In order to support the growth of the ECHO movement, Project ECHO® collects participation data for each teleECHO™ program. This data allows Project ECHO to measure, analyze, and report on the movement’s reach. It is used in reports, on maps and visualizations, for research, for communications and surveys, for data quality assurance activities, and for decision-making related to new initiatives.
Thrombolytics in Intermediate Pulmonary Embolism (PE)

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Intermountain Medical Center/Tele-Critical Care
Objectives

• Discuss risk stratification of massive and intermediate PE requiring thrombolytics
• Review guideline recommendations and key randomized controlled trials for/against thrombolytic use in intermediate PE
• Patient case-based application of literature
Abbreviations

Alteplase – tPA or r-tPA
American Heart Association – AHA
American College of Chest Physicians – CHEST
Anticoagulation Forum – AC Forum
Blood pressure – BP
Cardiopulmonary resuscitation – CPR
CT pulmonary angiography – CTPA
Direct oral anticoagulant – DOAC
Electrocardiogram – ECG or EKG
Emergency department – ED
European Society of Cardiology – ESC
Gastrointestinal bleed – GIB
Heart rate – HR
Hemoglobin – Hgb
Hypertension – HTN
Intensive care unit – ICU
Intravenous – IV
Left ventricle – LV
Length of stay – LOS
Low molecular weight heparin – LMWH
Mean arterial pressure – MAP
National Institute for Health and Care Excellence – NICE
Past medical history – PMH
Pulmonary arterial systolic pressure- PASP or SPAP
Pulmonary embolism – PE
Pulmonary embolism severity index – PESI
Pulmonary embolism rule out criteria – PERC
Pulmonary hypertension – pHTN
Respiratory rate – RR
Revised Geneva score – RGS
Right ventricle – RV
Right/left ventricle end-diastolic diameter ratio – RVED/LVED
Shortness of breath – SOB
Systolic blood pressure – SBP
Transient ischemic stroke – TIA
Unfractionated heparin – UFH
Upper limit of normal – ULN
Venous thromboembolism – VTE
Ventilation perfusion – V/Q
Background
Background

- **PE is considered the third most common cause of cardiovascular death after heart attack and stroke**
- **Approximately 60,000 to 100,000 deaths reported each year**

<table>
<thead>
<tr>
<th>Hereditary risk factors</th>
<th>Acquired risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin, Protein C, Protein S deficiencies</td>
<td>Reduced mobility</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>Cancer</td>
</tr>
<tr>
<td>Plasminogen deficiency</td>
<td>Acute medical illness/major surgery</td>
</tr>
<tr>
<td>Antithrombin, Protein C, Protein S deficiencies</td>
<td>Trauma/Spinal cord injury</td>
</tr>
<tr>
<td></td>
<td>Pregnancy and post-partum period</td>
</tr>
<tr>
<td></td>
<td>Hormone replacement therapy, oral contraception</td>
</tr>
</tbody>
</table>

**Presentation**

- **PE presenting symptoms can be variable**

<table>
<thead>
<tr>
<th>Common presenting symptoms</th>
<th>Common presenting signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>Tachypnea (≥ 20 breaths/min)</td>
</tr>
<tr>
<td>Pleuritic pain</td>
<td>Tachycardia (&gt; 100 bpm)</td>
</tr>
<tr>
<td>Cough</td>
<td>Rales</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Decreased breath sounds</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Jugular vein distention</td>
</tr>
</tbody>
</table>

Pre-test risk assessment can help to rule out a PE before additional imaging is performed

- **Pulmonary Embolism Rule Out Criteria (PERC)**
- **Revised Geneva Score (RGS)**
  - Assesses patients' likelihood of having a PE based on risk factors and signs/symptoms present
  - If no criteria met, PE can be ruled OUT (no further imaging needed)
Imaging and further testing is the next step in risk stratification

- CT pulmonary angiography (CTPA)
- Ventilation/perfusion (V/Q) scan
- Electrocardiogram
- Echocardiogram
- Cardiac biomarker labs

Pathophysiology

Why are PE’s so deadly if not caught and treated?

• Acute PEs interfere with circulation and gas exchange
• Patients with enough clot burden to create right ventricular dysfunction are at risk for further hemodynamic decompensation

Traditional definitions and terms for PE included massive, submassive and low-risk

<table>
<thead>
<tr>
<th>PE classification</th>
<th>Hypotension (SBP &lt; 90 mmHg)</th>
<th>RV dysfunction or elevated troponin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massive</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Submassive</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Low-risk</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Pulmonary Embolism Severity Index (PESI)

- *Predicts 30-day mortality and morbidity*

<table>
<thead>
<tr>
<th>Class</th>
<th>Score</th>
<th>30-day mortality</th>
<th>Risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>&lt; 65</td>
<td>0-1.6%</td>
<td>Very low</td>
</tr>
<tr>
<td>Class 2</td>
<td>66-85</td>
<td>1.7-3.5%</td>
<td>Low</td>
</tr>
<tr>
<td>Class 3</td>
<td>86-105</td>
<td>3.2-7.1%</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Class 4</td>
<td>106-25</td>
<td>4.0-11.4%</td>
<td>High</td>
</tr>
<tr>
<td>Class 5</td>
<td>&gt; 125</td>
<td>10.0-24.5%</td>
<td>Very high</td>
</tr>
</tbody>
</table>
## PE Clinical Classification

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Shock or hypotension</th>
<th>PESI class III-V</th>
<th>Signs of RV dysfunction on imaging</th>
<th>Cardiac biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intermediate</td>
<td>High</td>
<td>-</td>
<td>+</td>
<td>Both positive</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>-</td>
<td>+</td>
<td>Either one (or none) positive</td>
</tr>
<tr>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

PE Treatment Algorithm

Adapted from IHC Diagnosis and Management of Venous Thromboembolism CPM, June 2021
Clinical Treatment Guidelines
PE Treatment Guidelines

- 2011: AHA guideline
- 2014: ESC guideline
- 2019: ESC guideline update
- 2020: ASH guideline
- 2012: CHEST guideline
- 2016: CHEST guideline
- 2020: AC Forum guideline
- 2020: NICE guideline
- 2021: CHEST guideline update
## Guideline Summary

<table>
<thead>
<tr>
<th>Guideline (Year)</th>
<th>“Submassive” or &quot;intermediate-risk&quot; PE Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA (2011)</td>
<td>Can consider in those who have evidence of adverse prognosis</td>
</tr>
<tr>
<td>AC Forum (2016)</td>
<td>Can consider on an individual case-by-case basis</td>
</tr>
<tr>
<td>ESC (2019)</td>
<td>No recommendation can be made until solid evidence has been published</td>
</tr>
<tr>
<td>NICE (2020)</td>
<td>Recommend against administration in patients who are hemodynamically stable regardless of presence of RV dysfunction</td>
</tr>
<tr>
<td>ASH (2020)</td>
<td>Recommend against administration in patients who are hemodynamically stable</td>
</tr>
</tbody>
</table>
| CHEST (2016;2021)| Recommend against administration in most patients who are hemodynamically stable  
Recommend administration in select patients who decompensate after anticoagulation initiation |

TJ is a 70M brought in by EMS after GLF

**HPI:** SOB, severe chest pain, became dizzy and fell

**PMH:** prior hx small DVT, HTN

**Home meds:** amlodipine

**Vitals:** BP 60/39 (MAP 50 mmHg), HR 100 bpm, RR 30 br/min, SpO2 70%

**Notable imaging, labs, other:** CTPA (+) PE, TTE shows enlarged right ventricle with strain, troponin 0.5 ng/mL, D-dimer 10.0 mcg FEU/mL (ug/mL)

• PESI score = 130
Patient Case 1

**TJ is a 70M brought in by EMS after GLF**

**HPI:** SOB, severe chest pain, became dizzy and fell

**PMH:** prior hx small DVT, HTN

**Home meds:** amlodipine

**Vitals:** BP 60/39 (MAP 50 mmHg), HR 100 bpm, RR 30 br/min, SpO2 70%

**Notable imaging, labs, other:** CTPA (+) PE, TTE shows enlarged right ventricle with strain, troponin 0.5 ng/mL, D-dimer 10.0 mcg FEU/mL (ug/mL)

* PESI score = 130

Based on guideline recommendations, should TJ receive thrombolytics?

1. YES
2. NO
Patient Case 2

WJ is a 62F admitted to the medical ICU

HPI: SOB and chest pain for 8 hours

PMH: HTN, HLD, hysterectomy 7 days ago

Home meds: rosuvastatin, lisinopril

Vitals: BP 93/59 (MAP 70 mmHg), HR 132 bpm, RR 38 br/min, SpO2 80%

Notable imaging, labs, other: CTPA (+) saddle PE, TTE shows enlarged right ventricle with strain, troponin 0.3 ng/mL, D-dimer 7.0 mcg FEU/mL (ug/mL)

• PESI score = 102
WJ is a 62F admitted to the medical ICU

**HPI:** SOB and chest pain for 8 hours

**PMH:** HTN, HLD, hysterectomy 7 days ago

**Home meds:** rosuvastatin, lisinopril

**Vitals:** BP 93/59 (MAP 70 mmHg), HR 132 bpm, RR 38 br/min, SpO2 80%

**Notable imaging, labs, other:** CTPA (+) saddle PE, TTE shows enlarged right ventricle with strain, troponin 0.3 ng/mL, D-dimer 7.0 mcg FEU/mL (ug/mL)

• **PESI score = 102**

Based on guideline recommendations, should WJ receive thrombolytics?
1. YES
2. NO
3. Maybe?
**Heparin + alteplase vs. heparin alone**

- **N=256**
  - Intermediate risk patients

- **Outcomes**
  - **Primary**: in-hospital death or clinical deterioration after alteplase infusion
  - **Secondary**: recurring PE, major bleeding, ischemic stroke

*MAPPET-3, 2002*

Primary outcomes

- All cause mortality = **no difference**
- Composite outcome = **statistically significant**
- Treatment escalation = **statistically significant**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Heparin + alteplase</th>
<th>Heparin alone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>3.4%</td>
<td>2.2%</td>
<td>0.71</td>
</tr>
<tr>
<td>Composite end point</td>
<td>11%</td>
<td>24.6%</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Treatment escalation</td>
<td>10.2%</td>
<td>24.6%</td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>
Secondary outcomes

• Recurrent PE = no difference
  o Alteplase group (3.4%) vs placebo group (2.9%), p=0.89

• Major bleeding = no difference
  o Alteplase group (0.8%) vs placebo group (3.6%), p=0.29
    • Fatal bleed – None in either group
    • Hemorrhagic stroke – 0% vs 0.7%, p=1.0

• Ischemic stroke = no difference
  o Alteplase group (0%) vs placebo group (0.7%), p=1.0
**TOPCOAT, 2013**

**LMWH + tenecteplase vs. LMWH alone**

- **N=83**
  - *Intermediate risk patients*

- **Outcomes**
  - *PE related*: death, circulatory shock or intubation within 5 days of diagnosis
  - *Treatment related*: death from hemorrhage, active bleed, surgery
  - *Functional*: progression or resolution of RV strain, pulmonary htn, exercise tolerance

## PE related outcomes

### Table 3 Breakdown of all adverse outcomes in each treatment group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Death</th>
<th>Shock/intubation</th>
<th>Within 5 days</th>
<th>Recurrent VTE* and poor functional capacity† and low perception of wellness‡</th>
<th>Poor functional capacity† and low perception of wellness‡</th>
<th>Recurrent VTE* and low perception of wellness‡ only</th>
<th>Poor functional capacity† only</th>
<th>Recurrent VTE only</th>
<th>Low perception of wellness‡ only</th>
<th>None§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N = 43)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>27 (63%)</td>
<td></td>
</tr>
<tr>
<td>Tenecteplase (N = 40)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>34 (85%)</td>
<td></td>
</tr>
</tbody>
</table>

### Functional outcomes at 90-day follow up

**Table 3** Breakdown of all adverse outcomes in each treatment group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Death</th>
<th>Shock/intubation</th>
<th>Within 5 days</th>
<th>At 90-day follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrent VTE* and poor functional capacity† and low perception of wellness‡</td>
<td>Poor functional capacity† and low perception of wellness‡</td>
</tr>
<tr>
<td>Placebo (N = 43)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Tenecteplase (N = 40)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Heparin + tenecteplase vs. heparin alone

- \( N=1005 \)
  - Intermediate risk patients
- Outcomes
  - **Primary**: clinical composite of death or hemodynamic decompensation within 7 days
  - **Secondary**: major adverse effects or mortality within 30 days
  - **Safety**: ischemic or hemorrhagic stroke within 7 days, extracranial bleeding and serious adverse events

PEITHO, 2014

Primary and secondary outcomes

- Mortality at 7 and 30-days = **no difference**
- Hemodynamic decompensation = higher in placebo group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase (N=506)</th>
<th>Placebo (N=499)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite end point – no. (%)</td>
<td>13 (2.6)</td>
<td>28 (5.6)</td>
<td>0.44 (0.23 - 0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>6 (1.2)</td>
<td>9 (1.8)</td>
<td>0.65 (0.23 - 1.85)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hemodynamic decompensation</td>
<td>8 (1.6)</td>
<td>25 (5.0)</td>
<td>0.30 (0.14 - 0.68)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death from any cause at day 30</td>
<td>12 (2.4)</td>
<td>16 (3.2)</td>
<td>0.73 (0.34 - 1.57)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

## Safety outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase (N=506)</th>
<th>Placebo (N=499)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding between randomization and day 7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major extracranial</td>
<td>32 (6.3)</td>
<td>6 (1.2)</td>
<td>5.55 (2.3-13.99)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>165 (32.6)</td>
<td>43 (8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>58 (11.5)</td>
<td>12 (2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke between randomization and day 7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>12 (2.4)</td>
<td>1 (0.2)</td>
<td>12.10 (1.57 - 93.39)</td>
<td>0.003</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2 (0.4)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>10 (2.0)</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events, randomization to day 30</strong></td>
<td>55 (10.9)</td>
<td>59 (11.8)</td>
<td>0.91 (0.62 - 1.34)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

## Thrombolytics vs. Placebo Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>MAPPET-3</th>
<th>TOPCOAT</th>
<th>PEITHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>N=256</td>
<td>N=83</td>
<td>N=1005</td>
</tr>
<tr>
<td>Lytic agent used</td>
<td>Alteplase</td>
<td>Tenecteplase</td>
<td>Tenecteplase</td>
</tr>
<tr>
<td>NNT</td>
<td>7.5</td>
<td>4.5</td>
<td>33.3</td>
</tr>
<tr>
<td>Mortality benefit?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Increase bleeding?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Composite outcome (death or clinical deterioration)</td>
<td>Composite outcome (considered death = a low score on a QOL survey)</td>
<td>Composite outcome (death or hemodynamic collapse within 7 days)</td>
</tr>
<tr>
<td>Other considerations</td>
<td>Clinical deterioration not objectively defined</td>
<td>Study terminated early</td>
<td>Enrolled patients with active cancer, older age and surgical history within 6 weeks</td>
</tr>
</tbody>
</table>
Dosing and Administration
What do these famous people have in common?
TJ is our 70M brought in by EMS after GLF

• Having a massive PE with hemodynamic decompensation
• ER physician requests alteplase
• Package insert dosing options for alteplase in massive PE:
  o 100 mg over 2 hours
  o 20 mg bolus, 80 mg over 2 hour
  o 50 mg bolus over 2 min, can repeat in 15 min if warranted (associated with cardiac arrest)
WJ is a 62F admitted to the medical ICU

- Intermediate risk PE with evidence of RH strain
- On admission she was hemodynamically stable but now has soft pressures, MAP of 65 mmHg
- Additional considerations: hysterectomy 7 days prior

ICU team wants to give her alteplase given she is starting to clinically decompensate, what dose should they give?
Wang et al, 2010

Full dose (100 mg) vs. half dose (50 mg) alteplase

• N=127
  o Hemodynamically massive and anatomically massive (intermediate) PE

• Outcomes
  o **Efficacy**: PE recurrence, mortality, improvement in RV function, pulmonary artery pressure, lung perfusion
  o **Safety**: bleeding

### Efficacy outcomes

- **Mortality, bleeding = no difference**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hemodynamically Massive</th>
<th>Anatomically Massive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg (n=19)</td>
<td>50 mg (n=18)</td>
</tr>
<tr>
<td>Death, n(%)</td>
<td>1 (5)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Due to PE</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Due to bleeding</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Recurrent PE, n(%)</td>
<td>1 (5)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Bleeding complications, n(%)</td>
<td>7 (37)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2 (11)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>5 (26)</td>
<td>3 (17)</td>
</tr>
</tbody>
</table>
Safety outcomes

• What about body weight?

Wang et al, 2010

50 mg alteplase vs. placebo

• N=121
  o Moderate PE
    • ≥ 2 signs/symptoms of PE AND
    • CTPA with >70% thrombus in left main, right main, or ≥ 2 lobar pulmonary arteries OR V/Q mismatch in ≥ lobes

• Outcomes
  o **Primary**: composite of pulmonary HTN AND recurrent PE at 28 months
  o **Secondary**: mortality, hospital LOS, recurrent PE, composite of recurrent PE, mortality or bleed

MOPETT, 2013

**Primary outcomes**

- *Mortality = no difference*
- *Bleeding = no difference*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>tPA + AC</th>
<th>Placebo + AC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pHTN and recurrent PE, n (%)</td>
<td>9 (16)</td>
<td>35 (63)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mortality and recurrent PE, n (%)</td>
<td>1 (1.6)</td>
<td>6 (10)</td>
<td>0.049</td>
</tr>
<tr>
<td>pHTN</td>
<td>9 (16)</td>
<td>32 (57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>2.2</td>
<td>4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 48 hours</td>
<td>34</td>
<td>41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 months</td>
<td>31</td>
<td>49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>28 months</td>
<td>28</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Alteplase 30 mg vs. placebo**

- **N=66**
  - *Intermediate risk PE*

- **Outcomes**
  - *Primary*: changes in LV/RV ratio, PAP, subjective improvement at 24 hours
  - *Secondary*: bleeding, mortality, decompensation, recurrent PE at f/u

*Zhang et al, 2018*

**Primary outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>tPA + LMWH</th>
<th>Placebo + LMWH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP, mmHg</td>
<td>17.0 ± 10.2</td>
<td>4.6 ± 9.8</td>
<td>0.001</td>
</tr>
<tr>
<td>RV/LV</td>
<td>0.31 ± 0.18</td>
<td>0.04 ± 0.16</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptom severity</td>
<td>5.6 ± 1.5</td>
<td>1.0 ± 0.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Difference from baseline at 24 hours (mean ± SD)
Secondary outcomes

- Mortality = no difference

<table>
<thead>
<tr>
<th>Variable</th>
<th>tPA + LMWH</th>
<th>Placebo + LMWH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Hemodynamic decompensation</td>
<td>0 (0)</td>
<td>9%</td>
<td>0.24</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>3%</td>
<td>6%</td>
<td>1.0</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>24%</td>
<td>3%</td>
<td>0.0268</td>
</tr>
</tbody>
</table>
Alteplase 50 mg vs. placebo

• N=76
  - Intermediate risk PE

• Outcomes
  - **Primary**: death from any cause, death or decompensation at 7 and 30 days
  - **Secondary**: recurrent PE, pHTN at 6-months
  - **Safety**: ischemic or hemorrhagic stroke within 7 days, major extracranial bleeding within 7 days
**Outcomes**

- **Total mortality at 7/30 days = no difference**
- **Major/minor bleeding = no difference**

<table>
<thead>
<tr>
<th>Variable</th>
<th>tPA + LMWH</th>
<th>LMWH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/hemodynamic decompensation at 7 days</td>
<td>1 (3)</td>
<td>8 (21)</td>
<td>0.028</td>
</tr>
<tr>
<td>Death/hemodynamic decompensation at 30 days</td>
<td>1 (3)</td>
<td>10 (26)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
## Dosing Trials Summary

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, 2010</td>
<td>50 mg vs 100 mg tPA</td>
<td>• No difference in mortality, recurrent PE, or pulmonary artery obstruction improvement</td>
<td>• Increased bleeding in patients &lt; 65 kg or BMI &lt; 25</td>
</tr>
<tr>
<td>MOPPET, 2013</td>
<td>50 mg tPA vs placebo</td>
<td>• Improvement in PASP, reduced mortality, decreased occurrence of recurrent PE, and shorter LOS</td>
<td>• No difference in bleeding</td>
</tr>
<tr>
<td>Zhang, 2018</td>
<td>30 mg tPA vs placebo</td>
<td>• Improvement in PASP and symptom severity</td>
<td>• Increased minor bleeding</td>
</tr>
<tr>
<td>Yilmaz, 2021</td>
<td>50 mg tPA vs placebo</td>
<td>• Reduced occurrence of composite outcome (death or hemodynamic decompensation) • No difference in mortality alone, recurrent PE, or pHTN</td>
<td>• No difference in bleeding</td>
</tr>
</tbody>
</table>
Additional Considerations

**Patient specific factors**
- Past medical history
- Past or recent surgical history
- Active home medications
- Weight/BMI
- Quality of life
### Additional Considerations

#### Contraindications to thrombolytics

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of intracranial hemorrhage</td>
<td>Systolic BP &gt; 180 mmHg or diastolic BP &gt; 110 mmHg</td>
</tr>
<tr>
<td>Known cerebral arteriovenous malformation</td>
<td>Prolonged CPR (&gt; 10 min)/Traumatic CPR</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Ischemic stroke &gt; 3 months prior</td>
</tr>
<tr>
<td>Significant trauma in the past 3 months</td>
<td>Major surgery in past 3 weeks</td>
</tr>
<tr>
<td>Active bleeding (excluding menses)</td>
<td>Recent bleeding (non-intracranial)</td>
</tr>
<tr>
<td>Ischemic stroke in past 3 months</td>
<td>Pregnancy or week one post-partum</td>
</tr>
<tr>
<td>Neoplasm in central nervous system</td>
<td>Anticoagulated</td>
</tr>
<tr>
<td><em>Age &gt; 75</em></td>
<td><em>Dementia</em></td>
</tr>
</tbody>
</table>
Additional Considerations

Dosing and administration of thrombolytics
• 50 mg vs 30 mg vs something else?
• No need for 100 mg
• Bolus then infusion
• Infusion alone
• Is catheter directed an option?
WJ is a 62F admitted to the medical ICU

- Intermediate risk PE with evidence of RH strain
- On admission she was hemodynamically stable but now has soft pressures, MAP of 65 mmHg
- Additional considerations: hysterectomy 7 days prior

ICU team wants to give her alteplase given she is has a soft blood pressure, what dose should they give, or should you ask some more questions?
Do what's best for your patient and remember the literature!

- **Risk versus benefit**
- **Lytics versus anticoagulation alone**
  - No mortality benefit
  - Potential reduction in hospital stay
  - Potential reduction in occurrence of pHTN
  - Outcomes included subjective variables, that make results hard to interpret
- **Dosing strategies**
  - Reduced dose tPA can be considered
  - No primary outcome differences between 100 mg dose and reduced dose, but reduced dose is still superior to placebo
  - Potentially an increase in bleeding when comparing 100 mg to reduced dose (especially in smaller patients), but inconsistent results when comparing reduced dose to placebo
Discussion

Should you give thrombolytics to a patient with intermediate risk PE?
References


References


Thrombolytics in Intermediate Pulmonary Embolism (PE)

Rachel Belcher, PharmD
PGY2 Critical Care Pharmacist Resident
Intermountain Medical Center/Tele-Critical Care