

Possible New Diagnostic Strategies for Pulmonary Embolism
Is Outpatient Management of Pulmonary Embolism Ready for Implementation?

Exclusion of PE is a daily task for Emergency Physicians. We must balance the risk of a missed diagnosis with the risk of testing since the current accepted “gold standard” test in the ED is CT Pulmonary Angiography. The risks associated with this are not trivial:

- Published studies demonstrate there is up to a 6–10% false positive rate in low-risk populations, possibly leading to over-diagnosis and unnecessary anticoagulation.
- CTPA imparts approximately 10 to 20 mSv of radiation, with an estimated increased lifetime risk of fatal cancer of at least 1 in 500 per chest CT. This cancer risk is likely highest in young patients, particularly female patients due to radiation to breast tissue.

Tools available to us to risk stratify patients include clinical gestalt, and 2 major clinical scoring systems: the Wells and Simplified Revised Geneva Score. The Pulmonary Embolism Rule out Criteria (PERC rule) can be used to exclude PE in low risk patients. When the PERC rule cannot be used, quantitative D-Dimer assays are the next step in the diagnostic algorithm for low and moderate pre-test probability patients.

The D-Dimer has limitations, most troublesome is the rate of false positive results. Table below is taken from Kline et al 2015 and lists factors that create a false positive D-Dimer.

False Positives
Patient factors:
• Increasing age: (60–69 years [OR 2.6], 70–79 years [OR 4.5], ≥80 years [OR 10.5])
• Cocaine use (OR 2.0)
• Immobility: general (OR 2.3), limb (OR 2.8), or neurologic (OR 3.0)
• Hemoptysis (OR 2.0)
• Hemodialysis (OR 2.2)
• Malignancy, active (OR 2.6)
• Rheumatoid arthritis (OR 2.8)
• Systemic lupus erythematosus (OR 2.1)
• Sickle cell disease (OR 24.2)
• Pregnancy and postpartum state: (2nd trimester [OR 7.3], 3rd trimester [OR 51.3], postpartum [OR 4.2])
• Surgery (<4 weeks prior): abdominal (OR 3.5), chest (OR 2.7), orthopedic (OR 2.2), other surgery (OR 3.2)

Today we will discuss two of these factors for which there is some recent evidence that may support the use of increased thresholds of D-Dimer. Age Adjusted D-Dimer, and Pregnancy Adjusted D-Dimer by trimester.

Additionally, we will discuss an article supporting the strategy for outpatient treatment of low-risk pulmonary embolism patients.

ARTICLE:

Righini M, Van Es J, Den Exter PL, et al. **Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study.** JAMA 2014;311:1117–24. doi:10.1001/jama.2014.2135

PURPOSE:

- Research Question(s): Does using an age adjusted D-Dimer threshold safely exclude PE in patients > 50?

DESIGN:

- Study Design: Multicenter prospective cohort
- Dependent / outcome Variable(s): Failure of diagnostic strategy (Thromboembolic not treated based on negative D-Dimer result)

SETTING / SUBJECTS:

- Research Setting: 19 hospitals in 4 european countries
- Subjects: 3346 ED patients
 - Study population:
 - Inclusion Criteria: Consecutive outpatients who presented to the emergency department with a clinical suspicion of PE defined as an acute onset or worsening shortness of breath or chest pain without another obvious etiology.
 - Exclusion Criteria: PE suspicion was raised more than 24 hours after admission to the hospital, if they were receiving anticoagulant therapy for another indication, if they had an allergy to contrast medium, impaired renal function, life expectancy of less than 3 months, ongoing pregnancy, or inaccessibility for follow-up

METHODS: (See figure) Patients risk stratified by either Well's or Geneva score. Low/moderate pretest probability underwent D-Dimer testing. If < 50 cutoff of 500 was used. If greater than 50, age adjusted (age x 10) was used as the cutoff. Negative D-Dimer stopped the workup. If D-Dimer testing was positive, CTPA was utilized.

Patients that were high risk for PE underwent CTPA and D-Dimer Testing.

3 month follow up by phone call. Possible VTE events were adjudicated by 3 blinded reviewers

RESULTS: (See Table 3)

D-Dimer < 500: 1 of 810 patients had VTE (failure rate of 0.1% [95% CI, 0.0%-0.7%])

Age Adjusted: 1 of 331 patients had VTE (failure rate of 0.3% [95% CI, 0.1%-1.7%])

Elderly Patients (>75) benefited most. Much improved specificity without loss of sensitivity

ARTICLE:

Kovac M, Mikovic Z, Rakicevic L, et al. **The use of D-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy.** Eur J Obstet Gynecol Reprod Biol 2010;148:27–30. doi:10.1016/j.ejogrb.2009.09.005

PURPOSE:

- Research Question(s): Can new reference ranges be established for D-Dimer in pregnancy?

DESIGN:

- Study Design: prospective, 88 women were followed during pregnancy and had serial d-dimer testing

SETTING / SUBJECTS:

- Research Setting: patients referred to center for hemostasis research with purpose of determining new reference ranges.
- Subjects:
 - Study population:
 - Inclusion Criteria: Healthy pregnant women without personal or family history of thrombosis.
 - Exclusion Criteria: patients with diabetes, SLE, chronic hypertension, hepatic or renal diseases. Patients who tested positive for thrombophilia were excluded.

METHODS: Patients were tested at their 1st, 2nd and 3rd trimester visits.

RESULTS: Similar to two previous studies, In the first Trimester 84% women had normal Ddimer, in the second 33%, and by the third trimester 1% of women had a normal D Dimer when traditional reference ranges were used.

Proposed new reference ranges for D-Dimer in pregnancy

First Trimester: 286 Second Trimester: 457 Third Trimester of 644 ng/mL

(These are D-Dimer units. Most testing we are used to seeing are in Fibrinogen equivalent units, FEU. the conversion is 2:1. They would be 572, 914, 1288 respectively)

ARTICLE:

Aujesky D, Roy P-M, Verschuren F, et al. **Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial.** Lancet (London, England) 2011;378:41–8. doi:10.1016/S0140-6736(11)60824-6

PURPOSE:

- Research Question(s): compare the effectiveness, safety, and efficiency of outpatient versus inpatient care for low-risk patients with acute, symptomatic pulmonary embolism as established with a validated clinical prognostic model.

DESIGN:

- Study Design: open-label, randomized, non-inferiority clinical trial
- Primary Outcome: recurrence of symptomatic, objectively confirmed VTE, defined as recurrent pulmonary embolism or new or recurrent deep vein thrombosis within 90 days of randomization
- Secondary Outcomes: major bleeding, 14 and 90 days of randomisation and all-cause mortality within 90 days

SETTING / SUBJECTS:

- Research Setting: 19 ED's in Switzerland, Belgium, France and USA
- Subjects:
 - Study population: 344 ED PE patients evenly divided between groups.
 - Inclusion Criteria: Consecutive adults aged 18 years of age or older with acute, symptomatic, and objectively verified pulmonary embolism who were at low risk of death based on the pulmonary embolism severity index (PESI)
 - Exclusion Criteria: hypoxemia < 90%, SBP < 100 mmHG, needing opioids, active bleeding, high risk of bleeding (stroke in last 10 days, GI bleed last 14 days, thrombocytopenia, renal failure, obesity, HIT/heparin allergy, already on oral anticoagulation, barriers to treatment adherence, pregnancy, patients diagnosed >23 hr before time of screening.

METHODS: At time of diagnosis, patients low risk by PESI score were randomly assigned to inpatient or outpatient treatment. Initially anticoagulated with LMWH, with Vitamin K antagonists started concomitantly. LMWH discontinued when INR >2 for 2 consecutive days. PCM managed anticoagulation.

RESULTS: One patient in outpatient arm had recurrent VTE, three outpatients and no inpatients had major bleeding. One patient in each arm died (outpt: traumatic aortic rupture, inpatient: pneumonia).

SUMMARY OF DISCUSSION

ARTICLE 1:

Overall, a well done study. This was the 3rd in a series of studies looking at age adjusted D-Dimer. The two priors had been the derivation and retrospective validation studies. This was the prospective study. There are a few other similar studies since. A drawback to the study was that the potential thromboembolic embolic events that occurred in the follow up period were determined by “adjudication,” a process by which blinded reviewers determine whether the patient had the outcome of interest by reviewing the chart (I.e instead of autopsy in patients who had died). However, adjudication is widely used for this purpose in many clinical studies similar to this one.

It seemed like there was agreement that implementing this strategy for PE in the ED would be acceptable. A few were currently using this strategy.

The major objection to using this strategy by a few providers at the meeting was that CT in elderly patients with dyspnea reveals alternative diagnoses sometimes, and the elderly population will be at lowest risk from radiation, though they will be at higher risk from renal complications associated with IV contrast.

ARTICLE 2:

This study was not an outcome based study, nor did it assess the actual performance of using trimester adjusted D-Dimer to exclude PE in pregnancy. However, it is unlikely this study will ever be undertaken as pregnant patients are very difficult to study from an IRB standpoint.

In the discussion, most providers at the meeting felt that clinical gestalt was the major tool they used for risk stratifying pregnant patients for PE, and were fairly aggressive about not CT scanning patients unless they were very concerned.

A discussion ensued about radiation exposure. I found 3 good resources I found in follow up to address these:

If you only read one, read this one:

CDC Publication about radiation in pregnancy (for both cancer and non-cancer health effects)

<http://emergency.cdc.gov/radiation/prenatalphysician.asp>

Powerpoint File from International Commission on Radiological Protection

<http://www.icrp.org/publication.asp?id=ICRP%20Publication%2084>

Review Article:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3259315/>

Take Home Points from them:

Radiation exposure of <100 mGy (.1 Gy) in a single dose is very unlikely to cause harm (very low risk of malformation, 99% of child being cancer free [ages 0-19])

Risk increases between 100-500 mGy (0.1-0.5 Gy). Above 0.5 Gy risk increases rapidly

Avg Dosages to fetus:

CT PE

0.013 and 0.026 mGy in early pregnancy

0.06–0.1 mGy late pregnancy

V/Q (Authors advocate performing a Chest x-ray, if normal, then proceed with half dose perfusion scintigraphy only, and omit ventilation phase)

0.1–0.6 mGy in early pregnancy

0.6–0.8 mGy in late pregnancy

Bottom Line: Both Modalities expose the fetus to a fraction of the radiation threshold thought to be harmful. (at .02 mGy per CT it would take 5000 CT's to reach the threshold of 100mGy)

A statement from the ICRP:

“Communication should be related to the level of risk. Communication that risk is negligible is adequate for very low dose procedures (<1 mGy to the fetus)”

CT scanning seems attractive because of the lower fetal exposure, however it is a much higher absorbed dose to the vulnerable breast tissue, the risks of which are not well quantified.

Another question that came up was the value of echocardiography in testing for PE in patients.

While not an exhaustive review, the most recent article I could find demonstrated it had very little utility in ruling out PE, while in patients with high clinical suspicion for PE with findings of RV strain, it does increase the post test probability of PE. (sensitivity 56%, specificity 90%)

<http://www.ncbi.nlm.nih.gov/pubmed/11343666>

ARTICLE 3:

Well done study, though with the average LOS in the outpatient arm being almost half a day, it raises the question whether these are truly the “outpatients” we would send home from the ED after only several hours. Additionally, since this study was performed before the widespread use of the novel anticoagulants (rivaroxaban, apixaban, etc.), sending a patient home on these agents has not been with PE from the ED has not been explicitly studied in large trials.

A small study did come out after the articles for journal club had been selected that did look at this.

<http://onlinelibrary.wiley.com/doi/10.1111/acem.12711/epdf>

After being risk stratified as low risk thromboembolism 106 patients (71 DVT, 30 PE, 5 both) were treated with rivaroxaban as outpatients after receiving a single dose of enoxaparin in the ED (one reason for enoxaparin was that most patients in the original trial of rivaroxaban were therapeutically anti-coagulated with heparin before starting rivaroxaban.)

Patients did well, with no adverse outcomes.

Obvious limitations include not a randomized controlled trial, no control group whatsoever.

A few providers at Journal club currently do send home patients with low-risk PE already, and many thought the idea was viable at their institutions.