Diagnosis and Treatment of Pulmonary Embolism: High-Tech versus Low-Tech, which way to go?

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Dr. Wells has declared no conflicts of interest related to the content of his presentation.
## Disclosures

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<td>Bayer Healthcare, Sanofi-aventis, Pfizer, Biomerieux, Daiichi Sankyo</td>
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<td>Scientific advisory board *</td>
<td>Bayer Healthcare, Sanofi-aventis, Pfizer, Boehringer Ingelheim</td>
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* last 3 years
VTE Epidemiology - Incidence

• Incidence
  – 1.3 cases per 1,000 people every year
  – Reaches 1.2% per year after 75 y of age
  – Mean age 70 years
  – 650,000 to 700,000 persons affected every year in the USA
Epidemiology

• Mortality
  – 3rd leading cause of cardiovascular death (after myocardial infarction and stroke)
  – PE cause 10% of in-hospital deaths
  – 22% of patients with PE die before diagnosis or on the first day
  – Untreated episode: mortality from PE up to 30% in first 3 months
  – On treatment mortality
    • In clinical trials: 1.3% for PE
    • In ‘real-life’ cohorts: 3.0% for PE
Why Discuss High-Tech versus Low-Tech?

• Issues of Cost
• Efficiency or timing to initiation of treatment
• Side effects of investigations and drugs
• Diminishing thinking with high-tech?
Total health expenditures as a percentage of gross domestic product (1970-2011)

OECD, 2013
Canada

- 2010 – $192 billion on health care in Canada
- 11.7% of GDP
- 25% of growth in expenditures due to new technology

* data from CIHI
“Business as usual” national health care expenditures

- Failures of care delivery
- Failures of care coordination
- Overtreatment
- Administrative complexity
- Pricing failures
- Fraud and abuse
- Growth in national health care expenditures matches GDP growth

US National Health Expenditures, % of GDP

Year


17.5 18.0 18.5 19.0 19.5 20.0 20.5
Physicians determine care

1. Which patients are seen and how frequently
2. Which patients are hospitalized
3. Which tests, procedures and surgical operations are administered
4. Which technologies are used
5. Which medications are prescribed
I’ve always done this

Patients want it

Fear of litigation

Referring doctor wants it

New tests are good

Better to get a test than “do nothing”

$$
“We — physicians — are the only people that can get health care costs under control”.

- Zeke Emanuel

“Somebody has to do something, and it's just incredibly pathetic that it has to be us”.

- Jerry Garcia
A campaign to help physicians and patients engage in conversations about the overuse of tests and procedures and support physician efforts to help patients make smart and effective care choices.
First 9 — now 56 societies

American Academy of Allergy Asthma & Immunology

American Gastroenterological Association
Advancing the Science and Practice of Gastroenterology

American Academy of Family Physicians
Strong Medicine for America

American College of Physicians®
Internal Medicine | Doctors for Adults

American College of Cardiology

American Society of Clinical Oncology

American Society of Nuclear Cardiology
How are we taught?

- Patients want it
- New tests are good
- Better to get a test than “do nothing”
- Demonstrate thoroughness
- Lack of feedback
- Preemptive ordering
Diagnosis
Is CTPA Better Than VQ Scanning?
CTPA has the following Advantages Compared to VQ Scans

a) A normal result more reliably rules out PE
b) Much higher positive predictive value in low clinical probability patients
c) Higher reader agreement
d) All of the above
e) None of the above
CTPA has the following advantages compared to VQ scan

a. A normal result more reliably rules out PE
b. Much higher positive predictive value in low clinical probability patient
c. Higher reader agreement
d. All of the above
e. None of the above

0% 0% 0% 0% 0%
RCT of CTPA versus VQ

• 694 randomized to CTPA vs 711 VQ
• PE was diagnosed in 19.2% of CT patients vs 14.2% of VQ patients
• In the patients in whom PE was excluded 3 month follow-up events occurred in 0.4% of the CT group and 1.0% (one fatal PE) in VQ group
• Suggests that small PE (with no DVT) can safely go untreated
False positives, the math

• CTPA has a specificity < 94%

• Hayashino’s meta-analysis: the false positive rate was 70% in low pretest probability patients and 16% in patients with moderate

• Modeled through Bayes Theorem, assuming a generous sensitivity of 92% and a specificity of 94% for CTPA, the false positive rate would be 55% if low probability and 20% if moderate
False positives, the studies

• PIOPED II reported that the positive predictive values for PE detected by CTPA in the lobar, segmental and subsegmental vessels were 97%, 68% and 25% respectively.

• A recent comparative study of a multidetector row CT to digital subtraction pulmonary angiography demonstrated a false positive CT rate of 30% with most false CT results incorrectly detecting PE in isolated segmental or subsegmental vessels.
False positive or clinically irrelevant PE?

- Small pulmonary emboli may be of lower or even no clinical significance if such emboli are not accompanied by DVT.
- Hull et al in 1989: PE rate with non-high VQ was 10%, far less than was suggested by the original PIOPED study (21%).
- Treated far fewer than 21% of patients; despite this follow-up event rates were only 2.7%.
A prognostic perspective

Annual incidence of central (♦) and peripheral (segmental ■ and subsegmental ▲) pulmonary embolism during the 2000 to 2005 study periods.
# Low Tech Helper: Clinical Assessment Tools

<table>
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<tr>
<th>Modified Geneva</th>
<th>PERC</th>
<th>Wells</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
<td><strong>Points</strong></td>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Age 65 years or over</td>
<td>1</td>
<td>Hypoxia-SaO2 &lt;95%</td>
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<tr>
<td>Previous DVT or PE</td>
<td>3</td>
<td>Unilateral leg swelling</td>
</tr>
<tr>
<td>Surgery or fracture within 1 month</td>
<td>2</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Active malignant condition</td>
<td>2</td>
<td>Prior DVT or PE</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>3</td>
<td>Recent surgery or trauma</td>
</tr>
<tr>
<td>Pain on deep palpation of lower limb and unilateral oedema</td>
<td>4</td>
<td>Age &gt;50</td>
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<tr>
<td>Haemoptysis</td>
<td></td>
<td>Hormone use</td>
</tr>
<tr>
<td>HR 75 to 94 bpm</td>
<td>3</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>HR 95 or more beats per minute</td>
<td>5</td>
<td></td>
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**Modified**
- <3 points - Low
- 4 - 10 points - Intermediate
- >10 points - High

**Simplified**
- 2 points or less PE unlikely

**Absence of all variables classifies the patient as ‘no risk’ of PE**

**Traditional**
- Score > 6.0 - High
- Score 2.0 to 6.0 - Moderate
- Score < 2.0 - Low

**Simplified**
- Score > 4 - PE likely
- Score 4 or less - PE unlikely

**Abbreviations:** DVT, deep vein thrombosis; PE, pulmonary embolism; HR, heart rate; bpm, beats per minute
Meta-analyses of over 52 studies and 55,000 patients demonstrate that the Wells and Modified Geneva rules are safe and accurate for pretest probability of PE.
D-Dimer

- D-Dimer ~ $15 per test
  - Fibrin degradation products
  - Measured through a simple, cheap, fast, blood test
  - Highly sensitive to the presence of a blood clot
    - Positive in *almost* all patients with DVT
    - **Low likelihood of DVT if D-dimer negative**
  - Not specific
    - Positive in many other conditions than DVT (infection, surgery, cancer, pregnancy, elderly, etc.)
Suspected PE - do clinical probability score

PE unlikely or low/intermediate and D-dimer negative

No therapy
Suspected PE - do clinical probability score

PE unlikely or low/intermediate and D-dimer negative
→ No therapy

PE likely or D-dimer positive
→ CTPA
  - PE present
    → Treat³
  - PE absent
    → No therapy⁴

ALTERNATIVE APPROACHES
If symptoms or signs of DVT use US first

If positive then treat

If negative proceed to pulmonary imaging
Normal chest X-ray

V/Q scan

- Normal or near normal² → No therapy
- High probability → Treat⁶
- Nondiagnostic → US

US

- Abnormal → Treat
- Normal
  - PE unlikely → No therapy
  - PE likely → Repeat US in one week
CTPA

**Normal chest X-ray**
- V/Q scan
  - Normal or near normal: No therapy
  - High probability: Treat
  - Nondiagnostic: US
    - Abnormal: Treat
    - Normal: PE unlikely
      - PE unlikely: No therapy
      - PE likely: Repeat US in one week

**Abnormal chest X-ray**
- CTPA
  - PE present: Treat
  - PE absent: No therapy
• Cost-effectiveness studies support the use of CPRs
• CPOE clinical decision support tools will decrease use of CT and increase yield (more true positives)
• Failure to use algorithms dramatically increases error rates
Advantages and Disadvantages of our PE diagnosis strategies?

• Advantage:
  o Enables less diagnostic imaging
  o Thinking may allow for consideration of false imaging results

• Disadvantage:
  o Doesn’t directly address possibility of false positives
  o DD may be used for screening
  o Pretest probability may be subject to inter-observer variability
  o Sensitive to accuracy of D-dimer
CTPA versus VQ: Emerging Issues

- Radiation dose high CT
- Detects very small clots which may not be real or may be important
- Expensive
- Need to inject dye
- Radiation
- Not available in most smaller towns
Conclusions on Diagnosis of PE

• VQ should not be allowed to die since CT can be inadequate and there are contraindications (renal dysfunction, pregnancy, contrast allergy, large size)
Acute Treatment

• The same regardless of etiology……..

• Short-term treatment with SC LMWH (1A), IV UFH (1A), monitored SC UFH* (1A), fixed-dose SC UFH (1A) or SC fondaparinux (1A)

• LMWH SC, as an outpatient if possible, is recommended over IV UFH*
LMWH vs UFH

• Most recent meta-analysis included 20 studies (17 used IV UFH, 3 used SC UFH)
• LMWH was associated with:
  ▪ Fewer recurrences (3.6% vs. 5.4%, Odds Ratio = 0.68)
  ▪ less major bleeding (1.2% vs. 2.0%, O.R. = 0.57)
  ▪ fewer deaths (4.5% vs. 6.0%, O.R. = 0.76)

• Rivaroxaban and Apixaban as monotherapies are also effective
Outpatient Treatment of PE

a) Has been studied in randomized trials
b) Has been used in Canada for 20 years
c) Is safe in at least 40% of PE cases
d) All of the above
e) None of the above
Outpatient Treatment of PE

a. Has been studied in randomized trials
b. Has been used in Canada for 20 years
c. Is safe in at least 40% of PE cases
d. All of the above
e. None of the above
Uniquely Canadian?

Outpatient Treatment of Pulmonary Embolism
Outpatient PE Treatment

- A systematic review supports outpatient therapy
  - Three month recurrence risk 1.5%
  - Major hemorrhage risk of 0.8%
  - 0.47% fatal PE
  - 30% to 50% of all PE cases would qualify as low risk

- **Low-Tech:** Several prediction rules accurately select patients for *in-hospital mortality of < 1%* Geneva rule, PESI rule, Aujesky CPR and the Murugappan CPR
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<td>Variable</td>
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<td>Variable</td>
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<td>Cancer</td>
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<td>Age</td>
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<td>Age</td>
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<td>Age &gt; 70 yrs</td>
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<tr>
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<td>&lt;100 mmHg</td>
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<td>Chronic Lung Disease</td>
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<tr>
<td>PaO₂ &lt; 8 kPa [60 mmHg]</td>
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<td>DVT (shown by US)</td>
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<td>Cerebro-Vascular disease</td>
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<td>&lt;100 mmHg</td>
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<td>Temperature</td>
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<tr>
<td>Respiratory rate</td>
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<tr>
<td>Temperature</td>
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<td>Temperature &lt;36° C</td>
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<td>Altered Mental status</td>
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<td>Altered Mental status</td>
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<td>Arterial blood Oxygen Saturation &lt; 90%</td>
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<td>Arterial blood Oxygen Saturation &lt; 90%</td>
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<td>I: Very low</td>
<td>≤65</td>
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<tr>
<td></td>
<td></td>
<td>II: Low</td>
<td>66-85</td>
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<td>III: Intermediate</td>
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<td>IV: High</td>
<td>106-125</td>
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<td>V: Very high</td>
<td>≥126</td>
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<td>I-II: Low</td>
<td>≤85</td>
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<td>IV-IV: High</td>
<td>≥126</td>
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High-Tech Prognosis Tools

– RV strain on Echocardiography
– RV strain on CTPA
– Biomarkers: NT-proBNP, Troponin
Using Biomarkers: One prospective management study

- Hemodynamically stable outpatients with acute PE and NT-proBNP level < 500 pg/ml; treated as outpatients
  - No deaths, major bleeding or recurrent VTE in the first 10 days or 3 months follow-up
- Second prospective study NT-proBNP level < 300 pg/ml was the only significant negative predictor of good outcomes (40% of patients)
Echo or CT

• Echo has not been consistent as a predictor
  – It would be an extra test. Therefore hi-tech
• CTPA is done in most patients for diagnosis
  – However results also vary between studies
  – Interobserver reliability has been poor and likely will always be thus
  – Volumetric RVV/LVV ratio seems most reliable; large differences most helpful
Pulse Oximetry or Clinical Risk Scores?

- Retrospective study of 168 patients in high altitude
- Measure short-term outcomes (AO) defined as utilization of vasopressors, thrombolytics or death
- Overall AO rate of 7.1%, with 3.0% mortality rate.
- A room-air pulse oximetry cutoff of 92.5%, classified 89/136 patients as low risk, 1.1% had an AO, and 47/136 patients as high risk, 10.6% had AO.
- Sensitivity of 83%, specificity of 68% and a NPV of 99%.
- PESI classified 91/168 patients as low risk: 2.2% had AO but none died, and 77/168 were classified as high risk (class III, IV, or V), with an AO rate of 13.0%
- The performance was better than the one from PESI
Does It Matter If We Identify High Risk PE Patients?

IVC Filters Likely Only Option to Help

• PREPIC 2
• RCT: IVCF + standard Rx vs Standard Rx alone in patients with unprovoked PE with DVT and high recurrence risk
  – age>75, cancer, RV dysfunction, bilateral or ilio-caval DVT, Cardiorespiratory insufficiency
• 6 vs 2 fatal PE and no overall mortality difference or recurrence difference
Does it matter if we identify High Risk? *IVC filters*

- **Nationwide Inpatient Sample, Healthcare Cost and Utilization Project:**

  IVC Filters significantly reduce mortality in patients with hemodynamically unstable PE and in patients who received thrombolytic therapy *(Stein et al 2012)*
Does It Matter If We Identify High Risk?

Thrombolysis vs Standard Therapy for PE

- Systemic administration of thrombolysis for submassive PE has been studied in two well-performed randomized trials
- PEITHO study most recent
  - PE, not with hemodynamic collapse, and with RV dysfunction and Myocardial injury
  - Randomized to tenectaplastase or placebo + UFH
Does it matter if we identify High Risk?

Thrombolysis vs Standard Therapy for PE

- All cause mortality 1.2% vs 1.8% at 7 days \( (p=0.43) \) and 2.4% vs 3.2% at 30 days
- Major bleed in 6.3% vs 1.5%, and strokes in 2.4% vs 0.2%
- All outcomes better if \( \leq 75 \) years of age but not statistically significant
- Therefore, recommended only for patients with PE and hemodynamic compromise or deterioration while receiving standard anticoagulant therapy
VKA management

• Genomic dosing versus nomogram vs gestalt
Genomic Testing to Predict Vitamin K Antagonist dosing

a) Has been proven to effect clinical outcomes?
b) Can be widely employed?
c) Works best in Caucasians?
d) Has been evaluated by appropriate study design?
Genomic testing predict VKA dosing

a. Has been proven to effect outcomes

b. Can be widely employed

c. Works best in Caucasians

d. Has been adequately studied
Low-Tech Nomogram- does it work?

- In 2003 we published a RCT comparing a 10 mg warfarin initiation protocol to a 5mg protocol
- 83% of those patients who followed the 10 mg nomogram reached a therapeutic INR level within the first 5 days
- Patients who were randomly assigned to the 10mg nomogram achieved therapeutic INRs 1.4 days earlier than those assigned to a 5mg nomogram
Validation

- INR of 2.0 to 3.0 by day 6 in 78% vs 58%
- INR of 2.0 to 3.0 by day 8 in 98% vs 93%
- INR of > 5.0 in 5.6% vs 5.5%
- INRs in first month 7 vs 8
- Maintenance dose (in mg) predicted by: 2.5 + 10% of the first week cumulative dose - INR value at Day 8 + 1.5 if INR was below 2.0 at Day 5.
Pharmacogenetic Dosing

• Two (3) recent RCTs in the NEJM
• Neither compared to a validated algorithm
• All used surrogate outcomes of TTR
• All demonstrated marginal or no benefit
5.1 Dose-Initiation Algorithms

Pharmacogenetic dose-initiation algorithm\(^2\)

The estimated daily dose in mg/day is:

\[
\exp[0.9751 - (0.2066 \times CYP2C9^{*2}) - (0.4008 \times CYP2C9^{*3}) - (0.3238 \times VKORC1) \\
- (0.00745 \times \text{age in years}) \\
- (0.0901 \times \text{black race}) \\
+ (0.0922 \times \text{smokes}) \\
+ (0.4317 \times \text{body surface area in m}^2) \\
- (0.2538 \times \text{amiodarone use}) \\
+ (0.2029 \times \text{target INR}) \\
+ (0.0664 \times \text{DVT/PE as indication for warfarin therapy})],
\]

for which: \(CYP2C9^{*2}\) and \(CYP2C9^{*3}\) SNPs are coded as 0 if absent (no variants), 1 if heterozygous, and 2 if homozygous; \(VKORC1\) is \(VKORC1\ 3673G>A\) (also known as \(VKORC1\ 1639,\ rs9923231\) and is coded 0 (homozygous GG), 1 (heterozygous), or 2 (homozygous AA). Race is coded as 1 if black and 0 if nonblack. Smokes, amiodarone use, and DVT/PE as indication for warfarin therapy are coded as 1 if yes and 0 if no. Body surface area is calculated as \[((\text{weight in kg})^{0.425} \times (\text{height in cm})^{0.725})/139.2\]. In the COAG trial, target INR was fixed at 2.5.
This was me a week ago in Ottawa, the coldest capital city in the world? True or false?