Pulmonary Embolism in The Time of Lytics:

Defining Optimal Therapy for Intermediate risk Pulmonary Embolism

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Contents

• Definitions

• Pathophysiology

• Predictors of Mortality

• Lytics and other Therapies

• Management Suggestions
It’s 6 AM and...

- 48 YO F acute onset Chest pain this AM. Mild dyspnea and tachypnea

- VS: HR: 105, BP: 100/60, RR: 24, Sat: 91% on 6L
Imaging/Labs

- TnI: 0.9
- BNP: 522
Decisions Decisions...

Admit to ICU w/ Heparin?

Give ½ dose lytics?

Give Full dose lytics?

Surgical Intervention

Give Catheter based lytics

Need more Information?
What if this was a medium sized stroke?

• How many would give tPA?
Decisions Decisions…

There is no one size fits all answer…
Key questions

• What defines a sub-massive/intermediate risk pulmonary embolism?

• Should we consider lysis in these patients?

• What are we preventing?
  • Death?
  • Decompensation?
  • Long term outcomes

• What are the risks vs. benefits?
Does it Matter?

- Approx 600,000 PE/year

- Mortality:
  - 75% deaths occur in 1st hour...
  - Overall ~16%

- By subtype:
  - Massive PE: 52-63%
  - HD stable PE (incl SMPE): ~5-10%

- There is likely a gray zone in definitions
Immediate Decompensation Physiology

![Diagram showing the pathophysiology of major pulmonary embolism](image)

Fig. 2. Pathophysiology of PE. (From Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002;121;877–905; with permission.)
Classification of PE

PE Suspected
- SBP < 90 or
- Arrest/PEA or
- HR < 40/Shock

Yes
- Massive PE

No
- SBP > 90

1. RV Strain:
   - New RBBB
   - Anteroseptal T wave changes
   - Echo/CT RV:LV > 0.9
   - BNP > 90/ntBNP > 500

OR
2. Myocardial Necrosis by TnI

Sub-massive PE

Lysis ??
Pulmonary Embolism and Mortality

- Few studies looked at SMPE alone.
Prognosis of intermediate risk PE

- M+M in SM-PE: 10% decompensated, 5% died

- ECHO has a 100% NPV for death but poor PPV

- Griffoni Et All, 2000 Circulation
Is the classification that simple?

Low Risk: Sub-segmental

Intermediate Risk: Sub-massive

High Risk: Massive
Prognosis of intermediate risk PE

- Definitions:
  - RV Strain:
    - New RBBB
    - Anteroseptal T wave changes
    - Echo/CT RV:LV >0.9
    - BNP>90/ntBNP>500
  - OR
    - Myocardial Necrosis by TnI

- 10% decompensated
- 5% died
- Probably there is a range of risk with Intermediate risk PE
What Should Worry Us?

- BNP?
- Troponin?
- Clot burden on CT?
- CT RV:LV?
- Clots in transit?
- Large DVT?
- Patient factors?
- Echo RV strain?
RV:LV ratio on CT and 30D Mortality

RV:LV<0.9

RV:LV>0.9

Schoepf, Et Al. Circulation 2004; 110:3276-80

N=431
RV:LV ratio on CT and 30D Mortality

- No dilation: 7.7%
- Dilated RV:LV: 15.6%
  - Sensitivity: 78.2%
  - Specificity: 38%

Schoepf, Et Al. Circulation 2004; 110:3276-80
Does Clot burden Matter?

Predictive value of thrombus load for short-term clinical outcomes in acute PE

A  All-cause mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Weight</th>
<th>Observed OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu</td>
<td>2004</td>
<td>59</td>
<td>7.3</td>
<td>44.2 [4.4, 443.6]</td>
</tr>
<tr>
<td>Engelke</td>
<td>2006</td>
<td>89</td>
<td>10.14</td>
<td>6.8 [1.5, 31.3]</td>
</tr>
<tr>
<td>Pech</td>
<td>2007</td>
<td>188</td>
<td>12.54</td>
<td>0.6 [0.2, 1.5]</td>
</tr>
<tr>
<td>Aviram</td>
<td>2008</td>
<td>145</td>
<td>12.43</td>
<td>0.6 [0.2, 1.5]</td>
</tr>
<tr>
<td>Nakada</td>
<td>2010</td>
<td>45</td>
<td>7.29</td>
<td>1.0 [0.1, 10.1]</td>
</tr>
<tr>
<td>Moroni</td>
<td>2011</td>
<td>226</td>
<td>11.36</td>
<td>0.5 [0.1, 1.7]</td>
</tr>
<tr>
<td>Chaosuvannakit</td>
<td>2012</td>
<td>81</td>
<td>8.14</td>
<td>17.7 [2.3, 138.0]</td>
</tr>
<tr>
<td>Guel</td>
<td>2012</td>
<td>61</td>
<td>14.29</td>
<td>0.8 [0.6, 1.2]</td>
</tr>
<tr>
<td>Rodrigues</td>
<td>2012</td>
<td>102</td>
<td>8.95</td>
<td>0.9 [0.1, 5.8]</td>
</tr>
<tr>
<td>Soares</td>
<td>2013</td>
<td>96</td>
<td>7.56</td>
<td>1.3 [0.1, 11.8]</td>
</tr>
</tbody>
</table>

Random Effects Model

Odds Ratio (log scale)

1.6 [0.7, 3.9]
RV:LV ratio seems a better predictor
R. Heart Strain on ECHO

- Tricuspid Regurgitation

- Loss of IVC Collapsibility
R. Heart Strain on ECHO

- McConnell Sign
- D Sign/Septal Bowing
Significance of ECHO RV Strain

HD stable PE’s: n=3,283

- 37%: RV Strain
- 63%: No RV Strain

Mortality = 13.7%
Mortality = 6.5%
Cardiac Thrombi: Particularly Risky

- 4% of all PE pt’s
- Untreated Mortality: 100%

Table 1—Effect of Treatment on Mortality in Right Heart Thromboembolism*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Age, yr</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>35 (19.8)</td>
<td>65.7 ± 14.0†</td>
<td>28.6%</td>
</tr>
<tr>
<td>Surgery</td>
<td>63 (35.6)</td>
<td>56.6 ± 18.4</td>
<td>23.8%</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>62 (35.0)</td>
<td>60.5 ± 15.6</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

Concomitant DVT Increases Mortality in PE

- HR for mortality:
  - 1.6 vs no DVT

- HR for PE specific mort:
  - 2.01 vs. no DVT

- Jimenez Et Al. AM JRCCM 2010
Imaging Findings and Increased Mortality

- Increased RV:LV and mortality:
  - CT RV:LV > 0.9 → 15.6%
  - Echo RV Strain → 13.7%
  - Clot burden has ½ the odds of mortality vs CT RV:LV

- Intra-cardiac thrombi: 100% mortality

- Concomitant DVT: 1.5X risk of death

- Jimenez et al, 2009 CHEST
What can labs and Comorbidities tell us?
BNP: Better At Ruling Out Risk

- OR for Adverse events: 15.6
- OR for death: 6.57
  - Sens: 93%
  - Spec: 48%
- “If BNP is Negative, death from SM PE is less likely”

- Guillaume, C Et Al. Crit Care 2008
Troponin I

- Pooled OR for death: 4.26
  - TnI>0.1 or TnT>0.4

- OR for death:
  - Rarely detected w/o +BNP
  - Increased OR to 8.4 w/ + BNP

- “Higher TnI are bad, we just don’t know how bad, but they are worse w/ BNP”

- Jimenez et Al, 2009 CHEST; Lega Et Al, 2008 Thorax
Additional Predictors of Poor Outcome

Decompensation (OR)

1

BNP > 250
Malignancy
Chronic Lung Dz
Pneumonia
>RV:LV ratio

3.5

Altered Mental Status

Death (HR)

Ref: Sanchez, Et Al 2010 AM JRCCM ; Schoepf Et Al 2004 Circulation
Determining Acute Outcomes-conclusions

• Factors that Increase mortality:
  • Elevated TnI (OR 4.3)
  • Elevated BNP (OR 6.5)
  • TnI + BNP (OR 8.4)

• Other RF’s for poor outcome:
  • Malignancy
  • Lung Disease
  • AMS

• Negative BNP and TnI mortality highly unlikely
Long Term Outcomes: CTEPH

Type I: Fresh Thrombus

Type II: fibrosis and Intimal thickening

Type III: Well organized, distal vessel re-organization
Pulmonary HTN following SM-PE

Goals of Lytic Intervention in SM PE

• **Short Term:**
  • Prevent decompensation and death
  • Relieve Symptoms
  • Decrease recurrent PE
  • Prevent mortality from assoc thrombi (DVT/ICT)
  • Improve RV Function

• **Long Term:**
  • Prevent CTEPH
  • Preserve Exercise tolerance
What We Knew Before 2013

- Cocharane: 8 RCT’s 2006-09
- Heparin + placebo vs. hep+lytics
- Most were all PE not SMPE
- Results:
  - Similar: death, recurrent PE, major and minor bleeding
  - Improved hemodynamics w/ thrombolytics

Cocharane Review: Dong Et Al, 2009
Currently Accepted interventions for SMPE

AHA-2011

• ACCP: SMPE lytics should be considered

• AHA: lytics if elevated BNP/TnI and echo +

• ACEP: insufficient evidence to make any recommendations regarding use of thrombolytics

• ESC: no clear recommendation

• ACC: lytics have an unfavorable risk-benefit ratio in intermediate-risk PE.
Which Lytics are Available?

https://www.slideshare.net/perf9753/fibrinolytic-therapy
### Which Lytics are Available?

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA-Approved Indications</th>
<th>IV Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase (rt-PA)</td>
<td>AIS</td>
<td>0.1 mg/kg bolus, then: 0.8 mg/kg infusion over 60 min</td>
<td>ICH: 0.4%-0.9% Max dose = 90 mg (AIS)</td>
</tr>
<tr>
<td></td>
<td>Acute PE</td>
<td>100 mg infusion over 2 h</td>
<td>Fibrin specific</td>
</tr>
<tr>
<td></td>
<td>STEMII</td>
<td>&gt;67 kg: 100 mg IV (total) 15 mg bolus over 1-2 min 50 mg over 30 min 35 mg over 60 min ≤67 kg: 100 mg IV (max) 15 mg bolus over 1-2 min 0.75 mg/kg over 30 min (max 50 mg) 0.5 mg/kg over 60 min (max 35 mg)</td>
<td>Fibrinogen sparing</td>
</tr>
<tr>
<td>Reteplase</td>
<td>STEMII</td>
<td>10 units IV push over 2 min Repeat in 30 min</td>
<td>Anaphylaxis ICH: 0.8%</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Acute PE/DVT</td>
<td>250,000 IU IV over 30 min, then: 100,000 IU/h for 24 h (PE) or 72 h (DVT)</td>
<td>Anaphylaxis ICH not reported</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>STEMII</td>
<td>&lt;60 kg: 30 mg IV bolus 60-69 kg: 35 mg IV bolus 70-79 kg: 40 mg IV bolus 80-89 kg: 45 mg IV bolus &gt;90 kg: 50 mg IV bolus</td>
<td>IV push over 5 sec Most fibrin specific Fibrinogen sparing ICH: 0.9%</td>
</tr>
<tr>
<td>Urokinase</td>
<td>Acute PE</td>
<td>4,400 IU/kg over 10 min bolus, then: 4,400 IU/kg/h IV for 12 h</td>
<td>Anaphylaxis ICH: &lt;1%</td>
</tr>
</tbody>
</table>

### ABSOLUTE CONTRAINDICATIONS

**Acute Myocardial Infarction or Pulmonary Embolism**
- Active internal bleeding
- History of cerebrovascular accident
- Recent intracranial or intraspinal surgery or trauma
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diathesis
- Severe uncontrolled hypertension

**Acute Ischemic Stroke**
- Evidence or suspicion of intracranial or subarachnoid hemorrhage on pretreatment evaluation
- Intracranial or intraspinal surgery, serious head trauma, or previous stroke within 3 months
- History of intracranial hemorrhage
- Uncontrolled hypertension (>185 mmHg/110 mmHg)
- Seizure at onset of stroke
- Active internal bleeding
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Known bleeding diathesis (current anticoagulant use or international normalized ratio >1.7, heparin administration within 48 h, or platelets <100,000/mm³)
Lytics: the Current Literature

• Heparin Vs. Lytics in SM-PE
  • MAPPET3-2002: tPA
  • PEITHO trial 2014: TNKase
  • PEITHO-2 2017: 36 MO pHTN 2017
  • Kline et. Al TOPCOAT 2014: TNKase
  • Chatterjee: 2014 Meta-all cause mortality and ICH

• Half/low dose tPA in SMPE
  • Sharifi MOPPETT 2013, Half dose tPA

• Catheter based:
  • SEATTLE II: 2015-All PE
  • ULTIMA: 2014-SMPE only
### MAPPETT-3: 2002 tPA for SMPE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>tPA+UFH</th>
<th>UFH+Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite:</td>
<td>11%</td>
<td>24.60%</td>
<td>0.006</td>
</tr>
<tr>
<td>Death</td>
<td>3%</td>
<td>2.20%</td>
<td>0.7</td>
</tr>
<tr>
<td>Decompensation</td>
<td>10.20%</td>
<td>24.60%</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Secondary end</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>3.40%</td>
<td>2.90%</td>
<td>0.89</td>
</tr>
<tr>
<td>Major bleeds</td>
<td>0.80%</td>
<td>3.60%</td>
<td>0.29</td>
</tr>
<tr>
<td>ICH</td>
<td>0.00%</td>
<td>0.00%</td>
<td>X</td>
</tr>
<tr>
<td>Fatal bleeds</td>
<td>0.00%</td>
<td>0.70%</td>
<td>1</td>
</tr>
<tr>
<td>Ischemic CVA</td>
<td>0.00%</td>
<td>0.70%</td>
<td>1</td>
</tr>
</tbody>
</table>

- RCT 2002: N=252 pts w/ RV strain and nml BP w/ PE

Konstantinides S Et al. MAPPET-3 NEJM 2002
MAPPET3 Conclusions

- Use of tPA + UFH
  - Decreased composite risk of death + decompensation
  - Fewer rescue thrombolysis
  - NO difference in bleeding and ICH

- Risk factors for morbidity and mortality
  - Female
  - Age >70
  - Hypoxia
PEITHO-2014: TNK for SMPE

- DB RCT ITT analysis
- UFH+ placebo vs. TNK + UFH
- N= 1006 pt w/ SM-PE
- Outcomes:
  - 7D Composite death/decompensation
  - Recurrent PE
  - ICH, CVA, major extracranial bleeds
<table>
<thead>
<tr>
<th>PEITHO Outcomes (0-7D)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
</tr>
<tr>
<td>Composite:</td>
</tr>
<tr>
<td>7D Death</td>
</tr>
<tr>
<td>Decompensation</td>
</tr>
<tr>
<td><strong>Secondary endpoint</strong></td>
</tr>
<tr>
<td>Recurrent PE</td>
</tr>
<tr>
<td>Major bleeds</td>
</tr>
<tr>
<td>All Stroke</td>
</tr>
<tr>
<td>ICH</td>
</tr>
<tr>
<td>Ischemic CVA</td>
</tr>
</tbody>
</table>
PEITHO in 2017: What About PHTN

- ~38 MO F/U PEITHO pt’s
- N=709 (of 1006), pre-planned analysis
- Outcomes:
  - 30 D All cause mortality
  - Rates of 3yr PHTN by ECHO

<table>
<thead>
<tr>
<th>Mortality: the Verdict…</th>
</tr>
</thead>
</table>

**Table 3: Overall and Cause-Specific 30-Day and Long-Term Mortality**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tenecteplase (N = 359)</th>
<th>Placebo (N = 350)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause between randomization and day 30</td>
<td>8 (2.2)</td>
<td>10 (2.9)</td>
<td>0.595</td>
</tr>
<tr>
<td>Hemodynamic collapse</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Stroke (ischemic or hemorrhagic)</td>
<td>4 (1.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Recurrent pulmonary embolism</td>
<td>0 (0.0)</td>
<td>2 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0 (0.0)</td>
<td>2 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Sudden unexplained death</td>
<td>0 (0.0)</td>
<td>2 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.6)</td>
<td>3 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Death from any cause between day 30 and long-term follow-up</td>
<td>65 (18.1)</td>
<td>53 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Sudden unexplained death</td>
<td>2 (0.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>8 (2.2)</td>
<td>9 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0.0)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>19 (5.3)</td>
<td>4 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown cause</td>
<td>32 (8.9)</td>
<td>35 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Death from any cause between randomization and long-term follow-up</td>
<td>73 (20.3)</td>
<td>63 (18.0)</td>
<td>0.430</td>
</tr>
<tr>
<td>Table 4: Findings in Patients With Echocardiographic Long-Term Follow-Up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Right ventricular end-diastolic diameter &gt;30 mm</strong></td>
<td>Tenecteplase (N = 144)</td>
<td>Placebo (N = 146)</td>
<td>p Value</td>
</tr>
<tr>
<td>Missing data</td>
<td>34 (23.6%)</td>
<td>22 (15.1%)</td>
<td>0.058</td>
</tr>
<tr>
<td><strong>Right/left ventricular end-diastolic diameter &gt;0.9</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>12 (8.3%)</td>
<td>11 (7.5%)</td>
<td>0.834</td>
</tr>
<tr>
<td><strong>Hypokinesia of the right ventricular free wall (any view)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>6 (4.2%)</td>
<td>5 (3.4%)</td>
<td>0.740</td>
</tr>
<tr>
<td><strong>Tricuspid annulus plane systolic excursion reduced</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, mm Hg</td>
<td>23.6 ± 4.8</td>
<td>23.9 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>Median, mm Hg</td>
<td>24.0 (20.0-27.0)</td>
<td>24.0 (21.0-26.0)</td>
<td>0.551</td>
</tr>
<tr>
<td>Missing data</td>
<td>19 (13.2%)</td>
<td>18 (12.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Tricuspid systolic velocity &gt;2.6 m/s</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>22 (15.3%)</td>
<td>27 (18.5%)</td>
<td>0.412</td>
</tr>
<tr>
<td><strong>Systolic pulmonary artery pressure, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>31.6 ± 12.3</td>
<td>30.7 ± 10.2</td>
<td>0.527</td>
</tr>
<tr>
<td>Median</td>
<td>30.0 (24.0-35.0)</td>
<td>30.0 (25.0-35.0)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>33 (22.9%)</td>
<td>39 (26.7%)</td>
<td></td>
</tr>
</tbody>
</table>
PEITHO in 2017 And the Verdict is?

- At 30 Days:
  - No difference in mortality

- At 3 years:
  - Equal CTEPH b/t groups

- Criticisms on measurement and F/U

- **Lytics may be best for the acute phase**
TOPCOAT 2014: TNK for SMPE

- LMWH vs. TNKase, DBRCT
- Included: RV strain (echo/TnI/BNP)
- Primary Outcomes: Composite
  - Death, shock, intubation, embolectomy or bleeds in 5 days
- Secondary outcomes: Functional outcomes at 90 days
Composite outcome measures

Treatment patients had shorter hospital LOS

Study Conclusions II: Topcoat

- Caveats: Small study + composite outcomes
- Observed ICH rate 2.5% in treatment group
- TNKase + LMWH shows
  - Lower rates of decompensation and complications
  - Shorter hospital stays
  - No difference in long term outcomes
What About all the Others...

- Since 1970 16 trials w/ lytics and PE
- We could go through all of them...
2014 Meta analysis, 16 total (1970-2014)

8/16: Sub Massive PE only

Primary Outcomes:
- Efficacy: All cause mortality
- Safety: Major bleeding

Secondary Outcomes:
- Efficacy: Recurrent PE and
- Safety: ICH

**Summary Lytics vs. Anticoagulation Alone**

<table>
<thead>
<tr>
<th>Lytics and PE Meta Analysis Data</th>
<th>+ Lytic (%)</th>
<th>Anticoag Alone (%)</th>
<th>NNT/H</th>
</tr>
</thead>
<tbody>
<tr>
<td>All PE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submassive PE</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Summary Lytics vs. Anticoagulation Alone

<table>
<thead>
<tr>
<th></th>
<th>+ Lytic (%)</th>
<th>Anticoag Alone (%)</th>
<th>NNT/H</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All PE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>2.17</td>
<td>3.89</td>
<td>NNT=59</td>
</tr>
<tr>
<td>Recurrent PE (%)</td>
<td>0.4</td>
<td>1.17</td>
<td>NNT=54</td>
</tr>
<tr>
<td>ICH (%)</td>
<td>1.46</td>
<td>0.19</td>
<td>NNH=78</td>
</tr>
<tr>
<td>Major Bleeding (%)</td>
<td>9.34</td>
<td>3.42</td>
<td>NNH=18</td>
</tr>
<tr>
<td><strong>Submassive PE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>1.39</td>
<td>2.92</td>
<td>NNT=65</td>
</tr>
<tr>
<td>Major Bleeding (%)</td>
<td>7.74</td>
<td>2.25</td>
<td>NNH=18</td>
</tr>
</tbody>
</table>
MOPPET-2013: What About Half the Dose?

- ½ dose tPA
  - 0.5mg/kg tPA, Max 50 mg
  - 20% in 10 min/rest 2H

- Total of 56 pts per group

- Outcomes:
  - 1: PHTN (at 2 days/6MO)
  - 2: Major bleeding

Sharifi et Al JACC 2103
**Conclusion: Half dose tPA vs. Placebo**

<table>
<thead>
<tr>
<th>MOPPET 1/2 Dose tPA Outcomes</th>
<th>1/2 tPA</th>
<th>Anticoag</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHTN</td>
<td>16%</td>
<td>57.00%</td>
<td>2</td>
</tr>
<tr>
<td>PHTN+ recurrent PE</td>
<td>16%</td>
<td>63.00%</td>
<td>2</td>
</tr>
<tr>
<td><strong>Secondary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>0.00%</td>
<td>5.00%</td>
<td>2</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.60%</td>
<td>5.00%</td>
<td>NS</td>
</tr>
<tr>
<td>Mort+ Recurrent PE</td>
<td>1.60%</td>
<td>10.00%</td>
<td>12</td>
</tr>
<tr>
<td>Major Bleeds**</td>
<td>0.00%</td>
<td>0.00%</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>2.2 D</td>
<td>4.9 D</td>
<td>NA</td>
</tr>
</tbody>
</table>
Summary ½ dose Lytics

- **Reduces:**
  - Pulmonary HTN: **NNT 2**
  - PHTN+Recurrence: **NNT 2**
  - Recurrence+mortality: **NNT 12**

- **Criticisms:**
  - Not powered for mortality alone
  - Small study
  - No ICH or Major Bleeding
    - Zhang Et Al: Meta data ½ dose ICH = 0.2%
Summary: Systemic Lytics in SM-PE

- **Benefits:**
  - Reduced mortality NNT=65
  - Reduced decompensation
  - ½ dose Appears better

- **Risks:**
  - ICH: 1.5% NNH=78 full dose; 0.5% ½ dose
  - Major Bleeds: 9% NNH = 18
  - Higher bleed rates > 65 YO

- **Controversial:**
  - PHTN/CTEPH: May reduce
How Does this Compare to the Lytics for Stroke?

- Stroke: **12 trials total**
- Mortality (All Stroke): 16-23%
  - 2 Trials: **Benefit** Functional only, *not mortality*
    - ECASIII: **NNT8**
    - NINDS: **NNT15**
  - 6 trials: **NO Benefit**, 
  - 5 trials stopped for **Harm**, Overall ICH: **NNH20**
Lytics for SMPE...

- SM-PE: 9 trials total
- Mortality SMPE: 5-10%
  - 8 Trials: Benefit
    - mortality: NNT=54
    - Recurrence: NNT=59
  - 1 trials: **NO Benefit**,
- 0 trials stopped for **Harm**, Overall ICH: **NNH=78**
How Does this Compare to the Lytics for Stroke?

- tPA Has mortality benefit in SMPE **Not** stroke
- 1/3 the ICH rate vs Stroke
- 90% studies w/ lytics in SMPE show benefit
- 17% of studies of tPA in Stroke show benefit
- You decide which indication is more controversial...

*Denotes ½ dose*
What About Patients With Higher Bleeding Risk?
Embolectomy?
Embolectomy

• May be riskier than the disease itself...

• Additive Surgical Mortality:

  Massive PE: 6.6%
  Sub-Massive MPE: 3.6%

• Better for:
  • Massive PE: Mortality 30-70% alone
  • Bleeding risks
  • Higher risk SM PE
Other Therapies... EKOS
SEATTLE II

- Massive PE n=31
- Submassive n=119
- UFH/LMWH vs Cath tPA

Outcomes:
- Primary Efficacy: CT RV/LV ratio
- Primary Safety: Major bleeding 72H
- No mortality related outcomes

SEATTLEII Piazza Et Al, JACC 2015
EKOS Improves Non Clinical Outcomes

SEATTLEII Piazza Et Al, JACC 2015
Bleeding AE Mostly Catheter Associated

- N=150
- 16 total bleeds
  - 8 hematoma + 1 pseudoaneurysm
  - 3 Symptomatic anemia
  - 2 hemoptysis
  - 1GU
  - 1 mucosal
- No ICH

SEATTLEII Piazza Et Al, JACC 2015
SEATTLE II Conclusions

- Catheter based lytics improve
  - RV:LV ratio and PA systolic pressures
- True clinical outcomes more nebulous
- No ICH
- Bleeding mostly catheter associated

SEATTLEII Piazza Et Al, JACC 2015
ULTIMA: EKOS for SM PE

- 59 pts total UFH vs. tpa/cath (10-20mg)

- Only for SM PE

- Results similar to SEATTLEII
  - Significantly Improved RV/LV ratios
  - Significantly improved PASP

- No Major bleeding, no ICH

ULTIMA. Kucher Et Al, Circulation 2014
What’s the Bottom Line

• Embolectomy Reserved for high risk pts

• Catheters:
  • Less bleeding
  • No ICH
  • Mortality Benefit nebulous
  • Improved RVSP and RV/LV

• CD-tPA: Best for Semi Stable pt w/ moderate bleeding risk
So How do we decide who gets what therapy?
Not All SM PE Are Created Equal

- Chronic Lung Dz
- Malignancy
- Pneumonia
- Elevated BNP
- $\text{RV:LV ratio}$
- TnI > 0.1
- Cardiac thrombi
- Worsening VS
- Altered Mental Status
- Proximal DVT
Not All Treatment Risks Are Equal

**Intracranial Hemorrhage**

- tPA + UFH (1.5%)
- ½ dose tPA (0.5%)
- Catheter tPA (0%)

**Major Bleeding**

- tPA-stroke (6%)
- UFH-MI (1.0%)*
- UFH SM-PE (2.3%)
- tPA+UFH (7.7%)
- Cath tPA (0%)
- tPA+UFH (7.7%) - Cath tPA (0%)
- All PE (9.4%)
- tPA - All PE
Therapy Is Based on Risk

<table>
<thead>
<tr>
<th>BLEED</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>½ dose tPA W/O UFH Or Embolectomy</td>
<td>UFH Alone</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>½ Dose tPA Or Full Dose if Worse</td>
<td>EKOS Catheter</td>
</tr>
</tbody>
</table>

Death
What do I tell My Patient?

• Your risk of brain bleed is about 1-2%
• 1 in 10 will bleed anywhere
• We are probably preventing recurrence
• Some may feel better in 6 months
• This treatment cuts your risk of hospital complications and death in half (from 10% to 5%)
• This data is much better and more consistent than tPA for stroke
Questions?


14. NICE 2012 clinical guideline 144: guidance.nice.org.uk/cg144