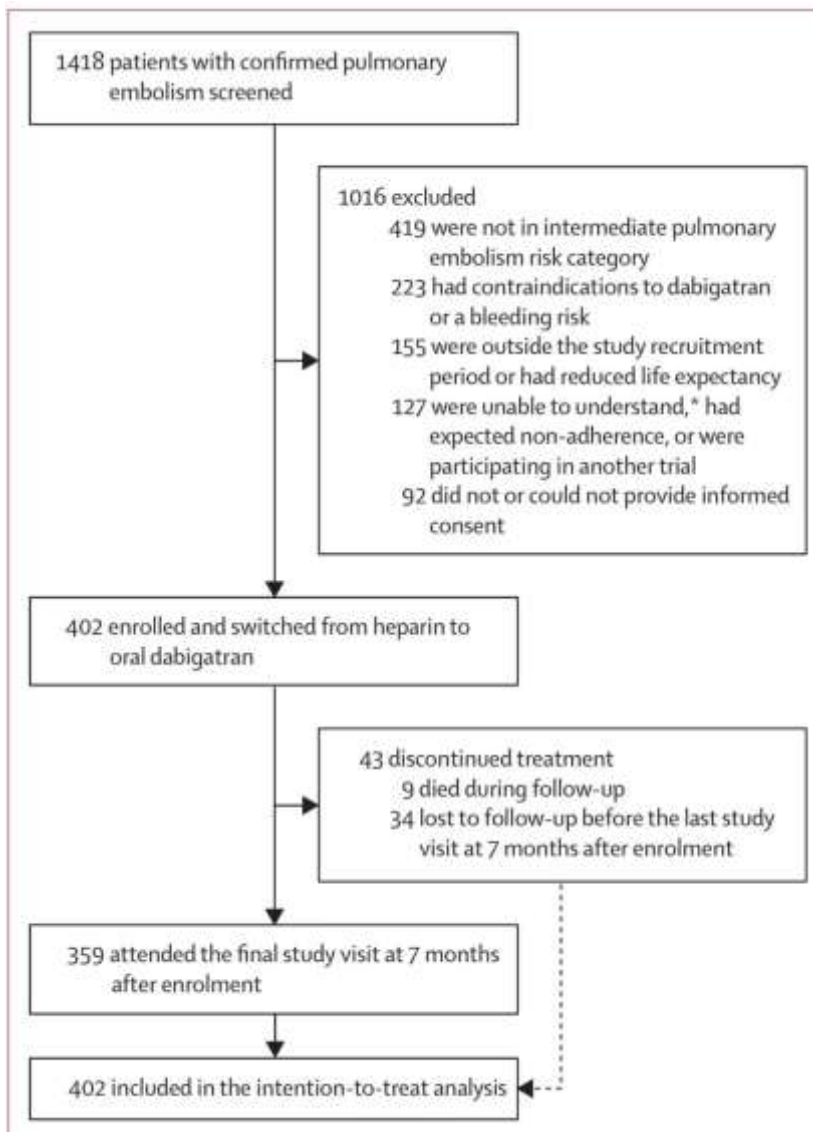


Frederikus A Klok, Gerrit Toenges, Anna C Mavromanoli, Stefano Barco, Walter Ageno, H  l  ne Bouvaist, Marianne Brodmann, Claudio Cuccia, Francis Couturaud, Claudia Dellas, Konstantinos Dimopoulos, Daniel Duerschmied, Klaus Empen, Pompilio Faggiano, Emile Ferrari, Nazzareno Gali  , Marcello Galvani, Alexandre Ghuysen, George Giannakoulas, Menno V Huisman, David Jim  nez, Matija Kozak, Irene Marthe Lang, Mareike Lankeit, Nicolas Meneveau, Thomas M  nzel, Massimiliano Palazzini, Antoniu Octavian Petris, Giancarlo Piovaccari, Aldo Salvi, Sebastian Schellong, Kai-Helge Schmidt, Franck Verschuren, Irene Schmidtman, Guy Meyer, and Stavros V Konstantinides, on behalf of the PEITHO-2 investigators*

Aim-whether treatment of acute intermediate-risk pulmonary embolism with parenteral anticoagulation for a short period of 72 h, followed by a switch to a direct oral anticoagulant (dabigatran), is effective and safe.

Klok FA et al; Early switch to oral anticoagulation in patients with acute intermediate-risk pulmonary embolism (PEITHO-2): a multinational, multicentre, single-arm, phase 4 trial. *Lancet Haematol.* 2021 Sep;8(9):e627-e636.

Study	Outcomes	Results
<ul style="list-style-type: none"> • Multinational, multicentre, single-arm, phase 4 trial • 402 patients • Adult patients (aged ≥ 18 years) with symptomatic intermediate-risk pulmonary embolism, with or without DVT • Patients received parenteral LMWH/UFH 72 h after diagnosis of pulmonary embolism before switching to oral dabigatran 150 mg twice per day following a standard clinical assessment. 	<ul style="list-style-type: none"> • The primary outcome - recurrent symptomatic venous thromboembolism or pulmonary embolism-related death within 6 months. • The primary and safety outcomes were assessed in the intention-to-treat population 	<ul style="list-style-type: none"> • Recurrent symptomatic VTE occurred seven (2%) patients, • At 6 months, 11 (3%) had at least one major bleeding event and 16 (4%) had at least one clinically relevant non-major bleeding event • Conclusion-intermediate-risk pulmonary embolism found that a management strategy of early switch from heparin to dabigatran after rigorous clinical assessment of stabilization at 72 h was both effective and safe.



Study population (n=402)	
Age, years	
Median	69.5 (60.0-78.0)
>80 years	67 (17%)
Sex	
Women	192 (48%)
Men	210 (52%)
Risk factors and comorbidities	
Major trauma in the past 30 days	13 (3%)
Major surgery in the past 30 days	14 (3%)
Immobilisation (for at least 3 days)	52 (13%)
Previous pulmonary embolism or deep vein thrombosis	107 (27%)
Active cancer	10 (2%)
History of cancer	38 (9%)
Ongoing chemotherapy	3 (<1%)
History of chronic cardiopulmonary disease	83 (21%)
Clinical features at presentation	
Body-mass index, kg/m ² *	28.05 (25.05-31.82)
Heart rate, beats per minute	84 (72-97)
Heart rate >100 beats per minute	40 (10%)
Systolic/diastolic blood pressure, mm Hg	130 (119-140)/76 (70-82)
Systolic blood pressure <100 mm Hg	7 (2%)
Oxygen saturation <90%	27/399 (7%)
Indicators of pulmonary embolism severity	
Simplified Pulmonary Embolism Severity Index ≥1	213 (53%)
Signs of right ventricular dysfunction on at least one imaging method	371/377 (98%)
Signs of right ventricular dysfunction on echocardiography	338/350 (97%)
Signs of right ventricular dysfunction on CT pulmonary angiography	202/248 (81%)
Elevated cardiac troponin concentrations	308/382 (81%)

Data are median (IQR), n (%), or n/N (%). *Data were missing for four patients.

Table 1: Baseline characteristics

Study population (n=402)	
Primary efficacy outcome	
Recurrent symptomatic venous thromboembolism or death related to pulmonary embolism within the first 6 months	7 (2%; 3)
Recurrent pulmonary embolism	5 (1%)
Recurrent deep-vein thrombosis	3 (<1%)
Death related to pulmonary embolism	2 (<1%)
Secondary efficacy outcomes	
Pulmonary embolism-related death, haemodynamic collapse, or haemodynamic decompensation within the first 30 days	3 (<1%)
Death from any cause, haemodynamic collapse, or decompensation within the first 30 days	5 (1%)
Death from any cause within the first 6 months	8 (2%)
Safety outcomes	
At least one major bleeding event within 6 months	11 (3%; 1-5)
At least one clinically relevant non-major bleeding within 6 months	16 (4%; 2-6)
At least one major or clinically relevant non-major bleeding event within 6 months	26 (7%; 4-9)
At least one serious adverse event within 30 days	34 (9%)
At least one serious adverse event within 6 months	71 (18%)

Data are n (%; upper bound of right-sided 95% CI), n (%), or n (%; 95% CI).

Table 2: Efficacy and safety outcomes

Klok FA et al; Early switch to oral anticoagulation in patients with acute intermediate-risk pulmonary embolism (PEITHO-2): a multinational, multicentre, single-arm, phase 4 trial. Lancet Haematol. 2021 Sep;8(9):e627-e636.

Survival and recurrence after acute pulmonary embolism treated with pulmonary embolectomy or thrombolysis in New York State, 1999 to 2013



Timothy Lee, BS,^a Shinobu Itagaki, MD, MS,^a Yuting P. Chiang, MD, MS,^b Natalia N. Egorova, PhD,^c David H. Adams, MD,^a and Joanna Chikwe, MD^{a,d}

- Retrospective cohort (257 pts vs 1854 of thrombolytic therapy)
- No difference between Surgical/Thrombolysis in 30day mortality(15.2% vs13.2%) or 5yr survival(72.4vs 76.1)
- Stroke (1.9% vs0.8%) and recurrent PE(3.8% vs1.2%) higher in thrombolysis group
- Thrombolysis was associated with a higher rate of recurrent PE necessitating inpatient readmission
- Pulmonary embolectomy and thrombolysis are associated with similar early and long-term survival, supporting guideline recommendations for embolectomy when thrombolysis is contraindicated.
- Limited to large centers-experienced surgeon and cardiopulmonary bypass required

Lee, Timothy et al. "Survival and recurrence after acute pulmonary embolism treated with pulmonary embolectomy or thrombolysis in New York State, 1999 to 2013." *The Journal of thoracic and cardiovascular surgery* vol. 155,3 (2018): 1084-1090.

RESEARCH ARTICLE

Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis

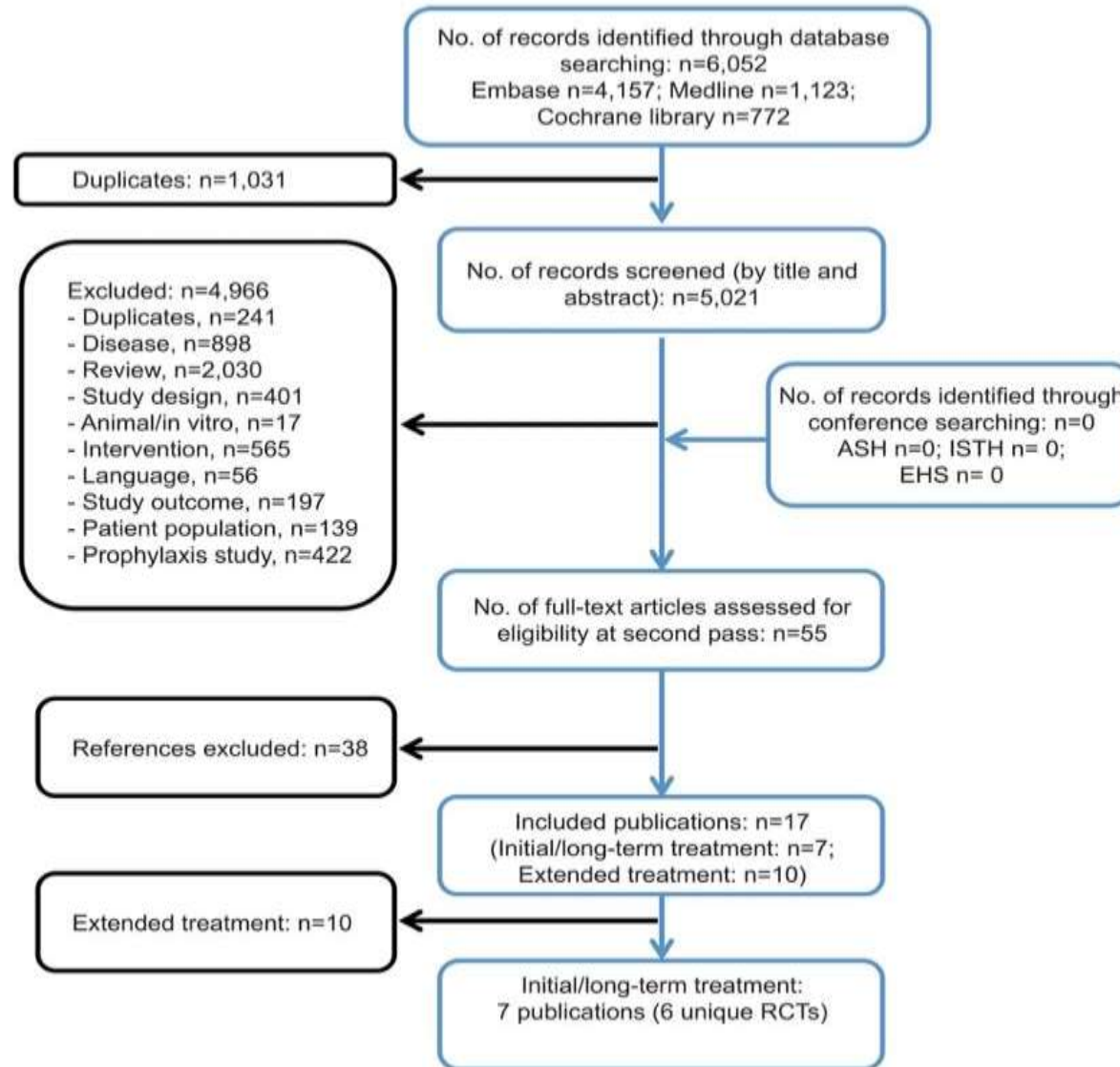
A. T. Cohen¹, M. Hamilton², S. A. Mitchell^{3*}, H. Phatak², X. Liu⁴, A. Bird⁵, D. Tushabe⁶, S. Batson³

1 Guy's and St Thomas' Hospitals, King's College, London, United Kingdom, **2** BMS, Princeton, United States of America, **3** Abacus International, Bicester, United Kingdom, **4** Pfizer, New York, United States of America, **5** Pfizer, Walton Oaks, United Kingdom, **6** TUSH-D UK LTD, Birmingham, United Kingdom

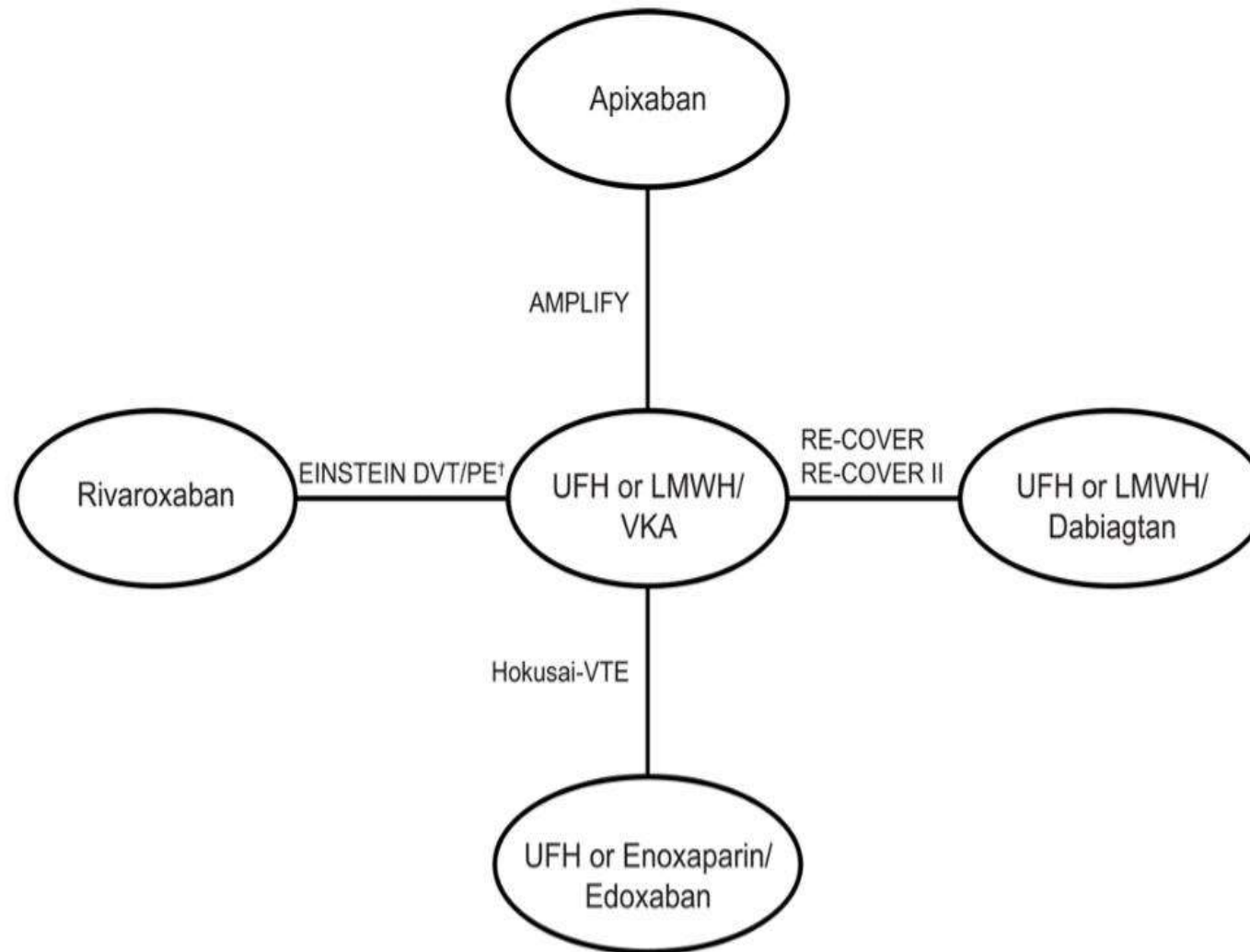


Cohen, A T et al. "Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis." *PloS one* vol. 10,12 e0144856. 30 Dec. 2015,

Population	Adult patients (18 years of age) with an objectively confirmed symptomatic VTE (DVT and/or PE), who were receiving initial/long-term treatment following an acute VTE event.
Study design	Prospective, phase III RCTs, with no restriction on randomisation procedure: double-blind or open label
Intervention	Treatments of interest include the following NOACs: • Apixaban • Dabigatran • Rivaroxaban • Edoxaban
Outcomes	Recurrent VTE and VTE-related death • Major bleeding • CRNM bleeding • All-cause mortality



Cohen, A T et al. "Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis." *PloS one* vol. 10,12 e0144856. 30 Dec. 2015.



Cohen, A T et al. “Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis.” *PloS one* vol. 10,12 e0144856. 30 Dec. 2015,

Trial	Treatment,	Mean	Female,	Unprovoked	Unprovoked	Patients	Index	Index	Index	Time on treatment
AMPLIFY Double- RCT										
RE-CC Double RCT										
RE-CC [22] Do RCT										
EINST EINST pooled [28] Op RCTs										
Hokusa [23] Do RCT										

- Apixaban treatment was associated with the most favourable safety profile of the NOACs, showing a statistically significantly reduced risk of 'major or clinically relevant non-major (CRNM) bleed' compared with rivaroxaban (0.47 [0.36, 0.61]), dabigatran (0.69 [0.51, 0.94]), and edoxaban (0.54 [0.41, 0.69]).
- Dabigatran was also associated with a significantly lower risk of 'major or CRNM bleed' compared with rivaroxaban (0.68 [0.53, 0.87]) and edoxaban (0.77 [0.60, 0.99]).

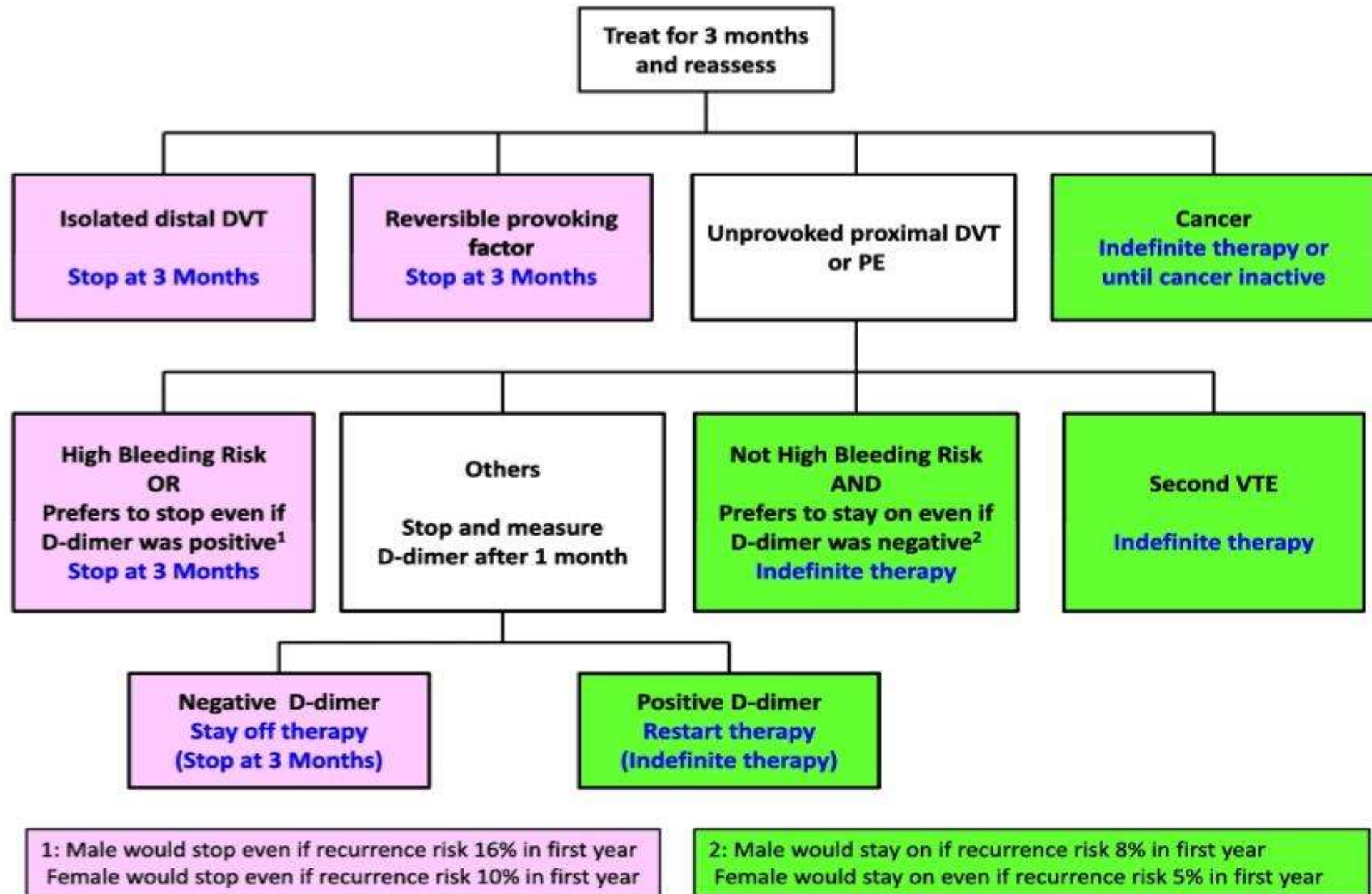
Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis." *PloS one* vol. 10,12 e0144856. 30 Dec. 2015,

Treatment comparison

RR (95% CrI)

	VTE and VTE-related-death	Major or CRNM bleeding	Major bleeding	CRNM bleeding	All-cause mortality
Apixaban vs. VKA	0.83 (0.59, 1.18)	0.44 (0.35, 0.55)	0.30 (0.16, 0.53)	0.48 (0.38, 0.60)	0.79 (0.52, 1.19)
Apixaban vs. rivaroxaban	0.93 (0.59, 1.46)	0.47 (0.36, 0.61)	0.55 (0.27, 1.09)	0.47 (0.36, 0.62)	0.82 (0.50, 1.34)
Apixaban vs. dabigatran	0.76 (0.47, 1.27)	0.69 (0.51, 0.94)	0.40 (0.19, 0.81)	0.80 (0.57, 1.12)	0.79 (0.44, 1.41)
Apixaban vs. edoxaban	1.01 (0.63, 1.63)	0.54 (0.41, 0.69)	0.36 (0.18, 0.69)	0.59 (0.45, 0.78)	0.75 (0.47, 1.21)
Rivaroxaban vs. VKA	0.90 (0.67, 1.20)	0.94 (0.82, 1.07)	0.55 (0.37, 0.81)	1.02 (0.88, 1.18)	0.96 (0.73, 1.27)
Rivaroxaban vs. dabigatran	0.82 (0.52, 1.31)	1.48 (1.15, 1.89)	0.73 (0.40, 1.31)	1.70 (1.28, 2.25)	0.96 (0.59, 1.58)
Rivaroxaban vs. edoxaban	1.09 (0.71, 1.69)	1.14 (0.94, 1.38)	0.65 (0.38, 1.09)	1.26 (1.03, 1.55)	0.92 (0.64, 1.33)
Dabigatran vs. VKA	1.09 (0.76, 1.57)	0.64 (0.51, 0.78)	0.76 (0.48, 1.17)	0.60 (0.47, 0.76)	1.00 (0.66, 1.50)
Dabigatran vs. edoxaban	1.32 (0.81, 2.16)	0.77 (0.60, 0.99)	0.89 (0.51, 1.57)	0.74 (0.56, 0.98)	0.95 (0.59, 1.52)
Edoxaban vs. VKA	0.83 (0.60, 1.14)	0.82 (0.72, 0.95)	0.85 (0.59, 1.21)	0.81 (0.70, 0.94)	1.05 (0.82, 1.34)

Clinical trial	Study drug	Comparator	Follow-up length	Number of patients	Efficacy outcome	Incidence of efficacy outcome	Incidence of major Bleeding
Hokusai VTE Cancer	Edoxaban	Dalteparin	12 months	1050	Recurrent VTE	Edoxaban:7.9% Dalteparin:11.3% HR:0.71 (0.48-1.06)	Edoxaban:6.9% Dalteparin:4.0% HR: 1.77 (1.03-3.04)
SELECT-D	Rivaroxaban	Dalteparin	6 months	406	Recurrent VTE	Rivaroxaban:4% Dalteparin:11% HR: 0.43 (0.19-0.99)	Rivaroxaban:6% Dalteparin:4% HR: 1.83 (0.68-4.96)
ADAM VTE	Apixaban	Dalteparin	6 months	300	Venous or arterial thromboembolism	Apixaban:6% Dalteparin:6% HR: 0.93 (0.43-2.02)	Apixaban:0% Dalteparin:1.4% HR: not estimable
CARAVAGGIO	Apixaban	Dalteparin	6 months	1155	Recurrent VTE	Apixaban:5.6% Dalteparin:7.9% HR: 0.63 (0.37-1.07)	Apixaban:3.8% Dalteparin:4.0% HR: 0.82 (0.40-1.69)



Extended phase Anticoagulation

- Unprovoked VTE or provoked by persistent risk factor- extended-phase anticoagulation with a DOAC (strong recommendation, moderate-certainty evidence).
 - Patients on extended-phase anticoagulation - reevaluated at least on an annual basis, and at times of significant change in health status.
 - Extended-phase anticoagulation- the use of reduced-dose apixaban or rivaroxaban over full-dose apixaban or rivaroxaban (weak recommendation, very low certainty evidence).
- (Eg. Reduced dose refers to apixaban 2.5 mg twice daily and rivaroxaban 10 mg once daily.)
- Extended-phase anticoagulation, - reduced-dose DOAC over aspirin or no therapy (strong recommendation, low-certainty evidence) and suggest rivaroxaban over aspirin (weak recommendation, moderate-certainty evidence)

Original Investigation

Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism

A Randomized Clinical Trial

Patrick Mismetti, MD, PhD; Silvy Laporte, MS, PhD; Olivier Pellerin, MD, MSc; Pierre-Vladimir Ennezat, MD, PhD; Francis Couturaud, MD, PhD; Antoine Elias, MD, PhD; Nicolas Falvo, MD; Nicolas Meneveau, MD, PhD; Isabelle Quere, MD, PhD; Pierre-Marie Roy, MD, PhD; Olivier Sanchez, MD, PhD; Jeannot Schmidt, MD, PhD; Christophe Seinturier, MD; Marie-Antoinette Sevestre, MD; Jean-Paul Beregi, MD, PhD; Bernard Tardy, MD, PhD; Philippe Lacroix, MD; Emilie Presles, MSc; Alain Leizorovicz, MD; Hervé Decousus, MD; Fabrice-Guy Barral, MD; Guy Meyer, MD; for the PREPIC2 Study Group

<ul style="list-style-type: none"> • Randomized, open-label, blinded end point trial • Retrievable IVC filter implantation plus anticoagulation (filter group; n = 200) or anticoagulation alone with no filter implantation (control group; n = 199) 	<ul style="list-style-type: none"> • Primary outcome: Symptomatic recurrent PE at 3 months • Secondary Outcomes: Recurrent PE at 6 months/ Symptomatic DVT/Major Bleeding/Death at 3 and 6 months/Filter complications 	<ul style="list-style-type: none"> • Use of a retrievable inferior vena cava filter plus anticoagulation compared with anticoagulation alone did not reduce the risk of symptomatic recurrent pulmonary embolism at 3 months • Does not support the use of this type of filter in patients who can be treated with anticoagulation

Mismetti, Patrick et al. "Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial." *JAMA* vol. 313,16 (2015): 1627-35.

	Group, No. (%)	
	Filter (n = 200)	Control (n = 199)
Thrombolytic therapy	4 (2.0)	2 (1.0)
Main initial parenteral anticoagulation ^a	200 (100.0)	199 (100.0)
Low-molecular-weight heparin	120 (60.0)	113 (56.8)
Unfractionated heparin	46 (23.0)	44 (22.1)
Fondaparinux	34 (17.0)	42 (21.1)
Duration in patients receiving subsequent vitamin K antagonist therapy, median (IQR), d ^{b,c}	12 (8-24)	11 (7-22)
Long-term parenteral therapy	34 (17.0)	22 (11.1)
Duration in patients not receiving subsequent vitamin K antagonist therapy, median (IQR), d ^b	184 (171-196)	183 (171-187)
Vitamin K antagonist ^d	166 (83.0)	177 (88.9)
INR at the time initial parenteral therapy was stopped, median (IQR) ^e	2.3 (2.0-2.7)	2.3 (2.1-2.7)
Duration, median (IQR), d ^{b,c}	182 (170-187)	181 (171-187)
Median percentage of time spent with INR in a given range, %		
<2.0	19.7	15.9
2.0-3.0	58.3	61.5
>3.0	11.8	13.7

Mismetti, Patrick et al. "Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial." *JAMA* vol. 313,16 (2015): 1627-35.

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

Mismetti, Patrick et al. "Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial." *JAMA* vol. 313,16 (2015): 1627-35.

Subsegmental and Incidental PE

- Subsegmental PE (SSPE)- small peripheral clot beyond 5th order of pulmonary artery.
- Isolated SSPE can be unique (one subsegmental vessel involved) or multiple (two or more subsegmental vessels involved)
- Incidental SSPE is found casually in asymptomatic patients, usually by diagnostic imaging performed for other reasons
- Symptomatic SSPE is found in patients presenting with pleuritic pain or acute dyspnea ,or both.

Yoo HHB, Nunes-Nogueira VS, Fortes Villas Boas PJ. Anticoagulant treatment for subsegmental pulmonary embolism. Cochrane Database of Systematic Reviews 2020, Issue 2. Art. No.: CD010222.

Subsegmental and Incidental PE

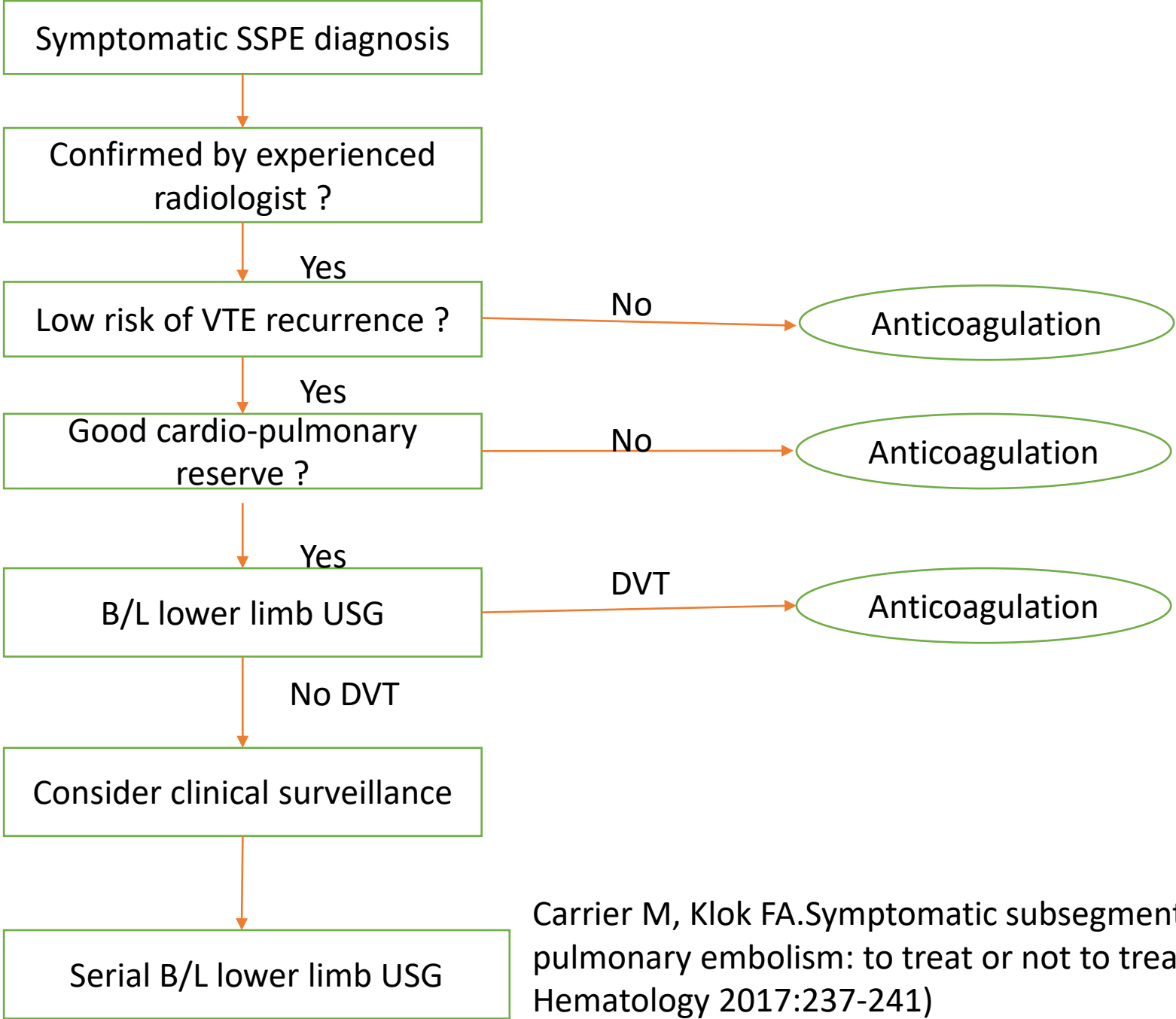
In patients with subsegmental pulmonary embolism (PE) (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a

- (I) low risk for recurrent VTE - clinical surveillance over anticoagulation (weak recommendation, low-certainty evidence)
- (II) high risk for recurrent VTE - anticoagulation over clinical surveillance (weak recommendation, low-certainty evidence).

In patients who are incidentally found to have asymptomatic PE- the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (weak recommendation, moderate-certainty evidence).

Stevens Scott M. et al. Antithrombotic Therapy for VTE Disease CHEST 2021; 160(6):2247-2259

Management strategy for symptomatic subsegmental PE



Carrier M, Klok FA. Symptomatic subsegmental pulmonary embolism: to treat or not to treat? Hematology 2017:237-241)

CONCLUSION

- Therapeutic dose anticoagulation is the main treatment of intermediate risk PE.
- Systemic fibrinolysis and Catheter-based therapy indicated in patients who develop hemodynamic decompensation.
- Purely mechanical catheter embolectomy techniques may be advantageous in patients with PE with contraindication to fibrinolytic therapy.
- Catheter-based therapy may be as an alternative to
 - 1) Surgical embolectomy for patients whom systemic fibrinolysis has failed
 - 2) Systemic fibrinolysis contraindicated
 - 3) Hemodynamic deterioration despite anticoagulation as alternative to systemic fibrinolysis
- More precise risk stratification tools to pre-emptively identify patients with intermediate-risk PE with the highest risk of clinical deterioration will be necessary for selection of those who would benefit from advanced therapies.