Management of sub-massive and massive pulmonary embolism:

Evidence and Controversy

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AGENDA

• CLINICAL SPECTRUM OF ACUTE PULMONARY EMBOLISM (APE)
• CLASSIFICATION OF APE: THEN AND NOW
• WHAT IS LIFE THREATENING (CRITICAL, SEVERE) VTE?
• SUB-MASSIVE VS MASSIVE PULMONARY EMBOLISM
• CURRENT EVIDENCE-BASED APPROACH ON MANAGEMENT OF APE
  • ANTI-CoAGULANT THERAPY
  • MANAGEMENT OF MASSIVE PE
    • THROMBOLYTIC THERAPY
    • UNSUCCESSFUL INITIAL THROMBOLYSIS: CATHETER-BASED THERAPY, SURGICAL EMBOLECTOMY, OR REPEAT THROMBOLYSIS,
  • MANAGEMENT OF SUB-MASSIVE PE
    • IS THERE ROLES OF THROMBOLYSIS IN SUB-MASSIVE PE?
  • IVC FILTER FOR APE & EXTENSIVE PROXIMAL DVT
• SUMMARY
CONFLICT OF INTEREST

I have no conflict of interest about methods, machines, and products use in this lecture.
Incidence of Pulmonary Embolism Per Year in the United States

**Total Incidence 630,000**

- **Death within 1 hr** 67,000 (11%)
  - **Dx not made** 400,000 (71%)
    - Survival >1 hr 563,000
    - **Dx made, therapy instituted** 163,000 (29%)
      - Survival 150,000 (92%)
      - Death 120,000
  - **Survival** 280,000 (70%)
  - **Death** 120,000 (30%)

*Progress in Cardiovascular Diseases, Vol. XVII, No. 4 (Jan/Feb 1975)*
Classification of APE:

Then and now
Pathological Classification According to “Clot Burden”

- **Small PE**: Pulmonary vascular bed (PVB) occlusion ~30-50% PAP ~ normal or slightly elevate

- **Moderate PE**: PVB occlusion ~50-75 %, significantly elevate PAP & evidence of RV dilatation/akinesia

- **Massive PE**: PVB occlusion >75 %,

Risk Stratification In APE: Clinical Features & Diagnostic Tests

Mortality
- 65% Cardiac Arrest
- 25% Shock
- 15% Hypotension without hypoperfusion
- 8.1% Normal BP with RV dysfunction
- 0-1% Normal BP and RV function

Clinical Status At Presentation

Higher Risk
- EKG
- CXR
- ABG
- D-Dimer
- Troponin, BNP
- Echocardiography

Predictions

Lower Risk
- V/Q
- CT Angiography
- Angiography

MAPPET – Kasper JACC 1997; 30:1165-1171
Initial risk stratification of acute PE

Suspected acute PE

Shock or hypotension\(^a\)?

Yes

High-risk\(^b\)

No

Not High-risk\(^b\)

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\(^a\) Defined as systolic blood pressure < 90 mmHg, or a systolic pressure drop by ≥ 40 mmHg, for > 15 minutes, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis.

\(^b\) Based on the estimated PE-related in-hospital or 30-day mortality.
RV dysfunction-Echocardiogram

Survival, %

Days

No RV Hypokinesis
RV Hypokinesis

Arch Intern Med. 2005;165:1777-1781
## Classification of early mortality risk

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Risk parameters and scores</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Shock or hypotension</td>
<td>PESI Class III-V or sPESI &gt;1</td>
</tr>
<tr>
<td>High</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate-high</td>
<td>−</td>
</tr>
<tr>
<td>Low</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

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# Prognostic Categories of Pulmonary Embolism

<table>
<thead>
<tr>
<th>Category</th>
<th>Presenting Symptoms and Signs</th>
<th>Prevalence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac arrest/ Need CPR</td>
<td>Shock</td>
<td>RV. Dysfunction</td>
</tr>
<tr>
<td>Massive</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Massive</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sub-massive</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-massive</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

CPR, cardiopulmonary resuscitation; RVD, right ventricular dysfunction
Clinical Presentations and Outcomes of Pulmonary Embolism

- Non-massive: 48%
- Sub-massive: 32%
- Massive: 20%

Mortality:
- Normotensive, normal RV function: 0%
- Normotensive, RV dysfunction: 10%
- Shock: 30%
- Cardiac arrest: 50%
- Sudden death: 100%

Severity Spectrum:
- Embolism size
- Cardiopulmonary reserve
What is life threatening APE?

Sub-massive VS Massive PE
Classification based on Severity Spectrum of Acute Pulmonary embolism

- Asymptomatic
- Mild Symptoms
- RV Dysfunction
- Non-massive
- Sub-massive
- Massive
- Shock >> CPR
- Normotensive
- Hypotensive
- Life-threatening APE

APE: Acute Pulmonary Embolism
Sub-massive or Massive PE?

Sub-massive PE

- APE without systemic hypotension but with either **RV dysfunction** or **myocardial necrosis**

- **RV dysfunction**: the presence of at least 1 of the following
  - ECG: new RBBB or anteroseptal elevation or T-wave inversion
  - RV dilatation (RV/LV Ø > 0.9) by echo. or CT.
  - BNP > 90 pg/mL
  - NT pro BNP >500 pg/mL. &
  - either
    - Troponin I > 0.4 ng/mL or
    - Troponin T> 0.1 ng/mL

Massive PE

- APE with **sustained hypotension** (BPs <90 mmHg.) for at least 15 min. or requiring **vasopressor** (not for other explainable cause(s) of shock)

- APE present with **cardiac arrest**

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The International Cooperative Pulmonary Embolism Registry (ICOPER)
Current evidence-based approach on Management of Acute pulmonary Embolism (APE)
2014 ESC Guidelines on The Diagnosis & Management of Acute Pulmonary Embolism

Chairpersons
Stavros Konstantinides (Germany/Greece)
Adam Torbicki (Poland)
Antithrombotic Therapy for Venous Thromboembolic Diseases

Antithrombotic Therapy and Prevention of Thrombosis: ACCP Evidence-Based Clinical Practice Guidelines, 9th ed

2012
Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing

Issued: June 2012

NICE clinical guideline 144
guidance.nice.org.uk/cg144
Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension


Circulation
Volume 123(16):1788-1830
April 26, 2011
Options of APE Management

- Heparin & anticoagulants
- Thrombolystics
- Catheter-based therapy
- Surgical embolectomy
Anticoagulant Therapy
RECOMMENDATIONS FOR **INITIAL ANTICOAGULATION FOR ACUTE PE**

1. Therapeutic anticoagulation during the diagnostic workup **should be given** to patients with intermediate or high clinical probability of PE and no contraindications to anticoagulation

*(Class I; Level of Evidence C).*
In Critical (Major) Pulmonary Embolism

- Diagnostic confirmatory studies can delay definitive treatment and contribute to additional mortality; 14%-67%

- Mortality decreasing with early anticoagulant therapy, but variable (16% - 46%)

- Sub-therapeutic level of anticoagulant in the first 24 hours may contribute additional mortality
Thrombolytics Therapy
In Massive PE
Massive Pulmonary Embolism (MPE)  
Prevalence and mortality

• The MAPPET (Germany based) APE with **hypotension** MR 25 %,

• APE **required CPR** MR 65% as compared to other

• **Massive PE**: 90 day Mortality rate 52.4 %

• Hemodynamic stable APE (non-massive & submassive) MR 8 %

*ICOPER 2005*

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

Odds of Mortality in Patients With Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation Evaluated using the Peto method of meta-analysis. MOPETT indicates Moderate Pulmonary Embolism Treated with Thrombolysis trial; PEITHO, Pulmonary Embolism Thrombolysis trial; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; TIPES, Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT, Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism trial; UPETSG, Urokinase Pulmonary Embolism Trial Stage 1.
From: *Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: A Meta-analysis*


Odds of Mortality in Patients With Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation Evaluated using the Peto method of meta-analysis. MOPETT indicates Moderate Pulmonary Embolism Treated with Thrombolysis trial; PEITHO, Pulmonary Embolism Thrombolysis trial; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; TIPES, Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT, Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism trial; UPETSG, Urokinase Pulmonary Embolism Trial Stage 1.
RECOMMENDATIONS FOR FIBRINOLYSIS FOR ACUTE PE-1

1. Fibrinolysis is **reasonable** for patients with **massive acute PE** and acceptable risk of bleeding complications

   *(Class IIa; Level of Evidence B).*
Cardiac Arrest

Shock > 15 min.

NO Absolute contraindications

Prolonged CPR not CI
# Thrombolytic treatment of PE

## Approved thrombolytic regimens for pulmonary embolism

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>250,000 IU as a loading dose over 30 minutes, followed by 100,000 IU/h over 12-24 hours.</td>
</tr>
<tr>
<td></td>
<td>Accelerated regimen: 1.5 million IU over 2 hours.</td>
</tr>
<tr>
<td>Urokinase</td>
<td>4,400 IU/kg as a loading dose over 10 min, followed by 4,400 IU/kg per hour over 12-24 hours.</td>
</tr>
<tr>
<td></td>
<td>Accelerated regimen: 3 million IU over 2 hours.</td>
</tr>
<tr>
<td>rtPA</td>
<td>100 mg over 2 hours; or</td>
</tr>
<tr>
<td></td>
<td>0.6 mg/kg over 15 minutes (maximum dose 50 mg).</td>
</tr>
</tbody>
</table>
# Contraindications to Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major trauma, surgery, head trauma (within 3 weeks)</td>
<td>Cancer</td>
</tr>
<tr>
<td>Prior hemorrhagic stroke</td>
<td>Age &gt; 75-80</td>
</tr>
<tr>
<td>Ischemic stroke within prior 6 months</td>
<td>Transient ischemic attack within 6 months</td>
</tr>
<tr>
<td>Central nervous system neoplasm</td>
<td>Oral anticoagulant therapy</td>
</tr>
<tr>
<td>Gastrointestinal bleeding within one month</td>
<td>Non-compressible punctures</td>
</tr>
<tr>
<td>Concurrent active bleeding</td>
<td>Traumatic resuscitation</td>
</tr>
<tr>
<td></td>
<td>Refractory hypertension</td>
</tr>
<tr>
<td></td>
<td>Advanced liver disease</td>
</tr>
<tr>
<td></td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td></td>
<td>Active peptic ulcer</td>
</tr>
<tr>
<td></td>
<td>Pregnancy or within one week postpartum</td>
</tr>
</tbody>
</table>

Thrombolytics Therapy
In Sub-massive PE
Key factors contributing to haemodynamic collapse in acute pulmonary embolism

Increased RV afterload

- RV Necrosis
- RV O₂ delivery
- RV coronary perfusion
- Systemic BP
- Low CO
- LV pre-load

Cardiogenic shock
- Death

RV dilatation
- TV insufficiency
- RV wall tension
- Neurohormonal activation
- Myocardial inflammation
- RV O₂ demand
- RV ischaemia
- RV contractility
- RV output

BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.
Clinical Presentations and Outcomes of Pulmonary Embolism

Mortality

Non-massive
48%

Sub-massive
32%

Massive
20%

Severity Spectrum

» Embolism size
» Cardiopulmonary reserve

Normotensive, normal RV function

Normotensive, RV dysfunction

Shock

Sudden death

Cardiac arrest

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
How many subgroups in Sub-massive Acute Pulmonary Embolism:

FIFTY SHADES OF GREY
Central Debate for last 3 Centuries

Thrombolytic in Sub-massive PE

**Pros**
- Feel better quicker
- Resolve clots faster?
- Improved RV function
  - Decrease PA pressure

**Cons**
- Increased ICH rate
- Increased other life threatening hemorrhage
  - Increased cost
- No survival benefit
Indicators of RV dysfunction use in studies

**EKG**

- \(S_1, Q_3, T_3\) and T wave changes

**Cardiac Biomarkers:**
- BNP >100 pg/mL or
- pro-BNP >900 pg/mL

**Echocardiography**

- RV Dilation, RV: LV \(\geq 1\), leftward septal bowing
- RV hypokinesia
- Estimated RVSP> 40 mmHg
NO CLEAR TREND IN BENEFIT

Wan S, Circ 110:744, 2004
No SURVIVAL BENEFIT but with significant risk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials That Included Patients With Major PE</th>
<th>Trials That Excluded Patients With Major PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombolysis, n/N (%)</td>
<td>Heparin, n/N (%)</td>
</tr>
<tr>
<td>Recurrent PE or death</td>
<td>12/128 (9.4)</td>
<td>24/126 (19.0)</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>5/128 (3.9)</td>
<td>9/126 (7.1)</td>
</tr>
<tr>
<td>Death</td>
<td>8/128 (6.2)</td>
<td>16/126 (12.7)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>28/128 (21.9)</td>
<td>15/126 (11.9)</td>
</tr>
</tbody>
</table>

PE indicates pulmonary embolism.
30% of normotensive PE have RV dysfunction

10% further developed hypotension

5% mortality during admission
Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaux, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., Ana Franca, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kupatt, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Mareike Lankeit, M.D., Nicolas Meneveau, M.D., Ph.D., Gerard Pacouret, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pruszczyk, M.D., Matteo Rugolotto, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Thiele, M.D., Adam Torbicki, M.D., Franck Verschuren, M.D., Ph.D., and Stavros V. Konstantinides, M.D., for the PEITHO Investigators*
**Figure 1. Efficacy and Safety Outcomes in Prespecified Subgroups.**

Panel A shows the primary efficacy outcome (death or hemodynamic decompensation), and Panel B shows a safety outcome (major extracranial bleeding), both within 7 days after randomization.
In conclusion, in normotensive patients with intermediate-risk pulmonary embolism, the composite primary outcome of early death or hemodynamic decompensation was reduced after treatment with a single intravenous bolus of tenecteplase. However, tenecteplase was also associated with a significant increase in the risk of intracranial and other major bleeding. Therefore, great caution is warranted when considering fibrinolytic therapy for hemodynamically stable patients with pulmonary embolism, right ventricular dysfunction, and a positive cardiac troponin test.
From: **Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: A Meta-analysis**


<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>No. of Patients</th>
<th>OR (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhaber et al,1993</td>
<td>0</td>
<td>46</td>
<td>2</td>
<td>55</td>
<td>0.16 (0.01-2.57)</td>
<td></td>
<td></td>
<td>5.3</td>
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<tr>
<td>Konstantinides et al,2002</td>
<td>4</td>
<td>118</td>
<td>3</td>
<td>138</td>
<td>1.58 (0.35-7.09)</td>
<td></td>
<td></td>
<td>18.4</td>
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<tr>
<td>TIPES,29 2010</td>
<td>0</td>
<td>28</td>
<td>1</td>
<td>30</td>
<td>0.14 (0.00-7.31)</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Fasullo et al,2011</td>
<td>0</td>
<td>37</td>
<td>6</td>
<td>35</td>
<td>0.11 (0.02-0.58)</td>
<td></td>
<td></td>
<td>15.1</td>
</tr>
<tr>
<td>MOPETT,10 2012</td>
<td>1</td>
<td>61</td>
<td>3</td>
<td>60</td>
<td>0.35 (0.05-2.57)</td>
<td></td>
<td></td>
<td>10.5</td>
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<td>ULTIMA,30 2013</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>29</td>
<td>0.13 (0.00-6.59)</td>
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<td>2.7</td>
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<tr>
<td>TOPCOAT,9 2014</td>
<td>1</td>
<td>40</td>
<td>1</td>
<td>43</td>
<td>1.08 (0.07-17.53)</td>
<td></td>
<td></td>
<td>5.3</td>
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<tr>
<td>PEITHO,8 2014</td>
<td>6</td>
<td>506</td>
<td>9</td>
<td>499</td>
<td>0.66 (0.24-1.82)</td>
<td></td>
<td></td>
<td>40.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>12</td>
<td>866</td>
<td>26</td>
<td>889</td>
<td>0.48 (0.25-0.92)</td>
<td></td>
<td></td>
<td>100.0</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 7.63; P = .37; I^2 = 8\%$

Overall effect: $z = 2.22; P = .03$

Odds of Mortality in Patients With **Intermediate-Risk Pulmonary Embolism Treated With Thrombolytic Therapy** vs Anticoagulation Evaluated using the Peto method of meta-analysis. The standard practice in meta-analysis of odds ratios (ORs) and risk ratios is to exclude studies from the meta-analysis where there are no events in either group. A 0-cell or continuity correction was not used based on recommendations regarding calculation of a Peto OR for studies with 0 events in only 1 group. MOPETT indicates Moderate Pulmonary Embolism Treated with Thrombolysis trial; PEITHO, Pulmonary Embolism Thrombolysis trial; TIPES, Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT, Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism trial.
Why not lyse a pt with RVD

20% incidence of major bleeding

3-5% risk of hemorrhagic stroke

*note: in ICOPER registry bleeding 24% in lysis, 15% with heparin alone. (common in both)

RECOMMENDATIONS FOR FIBRINOLYSIS
FOR ACUTE PE-2

2. Fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications

(Class IIb; Level of Evidence C)
3. Fibrinolysis is **not recommended** for patients with *low-risk PE* 
(*Class III; Level of Evidence B*) or *submassive acute PE* with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening

(*Class III; Level of Evidence B*).

4. Fibrinolysis is **not recommended** for *undifferentiated cardiac arrest*

(*Class III; Level of Evidence B*).
Risk-adjusted management algorithm

Clinical suspicion of PE
- Shock / Hypotension?
  - Yes
    - Diagnostic algorithm as for suspected high-risk PE
      - PE confirmed
      - Consider further risk stratification
        - Intermediate risk
          - RV function (echo or CT)
            - Laboratory testing
              - Both positive
                - High risk
                  - Primary reperfusion
                  - A/C; monitoring; consider rescue reperfusion
              - One positive or both negative
                - Intermediate-high risk
                - Intermediate-low risk
            - Low risk
              - A/C; consider early discharge and home treatment, if feasible
  - No
    - Diagnostic algorithm as for suspected not high-risk PE
      - PE confirmed
      - Assess clinical risk (PESI or sPESI)
        - PESI Class III-IV or sPESI ≥1
          - Intermediate-high risk
          - A/C; monitoring; consider rescue reperfusion
        - PESI Class I-II or sPESI = 0
          - Intermediate-low risk
          - A/C; hospitalization

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Probability of PE above treatment threshold

Submassive without RV Strain (Low risk PE)
- Heparin Anticoagulation

Submassive with RV strain (Abnormal echo or biomarkers)
- Heparin Anticoagulation

Systolic blood pressure < 90 mmHg for >15 min
- Heparin Anticoagulation

Assess for evidence of increased severity that suggests potential for benefit of fibrinolysis

1. EVIDENCE OF SHOCK OR RESPIRATORY FAILURE:
   - Any hypotension (SBP<90 mm Hg) OR
   - Shock index >1.0 OR
   - Respiratory distress (SaO2 <95% with Borg score >8, or altered mental status, or appearance of suffering)

2. EVIDENCE OF MODERATE TO SEVERE RV STRAIN:
   - RV dysfunction (RV hypokinesis or estimated RVSP> 40 mmHg) OR
   - Clearly elevated biomarker values (e.g., troponin above borderline value, BNP >100 pg/mL or pro-BNP >900 pg/mL)

No contraindications to fibrinolysis

Alteplase 100 mg over 2 h IV
Guidelines Support Thrombolysis for Massive PE but are purposely vague about Submassive PE
Suggested algorithm for acute life threatening pulmonary embolism. PE, pulmonary embolism; RV, right ventricle; ECG, electrocardiography; BNP, brain natriuretic peptide; TTE, transthoracic echocardiography, TEE, trans-esophageal echocardiography; CTPA, computerized tomography pulmonary angiography; UFH, unfractionated heparin; LMWH, low molecular weight heparin.
Catheter-Based Interventions
Contemporary Catheter Techniques

1. Conventional Catheter-Directed Thrombolysis
2. Thrombus Fragmentation
3. Rheolytic Thrombectomy
4. Suction Thrombectomy
5. Rotational Thrombectomy
6. Ultrasound Assisted Catheter-Direct Thrombolysis (USAT)
7. Pharmaco-mechanical Thrombolysis

Catheter Embolectomy & Fragmentation

An alternative in high-risk PE patients when thrombolysis is **absolutely contraindicated** or has **failed**

*Kucher N Chest 2007;132:657-663*
Goals of Catheter-Based Therapy

1. Rapidly reducing pulmonary artery pressure, RV strain, and pulmonary vascular resistance
2. Increasing systemic perfusion
3. Facilitating RV recovery
AngioJet-a catheter that breaks up the clot with a high speed jet of saline, heparin, or tPA that then sucks up clot using Bernoulli physics.
Very little systemic drug is delivered.

Angio-Vac

This **device** uses an ECMO-like system to suck up clot and then return the de-clotted blood to the venous circulation. It requires huge introducer sheaths.

Oren alluded to its main benefit being **intra-cavitary** or **vena cavae clots**. Some are billing this as a replacement for embolectomy in many cases.

Figure 1. A. The EkoSonic endovascular system consists of a multiple-lumen infusion catheter (larger arrow) with a removal coaxial ultrasound transducer core (smaller arrow), which is connected to a control unit that delivers lower-energy high-frequency ultrasound energy with concomitant thrombolytic drug infusion into the thrombus. B. Schlieren photograph of an EkoSonic catheter, which emits ultrasound energy. The acoustic streaming energy dissociates the fibrin and increases the fibrin porosity without causing distal embolization, which also facilitates the penetration of thrombolytic agent into the thrombus for receptor binding.
Catheter-directed Therapy for the Treatment of Massive Pulmonary Embolism: Systematic Review and Meta-analysis of Modern Techniques

William T. Kuo, MD, Michael K. Gould, MD, MS, John D. Louie, MD, Jarrett K. Rosenberg, PhD, Daniel Y. Sze, MD, PhD, and Lawrence V. Hofmann, MD

ARTICLE in JOURNAL OF VASCULAR AND INTERVENTIONAL RADIOLOGY: JVIR · NOVEMBER 2009
Impact Factor: 2.15 · DOI: 10.1016/j.jvir.2009.08.002 · Source: PubMed
Catheter-directed Therapy for Massive Pulmonary Embolism

From the overall 35 studies: 594 patients treated with catheter-based therapy, **86.5 % success rate**, 2.5 % major bleeding

WT Kuo 2009
Surgical Thrombo-embolectomy
Surgical Embolectomy in APE: Massive
Representative pulmonary endarterectomy specimens

A, **Type 1 disease** (25% of cases of thromboembolic pulmonary hypertension): Fresh thrombus in the main or lobar pulmonary arteries. 

B, **Type 2 disease** (40% of cases): Intimal thickening and fibrosis with or without organized thrombus proximal to segmental arteries. In these cases, only thickened intima can be seen on initial dissection into the pulmonary arteries, occasionally with webs in the main or lobar arteries. 

C, **Type 3 disease** (30% of cases): Fibrosis, intimal webbing, and thickening with or without organized thrombus within distal segmental and subsegmental arteries only. No occlusion of vessels can be seen initially.
Modern surgical treatment of massive pulmonary embolism: Results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach

Marzia Leacche, MD, Daniel Unic, MD, Samuel Z. Goldhaber, MD, James D. Rawn, MD, Sary F. Aranki, MD, Gregory S. Couper, MD, Tomislav Mihaljevic, MD, Robert J. Rizzo, MD, Lawrence H. Cohn, MD, Lishan Aklog, MD, and John G. Byrne, MD

TABLE 2. Indications for surgical embolectomy (n = 47)

<table>
<thead>
<tr>
<th>Indication</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindications to thrombolysis</td>
<td>21 (45%)</td>
</tr>
<tr>
<td>Recent surgical intervention</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Failed medical treatment</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Failure of thrombolytics</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Failure of catheter embolectomy</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Large RA-RV thrombus</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>RV hemodynamic dysfunction</td>
<td>15 (32%)</td>
</tr>
<tr>
<td>Large PFO</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

RA-RV, Right atrium–right ventricle; PFO, patent foramen ovale.

Figure 3. Kaplan-Meier survival curve after surgical pulmonary embolectomy (n = 47 patients, including the 3 operative deaths).
Repeated thrombolytic Therapy

Repeated thrombolytic therapy after initial unsuccessful thrombolysis in massive pulmonary embolism

R J M van den Biggelaar¹, D-J Slebos¹, J van der Meer²

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Management of Unsuccessful Thrombolysis in Acute Massive Pulmonary Embolism

Table 3---In-Hospital Evolution

<table>
<thead>
<tr>
<th>Variables</th>
<th>Rescue Embolectomy (n = 14)</th>
<th>Repeat Thrombolysis (n = 26)</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (7)</td>
<td>10 (38)</td>
<td>0.13</td>
<td>0.003-1.12</td>
<td>0.07</td>
</tr>
<tr>
<td>PE related death</td>
<td>1 (7)</td>
<td>6 (23)</td>
<td>0.28</td>
<td>0.01-2.68</td>
<td>0.39</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>0</td>
<td>3 (11.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory shock</td>
<td>1 (7)</td>
<td>3 (11.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>2 (14)</td>
<td>6 (23)</td>
<td>0.56</td>
<td>0.05-3.66</td>
<td>0.82</td>
</tr>
<tr>
<td>Major bleeding episodes</td>
<td>2 (14) [0 fatal]</td>
<td>4 (15) [4 fatal]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0</td>
<td>1 (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent PE (fatal and nonfatal)</td>
<td>0</td>
<td>0 (35)</td>
<td>0.12</td>
<td>0.0-0.87</td>
<td>0.015</td>
</tr>
<tr>
<td>Uneventful evolution</td>
<td>11 (70)</td>
<td>8 (31)</td>
<td>8.25</td>
<td>1.49-51.71</td>
<td>0.004</td>
</tr>
</tbody>
</table>

8% (40 of 488 massive PE need further Mx after 1st thrombolysis)
RECOMMENDATIONS FOR CATHETER EMBOLECTOMY AND FRAGMENTATION & SURGICAL EMBOLECTOMY

1. Depending on local expertise, either catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE and contraindications to fibrinolysis *(Class IIa; Level of Evidence C)*.

2. Repeat thrombolysis or catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE who remain unstable after receiving fibrinolysis *(Class IIa; Level of Evidence C).*( with in 1 hour)
3. Either catheter embolectomy or surgical embolectomy may be considered for patients with **submassive acute PE** judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory failure, severe RV dysfunction, or major myocardial necrosis) *(Class IIb; Level of Evidence C).*

4. Catheter embolectomy and surgical thrombectomy are **not recommended** for patients with **low-risk PE** or **submassive acute PE** with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening *(Class III; Level of Evidence C).*
Inferior Vena Cava Filters
Inferior Vena Cava Filter

A filter placed in IVC to prevent emboli from moving into pulmonary circulation while maintaining caval patency. Firstly placed in 1967, but most of the IVC filter insertion (>70%) performed in the 1990s.
**Inferior Vena Cava Filter**

**Type of IVC Filters**
- The Greenfield filter
- The Vena Tech filter
- The Bird’s Nest filter
- The Nitinol filter

**Indications:**
- Contraindication to anticoagulation
- Complication of anticoagulation
- Failure of anticoagulation
- Prophylaxis in patient with already significantly compromised pulmonary vascular bed & after embolectomy
Inferior Vena Cava Filter

- Theoretically benefits by prevent recurrent PE

- Fatal complication 0.12 %,

- Other complications
  - thrombosis,
  - filter migration,
  - filter erosion,
  - IVC obstr. (5-18 %)
RECOMMENDATIONS ON IVC FILTERS IN ACUTE PE

1. Adult patients with any confirmed acute PE (or proximal DVT) with **contraindications to anticoagulation** or **with active bleeding complication** should receive an IVC filter

   *(Class I; Level of Evidence C).*

2. Anticoagulation should be resumed in patients with an IVC filter once contraindications to anticoagulation or active bleeding complications have resolved

   *(Class I; Level of Evidence B).*

3. Patients who receive retrievable IVC filters should be evaluated periodically for filter retrieval within the specific filter’s retrieval window

   *(Class I; Level of Evidence C).*
4. For patients with recurrent acute PE despite therapeutic anticoagulation, it is reasonable to place an IVC filter "(Class IIa; Level of Evidence C)."

5. For DVT or PE patients who will require permanent IVC filtration (eg, those with a long-term contraindication to anticoagulation), it is reasonable to select a permanent IVC filter device "(Class IIa; Level of Evidence C)."
RECOMMENDATIONS ON IVC FILTERS IN ACUTE PE

5. For DVT or PE patients with a time-limited indication for an IVC filter (eg, those with a short-term contraindication to anticoagulation therapy), it is reasonable to select a retrievable IVC filter device

(Class IIa; Level of Evidence C).

6. Placement of an IVC filter may be considered for patients with acute PE and very poor cardiopulmonary reserve, including those with massive PE

(Class IIb; Level of Evidence C).

7. An IVC filter should not be used routinely as an adjuvant to anticoagulation and systemic fibrinolysis in the treatment of acute PE

(Class III; Level of Evidence C).
Patient with clinical suspicious PE and evidence of hypotension or hypoperfusion need urgent evaluation of other possibility cause of shock and anatomically confirmation of MPE

When clinical suspicion for PE is reasonable high, anticoagulant therapy should be start during further work up

Anatomically confirmed Massive PE with persistent hypotension > 15 min. despite optimized fluid therapy, who don’t have an absolute contraindication for, should start thrombolysis promptly
The options for unsuccessful 1\textsuperscript{st} thrombolysis with confirmed residual clot are:

- Cather-based endovascular treatment
- Surgical embolectomy or
- 2\textsuperscript{nd} Thrombolysis

Patients with absolute C/I for thrombolysis, catheter-based clot fragmentation or surgical embolectomy should be considered.
Summary-III

- **UFH** is the preferred anticoagulant of choice for **submassive PE**

- Evidence support is limited regarding **thrombolytic therapy** in **sub-massive PE** (subgroup categorization)

- Need further large clinical trial or meta-analysis enough to demonstrate a **survival benefit & safety profile** of thrombolysis compared to anticoagulation alone in submassive PE

- Consider **IVC filter** for patients with **C/I**, serious hemorrhagic complications, or failure anticoagulation
E = m \cdot c^2

E = M \cdot c^2
E = Excellence in Critical Care Medicine
M = Mastering of Sciences
C₁ = Commitment
C₂ = Competence
C₃ = Compassion

E = m·c²

Albert Einstein
In Physics

E = m²·c³

Pat Boonsong
In Critical Care Medicine

Medical Science
Clinical Science
Epidemiology & Biostatistics
Health System Management
Health Economics
Good Governance, etc.
Thank you for your attention