PE: A new approach to low risk patients

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PE in ED

- Compared to what we were lead to believe:
  - It is more benign
  - Treatment is less effective
  - CT is less accurate and more risky
  - → *Our current approach harms more than it helps*
- Based on above
  - A new Test Threshold (TT) will be calculated
  - A new approach to low risk patients will be put forward

PE Test Threshold (TT)

- Pretest probability (PTP) of disease where benefits of investigation = harms of investigation

- If patient's PTP < TT
  - → more harm than benefit from investigation
    - → do not investigate

PE Test Threshold (TT)…

- Calculated using the Pauker and Kassirer method:
  - $T_{th} = (P_{pos/nd} \times R_{rx} + R_t)/(P_{pos/nd} \times R_{rx} + P_{pos/d} \times B_{rx})$
- Jeff Kline calculated 2% in 2004
  - → Created the PERC rule
- **THE TEST THRESHOLD IS NOW OUTDATED!**
  - Will recalculate it based on current data

More benign than we thought

- Previously untreated PE mortality was estimated at 18-35% based on *old methodologically flawed* studies of *inpatients*
  - Included extrapolations from autopsy studies

- Newer data on ED type patients suggest a *far* lower mortality

Mortality of untreated PE in ED patients…

- Calder, Herbert, Henderson Ann EM 2005:
  - *The mortality of untreated PE in ambulatory patients is likely < 5%*, based on the following:

Mortality of untreated PE in ED patients…

- PIOPED study, 1990
  - 30% were outpatients (ED or clinic)
  - 20 patients inadvertently not R(x) for d(x) PE
    - 1 died (5%)

Mortality of untreated PE in ED patients…

- Nielsen et al, 1994 study
  - 87 ambulatory patients at a primary care facility
  - DVT pt's with V/Q proven silent PE's
  - Mortality = 0% in no R(x) group
  - *Discussed later*

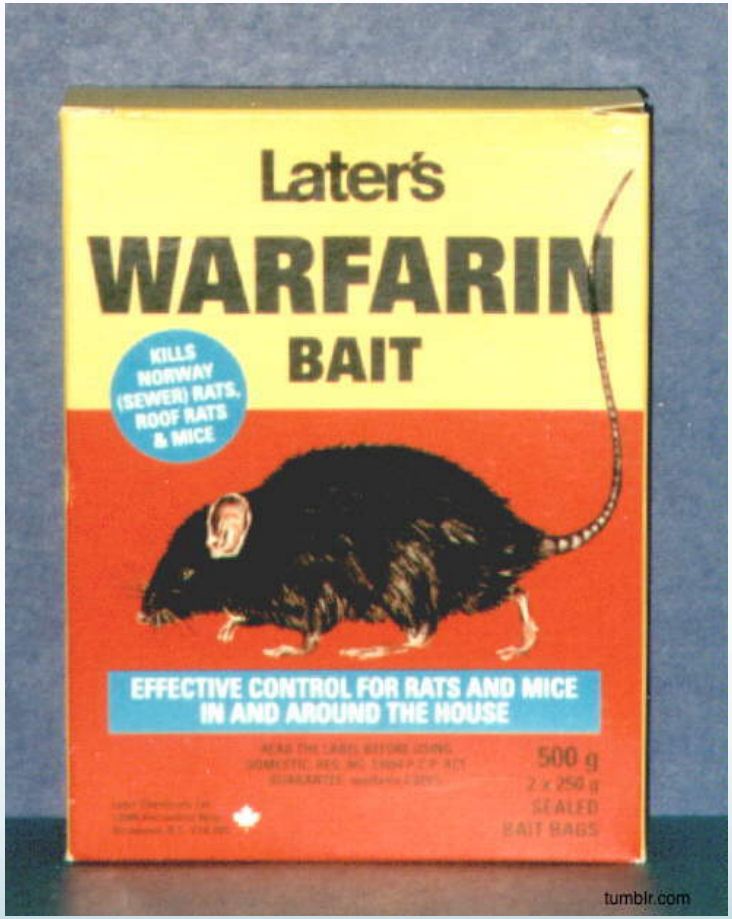
Mortality of untreated PE in ED patients…

- Several V/Q retrospective studies:
  - Examined long term outcome in untreated pts with low & intermediate probability scans (of which 12% & 34% respectively have PE from PIOPED)
  - 881 had low probability scans, 116 had intermediate scans
  - Approx 150 untreated PE's → **0 deaths**

Mortality of untreated PE in ED patients…

- Stein, 2000: Analysed 2 studies where AC withheld in patients with non diagnostic V/Q + serial negative LL imaging
  - 197 patients with untreated PE
    - 1 fatal PE = 0.5% mortality

What is the benefit of Anticoagulation (AC)?



Barritt & Jordan, Lancet 1960

- *"Anticoagulation in the treatment of Pulmonary Embolism, a controlled trial"*
- 35 Patients
- *Clinically Diagnosed* with PE:
  - Acute Right Sided HF or of pulmonary infarction using clinical exam, CXR and ECG. Pulmonary Infarction defined as:
    - *''pleuritic pain, haemoptysis, fever, pleural friction, loss of resonance at the lung base, and rales''*
      - **= Pneumonia**

Barritt & Jordan trial …

- No placebo, not blinded!
- No clear inclusion and exclusion criteria
- No information given comparing the 2 groups of pts
- All patients were confined to bed for 10 days!
- Most of the trial patients were *very sick inpatients*
  - → **not** representative of most ED patients

Barritt & Jordan trial …

- 5/19 patients died in the "no anticoagulation" group
  - Further audit of the autopsy data suggested PE was likely **not** the cause of death in 4 out of 5 of these patients
  - They all had major foci of infection including biliary sepsis, lung abscess and empyema.
- 1/16 patient died in treatment group from pneumonia + haemorrhage
- Stopped the trial early due to finding of "treatment benefit" → *chance*
- **If this trial was done today it would not even be published!**

Nielsen et al, 1994

- *Silent PE in Patients with DVT*, Journal of Internal Medicine
- 87 patients with proven DVT, half with asymptomatic PE on V/Q
- Randomised to 3/12 anticoagulation v's 10/7 of oral NSAID
- Repeat V/Q on day 10 and day 60

Nielsen et al, 1994

- Results
  - → **no difference in PE regression (45%)**
  - → **no difference in mortality (1 v 0 patients)**
- Remains the only RCT in actual PE patients in history and shows no benefit of AC
- Limitations
  - Small study
  - ? Relevance of asymptomatic PE

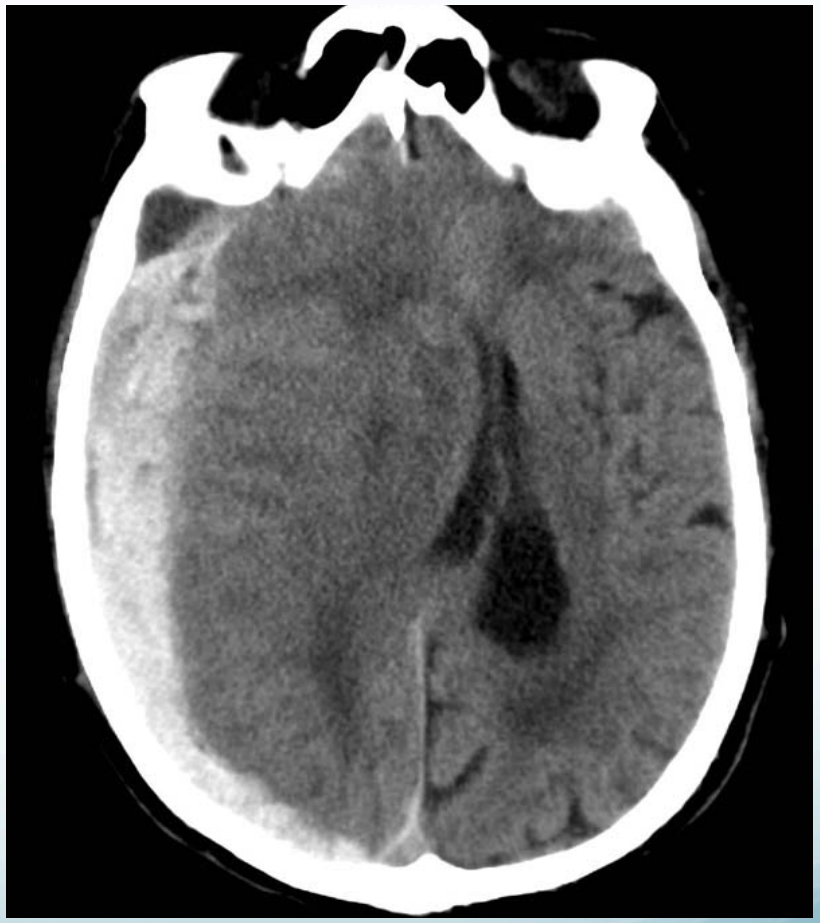
Benefit of Treatment?

- Given:
  - Mortality is <5%
  - Anticoagulation has no known mortality reduction
  - → Benefit of treatment assigned as 2.5%
    - Consistent with previous published TT calcs

Bleeding Risk

- Carrier et al, Ann of Intern Med 2010: Meta-analysis of bleeding risk *specifically in VTE patients*:

- Risks of AC with warfarin during first 3/12:
  - Major bleeding: 1.6%
  - **Fatal bleeding 0.2%**
  - *May underestimate the risk*



Source: Fanpop.com

Contrast Risk...

- Mitchell et al 2010, 663 patients
- 1st ever prospective study of CT with contrast with paired creatinine measurements in ED patients
- 11% developed Contrast Induced Nephropathy (CIN),
  - 9% of whom developed severe renal failure
  - 2/3 of whom died due to renal failure
- **Overall 0.6% mortality from contrast**

Contrast Risk Opposing View

- Radiology, April 2013
  - Macdonald et al:
    - Meta-analysis of *controlled* retrospective studies
    - *Gross* selection bias
      - → renal protective effect of contrast!
  - 2 papers Macdonald et al & Davenport et al attempted to adjust for this gross bias with “attribute matching”

TT: Contrast Risk

- The controlled studies are unhelpful
- TT calc: contrast risk = 0.1%
  - heavily discounted from 0.6% from the uncontrolled prospective study

CTPA Accuracy

- PIOPED II 2006, NEJM Multidetector CT
  - 83% sensitivity, 96% specificity

CTPA Accuracy

- Positive Predictive Value varies with PTP
  - High Risk = 96%
  - Moderate Risk = 92%
  - Low Risk = 58% (False Positives = 42%)
    - Dependant on location
      - Main or Lobar = 97%
      - Segmental = 68%
      - Subsegmental = 25%
      - Note the false positive rate doesn't take into account the possibility of true positives being *incidental*
  - *Further investigation to confirm segmental/sub-segmental PE's in low risk patients should be considered*
    - European Society Cardiology & PIOPED II

Reworking the Test Threshold

- Using Mortality Risks and Benefits
  - Risk of Test = 0.13%
    - (Contrast Risk (0.1%) +Radiation Risk (0.03%))
  - AC Risk = 0.2%
  - AC Benefit = 2.5%
  - False Positive rate = 42%

- **Test Threshold = 10%**

Lessler & Pines Test Threshold

- Annals EM 2010
- Used more complex Markov node model
  - Looked at both mortality and morbidity
  - Using Quality Adjusted Life Years lost
- Then later: using updated contrast risk figures but 0% AC risk
  - TT = 20%

Summarising Risk v Benefit of Investigation

- Newman & Schriger, *Rethinking Testing for PE: Less is More*, Annals of Emergency Medicine, June 2011

- ***"The current model of testing causes roughly 6 times as many deaths as lives saved"***

- *"A powerful first step would be to broadly acknowledge that testing under the current paradigm is a dubious, largely harmful endeavour and there must be an acceptable miss rate"*

Who is below the TT

PERC Rule

- Singh, PERC Meta-analysis, Ann of EM 2013
  - 15,000 patients in 6 countries
  - PE miss rate is 0.3%
- Endorsed by ACEP
  - Fesmire et al, Ann Emerg Med 2011

Wells <2

- Wells Score traditionally used to work out a PTP to decide which investigation to perform
- These are patients who you *don't* believe have PE but want to exclude
- What PTP does Wells <2 represent in ED patients?
  - Combined 2 meta-analyses
    - Ceriani, J Thromb Haemost 2010
    - Lucassen, Ann Intern Med 2011
  - Excluded retrospective and inpatient studies

Wells <2 table

Prospective evaluations of Wells Score (excluding inpatients)

		All Patients			Wells <2 Patients		
Study	**Year**	**N in Stud**	**Region**	**Study PE Prev**	**N**	**PE**	**PTP**
Wells et al	2001	930	Canada	9%	527	7	1.3%
Wolf et al	2004	134	US	12%	59	1	1.7%
Anderson et al	2005	858	Canada	10%	479	10	2.1%
Kabrhel et al	2005	607	US	10%	325	13	4.0%
Kline & Hogg	2006	178	US	14%	110	3	2.7%
Kline et al	2006	2302	US	5%	1704	50	2.9%
Kabrhel et al	2009	7940	US	7%	5482	173	3.2%
Legnani et al	2010	346	Europe+ N.America	15%	87	7	8.0%
Penaloza et al	2011	339	Belgium	19%	157	4	2.5%
Totals		13634			8930	268	**3.00%**

Wells <2 post PERC & d-dimer

- Wells <2 = 3.0% PTP
  - → *not* PERC negative (97% sens, 22% spec)
    - →3.7%
      - Positive d-dimer (98% sens, 45% spec)
        - → 6.4%

Still below 10% TT

Prognostication

- The patients in the source studies demonstrating untreated PE mortality were likely to be of low prognostic risk – it is safest to assume so.
- Therefore prudent to only consider exclusion of Wells <2 patients who are at *low prognostic risk*:
  - Well patients
  - Relatively normal vital signs
  - No major cardiorespiratory comorbidities
  - Absence of ongoing VTE risk factors


Source: Buypetmedicine.com

PPP approach

- **P**re-test Probability assessment
- **P**rognostication
- **P**atient-centred shared decision making

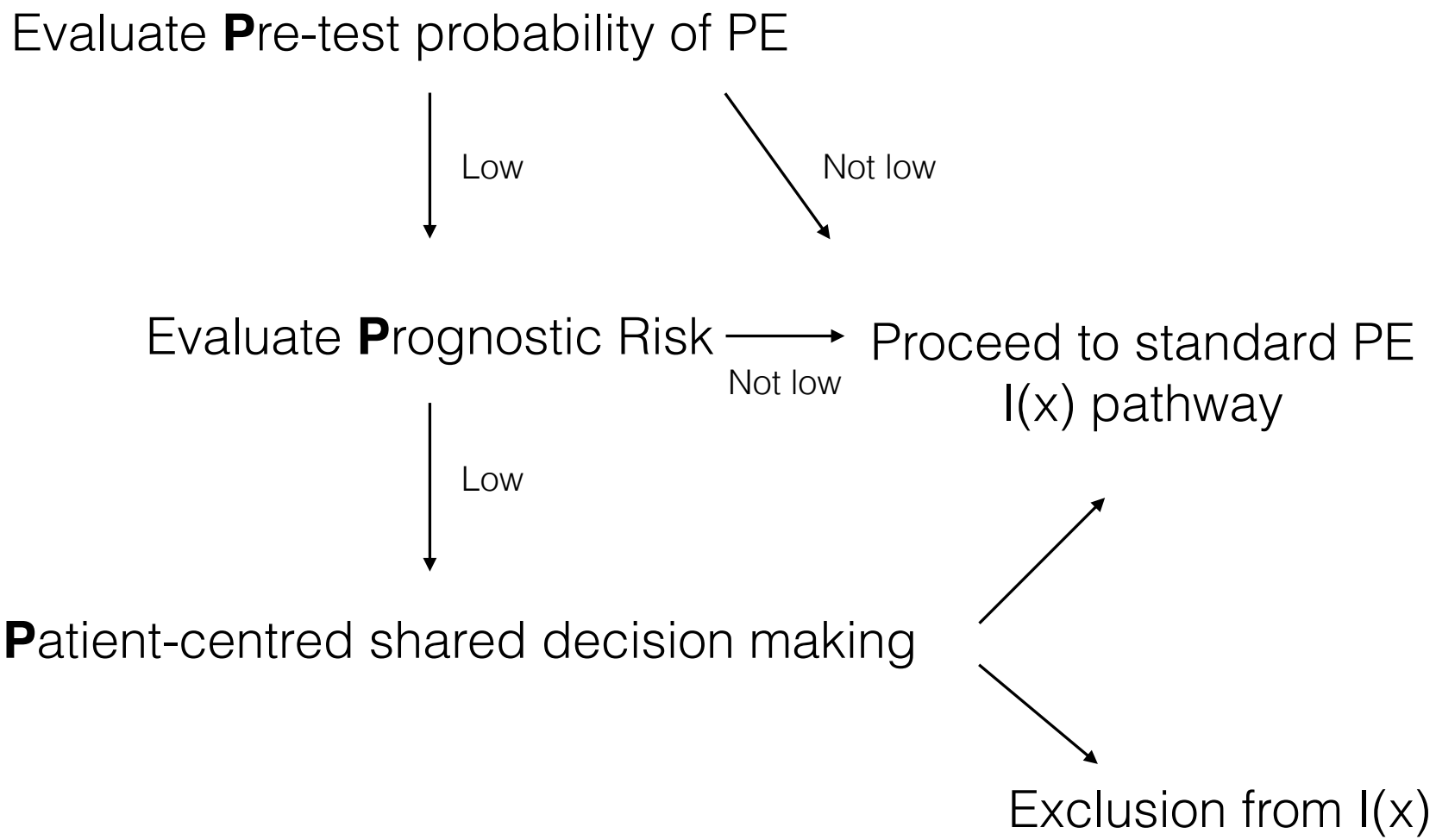


Figure 1: PPP PE Diagnostic Approach

Patient-centred decision making

- Decisions of uncertainty should be filtered through the risk tolerance of the patient *not the clinician*
- Numerous studies demonstrate when patients are faced with a very low risk of potentially serious event they usually choose to accept this risk
- This essentially represents an informed consent process regarding further investigation

Patient-centred decision making ...

- This will achieve 2 aims:
  - Empower the patient in their healthcare
  - Reduce unnecessary investigation that likely exposes the patient to more harm than benefit
- *Even a conservative explanation of the risk-benefit will achieve this*

Is *your* patient *above* the TT?

- The focus on definitively proving a patient is below TT is misguided
- We are guided by the principal of *"1st do no harm"*
- Under this principal the clinician must be confident the patient is *above* the TT *before* investigating
- This confidence simply *cannot* exist for low PTP patients with low prognostic risk
  - *They have an approx 1/1000 risk of death from PE*
- It is arguably unethical to *routinely* investigate this group of patients without *informed consent*

So what's the new approach?

- **Giving patients a choice!**

Questions?

- @drsenthi

- Emergucate.com
  - Talk posted here with all references