Critical Review Form
Diagnostic Test

Multidetector Computed Tomography for Acute Pulmonary Embolism (PIOPED II), *NEJM* 2006; 354:2317-2327

Objective: **"To determine whether multidetector CTA can reliably detect and rule out acute pulmonary embolism and whether the addition of CTV improves the ability to detect and rule-out pulmonary embolism. We also determined whether the addition of a validated clinical assessment (the Well's score – below) improves the ability to detect or rule out pulmonary embolism by CTA or CTA-CTV in patients with suspected pulmonary embolism." (p. 2318)**

Wells Score	
Clinical Feature	**Score**
Clinical signs and symptoms of DVT (objectively measured leg swelling and pain with palpation in the deep-vein system)	3.0
Heart rate >100 beats/min	1.5
Immobilization for ≥3 consecutive days (bed rest except to go to bathroom) or surgery in previous 4 weeks	1.5
Previous objectively pulmonary embolism or DVT	1.5
Hemoptysis	1.0
Cancer (with treatment within past 6 mo or palliative treatment)	1.0
Pulmonary embolism likely or more likely than alternative diagnoses (on the basis of history, physical examination, chest radiography, ECG, and blood tests)	3.0

Methods: **Prospective observational trial at 8 hospitals between Sep 2001 and July 2003 funded by the National Heart Lung and Blood Institute and conducted according to the Standards for Reporting of Diagnostic Accuracy. This was a convenience sampling during periods of staff availability (weekdays, day time). All patients underwent Well's score-defined pretest probability assessment before**

undergoing definitive testing for PE. The diagnosis of PE required one of the following scenarios:

1) **V/Q scan high probability in patient without a prior PE; or**
2) **Abnormal pulmonary digital subtraction angiography (DSA); or**
3) **Indeterminate V/Q scan and abnormal venous Doppler without prior DVT at that site.**

Exclusion of PE required one of the following scenarios:

1) **Normal findings on DSA;**
2) **Normal V/Q scan;**
3) **Low or very low probability V/Q scan and Well's score <2, and normal venous Doppler.**

Patients labeled as "no PE" at the index visit were followed up by telephone interview at 3- and 6-months to exclude initial false-negative labels.

CT scanners varied between centers from 4-row, 8-row and 16-row multidetector scans. Acute PE diagnosis required that there was failure of contrast material to fill the entire lumen because of a central filling defect. Acute DVT diagnosis required a central filling defect (complete or partial) on CTV. Two certified radiologists who were not at the center where the images were obtained had to agree on the image interpretation. To diagnose PE, two readers had to agree that at least one lobe had a filling defect on CTA or DSA. Similarly, two readers had to agree that PE was absent to exclude the diagnosis. Sensitivity, specificity and LR's were computed with 95% CI's. Investigators also report PPV and NPV stratified by disease pretest probability. Sensitivity analyses are reported using highest and lowest reported false-positive and false-negative rates for the composite criterion standards.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes, all patients had suspected PE and risk-assessment (Well's score) prospectively collected before CTA/CTA-CTU and criterion standard testing.
B.	**Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group?** **(Confirmation Bias)**	Yes, "Readers (of the CTA, CTA-CTV, DSA) were unaware of all clinical information and of the results of other imaging tests except chest radiographs, which were included with ventilation-perfusion scans." (p. 2319)

C.	**Did the results of the test being evaluated influence the decision to perform the gold standard?** **(Ascertainment Bias)**	No. "All patients consented to undergo diagnostic testing, including CTA-CTV, ventilation-perfusion scanning, venous compression ultrasonography of the lower extremities, and if necessary, pulmonary digital subtraction angiography." (p. 2318)
II.	**What are the results?**	
A.	**What likelihood ratios were associated with the range of possible test results?** **CTA** **PE + -** **CTA** **+ 150 25** **- 31 567** **Sen 83 (79-86)** **Spec 96 (95-97)** **LR^+ 19.6 (14-27)** **LR^- 0.18 (0.14-0.23)** **CTA-CTV** **PE + -** **CTA-CTV** **+ 164 30** **- 19 524** **Sen 90 (86-93)** **Spec 95 (93-96)** **LR^+ 16.5 (13-21)** **LR^- 0.11 (0.08-0.15)** **CTA – PPV declines with disease probability, NPV increases with disease probability.** **High Pre-test Prob** / **Int Prob 92%** / **Low Prob 58%** PPV: 96% / 92% / 58% NPV: 60% / NR / 96%	• From 7284 screened patients, 3262 were eligible and 1090 were enrolled with 62% female and mean age 52 years with 56% low probability by Well's criteria (and 38% intermediate probability) • 824 patients are included in this analysis since 28 did not get a CT and 238 did not receive a criterion standard test. • PE was diagnosed in 192/824 (23%) and among the 592 not initially diagnosed with PE and with an interpretable CT, only 2 were diagnosed with PE during the 6-month follow-up. • Initial CT non-diagnostic in 51/824 (6%) and CTA-CTV non-diagnostic in 87/824 (11%). • 105 patients had positive results on CTV with 3% IVC/pelvic vein alone, 85% in thigh veins alone, and 12% in both. • Sensitivity analysis using the lowest reported false positive and false negative rates for the criterion standards lower CTA sensitivity to 84% and CTA-CTV sensitivity to 92%. Using the highest reported false-negative and false positive rates lower CTA sensitivity to 82% and CTA-CTV 90%. Specificities changed < 1% in all scenarios. • Only 0.7% of patients had a complication (mild allergic reaction, urticaria, extravasation).

III.	How can I apply the results to patient care?	
A.	**Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?**	Yes, since Wash U was in fact one of the 8 medical centers from which patients were enrolled - we use the same equipment and Radiologists.
B.	**Are the results applicable to the patients in my practice?**	Yes, since Wash U was one of the 8 medical centers from which patients were enrolled – these are our patients.
C.	**Will the results change my management strategy?**	Yes, by understanding that CTA is insufficient to rule-in or rule-out PE with absolute certainty. In particular, when the CT-findings are discordant with the pre-test probability clinicians need to continue testing. In addition, PIOPED-II suggests that CTA-CTV may be superior to CTA to reduce the post test probability of VTE (LR^- 0.11 for CTA-CTV vs. 0.18 for CTA). Quantitatively, this means that an unremarkable CTA-CTV would reduce a pretest probability for PE from 23% to 3% while a negative CTA would reduce the same pretest probability to 5%. Moores' meta-analysis of single-detector CTA concluded that lower extremity imaging (CTV? Doppler US?) should be normal before anticoagulation is withheld in patients with suspected PE and unremarkable CTA. This is almost certainly not the standard of care and future research will be needed to determine the risks/benefits of LE imaging with/after CTA within the context of test-treatment thresholds.
D.	**Will patients be better off as a result of the test?**	Yes, by helping clinicians recognize the limitation of CTA and CTA-CTV for the diagnosis of PE. Future trials will be needed to determine how accurately clinicians complete and apply pre-test probabilities when utilizing CTA.

Limitations

1) **Likely selection bias (i.e. limited external validity) since convenience sampling (day light weekday hours) and exclusion of inconclusive imaging.**

2) **No stratification of results by CT-type (4-slice vs. 8-slice vs. 16-slice). Accuracy may be improved with more advanced scanners.**

3) **Possibly inadequate search for post-discharge PE diagnosis since the investigators relied upon telephone self-report which neglects death or hospitalization that prohibits the patient from reporting a PE. No loss to follow-up was reported, but more comprehensive methods would include review of hospital records and autopsy data.**

4) **No report of Kappa between cardiologists reviewing CTA, CTA-CTV, and DSA.**

5) **Who computed the Well's score? Clinicians (increased external validity)? Research assistants (increased internal validity)?**

Bottom Line

Although CTA (6%) and CTA-CTV (11%) are sometimes non-diagnostic, when images are of sufficient quality these CT studies rule-out PE (LR- = 0.18) in those with low pre-test probability (NPV = 96%) and rule-in PE (LR+ = 19.6) in those with high pre-test probability (PPV = 96%) when normal or abnormal, respectively. These results are robust to a sensitivity analysis adjusting for the flaws inherent in the criterion standards employed. It is essential to recognize that if the CT results are discordant with pre-test probability estimates, additional testing is necessary. PIOPED II does not provide any clinical direction for intermediate pre-test probability patients with positive or negative CTA. A key next step for researchers will be a diagnostic meta-analysis of multi-detector CT investigations stratified by 4-slice, 8-slice, etc. and evaluated within the context of test-treatment thresholds to help clinicians manage low, intermediate, or high pre-test probability patients based upon CTA results.