Submassive PE -- What’s new in 2015?

W. Graham Carlos MD, MSCR  11/6/2015

Objectives

- Define Submassive PE
- Predict which patients with PE will have poor outcomes and identify what those outcomes are
- Identify the risks and benefits of TPA treatment for submassive PE
- Recognize the emerging role of catheter directed thrombolysis for treatment of submassive PE

Disclosures

- Industry: None
- Practically: I am giving this talk on <24 hours notice

Some stats...

- 60-100 cases per 100,000 patients per year
- 30-day mortality rate of 10%-30%
- Accounts for 200,000 hospital discharges and 30,000 deaths each year

MASSIVE
- ~5% of PEs
- 58% 90-day mortality

SUBMASSIVE
- ~40% of PEs
- 22% 90-day mortality

LOW RISK
- ~55% of PEs
- <1% 90-day mortality
Low risk PE
Acute PE with:
• normal RV function
• no elevations in biomarkers

Massive PE
Acute PE with:
• sustained hypotension (SBP <90 mm Hg for at least 15 min or requiring inotropic support not due to a cause other than PE (arrhythmia, hypovolemia, sepsis, or LV dysfunction)
• pulselessness
or
• persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock)

Submassive PE
Acute PE:
• without systemic hypotension (SBP ≥90 mm Hg)
BUT
• with evidence of either RV dysfunction OR
• evidence of myocardial necrosis (elevation of troponin I (>0.4 ng/mL) or troponin T (>0.1 ng/mL)

RV dysfunction
• RV dilation on echo or CT (RV:LV diameter ratio >0.9)
• RV systolic dysfunction on echocardiography
• Elevated BNP (>90 pg/mL) or pro-BNP (>500 pg/mL)
OR
• ECG changes
new complete or incomplete RBBB anteroseptal ST elevation, ST depression, T-wave inversion
1. Fibrinolysis is reasonable for patients with **massive acute PE** and acceptable risk of bleeding complications (*Class Ila; Level of Evidence B*).

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*).

**Why the concern?**

- ~20% of all PE, BUT accounts for most deaths from PE
- 2-5% in-hospital mortality rate
- **Increased short-term morbidity:**
  - RV dysfunction on echo: OR = 2.53 (95% CI 1.17 - 5.50)
  - Myocardial necrosis: OR = 5.90 (95% CI 2.68 - 12.95)
- **Increased long-term morbidity:** chronic pulmonary hypertension, persistent RV dysfunction, increased rate of CTEPH and worse functional outcome/QOL

**Predictor of poor outcome...**

- 2-5% in-hospital mortality rate
Survival rate through 30 days in 1035 patients with pulmonary embolism with a systolic arterial pressure of 90 mm Hg or higher at presentation, according to the presence or absence of right ventricular (RV) hypokinesis on the baseline echocardiogram.

Prognostic value of right ventricular dysfunction for mortality in patients with pulmonary embolism without shock. The outcome was in-hospital mortality for all studies, except two: (*) 40-day mortality and (†) 90-day mortality.

Cardiac biomarkers and mortality

European Heart Journal (2008), 29, 1569-1577

Who should get the lytics? An ongoing debate...

The evidence...
MAPPET-3 (2002)

- Double-blinded RCT
- 256 pts with acute PE and RV strain (echo, ECG, or CT)
- 100mg tPA + heparin vs placebo + heparin over 2h

No difference for in-hospital mortality (3.4% vs. 2.2%; p=0.71)
More cases of clinical deterioration requiring escalation of care in heparin-alone group (24.6% vs 10.2%; p=0.004)

MOPETT Trial (2013)

- Single center, open label, RCT
- 114 patients with "moderate PE"
- Effect of low (half) dose t-PA on the reduction in pulmonary artery pressure at 28 months follow up
- 50 mg for pts >50kg and 0.5 mg/kg for <50kg vs anticoagulation alone
- Used old anatomical definition – NO RVD required prior to enrollment

Pulmonary HTN at 28 months

16% vs 57%, p<0.001

<table>
<thead>
<tr>
<th>Variable</th>
<th>TG</th>
<th>CG</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>9 (16%)</td>
<td>32 (57%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary hypertension + recurrent pulmonary embolism</td>
<td>9 (16%)</td>
<td>35 (59%)</td>
<td>&lt;0.001</td>
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</tbody>
</table>

NNT for pulmonary HTN = 2.4

MOPETT Trial (2013)

PEITHO Trial (2014)

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Decrease in total mortality + recurrent PE

1.6% vs 10%, p=0.049

Decrease in hospital LOS

2.2 vs 4.9 days, p=0.001

No difference in total mortality

No difference in bleeding (none in either group)

No recurrent PEs in treatment group although did not reach statistical significance (0% vs 5%, p=0.06)
• Double blinded, multi center, RCT
• 1006 normo-tensive patients with confirmed PE AND
  RVD by echo or CT and myocardial injury (+ Ti, Tt)
• Wt based (30-50mg) Tenecteplase bolus + heparin vs placebo + heparin

PEITHO (2014)

• Death within 7 days
• Hemodynamic collapse within 7 days
• Symptomatic recurrent of PE within 7 days
• Death within 30 days

Secondary Outcomes

Results

Safety Outcomes

Primary Outcome

Clinical composite of death from any cause OR hemodynamic collapse within 7 days

Table 3: Efficacy Outcomes.®

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tenecteplase (N=586)</th>
<th>Placebo (N=489)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome — no. (%)</td>
<td>23 (4.0)</td>
<td>28 (5.6)</td>
<td>0.44 (0.25-0.79)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>6 (1.0)</td>
<td>9 (1.8)</td>
<td>0.63 (0.29-1.37)</td>
<td>0.28</td>
</tr>
<tr>
<td>Hemodynamic deterioration</td>
<td>8 (1.4)</td>
<td>25 (5.1)</td>
<td>0.16 (0.06-0.44)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time between randomization and primary efficacy outcome — days</td>
<td>1.36 (0.7-2.2)</td>
<td>0.80 (0.4-1.5)</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>Recurrent pulmonary embolism — day 7 — no. (%)</td>
<td>2 (0.3)</td>
<td>5 (1.0)</td>
<td>0.20 (0.05-0.82)</td>
<td>0.034</td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>3 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal</td>
<td>2 (0.3)</td>
<td>2 (0.4)</td>
<td></td>
<td></td>
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<tr>
<td>Other non-hospital complications and procedures — no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mechanical ventilation</td>
<td>8 (1.4)</td>
<td>15 (3.1)</td>
<td>0.53 (0.25-1.12)</td>
<td>0.09</td>
</tr>
<tr>
<td>Surgical mortality</td>
<td>2 (0.4)</td>
<td>2 (0.4)</td>
<td></td>
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<tr>
<td>Catheter Thrombus Fragmentation</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>Venous cannulation interruption</td>
<td>5 (0.9)</td>
<td>2 (0.4)</td>
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</tr>
<tr>
<td>Thrombolytic treatment other than study medication</td>
<td>4 (0.7)</td>
<td>23 (4.7)</td>
<td></td>
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</tr>
<tr>
<td>Death from any cause between randomization and day 30 — no. (%)</td>
<td>27 (4.7)</td>
<td>10 (2.1)</td>
<td>0.71 (0.42-1.19)</td>
<td>0.14</td>
</tr>
<tr>
<td>Patient still hospitalized at day 30 — no. (%)</td>
<td>59 (10)</td>
<td>50 (10)</td>
<td></td>
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</tr>
<tr>
<td>Time between randomization and day 30 — no. (%)</td>
<td>10 (1.7)</td>
<td>23 (4.7)</td>
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Table 4: Safety Outcomes in the Intention-to-Treat Population.®

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<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Major bleeding</td>
<td></td>
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<tr>
<td>Subgroup</td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (1.9)</td>
<td>11 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt</td>
<td>5 (0.8)</td>
<td>5 (0.8)</td>
<td></td>
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<tr>
<td>Gender</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (1.9)</td>
<td>11 (2.2)</td>
<td></td>
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<tr>
<td>Wt</td>
<td>5 (0.8)</td>
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</tbody>
</table>

® Odds ratios and P values are prorated for efficacy and safety outcomes that were prespecified in the trial protocol. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis. Hemorrhagic death included hemorrhagic conversion of ischemic stroke.
Conclusions

• Substantial reduction in combined endpoint of early mortality OR hemodynamic collapse...

...at the expense of increased significant increase in major hemorrhage, esp in >75yrs

The role of thrombolytic therapy in pulmonary embolism

• Meta-analysis of 16 studies comparing thrombolysis to anticoagulation alone
• Total nb of patients = 2087

Mortality

OR of overall mortality comparing thrombolysis to anticoagulation in stable PE with clearly defined RVD

Bleeding Risk

OR of intracranial bleeding events comparing thrombolysis to anticoagulation
### Catheter-directed thrombolysis

**The theory...**

- Rapid debulking of thrombus
- Prevention of adverse outcomes
  - Early: worsening RV afterload /cardiac ischemia or respiratory/hemodynamic collapse
  - Late: Chronic thromboembolic pulmonary hypertension
- Lower dose and more localized administration makes it safer than systemic thrombolysis with reduction in hemorrhage rate

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**Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism**

Nils Kocher, MD; Peter Boekhoff, MD; Oliver J. Muller, MD; Christian Kopatz, MD; Jan Beyer-Westendorf, MD; Thomas Hellauer, MD; Ulrich Thaler, MD; Jan Honkompke, MD; Ralf Muller, MD; Kevin Blessing, MD; Martin Graef, MD; Philipp Lange, MD; Rüdiger Hoffmann, MD; Christian Wehr, MD; Achim Barwick, MD; Dirk Halter, MD; Henning Gerstwiek, MD; Klaus Elsner, MD; Iris Brausinger, MD

- Comparison of US-accelerated thrombolysis through EKOS catheter system vs Heparin
- Multi-center, open-label, RCT
- 59 patients with intermediate risk PE confirmed by echo
- Low dose (<20mg) r-tPA+ heparin vs heparin alone

**ULTIMA (2014)**

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**Baseline RV:LV ratio:**

- 1.28 in USAT vs 1.22 in no intervention (p=0.07)

- Mean decrease in RV:LV ratio at 24h:
  - 0.3 in USAT vs. 0.03 in no intervention (p<0.001)

- RV:LV ratio at 90d:
  - 0.92 in USAT vs 0.96 in no intervention (p=0.36)

No major bleeding in USAT group

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**SEATTLE-II Trial**

**ACC 2014**

Submassive and massive pulmonary Embolism treatment with **Accelerated Thrombolysis therapy**

- 150 patients (61 massive PE, 99 submassive PE)
- Ultrasound-facilitated, catheter-directed, endovascular low-dose thrombolysis
  - 2mg tPA, 1mg/hr for 24 hours

**RESULTS:**

- 98% successful completion rate
- No deaths in massive PE within 30 days
- RV/LV ratio reduction by 30% in 48 hours
- Pulmonary Artery Pressure reduction by 30% within few hours
- PA angiographic obstruction score (Miller Index) by 30% within few hours
- NO intracranial bleeding events
Acknowledgements

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- Dr. Aline Zouk – For help with slide compilation
- The Indiana ACP!

References