Pulmonary Embolism
The Past, Present, and Future

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OOA Convention 2024

Relevant Disclosure

Under the Oklahoma State Medical Association CME guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Parker Truong, DO

I have no relevant financial relationships or affiliations with commercial interests to disclose.

Objectives

- Definition and healthcare burden of pulmonary embolism.
- Learn the process of risk stratification for treatment.
- Details of current treatment technologies and guidelines.
- Discuss future directions of treatment for pulmonary embolism.

AHA SCIENTIFIC STATEMENT

Interventional Therapies for Acute Pulmonary Embolism: Current Status and Principles for the Development of Novel Evidence

A Scientific Statement From the American Heart Association

- Pulmonary embolism: Obstruction of pulmonary arteries by material (thrombus, tumor, air, fat) from parts of the body.
  - 100,000 deaths a year in the United States.
  - 30-day mortality 4%, 1-year mortality 13%.
  - A leading cause of in hospital death and #third common cause of CV death (after MI and stroke)*.

*CDC MMWR 2012

Risk Stratification

AHA, ESC, CHEST, ASH Guidelines

- Wide range of presentations from asymptomatic to death.
- Mainly divided into Low, Intermediate, and High Risk.
- To guide initial management and follow up but not absolute.
- Influenced by bleeding risks, thrombus burden, operator expertise, and individual patient preferences.

Low risk PE

- Patients who do not meet criteria for massive and submassive PE.
- Account for 40-60% of hospitalized patients with PE.
- Average mortality of 1% within one month*.
- Mainly treated with outpatient anticoagulation.
- Low risk of long-term complications.

*PROTECT Investigators 2014

Massive (High Risk) PE

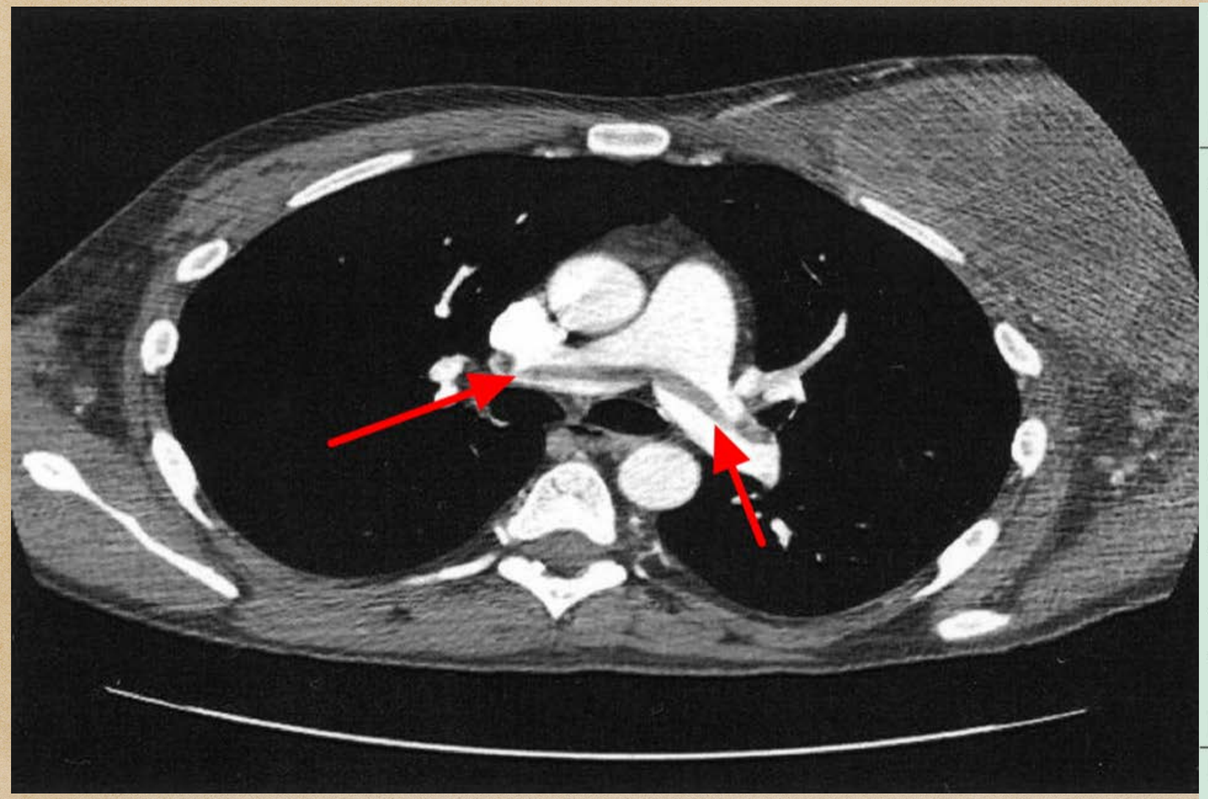
- Hypotension, SBP < 90 mmHg, drop > 40 mmHg for 15 min, need for pressors and hemodynamic support.
- Account for 5% of hospitalized patient.
- Mortality of 30% in one month*.

*ICOPER Registry 1999

Submassive (Intermediate Risk)PE

- Large PE (can be saddle) without hypotension.
  - AHA: RV strain(RV:LV ratio > 0.9)without hypotension.
  - ESC: simplified PESI score > 1, regardless of RV strain.
- Other markers: Elevated troponin, BNP, hypoxemia, tachycardia.
- Account for 35-55% of hospitalized patients.
- Mortality varies from 3% to 15% ==> Area of controversies for treatment.

*CDC MMWR 2012



PESI - Helpful in low risk patients for outpatient treatment

TABLE 1

Pulmonary Embolism Severity Index (PESI) in risk stratification

Parameter	PESI scoring	Simplified PESI
Age	Age in years	1 point if age > 80
Male sex	10 points	—
Cancer	30 points	1 point
Heart failure	10 points	1 point
Chronic pulmonary disease	10 points	1 point
Pulse ≥ 110 bpm	20 points	1 point
Systolic blood pressure < 100 mm Hg	30 points	1 point
Respiratory rate > 30 per minute	20 points	—
Temperature < 36°C (96.8°F)	20 points	—
Altered mental status	60 points	—
Arterial oxyhemoglobin saturation < 90%	20 points	1 point

Risk stratification	Total points		30-day mortality risk	
PESI	≤ 65	Class I	Very low	(0%–1.6%)
	66–85	Class II	Low	(1.7%–3.5%)
	86–105	Class III	Moderate	(3.2%–7.1%)
	106–125	Class IV	High	(4.0%–11.4%)
	> 125	Class V	Very high	(10.0%–24.5%)
Simplified PESI	0		1.0%	
	≥ 1		10.9%	

Based on information in references 2 and 3.

RIETE Investigators 2010

The Past

- Bedrest
- Oxygen
- Heparin transitioned to warfarin
- IVC filter placement?
- Surgical embolectomy for large massive PE
- Long-term CTEPH and Post PE Syndrome reported.

The Present

- Adverse outcomes of intermediate and high risk patients prompted escalation of therapeutic interventions.
- Systemic thrombolysis
- Catheter-directed therapies
- Surgical embolectomy
- Hemodynamic support: ECMO and percutaneous RV support*

*Elder et al, Interv Card Clin 2018

New Anticoagulants

- DOAC - Direct Oral Anticoagulants, since 2010.
  - Eliquis, Xarelto, Savaysa, Pradaxa, Bevyxxa (DC in 2020).
  - All are anti-Xa. Pradaxa is a Direct Thrombin Inhibitor.
  - Newer agent coming soon: Inhibitor of Factor XIa.
- All were non-inferior to warfarin therapy before FDA approval.
- Indicated for other reasons: non-valvular afib, PAD, post op prophylaxis.

American College of Chest Physicians Recommendations for Indication, Agent, and Duration of Anticoagulation Therapy

Indication	Agent	Duration
First episode of DVT of the leg or PE	Direct oral anticoagulants over vitamin K antagonists (grade 2B) and LMWH (grade 2C)	First episode of proximal DVT or PE attributed to reversible risk factor or surgery: Three months recommended over short-term use (grade 1B), longer use (grade 1B), or extended therapy (grade 1B) First episode of unprovoked proximal DVT or PE not attributed to a reversible risk factor: Low or moderate bleeding risk: extended use (lifelong) recommended over three months (grade 2B); high bleeding risk: three months recommended over extended use (grade 1B); recommend reassessing bleeding risk annually First episode of distal DVT attributed to a surgery or reversible risk factor: If without severe symptoms or risk factors of extension, suggest serial ultrasonography surveillance for two weeks instead of anticoagulation (grade 2C); if surveillance shows extension, recommend anticoagulation (grade 2C if it does not extend into proximal vessels; grade 1B if it extends into proximal vessels) If severe symptoms or risk factors of extension, recommend three months treatment over extended use (grade 1B) Risk factors for extension: unexplained D-dimer results; extensive DVT (> 5 cm) and/or involving multiple veins; close to proximal vein; unprovoked; cancer; previous VTE; inpatient

Cancer*	LMWH over direct oral anticoagulants (grade 2C) and vitamin K antagonists (grade 2B)	Extended therapy (lifelong) recommended (grade 1B if low bleeding risk, grade 2B if high bleeding risk)
Second episode of DVT of the leg or PE	Suggest changing to LMWH if recurrence while on vitamin K antagonist or direct oral anticoagulant (grade 2C) If recurrence while on LMWH, suggest increasing dose by one-fourth to one-third (grade 2C)	After two episodes of unprovoked DVT or PE, extended therapy if low (grade 1B) or moderate (grade 2B) bleeding risk, three months suggested over extended therapy (lifelong) if high bleeding risk (grade 1B)
Following completion of anticoagulation therapy, when indicated	Suggest aspirin if unprovoked proximal DVT or PE (grade 2B) and patient elects to discontinue anticoagulation	Extended therapy (lifelong)

Review - Contraindications for AC

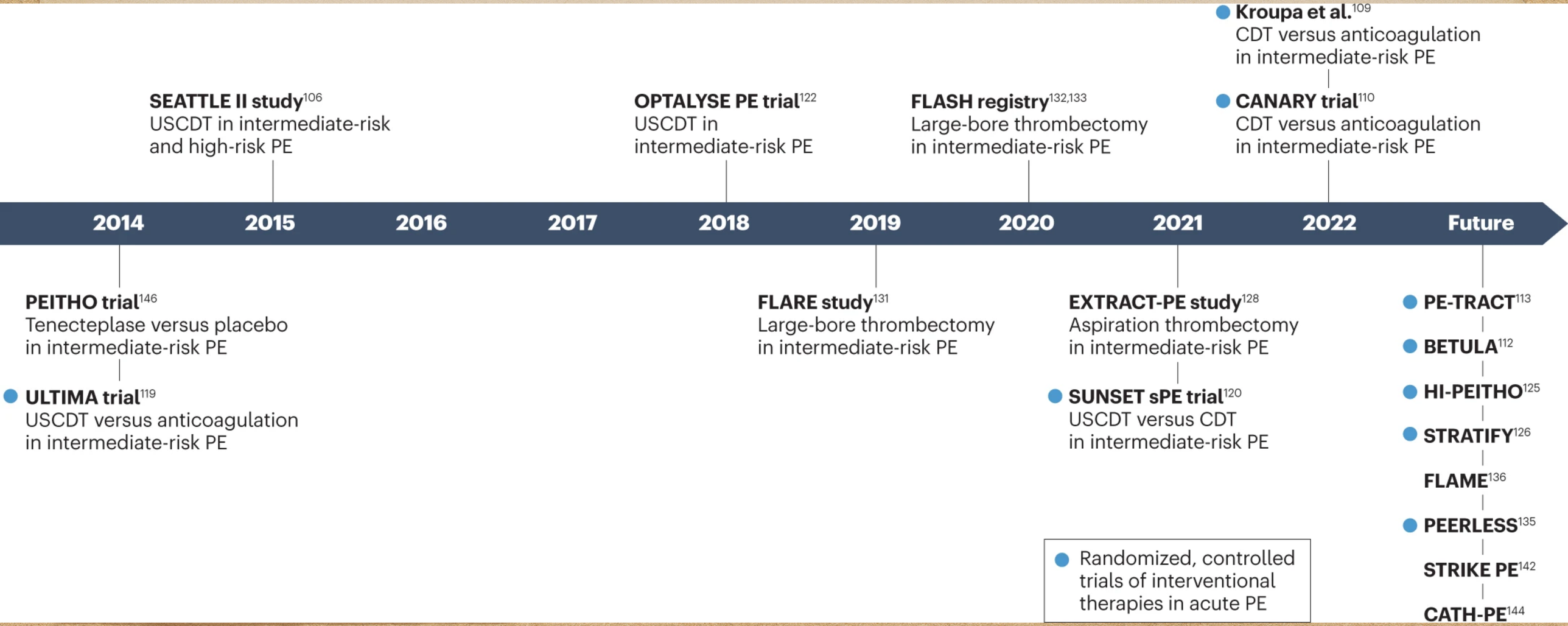
- Absolute
  - Major active bleeding, Platelet < 25K, spinal procedure, epidural placement, severe uncontrolled malignant hypertension.
- Relative
  - Brain mets (renal, choriocarcinoma, melanoma, thyroid cancer), intracranial bleeding within the past 4 weeks, recent high risk surgery or bleeding event, active but not-life threatening bleeding, active GI ulceration with high risk of bleeding, platelet < 50K. (Menstrual bleeding is not a contraindication).

Catheter-directed therapies

- Reserved for intermediate and high risks patients.
- According to a large meta-analysis systemic thrombolysis do not significantly reduce mortality in these patients, associated with bleeding events*.
- Catheter-directed therapies utilize less thrombolytic, much less bleeding risks.

*Marti C, et al. Eur Heart J, 2015

Clinical Trials for PE



Trial	n	Randomized Treatment	Comparator	Major Bleeding Criteria	Follow-Up, d	Low-Risk PE, n (%)	Intermediate-Risk PE, n (%)	High-Risk PE, n (%)	Mean Age (Range or SD), y	Male, n (%)	Efficacy	Safety
ULTIMA,[20] 2013	59	tPA-USAT (20 mg)	Heparin	ICH, spinal, joint, retroperitoneal, pericardial, hemoglobin drop >2 g/dL with transfusion	90	0 (0)	59 (100)	0 (0)	63.01 (13.51)	28 (47.46)	RV/LV ratio reduced from 1.28±0.19 to 0.99±0.17 at 24 h (P<0.001)	1 Death, 0 major bleeds, 3 minor bleeds, 0 recurrent VTE
SEATTLE II,[54] 2015	150	tPA-USAT (24 mg)	Single arm	ICH, hemodynamic compromise, need for intervention	30	0 (0)	119 (79)	31 (21)	59 (16.1)	73 (48.7)	RV/LV ratio reduced from 1.55 to 1.13 at 48 h (P<0.0001), PASP 51.4 reduced to 36.9 mm Hg (P<0.0001) at 48 h	1 GUSTO major bleed, 16 GUSTO moderate bleed, 0 ICH/death
PERFECT,[56] 2015	101	tPA or urokinase, CDL (variable dosing; mean, 28 mg tPA)	Single arm	ICH, fatal bleed	30	0 (0)	73 (72)	28 (28)	60.3 (14.9)	53 (52.5)	PASP 51.17±14.06 to 37.23±15.81 mm Hg (P<0.0001)	0 Major procedure-related complications, major hemorrhages, or hemorrhagic strokes
OPTALYSE PE,[36] 2018	101	tPA-USAT (8–24 mg)	Compared 4 tPA protocols	Fatal, ICH, bleeding in critical organ, drop of 2 g hemoglobin or need for 2 U RBC treatment	3	0 (0)	101 (100)	0 (0)	60.0 (29–77)	53 (52.5)	RV/LV ratio reduced in all arms	4 Major bleeding, 1 recurrent PE, and 1 death at 30 d; 1 additional death at 1 y
FLARE,[3] 2018	106	FlowTriever	Single arm	VARC-2 definition	30	0 (0)	104 (100)	0 (0)	55.6 (13.6)	58 (54.7)	RV/LV ratio 1.53 to 1.15 in 48 h	1 Hemoptysis, 1 clinical deterioration, 1 cardiogenic shock, 1 ventricular fibrillation, 1 death
PEITHO,[46] 2014	1006	Tenecteplase, systemic (30–50 mg)	Heparin/LMWH/fondaparinux	ICH, life-threatening, fatal, need for transfusion	30	0 (0)	1005 (100)	0 (0)	66.15 (15.29)	473 (47.06)	Death/decompensation at 7 d: 2.6% tenecteplase vs 5.6% placebo (odds ratio, 0.44; 95% CI, 0.23–0.87; P=0.02)	Tenecteplase arm: 2% ICH, 6.3% extracranial bleeding

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

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Table 3. Efficacy Outcomes.*

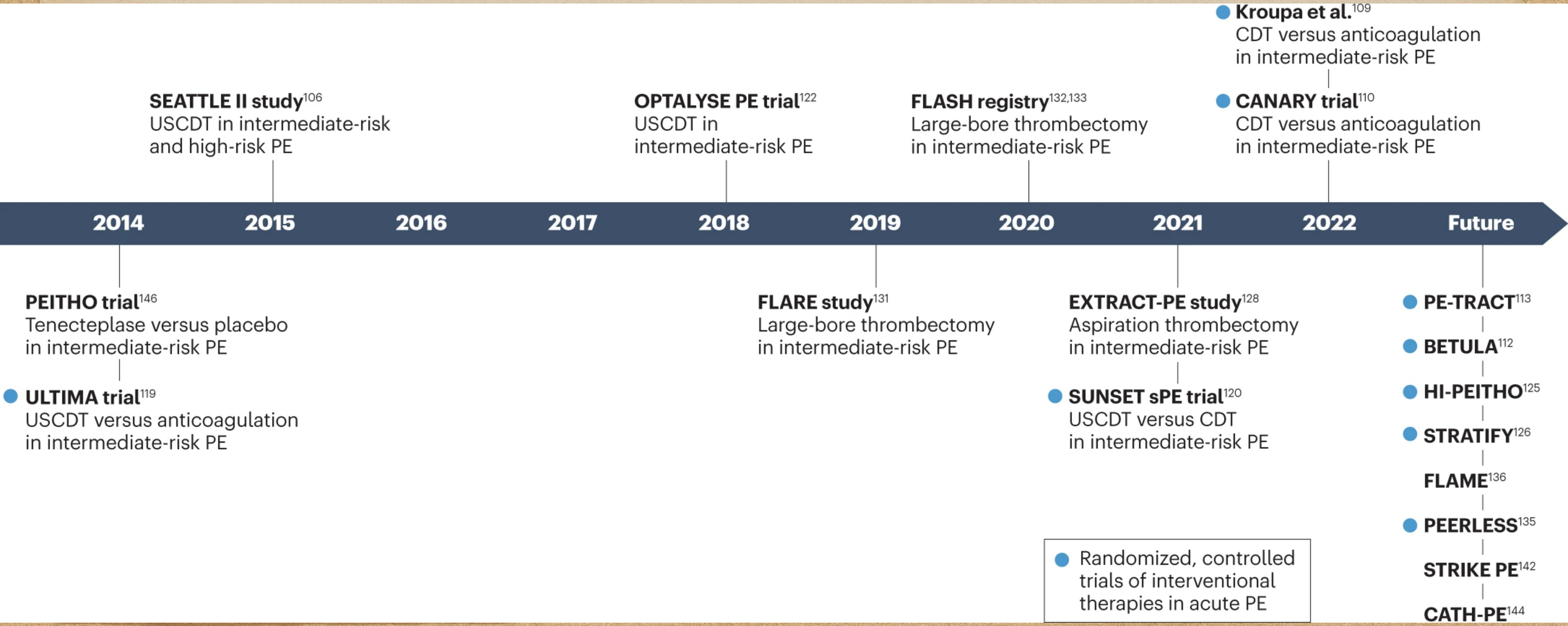
Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary 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
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		
Other in-hospital complications and procedures — no. (%)				
Mechanical ventilation	8 (1.6)	15 (3.0)		
Surgical embolectomy	1 (0.2)	2 (0.4)		
Catheter thrombus fragmentation	1 (0.2)	0 (0.0)		
Vena cava interruption	5 (1.0)	1 (0.2)		
Thrombolytic treatment other than study medication	4 (0.8)	23 (4.6)		
Death from any cause between randomization and day 30 — no. (%)	12 (2.4)	16 (3.2)	0.73 (0.34–1.57)	0.42
Patient still hospitalized at day 30 — no. (%)	59 (11.7)	50 (10.0)		
Rehospitalization between randomization and day 30 — no. (%)	22 (4.4)	15 (3.0)		

PEITHO*

- Largest PE Trial - Randomized, double-blind trial, 1006 patients.
- Thrombolytic (Tenecteplase)+ heparin vs. Heparin alone.
- Intermediate risk patients with RV strain, elevated biomarkers.
- End points: death and hemodynamic collapse after 7 days.
- **Conclusion**: Systemic lytic therapy prevented hemodynamic collapse with increased risk of bleeding (6.3% vs. 1.2%) and stroke (2.4% vs. 0.2%).
- **Gave rise to no lytic and localized lytic trials with lower dose for less bleeding.**

*Meyer, et al. NEJM 2014

Clinical Trials for PE



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

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CRF TCT

2 Attachments • Scanned by Gmail

Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a relevant financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship	Ineligible Company
Scientific Advisory Board	Abbott, Medtronic, RAPID.AI
Grant/Research Support	Abbott, Biotronik
Consultant Fees/Honoraria	Amgen, Boston Scientific, Medtronic, RAPID.AI

REAL-PE

- Technically not a trial.
- Comparing 2 PE treatment modalities (USCDT vs MT) side by side.
- Use the power of electronic medical records by Truveta:
  - 83 millions patient population
  - 535,567 with PE from 2009 to 2023
  - 1697 treated with local lytic, 742 non-lytic clot removal.

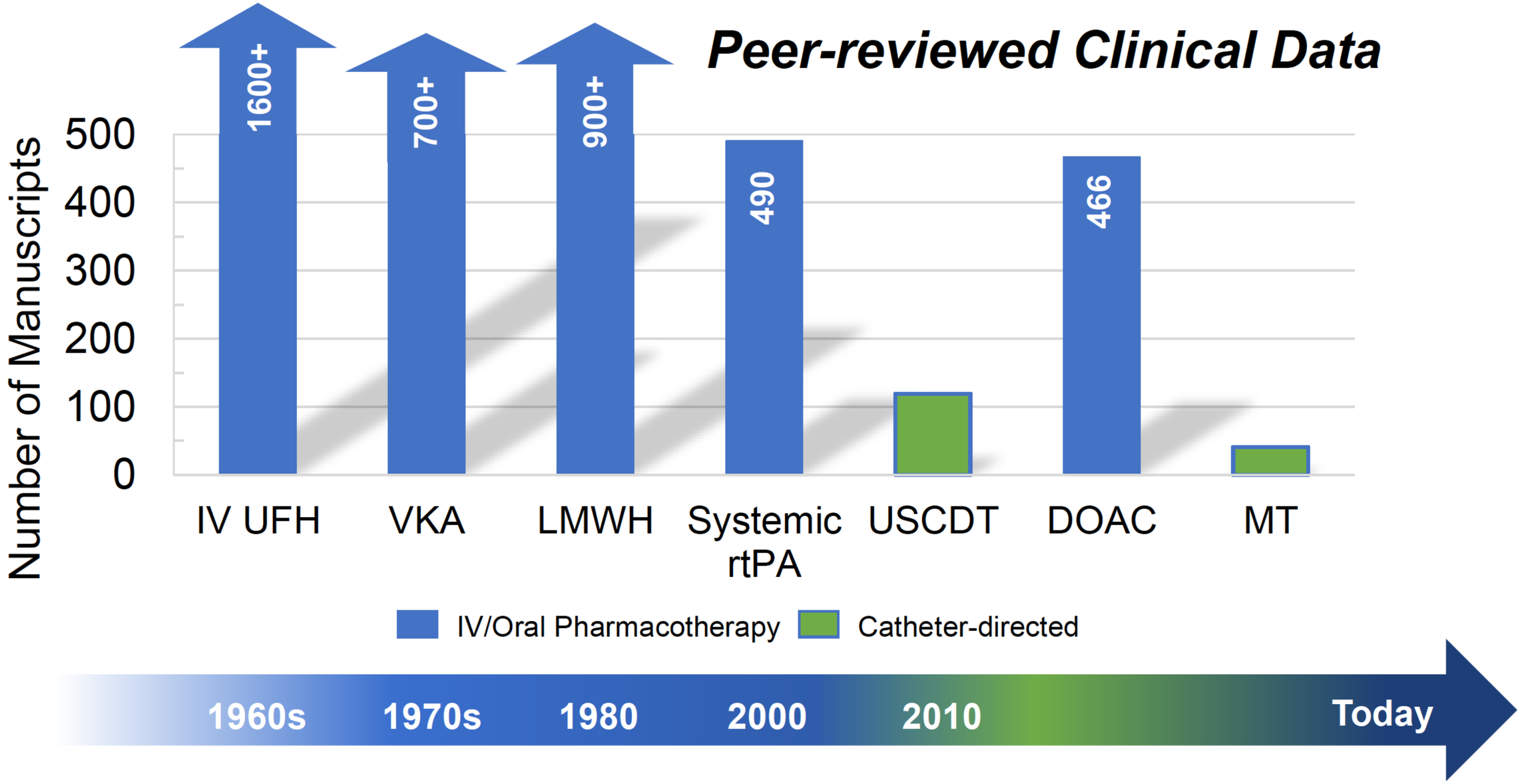
Results: Intracerebral Hemorrhage (post-procedure coding data)

	Primary (2009-2023)			Contemporary (2018-2023)		
	p-value	USCDT	MT	p-value	USCDT	MT
Ischemic stroke	0.368	26 (1.6%)	15 (2.2%)	0.450	20 (1.8%)	15 (2.3%)
Intracerebral hemorrhage	0.005	5 (0.3%)	9 (1.3%)	0.015	4 (0.4%)	9 (1.4%)
30 day readmission	0.777	81 (5.1%)	37 (5.4%)	0.730	56 (4.9%)	35 (5.3%)

Table 3: Adverse events derived from EHR data. Chi-square test p-values provided.

Take away point: Bleeding risks for either modalities are low.

Evolution of PE Therapy



MT, mechanical thrombectomy; USCDT, ultrasound assisted catheter directed thrombolysis

*Truveta True-PE

Summaries of Clinical Trials

- Invasive tx beneficial for intermediate/high risk. No benefits in low risk PE.
- Approved devices are safe and effective with low rate of complications.
- Bleeding risk in 1/2 with catheter based therapy compared to systemic.
- No long-term follow up studies for CTEPH or mortality data.
- Randomized controlled trials are difficult and expensive to conduct.
- Truveta may be the next emergent way of studying this disease.

The Future

Table 3. Future Directions of Research for Risk Stratification

Assessment Modality	Current AHA/ESC Focus	Future Directions
Clinical assessment	Systolic blood pressure Syncope Cardiac arrest	Diastolic blood pressure Mean blood pressure Heart rate Oxygen saturation and partial pressure Respiratory rate Objective functional capacity Patient-reported distress Acute cognitive impairment
Biomarker assessment	Troponin Brain natriuretic peptide	Lactate Arterial pH Worsened glomerular filtration rate
Echocardiographic assessment	RV dysfunction	Tricuspid annular plane systolic excursion RV fractional area change RV cardiac performance index RV outflow track acceleration/deceleration times RV outflow track Doppler notching Cardiac stroke volume

AHA/ESC indicates American Heart Association/European Society of Cardiology; and RV, right ventricular.

PERT

- *PERT Consortium Research Committee
- A multidisciplinary team: Interventionalist, cardiologist, radiologist, CV surgery, vasular surgery, endovascular medicine, pulmonologist, hematologist, intensivist.
- Similar concept for MI, Stroke (#Third common cause of death).
- Team available 24/7, respond within a set, short time period.
- An effort to reduce future PE mortality like cardiac arrest, MI and stroke.

*PERT Chest 2016

Thank you for your attention.