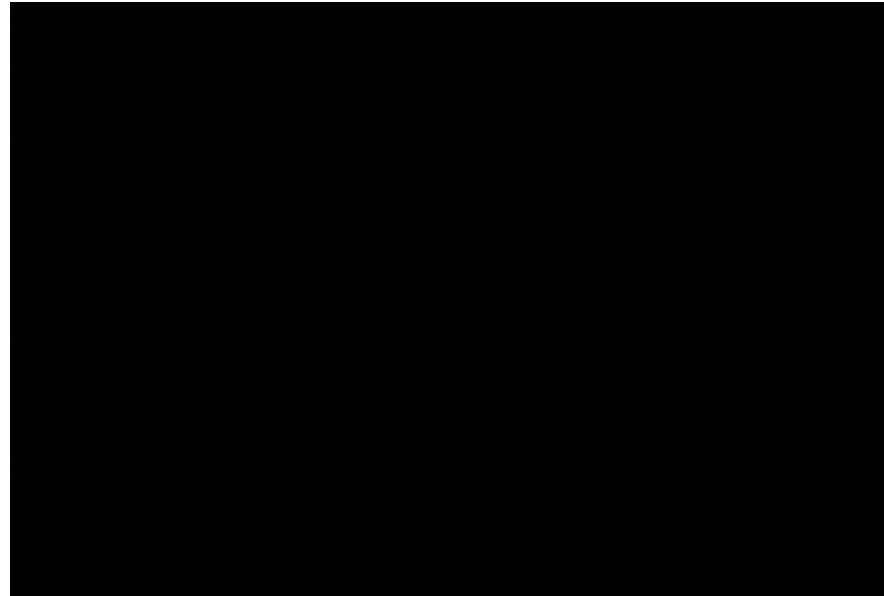


New Trends and Guidelines in the Diagnosis and Treatment of Pulmonary Embolism 2018



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Disclosures

- None relevant to this topic

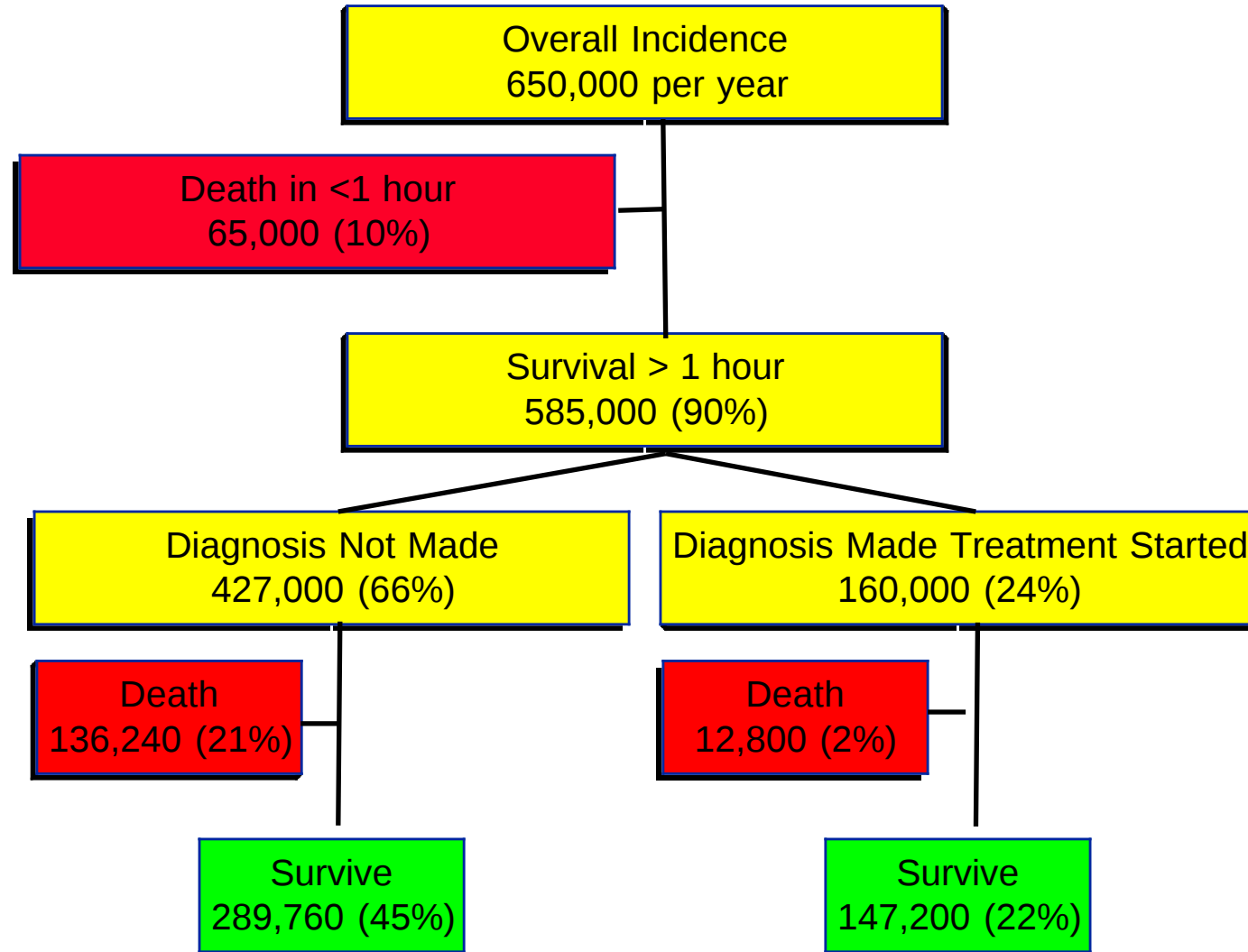
Objectives

- At the end of this lecture, participants will be able to discuss the following topics as reflected in most recent ERS and ACCP Guidelines
 - Clinical Probability Assessment +/- PERC Rule for Outpatient Diagnosis
 - Central Role of Severity Assessment in Treatment Setting, Testing and Therapy
 - Outpatient Management of PE
 - Role of Mechanical Disruption/CDT Thrombolysis in Patients with Hypotension or Shock
 - Role of DOACs (NOACs)
- At the end of this lecture, participants will be able to discuss the PERT initiative

Why Worry About Pulmonary Embolus?

- Fatal within 1 h after onset of symptoms in 10% of cases
- Untreated PE mortality rate ~30%
- Early mortality is closely linked to the probability of recurrent PE
- Recurrent PE mortality: ~ 25%
- US healthcare burden of PE estimated 2-10 billion dollars per year.

Overall Incidence and Survival



Current PE Guidelines



Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians

Ali S. Raja, MD; Jeffrey O. Greenberg, MD; Amir Qaseem, MD, PhD, MHA; Thomas D. Denberg, MD, PhD; Nick Fitterman, MD; and Jeremiah D. Schuur, MD, MHS, for the Clinical Guidelines Committee of the American College of Physicians*

[Evidence-Based Medicine]

CLINICAL GUIDELINE

Antithrombotic Therapy for VTE Disease CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

CHEST



European Heart Journal Advance Access published August 29, 2014



European Heart Journal
doi:10.1093/eurheartj/ehu283

ESC GUIDELINES

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

Authors/Task Force Members: Stavros Konstantinides* (Chairperson) (Germany/Greece), Adam Torbicki* (Co-chairperson) (Poland), Giancarlo Agnelli (Italy), Nicolas Danchin (France), David Fitzmaurice (UK), Nazzareno Galiè (Italy), J. Simon R. Gibbs (UK), Menno Huisman (The Netherlands), Marc Humbert† (France), Nils Kucher (Switzerland), Irene Lang (Austria), Mareike Lankeit (Germany), John Lekakis (Greece), Christoph Maack (Germany), Eckhard Mayer (Germany), Nicolas Meneveau (France), Arnaud Perrier (Switzerland), Piotr Pruszczyk (Poland), Lars H. Rasmussen (Denmark), Thomas H. Schindler (USA), Pavel Svtil (Czech Republic), Anton Vonk Noordegraaf (The Netherlands), Jose Luis Zamorano (Spain), Maurizio Zompatori (Italy)

Important Concept #1

Clinical Probability Assessment +/- PERC Rule for Outpatient Diagnosis

- ERS:
 - It is recommended that the diagnostic strategy be based on clinical probability assessed either by clinical judgement or a validated prediction rule. (I A)
- ACP:
 - **Best Practice Advice 1:** Clinicians should use validated clinical prediction rules to estimate pretest probability in patients in whom acute PE is being considered.
 - **Best Practice Advice 2:** Clinicians should not obtain D-dimer measurements or imaging studies in patients with a low pretest probability of PE and who meet all Pulmonary Embolism Rule- Out Criteria.

Traditional Guidelines for Diagnosis of Non-Shock PE

Wells Score for Assignment of Clinical Probability of PE

Clinical Characteristic	Score
Previous PE or deep vein thrombosis	+ 1.5
Heart rate >100 beats per minute	+1.5
Recent surgery or immobilization (within the last 30 d)	+1.5
Clinical signs of deep vein thrombosis	3
Alternative diagnosis less likely than pulmonary embolism	3
Hemoptysis	1
Cancer (treated within the last 6 mo)	1
Probability PE	Score
Low	0-1
Intermediate	2-6
High	>6

Why is Might Further Exclusion from Testing Be Important?

- Many patients will not have disease.
 - Typically 60% still tested
 - $<1/2$ of those will have PE
- Testing may not be benign
 - Dye
 - Radiation
- Problems with false positives
 - Generate more testing
 - Divert from true diagnosis
- Impact of applying testing in low prevalence populations

Relationship between disease prevalence and predictive value in a test with 95% sensitivity and 85% specificity

Study Challenging Initial ED Paradigm: Addition of Pulmonary Embolism Rule-out Criteria (PERC)

Pulmonary Embolism Rule-out Criteria (PERC)

- age < 50 years
- pulse < 100 bpm
- arterial oxygen saturation (SpO₂) > 94 %
- no unilateral leg swelling
- no hemoptysis
- no recent trauma or surgery
- no prior PE or deep venous thrombosis (DVT)
- no exogenous estrogen use

Results from PERC Prospective Validation Study (12 Hospitals, 8138 patients)

Summary of Sequential PERC use in low probability patients

- Has acceptably low false (-) rate
- Further excludes at least 10% of CT scans ordered

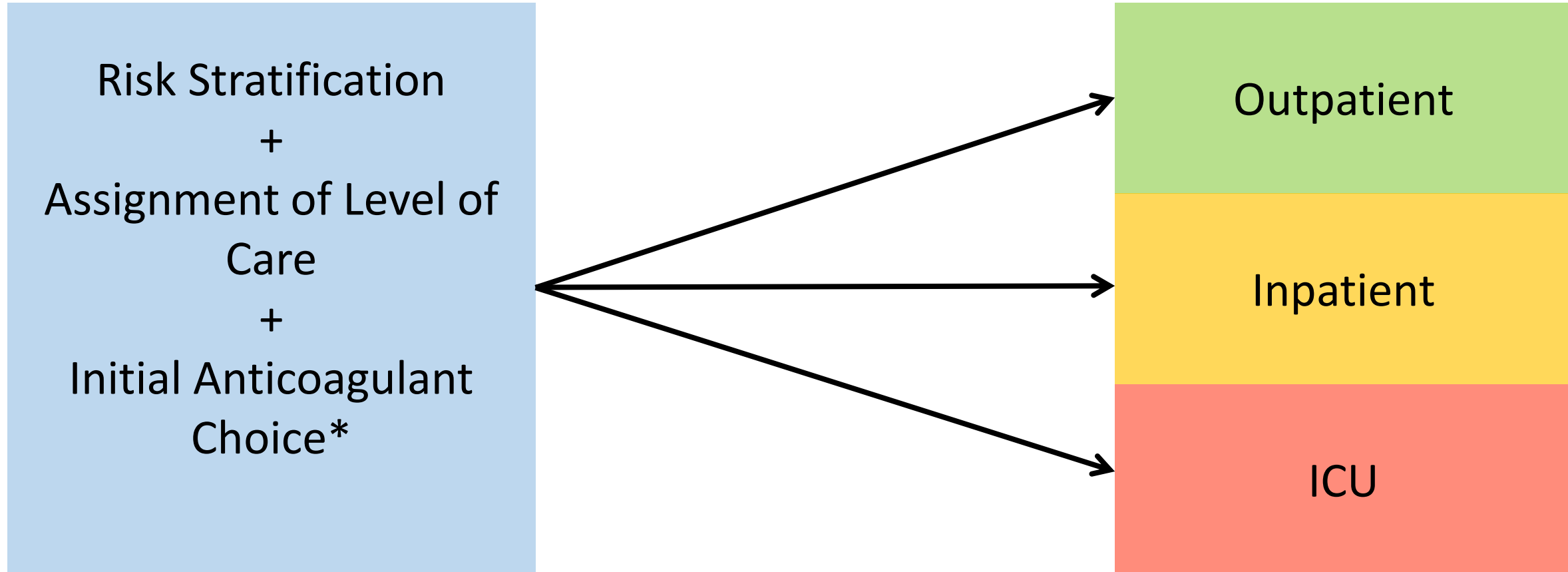
Important Caveats for Application of PERC Calculator

- The PERC rule **cannot be a substitute for gestalt**.
- Gestalt or some form of risk stratification should be employed **first before using** the PERC rule.
- The PERC rule should **not** be used in isolation to rule out PE in **pregnant or postpartum** patients.
- **It is unclear if patients on beta blockers can be included** in the PERC rule, and this significance has yet to be borne out in the data.
- The meta-analysis pooled negative LR is 0.17, which gives you a maximum pretest probability of about 15% to apply the PERC rule to risk stratify your patient down to the standard risk of 2%. However, your PE prevalence must be 7% or less (essentially a **Wells < 2**) before the PERC rule can be applied to patients presenting to ED with suspected PE in conjunction with clinical judgment to identify patients with a prevalence of PE that is below the 1.8% test threshold proposed by Kline.
- In high PE prevalence populations (which based on the literature, seem to be in Europe) the PERC score inclusive patients will not be able to have a post-test probability at or below the accepted standard risk level.*
- The only evidence we have about PERC rule-inclusive CT-PE or V/Q positive patients suggests that 56% of those will have **pleuritic chest pain**, which is not in a validated clinical decision rule despite having a higher OR for PE than hemoptysis and recent immobilization, which are both included in the Wells score.

Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians

Important Concept #2: Central Role of Severity Assessment in Treatment Setting, Testing and Therapy

Treatment of Pulmonary Embolism in the ED: Risk Stratification and Level of Care



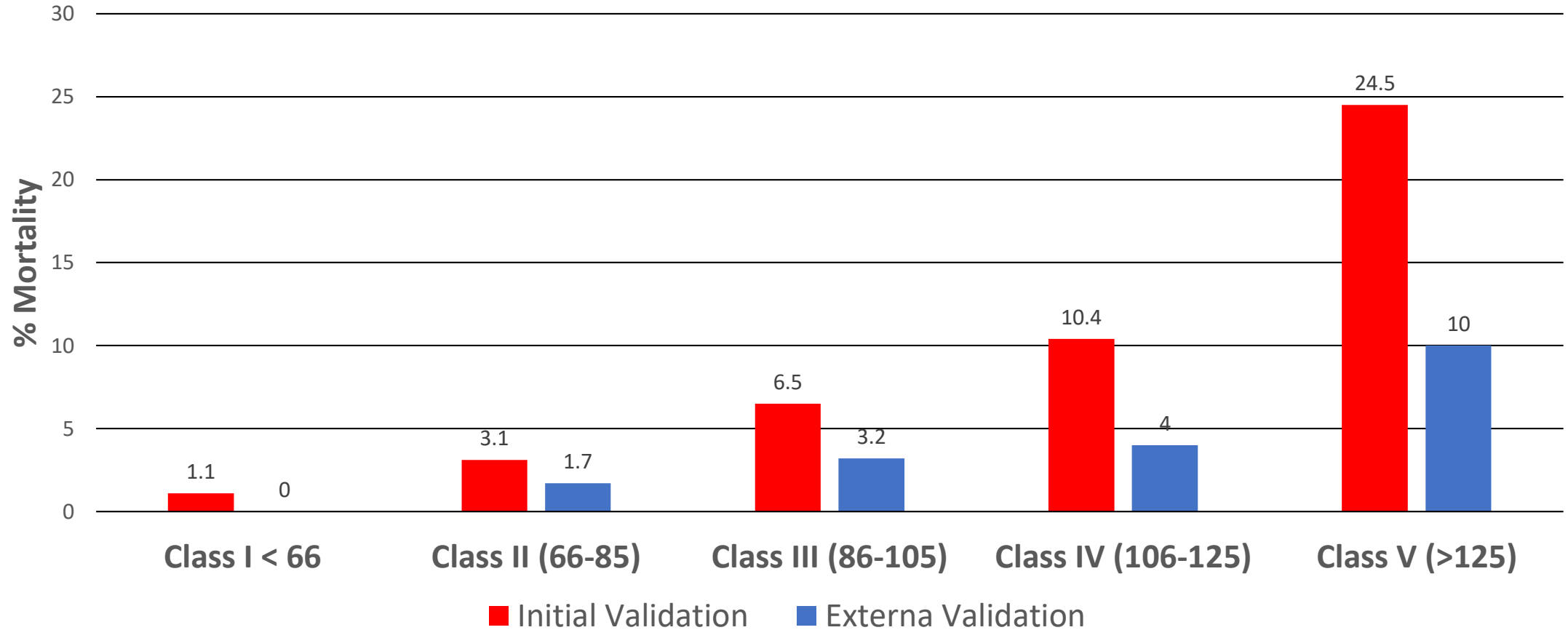
*Patients who have absolute contraindications to anticoagulation should be considered for IVC filters +/- Mechanical or surgical interventions depending on risk profile.

Independent predictors of 30-DAY mortality in the derivation sample and points assigned to the PESI risk score

Class	Risk	Score
I	Very Low	≤ 65
II	Low	66-85
III	Intermediate	86-105
IV	High	106-125
V	Very High	>125

Comparison of PESI and sPESI Scoring (0 or 1)

Risk of 30 Day PE Mortality by Severity Score



Adapted from: Aujesky D. et al. Am J Respir Crit Care Med. 2005 Oct 15; 172(8): 1041–1046

Assignment of Risk in PE Patients

Relevant data used to assess risk and determine treatments in PE?

- Assessment of Severity
 - Vital Signs (Evolution important)
 - HR
 - BP
 - SpO₂
- History
 - Personal history of prior VTE?
 - Personal history of RV dysfunction?
 - Active cardiac or pulmonary limitation?
- Proof of PE
 - CT
 - V/Q
 - DVT + pulmonary symptoms
 - Clinical suspicion in *extremis*
- Studies
 - Right Ventricular Appearance (Echo or CT RV/LV ratio)
 - Lactate
 - ECG
 - Troponin
 - BNP
 - Extent of Peripheral Clot

RV/LV Ratio and Risk Assessment

Images courtesy of Houston Methodist Sugar Land Hospital

Severity Scoring of PE and Decision of Appropriate Setting of Care

- Very Low Risk – Outpatient or early discharge, anticoagulation
- Intermediate Lower Risk – Inpatient, anticoagulation
- Intermediate Higher Risk – ICU monitoring, anticoagulation*
- Very High Risk/Hypotension/Shock – ICU, anticoagulation
 - +/- pressor
 - +/- thrombolysis
 - +/- mechanical treatment
 - +/- surgical embolectomy

*Prospective studies of ICU care improving outcome have not confirmed this recommendation

Risk-adjusted management strategies in acute PE.

Important Concept #3

Outpatient Management of PE

- ACCP: In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (eg, after the first 5 days of treatment) (Grade 2B).
- ERS: Patients with acute low-risk PE should be considered for early discharge and continuation of treatment at home if proper outpatient care and anticoagulant treatment can be provided. (IIa, B)

Who Can be Considered for Outpatient Treatment for PE?

- Low risk of death – defined as pulmonary embolism severity index (PESI) class I or II, or simplified PESI (sPESI) score = 0.
- No requirement for supplemental oxygen
- No requirement for narcotics for pain control
- No respiratory distress
- Normal pulse and blood pressure
- No recent history of bleeding or risk factors for bleeding
- No serious comorbid conditions (eg, ischemic heart disease, chronic lung disease, liver or renal failure, thrombocytopenia, or cancer)
- Normal mental status with good understanding of risk and benefits
- Are not needle averse (if low molecular weight (LMW) heparin chosen), and have good home support (eg, do not live alone, have access to a telephone and physician, can return to the hospital quickly if there is clinical deterioration)
- Absence of concomitant deep venous thrombosis (a high clot burden in the lower extremities may increase the risk of death or warrant additional therapy)

What Treatment Options Exist for Outpatient Treatment of PE?

- ¹LMWH (studied) or fondaparinux -> VKA
- DOACs

¹ Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet*. 2011 Jul 2. 378(9785):41-8

HESTIA Exclusion Guidelines

Is the patient hemodynamically unstable?*	Yes	No
Is thrombolysis or embolectomy necessary?	Yes	No
Active bleeding or high risk of bleeding?†	Yes	No
More than 24 h of oxygen supply to maintain oxygen saturation > 90%?	Yes	No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes	No
Severe pain needing intravenous pain medication for more than 24 h?	Yes	No
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?	Yes	No
Does the patient have a creatinine clearance of < 30 mL min ⁻¹ ?‡	Yes	No
Does the patient have severe liver impairment?§	Yes	No
Is the patient pregnant?	Yes	No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes	No

If the answer to one of the questions is 'yes', the patient cannot be treated at home in the Hestia Study

Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study

Outcome in HESTIA

Clinical outcome	No.	Percentage (95% CI)
Total recurrences	6	2.0 (0.75–4.3)
Fatal recurrent PE	0	0 (0–1.2)
Non-fatal recurrent PE	5	1.7 (0.55–3.9)
Non-fatal recurrent DVT	1	0.34 (0.0082–1.9)
Major bleeding complications	2	0.67 (0.082–2.4)
Fatal bleeding	1	0.34 (0.0082–1.9)
Non-fatal major bleeding	1	0.34 (0.0082–1.9)
Clinically relevant non-major bleeding	15	5.1 (2.9–8.2)
All-cause mortality	3	1.0 (0.21–2.9)
CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism.		

Patients fulfilling all low risk criteria and having adequate knowledge and support should be considered for homegoing or early release treatment of PE

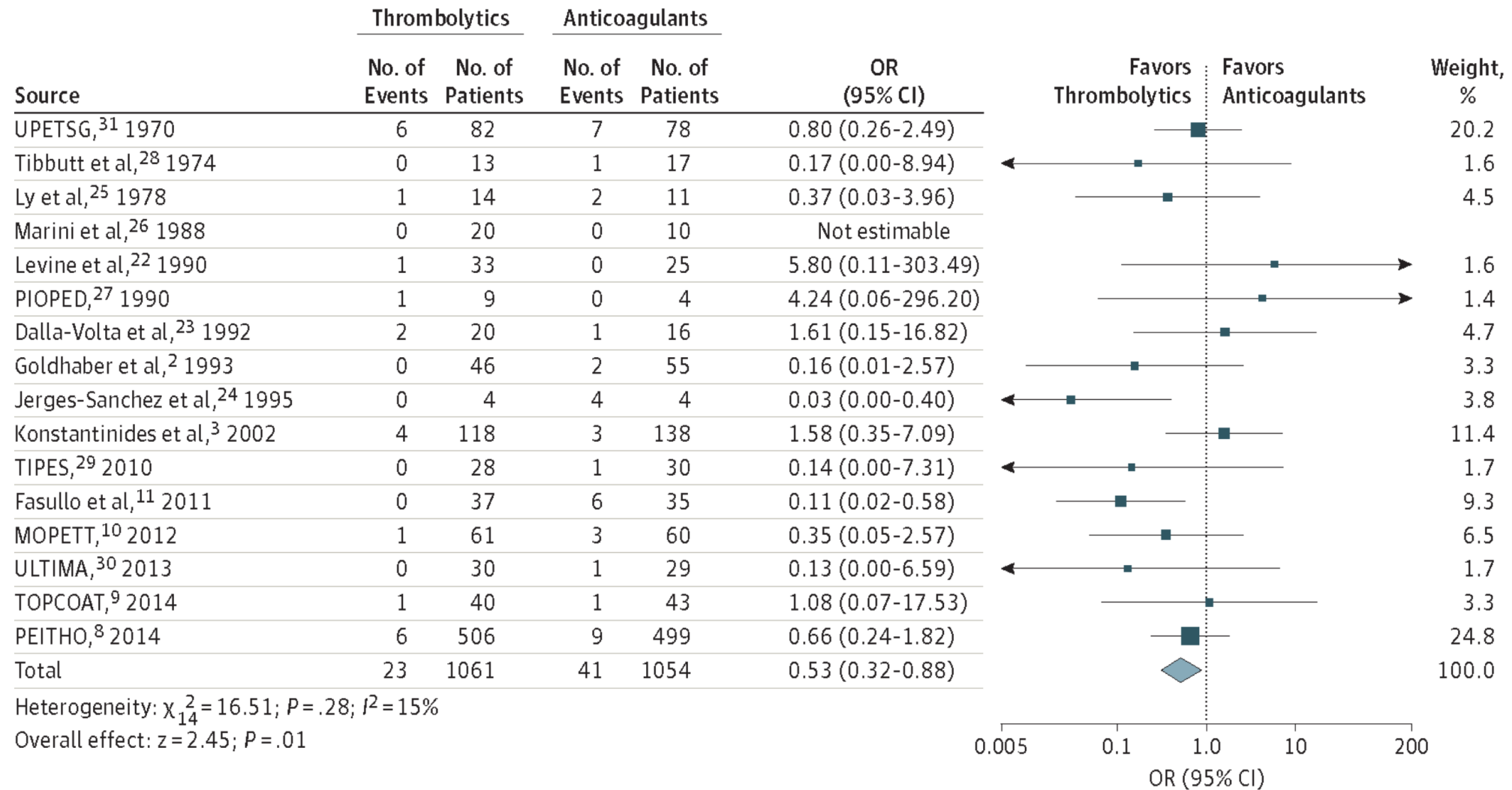
Important Concept #4

Role of Mechanical Disruption/CDT/ Thrombolysis in Patients with Hypotension or Shock

Historical Issue with Thrombolysis

- No superiority of catheter directed (CDT) vs system at full dose
- No studies conclusively powered to unequivocally demonstrate benefit
- Non-trivial incidence of serious or fatal hemorrhagic stroke
- Uncertainty of improvement in ill patients with anticoagulation only

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



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

Thrombolysis of Non-Shock PE

- Several studies have advocated on the basis of improvement of long term outcomes
 - Deterioration or death
 - Disability
 - Recurrence
 - Incidence of CTEPH
- No studies have really looked at this extensively
- Only marginal longitudinal study had been Pengo et al.(NEJM 2004) in which thrombolysis was actually associated with CTEPH.

Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism

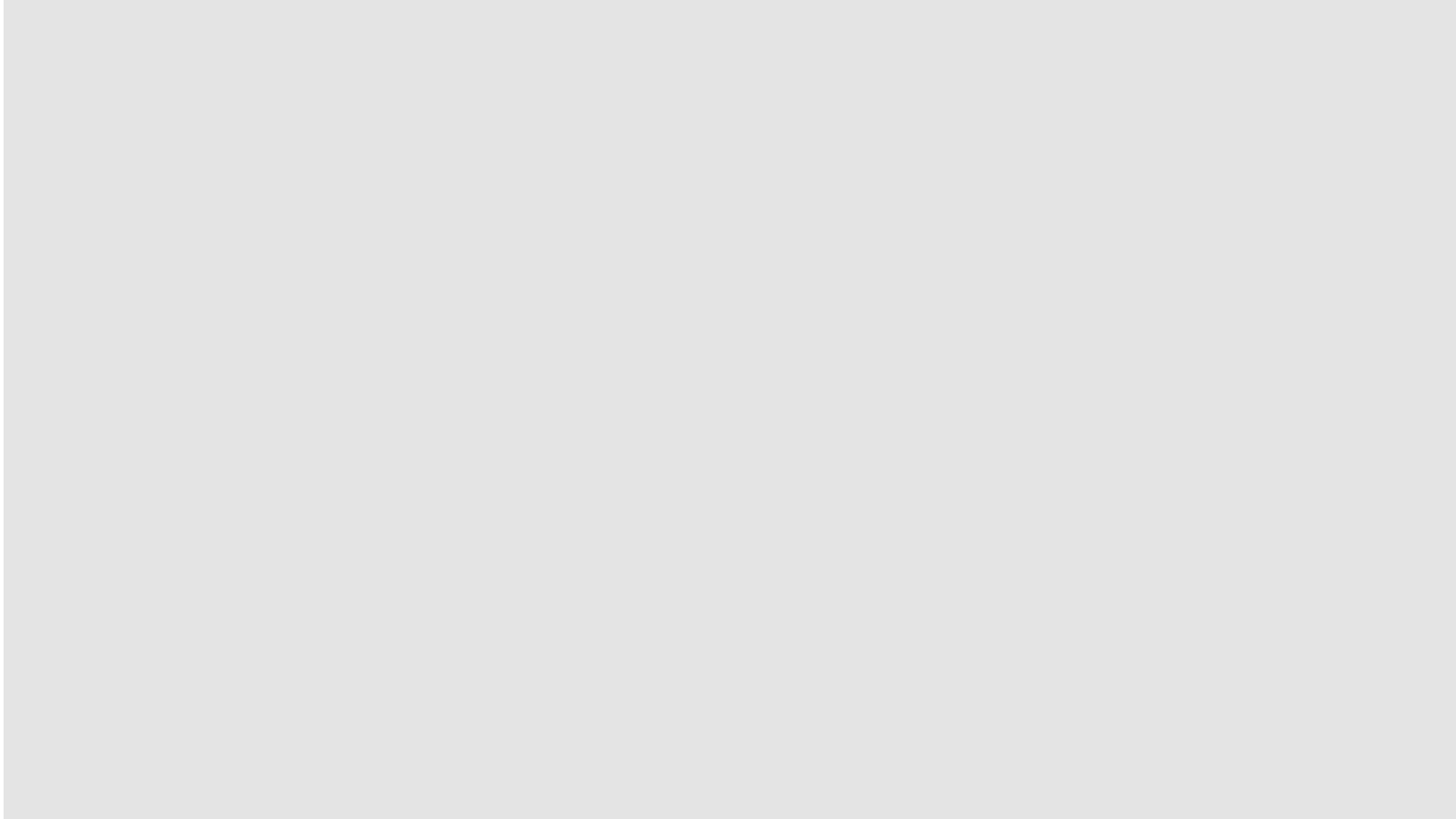
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Conclusions from Long Term Evaluation of PEITHO Trial

- No difference in mortality
- No difference in CTED
- No difference in RV (actually several echo parameters worse in thrombolysis)
- No difference in patient reported disability

EKOS Catheter

EKOS Catheter



Exclusion Criteria in ULTIMA Trial of EKOS CDT vs Heparin

- Exclusion criteria
 - age <18 or >80 years
 - index PE symptom duration >14 days
 - insufficient echocardiographic image quality in the apical 4-chamber view that prohibited the measurement of the RV/LV ratio
 - known significant bleeding risk
 - administration of thrombolytic agents within the previous 4 days
 - active bleeding; known bleeding diathesis; known coagulation disorder; platelet count <100 000/mm³
 - previous use of vitamin K antagonists with international normalized ratio >2.5 on admission
 - history of any intracranial or intraspinal surgery or trauma or intracranial/intraspinal bleeding
 - intracranial neoplasm, arteriovenous malformation, or aneurysm; gastrointestinal bleeding <3 months
 - internal eye surgery or hemorrhagic retinopathy <3 months
 - major surgery, cataract surgery, trauma, obstetric delivery
 - cardiopulmonary resuscitation, or other invasive procedure <10 days
 - allergy, hypersensitivity, or thrombocytopenia from heparin or rtPA
 - severe contrast allergy to iodinated contrast
 - known right-to-left cardiac shunt (eg, from a large patent foramen ovale or atrial septal defect)
 - large (>10 mm) right atrial or RV thrombus
 - hemodynamic decompensation, defined as the need for cardiopulmonary resuscitation, or systolic blood pressure <90 mm Hg for at least 15 minutes, or drop of systolic blood pressure by at least 40 mm Hg for at least 15 minutes with signs of end-organ hypoperfusion (cold extremities or low urinary output <30 mL/h or mental confusion), or need for catecholamine administration to maintain adequate organ perfusion and a systolic blood pressure of >90 mm Hg
 - severe hypertension on repeated readings (systolic >180 mm Hg or diastolic >105 mm Hg)
 - pregnancy, lactation, or parturition <30 days
 - participation in any other investigational drug or device study
 - life expectancy <90 days
 - inability to comply with study assessments.

Outcomes ULTIMA Trial

Outcomes ULTIMA Trial

Important Concept #5: Role of DOACs (NOACs)

- ERS
 - As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with:
 - rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.
 - apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.
 - As an alternative to VKA treatment, is recommended are following acute- phase parenteral anticoagulation
 - dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment)
 - edoxaban 60 mg daily is recommended following acute-phase parenteral anticoagulation.
- CHEST
 - In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).

Summary of Trials of DOACs in VTE

Anticoagulation: How Long and Why?

ACCP Guideline Recommendations

- **In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B),**

Rationale

- Lifelong risk of recurrent VTE (Unprovoked) is approximately 30%
- 15% risk in 5 years (Women)
- 25-30% 5 year for men.
- Increased with elevated d-dimer levels
- Increased with hypercoagulable states

Secondary Prevention Using DOACS

Summary

- At the end of this lecture, participants will be able to discuss the following topics as reflected in most recent ERS and ACCP Guidelines
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 - Role of DOACs (NOACs)
- At the end of this lecture, participants will be able to discuss the PERT initiative

Important Concepts #6: PERT

- PERT = Pulmonary Embolism Response Team
- Started at MGH
 - Non-Standard Care in spite of guidelines
 - Difficulty mobilizing care acutely for unstable patients
 - Framework for research
- Multidisciplinary Team
 - Pulmonary/Critical Care
 - Cardiology
 - Radiology
 - Cardiac Surgery
 - Hematology
 - Vascular Medicine

MGH PERT Activations

Initial Outcome of PERT Team Activations

University of Virginia, PERT Schema

PERT Consortium

UH is Part of PERT Consortium

- Currently a loose association involving
 - Pulmonary/Critical Care
 - Cardiology
 - Cardiothoracic Surgery
 - Vascular Medicine
 - Perfusion
- In process of formalizing activation