Incidental VTE. Who should we anticoagulate?

Anthony Maraveyas
VTE General Background

- VTE incidence is about 1:1000 persons annually
- >250,000 admissions for VTE annually
- >100,000 people die of PE annually
- >90% of PE’s arise from lower limb DVT
- 50% of DVT at diagnosis harbors PE
  - Only 33-40% of these are symptomatic
- About 70% of symptomatic PE will have a LL DVT at investigation

Cronin C.G. et al Am J. Roentgenol. 2007 189: 162-17
Natural acute history of untreated Pulmonary Embolism

• 10% of symptomatic PE are fatal within 1 hour of first symptoms.
  – Clinical diagnosis of PE is established in a minority of patients dying from PE

• Without treatment, 25% of patients die and 50% experience recurrent thrombosis within 3 months\(^1\)

\(^1\)Barritt & Jordan Lancet 1960; 1309-12
CAT: marker of shorter survival

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Patient Years</th>
<th>Deaths</th>
<th>MR per 100 PY (95%CI)</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>None</td>
<td>2777713</td>
<td>1750</td>
<td>0.63 (0.60-0.66)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>VTE Only</td>
<td>1317</td>
<td>67</td>
<td>5.1 (4.0-6.4)</td>
<td>2.6 (2.0-3.3)</td>
</tr>
<tr>
<td>Cancer Only</td>
<td>5650</td>
<td>721</td>
<td>12.7 (11.9-13.7)</td>
<td>7.4 (6.8-8.2)</td>
</tr>
<tr>
<td>Cancer &amp; VTE</td>
<td>131</td>
<td>72</td>
<td>55.0 (43.6-69.3)</td>
<td>31.2 (24.6-39.6)</td>
</tr>
</tbody>
</table>

CAT: marker of shorter cancer survival

Median OS 11.4 (8.95, 13.9) vs 6.71 (2.21, 11.2) p=0.02

Maraveyas et al EJC 2012
Definition of Incidental PE

• Incidental or Unsuspected interchangeable
  – NOT silent or asymptomatic
• No clinical suspicion of PE
• Diagnosed on imaging done for other reasons
  – Imaging performed with non-angiography protocols
• Has become a particular problem in Cancer patients due to frequent and repetitive scanning
i-PE in Cancer: a clinical problem

• Whole body rather than regional imaging becomes standard of care staging for cancer patients - driven by trial requirements (late 90s early 2000s) -

• Emerges as a problem when the new multi-slice scanners become standard of care (2003-2004)
  – 1mm CT slice thickness
VTE-Time from Randomization

Days

0 50 100 150 200 250 300

Control

Dalteparin

PM = Post-mortem

Clinical non-lethal VTE
Lethal VTE
Incidental VTE
Sudden death VTE-suspected

Maraveyas et al ESMO 2011
What is ‘Incidental’ PE?

- Clinical symptoms Absent ‘True Silent’
- Clinical Symptoms misattributed ‘False Silent’

Clinically undiagnosed

Incidentally diagnosed by multi-slice CT

Maraveyas A et al BJC 2009; 100:1837-41
The problem of ‘recognition’

• Recognition Gaps
  – Clinically Evident Vs Radiologically evident
  – Clinically suspected Vs Clinically unsuspected
    • But clinically apparent
    • Clinically ‘silent’ is easier to determine in a non-cancer setting

• Most data derived from trials with active ascertainment
  – Investigators ‘went looking’ for VTE
    • Venographic and V/Q scan endpoints
How common is incidental in Cancer related scanning?

- **HEYNHST (PRH)**
  - PE on 2.6% of all routine helical chest CTs in Cancer Patients
  - Literature 1.5% of all routine scans and 2.6-3.4% of scans associated with malignancy

- 6.3% of patients have unsuspected VTE on imaging
  - 25/397 PE, IVC, CI, IF- DVT or Both PE and DVT
    - Cronin C.G. et al Am J. Roentgenol. 2007 189: 162-170

- In HEY (0.5 million) we see between 52-57 iPE a year.
Site of i-PE in CT imaging and symptoms

<table>
<thead>
<tr>
<th>Site of PE</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral</td>
<td>59</td>
<td>38</td>
</tr>
<tr>
<td>Largest vessel involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main PA or L/R PA</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>Lobar PA</td>
<td>53</td>
<td>34</td>
</tr>
<tr>
<td>Segmental branches</td>
<td>55</td>
<td>36</td>
</tr>
<tr>
<td><strong>Subsegmental</strong></td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>branches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>1</td>
<td>1</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any new symptoms</td>
<td>66</td>
<td>43</td>
</tr>
<tr>
<td>Worsened pre-existing symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>74</td>
<td>48</td>
</tr>
<tr>
<td>Fatigue</td>
<td>117</td>
<td>76</td>
</tr>
<tr>
<td>Chest pain</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Lower limb oedema</td>
<td>51</td>
<td>33</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>PESI clinical parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hyperpnoea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Altered mental state</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Maraveyas et al. Thrombosis Res 2012 129: S183
Prognostic Relevance of Incidental VTE

Conclusions:
• Cancer patients with incidental or symptomatic VTE have a similar mortality rate at 6 months, highlighting the prognostic relevance of asymptomatic VTE

Age, gender, cancer site and stage were similar between all 3 groups
All patients with VTE were treated with LMWH or UFH

Dentali F et al. Thromb Res 2010; 125: S166-S191
Prognostic Relevance of i-PE

Fig 2. Kaplan-Meier cumulative survival curve until overall death for patients with cancer with incidental versus symptomatic pulmonary embolism (PE; \( P = .70 \)).

Prognostic Relevance of incidental PE.
To treat or not to treat?

- Untreated i-PE is more lethal than treated
  - From a cohort of 926 patients 53 were left untreated
    - 47% 6 month mortality vs. 28% (VKA) & 37% (LMWH)
  
  - 113 iPEs (Lung Cancer) 50% were treated at Clinicians discretion –some left untreated-no difference in stage PS, or treatment response
    - 30.9 months median survival (treated) Vs. 6.1 months (untreated)
      - HR 4.1 (95% CI 2.3-7.6)

Long-term Treatment of Patients With PE
ACCP Guidance (2011)

In patients who are incidentally found to have asymptomatic PE, we suggest the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (Grade 2B).

Kearon et al Chest 2011
Long-term Treatment of Patients With PE
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asymptomatic PE, we suggest the same initial and 
long-term anticoagulation as for comparable 
patients with symptomatic PE (Grade 2B).

Kearon et al Chest 2011
So where lies the controversy?

SSPE (Sub-segmental PE)
Example of an SSPE
SSPE Controversy

• Much of the data we rely on was generated when V/Q scans were standard of care
  – V/Q scans have very low sensitivity in SSPE
  – Likely SSPE was in the low probability for PE classification
    • No obvious adverse outcomes\(^1\)
• Anecdotally untreated SSPE in the non-Cancer setting does not seem to have adverse outcomes\(^2\)
• Epidemiological data in the NON cancer setting suggest that despite more PE being found mortality remains unchanged

\(^1\)Anderson et al JAMA 2007;298:2743-53
\(^2\)Donato AA et al Thromb Res 2010;126:e266-70.
Spiral CT scan staging starts to become standard

Weiner et al BMJ 2013 Jul 2;347:f3368
# True Increase in Disease

- **Before**: Nonfatal
- **After**: Nonfatal

- **Fatal**: Mortality

- **Apparent Increase**:
  - **Diagnosed PE per 100,000 US Adults**
  - **US population**

# Effective Test

- **Before**: Nonfatal
- **After**: Nonfatal

- **Fatal**: Mortality

- **Apparent Increase**:
  - **Diagnosed PE per 100,000 US Adults**
  - **US population**

# Overdiagnosis

- **Before**: Nonfatal
- **After**: Nonfatal

- **Fatal**: Mortality

- **Apparent Increase**:
  - **Diagnosed PE per 100,000 US Adults**
  - **US population**

### Scenario Description

- **Increase in risk factors results in more pulmonary emboli, with no change in disease severity.**

- **More sensitive test detects more pulmonary emboli, and new cases benefit from treatment -> fewer deaths.**

- **More sensitive test detects more pulmonary emboli, and new cases do not benefit from treatment (mild disease).**

### Apparent Incidence

- **Diagnosed PE per 100,000 US population**
  - **Increased**

- **US population**
  - **Increased**

### Mortality

- **Fatal PE per 100,000 US population**
  - **Increased**

### Case-Fatality

- **Fatal PE per Diagnosed PE**
  - **No change**

- **Diagnosed PE**
  - **Decreased**

- **Fatal PE**
  - **Decreased**

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Weiner et al Arch Intern Med. 2011;171: 831–7
## i-SSPE in Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>UPE</th>
<th>SSPE</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shinagare et al</td>
<td>202</td>
<td>13 (6.4%)</td>
<td>Cancer. 2011 15;117:3860-6</td>
</tr>
<tr>
<td>Maraveyas et al</td>
<td>155</td>
<td>14 (9%)</td>
<td>Thrombosis Res 129: S183</td>
</tr>
<tr>
<td>Sun et al</td>
<td>113</td>
<td>0 (0%)</td>
<td>Lung Cancer 2010;69:330–6.</td>
</tr>
<tr>
<td>O’Connell et al</td>
<td>70</td>
<td>17 (24%)</td>
<td>JTH, 2011 9: 305–311</td>
</tr>
<tr>
<td>Sahut D’Izarn et al</td>
<td>66</td>
<td>10 (15.2%)</td>
<td>JTH, 2012;10:2032-8.</td>
</tr>
<tr>
<td>Den Exter et al</td>
<td>45</td>
<td>4 (8%)</td>
<td>JCO 2011 29:2405-9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>669</strong></td>
<td><strong>61 (9.1%)</strong></td>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>
Does i-SSPE have a survival impact in Cancer?
The incidental SSPE in Cancer

- No UPE: 137
- Proximal UPE: 53
- Subsegmental UPE: 17

Months from staging CT scan:
- No UPE: 69, 45, 28, 16
- Proximal UPE: 16, 12, 10, 5
- Subsegmental UPE: 9, 6, 4, 4

P = 0.92
P = 0.027

O’Connel et al JTH, 2011 9: 305–311
The incidental SSPE in Cancer

Survival Functions

Cum Survival

Survival from IPE

Subsegmental vs others
1.00
2.00
1.00-censored
2.00-censored

Bozas et al unpublished
The ‘symptomatic’ SSPE
(Not a cancer patient study)

• CTPA for 3728 patients with clinically suspected PE
• PE confirmed in 748 patients,
  – of whom 116 (16%) had SSPE
  – Active malignancy, 21 (18.1%) SSPE and 113 (17.9) had Proximal PE

• ‘Proximal’ PE Vs SSPE
  – 3-month risk of recurrent VTE (3.6% vs 2.5%; P= .42), and mortality (10.7% vs 6.5%; P=.17)
  – SSPE were at an increased risk of VTE during follow-up (hazard ratio: 3.8; 95% CI: 1.3-11.1).

den Exter et al Blood 2013; 122: 1144-1149
Symptomatic Vs asymptomatic i-PE (Cancer Patients)

Fig 1. Kaplan-Meier curve for overall survival of patients with asymptomatic versus symptomatic unsuspected pulmonary emboli (UPE).

O’Connel et al JCO, 2011; 4208-4209
The Hull I-PE Prognostic Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>P</th>
<th>Points assigned</th>
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<tbody>
<tr>
<td>Palliative setting (metastatic or incurable disease)</td>
<td>Yes</td>
<td>&lt;.001</td>
<td>2</td>
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<tr>
<td></td>
<td>No</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>New or worsening symptoms</td>
<td>Yes</td>
<td>.010</td>
<td>1</td>
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<td></td>
<td>No</td>
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<td>Performance status</td>
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<td></td>
<td>1/2</td>
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<td>3</td>
</tr>
<tr>
<td></td>
<td>3/4</td>
<td>&lt;.001</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td></td>
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</table>

Grouping: Low Risk: 0, intermediate risk: 1-3 high risk: >3

Bozas et al. unpublished
Clinician survey of SSPE

• Cancer, Chest and palliative care physicians
  – 154 physicians responded.
  – In the **adjuvant setting**, oncologists were more likely to immediately anticoagulate for a single **asymptomatic** SSPE than palliative care physicians or chest physicians (84 vs 46 vs 56 %, respectively, \( p = 0.001 \)).
  – In the **metastatic setting** the differences were smaller (89 vs 69 vs 76 %, respectively, \( p = 0.057 \))
Clinician survey of SSPE

• In the adjuvant setting the percentage of surveyed physicians who would initiate anticoagulation immediately in the presence of new onset dyspnea and fatigue would rise to 93% (95%CI:88%-97%) for a single-site SSPE.

• In the metastatic setting this same percentage was 94% (95%CI:89%-97%).

Guideline Recommendations
ACCP 2016

- In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation (Grade 2C), and (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance (Grade 2C).

  - (Text) Patients hospitalized or have reduced mobility for another reason; have active cancer (particularly if metastatic or being treated with chemotherapy); or have no reversible risk factor for VTE such as recent surgery.

Kearon et al CHEST 2016
Conclusions

• Avoid terms like ‘asymptomatic’ or ‘silent’ when making the **radiological** diagnosis
  – Incidental, Unsuspected

• However symptomatic Vs. non symptomatic characterization is rational for further management.

• In the presence of a cancer diagnosis, treatment etc guidelines recommend anticoagulation of an IPE.
  – Some evidence exists for worse outcomes of untreated IPE patients
Conclusions

• If the patient has an SSPE
  – In the presence of active Cancer or Cancer treatment as a provoking factor anticoagulation is recommended (ACCP Grade 2 C)
  – In the **true absence of symptoms** and non-active cancer and or treatment > 6 months (e.g. Cancer surveillance period) one can consider clinical surveillance of the SSPE patient over treatment (ACCP Grade 2 C) after negative bilateral leg Doppler.

  – In the presence of **new symptoms however** consider anticoagulation (dan Exeter Blood 2013)
Conclusions

• If the patient has an SSPE
  – In the presence of active Cancer or Cancer treatment as a provoking factor anticoagulation is recommended (ACCP Grade 2 C)
  – In the **true absence of symptoms** and non-active cancer and or treatment > 6 months (e.g. Cancer surveillance period) one can consider *clinical surveillance* of the SSPE patient over treatment (ACCP Grade 2 C) after negative bilateral leg Doppler.
    • ‘...patients told to return for re-evaluation if symptoms persist or worsen’.
  – In the presence of **new symptoms however** consider anticoagulation (dan Exeter Blood 2013)
*Standard for clinical surveillance?

- NCT01455818 (OTTAWA, Carrier et al)
  - Weekly phone call for the first 4 weeks then monthly **up to 90 days**.
  - Questionnaire used to elicit signs and symptoms of recurrent VTE during the phone calls
  - Symptom resolution not formally assessed
  - Patients with suspected recurrent VTE are seen urgently in clinic.
Thank you