UPDATE ON MANAGEMENT IN PULMONARY EMBOLISM

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Scotland National Thrombosis Meeting
Stirling, May 2019
Outline

• Management of intermediate high risk PTE

• Ambulatory care and PTE
Why are we talking about this?
Acute PE

Massive: Thrombolyse

iv Heparin

Thrombophilia Screen

6/12 Warfarin

PE Management 1998
Acute PE
Massive:
Thrombolys
Thrombophilia
Screen
6/12 Warfarin
iv Heparin

PE Management 1998

PE Management 2019

Acute PE
Risk Stratify

High Risk: Thrombolys
Intermediate Risk: ?Thrombolysis

Low Risk: ? Early D/C

LMWH

3 – 6/12 Warfarin
3 – 6/12 Novel agent

LMWH

Risk Stratify

?Long Term Anticoagulation
CTEPH Screening
?Cancer Screening
### Risk stratification in PE

#### Table 9: Classification of patients with acute PE based on early mortality risk

<table>
<thead>
<tr>
<th>Early mortality risk</th>
<th>Risk parameters and scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shock or hypotension</td>
</tr>
<tr>
<td></td>
<td>PESI class III-V or sPESI ≥ 1</td>
</tr>
<tr>
<td></td>
<td>Signs of RV dysfunction on an imaging test^3</td>
</tr>
<tr>
<td></td>
<td>Cardiac laboratory biomarkers^c</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>(+)^4</th>
<th>+</th>
<th>(⊕)^d</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-high</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-low</td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td></td>
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</tbody>
</table>

- Both positive
- Either one (or none) positive
- Assessment optional; if assessed, both negative
hsTroponin 97
Assess cardiac risk

<table>
<thead>
<tr>
<th>Echo/CT parameters</th>
<th>biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV dilatation</td>
<td>Troponin</td>
</tr>
<tr>
<td>RV strain (RV/LV ratio &gt; 1)</td>
<td>BNP</td>
</tr>
<tr>
<td>Increased TRPG</td>
<td>NT-proBNP</td>
</tr>
<tr>
<td>Hypokinesis RV wall</td>
<td></td>
</tr>
</tbody>
</table>
PESI score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original version(^2\textsuperscript{14})</th>
<th>Simplified version(^2\textsuperscript{18})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age in years</td>
<td>1 point (if age &gt;80 years)</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10 points</td>
<td>–</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>+10 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>+10 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Pulse rate ≥110 b.p.m.</td>
<td>+20 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mm Hg</td>
<td>+30 points</td>
<td>1 point</td>
</tr>
<tr>
<td>Respiratory rate &gt;30 breaths per minute</td>
<td>+20 points</td>
<td>–</td>
</tr>
<tr>
<td>Temperature &lt;36 °C</td>
<td>+20 points</td>
<td>–</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60 points</td>
<td>–</td>
</tr>
<tr>
<td>Arterial oxyhaemoglobin saturation &lt;90%</td>
<td>+20 points</td>
<td>1 point</td>
</tr>
</tbody>
</table>

**Risk strata\(^3\)**

- **Class I: ≤65 points**
  - very low 30-day mortality risk (0–1.6%)
- **Class II: 66–85 points**
  - low mortality risk (1.7–3.5%)
- **Class III: 86–105 points**
  - moderately elevated mortality risk (3.2–7.1%)
- **Class IV: 106–125 points**
  - high mortality risk (4.0–11.4%)
- **Class V: >125 points**
  - very high mortality risk (10.0–24.5%)

0 points = 30-day mortality risk 1.0% (95% CI 0.0%–2.1%)

≥1 point(s) = 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)
Management of High Risk Massive PTE

• Alteplase is thrombolytic of choice in massive PE.
• For standard thrombolysis of massive PE:
  • 10mg alteplase IV over 2 minutes
• followed by 90mg alteplase over 2 hours
• N.B. max dosing is 1.5mg/kg for patients <65 kg
What would you do?
Young student

No previous medical history

Presents with sudden syncopal episode and acute dyspnoea

Admitted to local DGH
• On arrival, clammy, peripherally shut down
• Pleuritic chest discomfort
• BP 105mmHg systolic, tachycardic, resp rate 14
• Sats on air 92%, type 1 respiratory failure on ABG
• CXR normal
Progress

• Over next 24 hours becomes more breathless

• Progressive hypoxaemia

• Now needing 10 litres high flow oxygen via trauma mask to maintain Sats > 95%

• BP good
BP 110/50 mmHg
Troponin 310
SaO2 95% on 10l oxygen
Pulse 98bpm
What next?

- Anticoagulation alone
- Systemic thrombolysis
- Surgical embolectomy
- Catheter directed thrombolysis
- Panic! And Phone the Scottish Pulmonary Vascular Unit
Management for Intermediate High risk should be individualised
Intermediate High risk (Submassive)

- There is no accepted guideline on the best course of management for these patients but there is recognition that these patients have a higher mortality than patients with ‘low risk PE’.

- Therefore, clinical judgement is required as well as involving senior members of the medical staff.

- Anticoagulation with LMWH in the first instance should be first line.

- There should also be close monitoring in case of clinical worsening despite anticoagulation.
• If patient intermediate-high risk and clinically deteriorating (e.g. progressive hypoxaemia), there may be a role for the following:

• Full dose thrombolysis
• Low dose thrombolysis
  • Alteplase 10mg IV bolus followed by 40mg infusion over 1 hour.
• Catheter-directed intervention (via local interventional radiology)
### A  Death or Hemodynamic Decompensation

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Tenecteplase (N=506) no. of events/total no. (%)</th>
<th>Placebo (N=499) no. of events/total no. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤75 yr</td>
<td>6/344 (1.7)</td>
<td>17/335 (5.1)</td>
<td>0.33 (0.13–0.85)</td>
<td>0.36</td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>7/162 (4.3)</td>
<td>11/164 (6.7)</td>
<td>0.63 (0.24–1.66)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7/242 (2.9)</td>
<td>14/231 (6.1)</td>
<td>0.46 (0.18–1.16)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6/264 (2.3)</td>
<td>14/268 (5.2)</td>
<td>0.42 (0.16–1.12)</td>
<td></td>
</tr>
</tbody>
</table>

### B  Major Extracranial Bleeding

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Tenecteplase (N=506) no. of events/total no. (%)</th>
<th>Placebo (N=499) no. of events/total no. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤75 yr</td>
<td>14/344 (4.1)</td>
<td>5/335 (1.5)</td>
<td>2.80 (1.00–7.86)</td>
<td>0.09</td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>18/162 (11.1)</td>
<td>1/164 (0.6)</td>
<td>20.38 (2.69–154.53)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11/242 (4.5)</td>
<td>4/231 (1.7)</td>
<td>2.70 (0.85–8.61)</td>
<td>0.13</td>
</tr>
<tr>
<td>Female</td>
<td>21/264 (8.0)</td>
<td>2/268 (0.7)</td>
<td>11.49 (2.67–49.53)</td>
<td></td>
</tr>
</tbody>
</table>
Long term outcomes no different with Thrombolysis

Kaplan-Meier curves showing the cumulative risk of death in patients with intermediate-risk pulmonary embolism who were randomized to tenecteplase versus placebo in the PETHO (Pulmonary Embolism Thrombolysis) trial. A total of 709 patients, corresponding to 71% of the overall intention-to-treat population, were randomized by 28 study sites that signed the third protocol amendment extending the follow-up period to at least 24 months. Long-term follow-up extended over a median period of 37.6 months, with an interquartile range of 24.6 to 54.3 months. Survival status was assessed in 353 of 359 (98.3%) patients in the thrombolysis arm and in 343 of 359 (98.0%) patients in the placebo arm. Overall long-term mortality rates did not differ significantly between the 2 treatment arms: 20.3% and 18.0%, respectively (log-rank, p = 0.49).
Summary

• Reduces haemodynamic compromise at 7 days

• No effect on long term development of CTEPH

• Case by case discussion
Hospital vs Home
Historical/current management

• Patients with risk factors and clinical history of potential PTE are admitted

• Treated with low molecular weight heparin

• Admission depends on how long it takes to get appropriate investigation
What is low risk?
# Pivotal Evidence

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Inclusion criteria</th>
<th>Main exclusion criteria</th>
<th>Patients included</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aujesky$^{37}$</td>
<td>Open-label Randomized Non-inferiority 19 centres (ED) Discharge within 24 hours vs. inpatient therapy</td>
<td>Age $\geq$ 18 years Confirmed acute PE PESI Class I or II</td>
<td>BP $&lt;$ 100 mm Hg Pain needing opioids Active bleeding or high risk Extreme obesity CrCl $&lt;$ 30 ml/min HIT history Barriers to home treatment</td>
<td>344 (of 1557 screened)</td>
<td>Both arms: enoxaparin s.c. twice daily; overlap with VKA (starting 'early')</td>
</tr>
<tr>
<td>Otero$^{38}$</td>
<td>Open-label Randomized 9 centres Discharge after 3–5 days vs. inpatient therapy</td>
<td>Age $\geq$ 18 years Confirmed acute PE Low-risk by Uressesi clinical prediction rule$^{39}$</td>
<td>Haemodynamic instability Troponin T $\geq$ 0.1 ng/ml RV dysfunction (TTE) High bleeding risk Severe comorbidity $\mathrm{O}_2$ saturation $&lt;$ 93% COPO, asthma Extreme obesity</td>
<td>132 (of 1016 screened)</td>
<td>Both arms: LMWH s.c. overlap with VKA (starting day 10)</td>
</tr>
<tr>
<td>Zondag$^{40}$</td>
<td>Prospective cohort 12 centres (ED) All treated as outpatients, discharge within 24 hours</td>
<td>Age $\geq$ 18 years Confirmed acute PE</td>
<td>Haemodynamic instability Active bleeding or high risk Oxygen requirement CrCl $&lt;$ 30 ml/min Hepatic failure HIT history Barriers to home treatment</td>
<td>297 (of 581 screened)</td>
<td>Nadroparin s.c. once daily; overlap with VKA (starting day 1)</td>
</tr>
<tr>
<td>Agterof$^{41}$</td>
<td>Prospective cohort 5 centres (ED) Discharge within 24 hours</td>
<td>Age $\geq$ 18 years Confirmed acute PE NT-proBNP $&lt;$ 500 pg/mL</td>
<td>Haemodynamic instability Active bleeding or high risk Severe comorbidity Pain with i.v. analgesia Oxygen requirement Creatinine $&gt;$ 150 $\mu$mol/L Purine to home treatment</td>
<td>152 (of 351 screened)</td>
<td>LMWH s.c. once daily; overlap with VKA (starting 'early')</td>
</tr>
</tbody>
</table>
Major Outcomes are non-inferior in outpatient vs inpatient

- Open label, randomised, non-inferiority
- Look at inpatient vs outpatient care
- N=344
- 171 outpatients
- 1y outcome was incidence of recurrent VTE within 90 days
- Safety endpoints were major bleeding and mortality
Headlines

• 1 of 171 developed recurrent vte vs 0 of inpatients
• Slightly more bleeding complications in the OP arm (3vs0 at 90 days)
• Mortality no difference between groups

• Safe to do outpatient care
Time to keep management happy

### Medical Resource Utilisation

<table>
<thead>
<tr>
<th>Medical resources</th>
<th>Outpatient (n=171)</th>
<th>Inpatient (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean length of stay, days</td>
<td>0.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Hospital readmissions, n</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Emergency department visits, n</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Physician office visits, n</td>
<td>202</td>
<td>216</td>
</tr>
<tr>
<td>Home nursing visits, n</td>
<td>348</td>
<td>105</td>
</tr>
</tbody>
</table>

Aujesky et al., Lancet 2011;378:41
Cost effectiveness

- Estimated PTE cost in US > $1.5 billion
- UK post op VTE estimated £640 million

- Most studies have looked at cost effectiveness of LMWHeparin in early DVT treatment

- Aujesky showed that if 5% of PTE could be treated as outpatients then there would be an immediate cost saving

- Not yet sure about the NOACs

Aujesky Chest 2005
Is this applicable to UK?

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Median Length of Stay</th>
<th>Bed Days Saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies et al. [1]</td>
<td>n=157 (confirmed PE)</td>
<td>1.0 (0-3) days</td>
<td>990</td>
</tr>
<tr>
<td>Vali et al. [2]</td>
<td>n=971 (suspected PE)</td>
<td>1.59 days</td>
<td>692</td>
</tr>
</tbody>
</table>

1. Davies et al., 2007;30:708-14; 2. Vali et al., 2015;70:281-3
Hospital vs Home: Applicability in Leicester, UK

973 referrals:
- 66 admitted as unsuitable
- 497 from Primary care
- 309 from EDs
- 90 from other departments

905 patients assessed

569 Low probability
0-dimers checked

- 308 Negative
871 discharged
95 followed up in Respiratory Clinic
14 deaths

- 466 Negative

871 admissions to hospital avoided over 2 years

242 Intermediate Probability

- 499 Positive
401 CTPA
144 VQ
17 Both

91 High Probability

- 562 scanned:

- 96 Positive
34 patients admitted

Vali Thorax 2014
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>risk with inpatient setting</td>
</tr>
<tr>
<td></td>
<td>risk with outpatient setting</td>
</tr>
</tbody>
</table>

**Short-term all-cause mortality**
Follow-up: 7-10 days after randomisation

- Study population

  - 4 per 1000
  - 1 per 1000 (0 to 35)

**Long-term all-cause mortality**
Follow-up: 90 days after randomisation

- Study population

  - 4 per 1000
  - 4 per 1000 (0 to 68)

Low level evidence, small numbers
BTS Outpatient Management of Pulmonary Embolism Guideline Development Group

Dr Luke Howard (Chair), Dr Steve Barden, Dr Robin Condliffe, Dr Vincent Connolly, Dr Chris Davies, Dr James Donaldson, Mr Bernard Everett, Dr Catherine Free, Dr Daniel Horner, Dr Laura Hunter, Mr Jasvinder Kaler, Dr Cathy Nelson-Piercy, Dr Emma O’Dowd, Dr Raj Patel, Ms Wendy Preston, Dr Karen Sheares, Dr Campbell Tait

On behalf of the British Thoracic Society
Ambulatory PTE – BTS Guidelines

• Patients with pulmonary embolism should be assessed for suitability for management as outpatients. **Grade B**

• Patients assessed as low risk and suitable for outpatient management should be offered treatment in an outpatient setting where a robust pathway exists for follow-up and monitoring. **Grade B**
Summary

- Patients with suspected PE should, where reasonably practical, undergo investigation on the same day of presentation to exclude a diagnosis of PE.
- An alternative strategy of anticoagulation followed by outpatient imaging within 24 hours may be considered in patients with suspected PE, who have been deemed low risk and eligible for outpatient care as per confirmed PE.
- Robust systems should be in place to facilitate next day investigation and review.

GRADE D
In confirmed PE:

- Use PESI, sPESI or Hestia Criteria. **Grade B.**
- Where using PESI or sPESI, also apply some exclusion criteria. **Grade B**

  - Exclusion criteria include:
    - **Haemodynamic instability** (HR>110; SBP<100mmHg; requirement for inotropes and critical care; requirement for thrombolysis or embolectomy)
    - Oxygen **saturation**s ≤ 90% on air
    - Active **bleeding** or risk of major bleeding (e.g. recent GI bleed or surgery, previous intracranial bleeding, uncontrolled hypertension)
    - **On full-dose anticoagulation** at the time of the PE
    - Severe **pain** (e.g. requiring opiates)
    - Other medical **co-morbidities** requiring hospital admission
    - Chronic kidney disease (CKD) stages 4 or 5 (eGFR<30ml/min) or **severe liver disease**
    - **Heparin induced thrombocytopenia** (HIT) within the last year and where there is no alternative to repeating heparin treatment
    - **Social reasons** which may include inability to return home, inadequate care at home, lack of telephone communication, concerns over compliance, etc.
Patient information and point of contact
- Patients with confirmed pulmonary embolism who are eligible for outpatient care should be provided with verbal and written information on the signs and symptoms of recurrence, major bleeding and additional complications. Individual centres should also provide an appropriate point of contact in the event of complications or concerns, both in and out of hours. **Grade B**

Formal review within 1 week
- Patients should have a formal review (telephone/face to face) at least once during the first week after discharge to ensure therapeutic compliance along with the absence of complications. **Grade B**

Follow-up protocols for complications and anticoagulation
- Hospitals should have local protocols and pathways in place for follow-up of all PE patients, whether treated as an inpatient or outpatient. This should include assessment of ongoing symptoms (with further directed investigation as appropriate) and consideration of optimal duration / modality of anticoagulation. **Grade D**
Good practice points

Consultant review

- All pregnant and post-partum women presenting with suspected PE or confirmed PE should be reviewed by a consultant and discussed with maternity services prior to discharge.
- Outpatient care pathways may be considered for suspected or confirmed PE in pregnancy and/or the post-partum period.

No scores available

- Clinical risk scores derived for non-pregnant patients, such as PESI/sPESI, should not be used in pregnant women.

Use low molecular weight heparin

- DOACs or VKAs should not be used in pregnant patients with suspected or proven PE.

Research recommendation

Studies addressing the safety and efficacy of outpatient care pathways for pregnant and post-partum patients with suspected or confirmed PE are needed.
Summary

• OP management is safe

• Cost effective
Any Questions?
Cancer and VTE

• Historically quoted as 10% of unprovoked PTE

• Probably nearer 5% from more recent studies

• Associated with significant mortality

• Risk factors of recent diagnosis of cancer, chemotherapy, recent hospitalisation
Screening for VTE in unprovoked cancer

• Detailed screening is Not recommended

• Ensure detailed clinical history

• Clinical examination including breasts and urinalysis

• CXR

• Enrollment in routine age appropriate national screening programmes
Management of Cancer associated thrombosis

• Low molecular weight heparin still important

• New evidence suggesting DOACs can be used
  • But may be higher risk bleeding in GI cancers

• Recent ISTH guidance suggests DOACs can be used for CAT

• Shared Doctor and patient opinion though