Abstract: Massive Pulmonary Embolism (PE) requires immediate lifesaving intervention for the patient. For the submassive PE patient, characterized by presence of right ventricular (RV) dysfunction while hemodynamically stable, there is considerable debate regarding treatment options and best clinical practice. This white paper summarizes the current clinical research for risk assessment based upon RV dysfunction and a review of systemic thrombolytic treatment strategies for submassive PE patients.

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Epidemiology of Pulmonary Embolism (PE)

- A commonly underdiagnosed and lethal entity; over 600,000 cases annually in the United States\(^1\)
- Annual incidence of PE shown to be 69 per 100,000 in one 25-year population-based study\(^2\)
- PE most commonly originates from DVT of the legs: 79% of patients presenting with PE have evidence of DVT, and PE occurs in up to 50% of patients with proximal DVT\(^3\)

Acute PE: patient population profile\(^4\)

- Minor PE
  - Approx. 55% of the PE population
  - Good prognosis
  - Low mortality rate

- Submassive PE
  - 40% of the PE population
  - Mortality approx. 21% at 3 months

- Massive PE
  - <5% of the PE population
  - 58% mortality at 3 months
Right Ventricle Dysfunction (RVD) is Associated with Poor Clinical Outcomes

A) The presence of right-ventricular (RV) hypokinesis on baseline echocardiogram was associated with a 57% higher mortality rate at 3 months even though most of the patients (88.9%) were hemodynamically stable.\(^4\)

2454 consecutive pulmonary embolism patients at 52 hospitals in seven countries\(^4\)

- 88.9% of patients were symptomatic and hemodynamically stable. The overall mortality rate at three months was 17.4%
- 7.9% of patients had recurrent PE within 3 months and of these, 46.8% died
- The presence of RV hypokinesis on the baseline echo was associated with higher mortality at 2 weeks and 3 months compared to patients without RV hypokinesis (see figure\(^4\))

![Cumulative mortality according to status of right-ventricular function on baseline echocardiogram](image)

Approx. 15%

Approx. 21%
B) An echocardiographic RV/LV ratio >0.9 was shown to be an independent predictive factor of hospital mortality.\textsuperscript{5}

Registry of 1416 patients\textsuperscript{5}

- 1416 pulmonary embolism patients of which 950 underwent echocardiographic examination for which a right/left ventricular end-diastolic (RV/LV) ratio was obtained
- In patients with systolic BP ≥ 90 mmHg, the mortality rate was 3.3% in patients whose RV/LV ratio was ≥ 0.6 and 1.1% for those whose RV/LV ratio was < 0.6 (OR 2.66, p = 0.01)

C) Mortality risk increases with stepwise increase in RV/LV Ratio.\textsuperscript{6}

Retrospective analysis of 120 patients with hemodynamically stable PE and helical CT available for review\textsuperscript{6}

- CT signs of right ventricular dysfunction (RVD) (defined as RV/LV > 1.0) were seen in 69 patients (57.5%).
- All were administered intravenous unfractionated heparin for at least 5 days
- At three months, 18 (15%) patients had died, of which seven were PE related. Risk of PE-related death correlated to an RV/LV ratio > 1.0

<table>
<thead>
<tr>
<th>Increased mortality observed with stepwise increase in RV/LV ratio</th>
<th>Patients (%)</th>
<th>Deaths from PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/LV Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>18 (15%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>&gt;1.0 – 1.5</td>
<td>51 (42.5%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>≤1.0</td>
<td>51 (42.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

D) Pulmonary embolism patients with right heart dysfunction defined as RV/LV >0.9 have a significantly higher chance of adverse events within 30 days.\textsuperscript{7}

Retrospective Analysis of 63 patients\textsuperscript{7}

- 24 patients had adverse clinical events within 30-days including death, need for CPR, mechanical ventilation, pressors, rescue thrombolysis, or surgical embolectomy
- Measurements of ventricular dimensions demonstrated that either the CT 4-chamber view or echocardiogram measurements of RV/LV ratio were predictive of adverse events
- Patients with a CT 4-Chamber RV\textsubscript{d}/LV\textsubscript{d} > 0.9 had an 80.3% chance of adverse events within 30 days versus 51.3% for all others
E) Pulmonary embolism patients with Right Ventricle Dysfunction (RVD) which was not resolved prior to hospital discharge were 8-times more likely to have a recurrent PE than patients whose RVD resolved prior to discharge.8

Retrospective Analysis of 301 Patients with first episode acute PE8

146 (48.5%) patients had evidence of RVD; 87 of these patients showed complete RVD regression at discharge (23 underwent thrombolysis) whereas 59 patients retained 1 or more signs of RVD at discharge (7 underwent thrombolysis).

Mean Follow-up was 3.1 ± 2.7 years with the following observations:

- Patients with RVD persistence had increased likelihood of recurrent VTE (14/59, 24%) compared to those with RVD regression (3/87, 3%) at time of hospital discharge = 24%/3% = 8 times more likely.
- PE-related mortality was also significantly higher in patients with RVD persistence at time of hospital discharge (HR 15.18; 95% CI, 3.04-75.92; p<.001).

F) Patients that present with acute PE and elevated Right Ventricular Systolic Pressure (RVSP) treated only with heparin have worsening elevated RVSP, as well as dyspnea at rest or exercise intolerance at six months.9

Prospective observation of 200 normotensive patients with acute PE (CT angiography)9

- 144 of 162 patients that returned for follow up at 6 months had been treated with heparin only and 18 had been treated with heparin plus alteplase
- 50 of the heparin only treated patients followed up at 6 months had RVSP ≥ 40 mmHg at diagnosis; 39 of those 50 had higher RVSP at 6 months than at baseline (27%)
- Of these 39 patients with higher RVSP at 6 months, 18 (46%) had either dyspnea at rest or exercise intolerance
- 11 of the heparin plus alteplase treated patients followed up at 6 months had RVSP ≥40mm Hg at diagnosis; The RVSP at follow up was not higher than at time of diagnosis in any of the heparin plus alteplase treated patients
A) Thrombolytic treatment improves clinical outcomes however clinical benefit is associated with a risk of major bleeding (The PEITHO Investigation).  

Randomized multicenter trial: 1006 normotensive patients with acute intermediate-risk PE (characterized by RV dysfunction) randomized to tenecteplase or placebo.  

- At 7 days the all-cause mortality was similar in both groups, whereas hemodynamic collapse was 1.6% for patients treated with tenecteplase versus 5.0% for placebo (p=0.002)  
- More patients in the placebo-treated group required open-label thrombolysis than in the tenecteplase-treated group (4.6% versus 0.8%)  
- Clinical benefits of improved hemodynamics came at the cost of a significantly increased risk of major hemorrhage including intracranial bleeding  
- Non-intracranial major bleeding was 6.3% in the treatment group compared to 1.5% in the placebo group (p<0.001), and hemorrhagic stroke occurred in 2% of tenecteplase-treated patients compared to 0.2% of placebo patients (p=0.003)  
- Results of PEITHO justify risk stratification of normotensive patients with acute PE

B) Thrombolysis treatment results in trend towards improved clinical outcomes and RV Function.  

Prospective study of 72 Patients with first episode acute submassive PE and RV Dysfunction randomized to placebo versus alteplase, in addition to heparin.  

- The thrombolysis group showed a significant early improvement of RV function compared with heparin group as well as sustained improvement at 180 days

<table>
<thead>
<tr>
<th>RV/LV Ratio on admission, during hospitalization and follow-up</th>
<th>Admission</th>
<th>24 Hours</th>
<th>6 Days</th>
<th>3 mo</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin (35 pts)</strong></td>
<td>1.42±0.04</td>
<td>1.25±0.04</td>
<td>1.04±0.03</td>
<td>0.92±0.02</td>
<td>0.88±0.02</td>
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<tr>
<td><strong>Lytic (37 pts)</strong></td>
<td>1.41±0.05</td>
<td>1.12±0.04</td>
<td>0.82±0.01</td>
<td>0.68±0.01</td>
<td>0.67±0.01</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>&lt;0.354</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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- Thrombolytic treated patients had a lower incidence of combined adverse events (mortality, RVD, major bleeding and DVT) with 5.4% in the treatment group compared to 45.7% in the heparin group (p < 0.005)  
- The clinical benefit of thrombolysis treatment was associated with an increase in minor non-fatal bleeding events

<table>
<thead>
<tr>
<th>Total events during hospitalization and follow up</th>
<th>Heparin (n, %)</th>
<th>Lytic (n,% )</th>
<th><strong>P</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause Death</td>
<td>6 (17.1)</td>
<td>0</td>
<td>0.027</td>
</tr>
<tr>
<td>Recurrent PE (fatal)</td>
<td>4 (11.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Irreversible RVD</td>
<td>2 (5.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>1 (2.85)</td>
<td>2 (5.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>8 (22)</td>
<td>16 (43.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Combined AEs</td>
<td>16 (45.7%)</td>
<td>2 (5.4)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
C) Treatment with tenecteplase reduces RVD at 24 Hours in hemodynamically stable patients.\textsuperscript{12}

Prospective randomized multi-center trial of 58 hemodynamically stable patients with Echo confirmed RVD.\textsuperscript{12}

- Patients in the treatment group had reduced RVD of 0.31 ± 0.08 versus a reduction of 0.10 ± 0.07 in the control group (p = 0.04) at 24 hours
- One patient in the treatment group had a clinical event (recurrent PE) in comparison to three patients with clinical events in the control group (recurrent PE, clinical deterioration and non-PE related death)
- Two non-fatal major bleeds occurred in the treatment group (one being intracranial) compared to one with placebo

D) Treatment of Acute Submassive PE Patients with tenecteplase compared to placebo shows favorable outcomes.\textsuperscript{13}

83 normotensive patients with RV strain by echo or biomarkers. Prospective randomized multi-center trial.\textsuperscript{13}

- 37\% of placebo patients experienced adverse outcomes as compared to 15\% (p=0.017) of tenecteplase treated patients (adverse outcomes assessed at 5 and 90 days with 90 day endpoints including recurrent VTE and measurements of poor physical health using the SF36\textsuperscript{TM} questionnaire)
- One tenecteplase treated patient had a fatal intracranial hemorrhage occurring 5 hours after drug administration representing the only patient in the trial with a major bleed during the 5-day period of surveillance
- Three placebo treated patients had adverse outcomes within 5 days with one fatality directly attributed to PE and two who required endotracheal intubation, vasopressor support and catheter thrombectomy
- Proportion of patients who remained in the ICU on day 2 post-treatment was significantly higher with placebo (20.5\%) compared with tenecteplase (5\%, p = 0.03)

E) Long term follow-up of PE patients treated with IV thrombolytics showed lower PA pressures and pulmonary vascular resistance (PVR) than PE patients treated with heparin.\textsuperscript{14}

40 patients. Prospective Randomized Trial.\textsuperscript{14}

- Randomized to heparin or IV urokinase or streptokinase
- Follow-up mean 7.4 years
- Mean PA pressure and PVR significantly higher in heparin treated group (22 vs 17 mmHg (P<.05) and 351 vs 171 dynes s\textsuperscript{-1} cm\textsuperscript{-5} (p<.02), respectively)
- During exercise both parameters rose significantly higher in the heparin group, from rest to exercise PA pressure rose from 22 to 32 mmHg (p<.01) and PVR rose from 351 to 437 dynes s\textsuperscript{-1} cm\textsuperscript{-5} (p<0.01) but not in the thrombolytic treated group
**Guidelines from ACCP 2016 and AHA 2011**

<table>
<thead>
<tr>
<th>American College of Chest Physicians (ACCP) 2016&lt;sup&gt;16&lt;/sup&gt;</th>
<th>American Heart Association (AHA) 2011&lt;sup&gt;16&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>In selected patients with acute PE not associated with hypotension who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).</td>
<td>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).</td>
</tr>
<tr>
<td>In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over CDT (Grade 2C).</td>
<td>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).</td>
</tr>
</tbody>
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**American Heart Association (AHA) Scientific Statement (2011) recommendations support fibrinolysis and catheter-based interventions for the treatment of acute submassive PE.**<sup>16</sup>

- Percutaneous techniques to recanalize complete and partial occlusions in the pulmonary trunk or major pulmonary arteries are potentially life-saving in selected patients with massive or submassive PE.

- The goals of catheter-based therapy include (1) rapidly reducing pulmonary artery pressure, RV strain, and pulmonary vascular resistance (PVR); (2) increasing systemic perfusion; and (3) facilitating RV recovery.
References