Too much medicine and venous thromboembolism: How can we make things “Well” again?

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Canadian Society of Internal Medicine; November, 2017; Toronto, Canada
Objectives:

- Describe the root of the problem: over-diagnosis and overtreatment of venous thromboembolism
- Case of CT pulmonary angiogram (and venous Doppler) overuse
- Discuss when anticoagulation may not be required
- Discuss practitioner variability in the investigation of VTE
- Reduce over-investigation, over-diagnosis, and overtreatment of VTE within your practice
Conflicts of interest:

- Intellectual interest in reducing overuse and overtreatment and “winding back the harms of too much medicine”
- Grants received from the Canadian Institutes of Health Research and the Canadian Frailty Network to study deprescribing and co-creator of MedSafer, a tool to stop medications in older adults (patent pending)
- I’m not an expert in thrombosis
- I’ve not ever taken or received pharma-related money/merchandise
Thrombosis: a bit of history

- First written reference: in ancient Indian medical texts, physician and surgeon Susruta (circa 600 BCE) describes a patient with a painful swollen leg that is difficult to treat.
- Mid-1800s, Jean Cruveilhier, prominent French pathologist, proposed a central role for venous inflammation and thrombosis in all disease conditions “phlebitis dominates all of pathology”
And who is this?
Rudolph Virchow
Virchow’s triad

- Stasis
- Thrombosis
- Vessel wall injury
- Hypercoagulability
Once the pathology was identified, the challenge became diagnosis.

History of the diagnosis of pulmonary embolism
Diagnosis of PE

- Prior to the 1960s the clinical diagnosis was neither sensitive nor specific
- EKG (S1Q3T3), CXR (Westermark’s sign and Hampton’s hump), physical exam
Ref: Dalen JE, Alpert JS. Natural history of pulmonary embolism. Prog Cardiovasc Dis 1975;17:259–70
Diagnosis of pulmonary embolism

- Pulmonary angiograms (first case series 1964)
- Lung scan (1960s)
Pulmonary Angiography in PE

- Was the “gold standard”; a negative pulmonary angiogram excludes *clinically relevant* PE.

- Invasive method and no longer performed replaced by CT angiogram since 2000 in Europe and 2006 in North America.
Ventilation-Perfusion Scans

- Useful if normal (negative predictive value of 97%)
- Also useful if High probability (positive predictive value of 85 to 90%)
- Unfortunately, only diagnostic in 30 to 50% of patients
PIOPED study (1990 JAMA)--> the importance of pre-test probability

- In this landmark trial we learn: the combination of high clinical probability and a high probability scan equating to the presence of PE and a low clinical probability with a low probability scan excluding PE.
<table>
<thead>
<tr>
<th>Category</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE present (high probability)</td>
<td>Two or more segments of V/Q mismatch</td>
</tr>
<tr>
<td>PE absent (normal perfusion or very low probability)</td>
<td>Nonsegmental perfusion abnormalities; these were enlargement of the heart or hilum, elevated hemidiaphragm, costophrenic angle effusion, and linear atelectasis with no other perfusion defect in either lung</td>
</tr>
<tr>
<td></td>
<td>Perfusion defect smaller than corresponding radiographic lesion</td>
</tr>
<tr>
<td></td>
<td>Two or more matched V/Q defects with regionally normal chest radiograph and some areas of normal perfusion elsewhere in the lungs</td>
</tr>
<tr>
<td></td>
<td>One to three small segmental perfusion defects (&lt;25% of segment)</td>
</tr>
<tr>
<td></td>
<td>Solitary triple-matched defect (defined as a matched V/Q defect with associated matching chest radiographic opacity) in the mid or upper lung zone confined to a single segment</td>
</tr>
<tr>
<td></td>
<td>Stripe sign (a stripe of perfused lung tissue between a perfusion defect and the adjacent pleural surface; best seen on a tangential view)</td>
</tr>
<tr>
<td></td>
<td>Pleural effusion of one-third or more of the pleural cavity with no other perfusion defect in either lung</td>
</tr>
<tr>
<td>Nondiagnostic (low or intermediate probability)</td>
<td>All other findings</td>
</tr>
</tbody>
</table>
Ventilation-perfusion scans

- Despite PIOPED 2, concerns about specificity of V/Q reporting positive or negative findings in *shades of gray*
- Only diagnostic in 30 to 50% of patients
- Clinicians continued to search for a yes/no test for acute PE
- *CT rapidly evolved to fill this role*
- Were it not for definite **allergic and nephrotoxic risks** of contrast media and the **added radiation** burden of MDCTA, the ventilation/perfusion scan would virtually disappear from the diagnostic algorithm for pulmonary embolism.
CT scans- improvements mean greater detection rate

- In 1992, Remy-Jardin reported the use of spiral CT scanning for central PE. The study concluded that spiral CT had a sensitivity of 100% and specificity of 96% for a diagnosis of central PE.

- In 1995, Goodman and colleagues CT sensitivity 86%, specificity 92%, and likelihood ratio 10.7.

- When subsegmental vessels were included, however, sensitivity was 63%, specificity 89%, and likelihood ratio 5.7.
Case of over-investigation and overdiagnosis

- With this in mind let’s consider a case
Case example of over-investigation

- 40 female with no past medical history on the oral contraceptive pill presents to a community clinic after a flight home from France with new left calf pain

Reason for consultation:
40F L calf pain after flight today from Paris - on OCP - L=R calf size - rule out DVT
## Wells’ Criteria for DVT

Calculates Wells’ Score for risk of DVT.

**Note:** The Wells Score is less useful in hospitalized patients. [Silveira PC, 2013](#)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>+1</td>
</tr>
<tr>
<td>Treatment or palliation within 6 months</td>
<td></td>
</tr>
<tr>
<td>Bedridden recently ≥3 days or major surgery within 12 weeks</td>
<td>+1</td>
</tr>
<tr>
<td>Calf swelling &gt;3 cm compared to the other leg</td>
<td>+1</td>
</tr>
<tr>
<td>Collateral (nonvaricose) superficial veins present</td>
<td>+1</td>
</tr>
<tr>
<td>Measured 10cm below tibial tuberosity</td>
<td></td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>+1</td>
</tr>
<tr>
<td>Localized tenderness along the deep venous system</td>
<td>+1</td>
</tr>
<tr>
<td>Pitting edema, confined to symptomatic leg</td>
<td>+1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremity</td>
<td>+1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>+1</td>
</tr>
<tr>
<td>Alternative diagnosis to DVT at least as likely</td>
<td>-2</td>
</tr>
</tbody>
</table>
### Wells’ Criteria for Pulmonary Embolism

Objectifies risk of pulmonary embolism.

<table>
<thead>
<tr>
<th>Clinical Signs and Symptoms of DVT</th>
<th>+3</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE is #1 Diagnosis, or Equally Likely</td>
<td>+3</td>
<td>NO</td>
</tr>
<tr>
<td>Heart Rate &gt; 100</td>
<td>+1.5</td>
<td>YES</td>
</tr>
<tr>
<td>Immobilization at least 3 days, or Surgery in the Previous 4 weeks</td>
<td>+1.5</td>
<td>NO</td>
</tr>
<tr>
<td>Previous, objectively diagnosed PE or DVT</td>
<td>+1.5</td>
<td>NO</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>+1</td>
<td>NO</td>
</tr>
<tr>
<td>Malignancy w/ Treatment within 6 mo, or palliative</td>
<td>+1</td>
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#### 1.5 points

Low risk group: 1.3% chance of PE in an ED population. Another study assigned scores ≤ 4 as ‘PE Unlikely’ and had a 3% incidence of PE.
Impression and plan:

- “High risk for DVT and PE” (likely because of the history of airplane travel)
- No mention of the Well’s score
- CT pulmonary angiogram is performed
- No CXR
- No D-dimer
- No doppler
CT-Pulmonary embolus

- **Despite two injections, the bolus of contrast is less than adequate** for assessing segmental and subsegmental branches. No filling defects identified within the main pulmonary arteries.

- There is a questionable filling defect in a lateral lower lobe segmental branch see image 151 series 5.

- **If pulmonary embolism strongly suspected** would recommend a repeat examination in this patient or a ventilation perfusion scan.
CTPA for subsegmental PE

False Positive

Apparent filling defects
Lung window reveals motion artifact
CTPA for subsegmental PE

False Positive / Reproducibility

There is relatively poor interobserver agreement for subsegmental and/or small pulmonary artery defects, especially in CT pulmonary angiograms degraded by technical artifacts.
Take home point:

- CTPA as first-line imaging for suspected pulmonary embolism can increase the detection of small, subsegmental pulmonary embolism, which might have a questionable clinical relevance (false positive/overdiagnosis)
A case inspires a study
Study performed at the MUHC

- We retrospectively reviewed all CTPA at an academic teaching hospital in Montréal, Canada, from September 2014 to January 2016.
- A total of 1394 examinations ordered by 182 physicians were included, of which 199 (14.3%) were positive. A multivariable logistic regression analysis was performed to explore whether physician specialty, years in practice, physician sex, or total numbers of studies ordered per physician were associated with CTPA diagnostic yield.

Chong J, Lee T, Sivakumaran L, Gallix B, McDonald EG; accepted for publication Nov 1st, 2017; JAMA internal medicine (IN PRESS)
Study performed at the MUHC

- Via GEE logistic regression, **the odds of a positive CTPA decreased as the total number of scans ordered per physician increased.**
- For each additional ten studies ordered, the odds of a positive result decreased [OR 0.76; (95% CI 0.73-0.79)].

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**TABLE 1: Positive CTPA Examinations for All Physicians**

Table of the Number of Physicians, Studies, and Number/Percentage of Positive CTPA with Major Specialty Groupings. Physicians were stratified by the total study volume they ordered during the observation period.

<table>
<thead>
<tr>
<th>Study Volume</th>
<th>Number of Physicians</th>
<th>Number of CTPA Studies</th>
<th>Number of Positive CTPA (%</th>
<th>Physician Specialty Group: ER, Other (%)</th>
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</thead>
<tbody>
<tr>
<td>1-10</td>
<td>145</td>
<td>411</td>
<td>85 (20.7)</td>
<td>ER: 13 (9.0) Other: 132 (91.0)</td>
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<tr>
<td>11-20</td>
<td>14</td>
<td>228</td>
<td>37 (16.2)</td>
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<td>21-30</td>
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<td>198</td>
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<td>41-50</td>
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<td>&gt;50</td>
<td>3</td>
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**TOTAL** 182 1,394 199 (14.2) ER: 42 (23.1) Other: 140 (76.9)

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Eight emergency room physicians in the institution are responsible for ordering more than 1/3 of the institution’s scans! And their yield is LOW! <9%
MUHC Study on CTPA

Our institutional yield was 14.3% (similar to prior reported studies). However, closer inspection demonstrated that there was substantial inter-physician variability, with individual positivity rates ranging between 0% to 33.3%.

TAKE HOME MESSAGE: Peer-relative rates of utilization are easily quantified from electronic databases, and can identify physicians most likely to benefit from individual performance feedback and decision support tools (at the MUHC this a program we are working on instituting).

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Stratify all patients according to an objective clinical probability assessment.

**RESULTS:** The PIOPED II investigators recommend stratification of all patients with suspected pulmonary embolism according to an objective clinical probability assessment. D-dimer should be measured by the quantitative rapid enzyme-linked immunosorbent assay (ELISA), and the combination of a negative D-dimer with a low or moderate clinical probability can safely exclude pulmonary embolism in many patients. If pulmonary embolism is not excluded, contrast-enhanced computed tomographic pulmonary angiography (CT angiography) in combination with venous phase imaging (CT venography), is recommended by most PIOPED II investigators, although CT angiography plus clinical assessment is an option.

In pregnant women, ventilation/perfusion scans are recommended by many as the first imaging test following D-dimer and perhaps venous ultrasound. In patients with discordant findings of clinical assessment and CT angiograms or CT angiogram/CT venogram, further evaluation may be necessary.

- **10 years ago** → stratify according to an objective clinical probability assessment;
- **D-dimer for low or intermediate risk**
Patients with Low Probability Clinical Assessment

Low Probability Clinical Assessment
Positive D-dimer Rapid ELISA

CT Angiography or
CT Angiography/CT Venography

CT Angiogram Negative, NPV 96%
CT Angiogram/CT Venogram Negative, NPV 97%
No Treatment

CT Angiogram Positive, PPV 58%
CT Angiogram/CT Venogram Positive, PPV 57%
Segmental PPV 68%
Subsegmental PPV 25%
Main or Lobar Pulmonary Embolism
PPV 97%
Treat

Options:
- Repeat CT Angiogram or CT Angiogram/CT Venogram if Poor Quality
- If CT Angiography only, Ultrasound or MRI Venography
- Pulmonary Scintigraphy
- Digital Subtraction Angiography
- Serial Ultrasound
Overreliance on investigative imaging may lead to several inefficiencies in healthcare delivery

- Increased patient waiting time
- Opportunity cost
- Direct and indirect financial costs
- Harm related to the detection and treatment of false positives or findings of unclear significance, such as isolated distal DVT

When patients are appropriately selected for Doppler ultrasound, the positivity rate for proximal DVT studies is expected to be on the order of 10-20%.
Practitioner variability of Doppler ultrasound positivity rates as an indicator of overuse: a retrospective cohort study

- Retrospectively reviewed all lower extremity Doppler ultrasounds performed over a period of 18 months at the Montreal General Hospital, Canada. Physicians ordering >10 examinations over the study period were included.

- Acute DVT was identified in 394/2030 studies (16.5%). There was marked variability in positivity rate by physician (range 0%-42.9%). Of 79 practitioners who ordered ≥10 examinations over the study period, one in four achieved a positivity rate above 15%, while one in three had a positivity rate below 5%.
Proportion of physicians—by specialty—whose positivity rates for diagnosing proximal DVT fall within given intervals
Take home message

- Step 1: Do you think this patient has a PE or DVT?
- If you DON’T think this patient has a DVT or PE then STOP here.
- Step 2: If you do think there is a possibility of a PE or DVT then proceed to use a clinical prediction tool (ex. Well’s score or the PERC score)
- Step 3: Based on the pre-test probability, proceed to D-dimer or appropriate imaging
When in doubt, follow the tenets of the Choosing Wisely STARS!

<table>
<thead>
<tr>
<th>#</th>
<th>Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Don't suggest ordering the most invasive test or treatment before considering other less invasive options.</td>
</tr>
<tr>
<td>2</td>
<td>Don't suggest a test, treatment, or procedure that will not change the patient's clinical course.</td>
</tr>
<tr>
<td>3</td>
<td>Don't miss the opportunity to initiate conversations with patients about whether a test, treatment or procedure is necessary.</td>
</tr>
<tr>
<td>4</td>
<td>Don't hesitate to ask for clarification on tests, treatments, or procedures that you believe are unnecessary.</td>
</tr>
<tr>
<td>5</td>
<td>Don't suggest ordering tests or performing procedures for the sole purpose of gaining personal clinical experience.</td>
</tr>
<tr>
<td>6</td>
<td>Don't suggest ordering tests or treatments pre-emptively for the sole purpose of anticipating what your supervisor would want.</td>
</tr>
</tbody>
</table>
Case resolution

- 3 Doppler ultrasounds (all negative)
- 1 CT pulmonary angiogram (indeterminate)
- 2 Ventilation Perfusion studies (indeterminate and then negative)
- Recommended against anticoagulation
- Rivaroxaban stopped after 10 days of treatment
- No bleeding or thrombotic complications over the subsequent three months
Overtreatment
Antithrombotic therapy for VTE disease: CHEST guideline 2016 update

- For patients with subsegmental PE and no DVT, the guideline suggests clinical surveillance over anticoagulation when the risk of VTE recurrence is low (Grade 2C).

- The guideline recommends the use of anticoagulation over surveillance when the risk of VTE recurrence is high (Grade 2C).

- From local data: 87% of our SSPEs are anticoagulated (72/82).
What is the risk for progression or recurrence?

- Not hospitalized (i.e. outpatients)
- Not immobilized
- No active malignancy
- Other factors:
  - Patient preference
  - Low cardiopulmonary reserve
  - Absence of an alternative explanation for symptoms
  - RISK OF BLEEDING
What is the risk for progression or recurrence?

- Not hospitalized (i.e. outpatients)
- Any risk of bleeding in the absence of a TRUE PE is likely unacceptable!
- Other factors:
  - Patient preference
  - Low cardiopulmonary reserve
  - Absence of an alternative explanation for symptoms
  - RISK OF BLEEDING
Improving your TRUE positives

- Marked, unexplained high d-dimer
- High pre-test probability and symptomatic
- The CT is good quality with good opacification of the distal arteries
- There are multiple filling defects with contrast around the defect
- Defects involve larger subsegmental arteries
- Seen on more than one image, more than one projection
Have we met our objectives?

- Describe the root of the problem: overdiagnosis and overtreatment of venous thromboembolism—*CTPA has become more and more sensitive and there is an increased detection of PE of questionable clinical significance*.
- Case of venous Doppler and CT pulmonary angiogram overuse (*3 chest scans in a young woman!*)
- Discuss when anticoagulation may not be required
- Discuss practitioner variability
- Reduce over-investigation, overdiagnosis and overtreatment of VTE within your practice—*armed with this new knowledge, hopefully so!*
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Questions or comments

- emily.mcdonald@mcgill.ca