Biomarkers of Venous Thromboembolism

Benjamin Jacobs, M.D.
Thomas W. Wakefield, M.D.
Stanley Professor of Surgery
Section of Vascular Surgery
University of Michigan USA
Director Samuel and Jean Frankel Cardiovascular Center

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Nothing To Disclose

What is a Biomarker?
A Biomarker is a measurable indicator of the severity or presence of some disease state. More generally, a biomarker is anything that can be used as an indicator of that particular disease state.

D-dimer Assay

DVT
96%/40%/48%/95%

PE
Sensitivity 96%-98%, Specificity 39%-52%

False Positives:
Pregnancy, Infection, Malignancy, Recent Postoperative, Total Bilirubin >2mg

D-Dimer Investigation

• In patients with low pre-test probability:
  – High-sensitivity D-dimer (2B)
  – Moderately sensitive D-dimer (2C)

• Negative D-dimer ➔ No further testing (1B)
• Positive D-dimer ➔ Compression US Proximal Veins

• Low-probability Wells Score is insufficient to rule-out DVT without addition of D-dimer.
Outpatient Safety of Combining Negative D-Dimer with Clinical Presentation (< 2 points)

39% Fewer Ultrasounds Used in 566 Cases
Only 2 cases went on to DVT (within 3 Mo)
NPV 96.1%


Non-outpatient populations

- Whether D-dimer has reduced diagnostic efficacy in non-outpatient populations is unknown.
- Meta-analyses by Geersing (2014)
  - Wells Score plus D-dimer is safe for the exclusion of deep vein thrombosis in hospital care patients with suspected DVT.
  - This strategy has reduced efficacy in patients with malignancy.

D-dimer in Pregnant Patients

- Sensitivity 100% (CI, 77% to 100% [13 of 13 patients])
- Specificity 60% (CI, 52% to 68% [81 of 135])
- Negative Predictive Value 100% (CI, 95% to 100% [81 of 81])

Specificity decreases as pregnancy progresses, limiting usefulness in the third trimester.

D-dimer Cutoffs

- Best D-dimer cutoff is currently unclear.
- 500ng/mL is most common “positive”
- A higher cutoff (1000ng/mL) may be as effective in patients with low-pretest probability.
- Age adjustment of cutoff values may increase specificity for DVT in elderly patients.
  - Specificity < 50 years 49%-67%; ≥80 years 0%-18%
  - Age x 10 D-dimer cutoff increases specificity in > 80 years to 35.2%
- Similar results have been shown for PE, ADJUST-PE.

Variation by Assay

- Significant variation is found by assay type
- Best performance:
  - ELISA
  - Rapid-quantitative ELISA
- Generally, a trade-off between sensitivity and specificity.

D-Dimer Testing to Determine the Duration of Anticoagulation Therapy

D-Dimer Abnormal 1 month after Stopping Coumadin
223 /608 Patients
Remaining off Anticoagulation - 13% Recurrence (1.4y FU)
Resumed Anticoagulation – 2.9% Recurrence
OR 4.26x (p=0.02)

D-Dimer Normal 1 month after Stopping Coumadin
385 Patients
6.2% Recurrence

Soluble P-selectin

Selectins are glycoproteins found primarily on endothelial cells, leukocytes and platelets. They are involved in trafficking of leukocytes in acute and chronic inflammatory processes, including:

- Post-ischemic inflammation in muscle, kidney and heart
- Skin inflammation
- Atherosclerosis
- Glomerulonephritis
- Lupus Erythematosus

DVT


Meta-analysis of sP-selectin

- 586 VTE patients, 1843 Controls
- Sensitivity: 0.57 (95% CI 0.30-0.82)
- Specificity: 0.73 (95% CI 0.51-0.90)
- Importantly, unlike D-dimer, sPsel appears to perform as well in patients with or without Malignancy.

sP-selectin

- P-selectin may be elevated to greater levels in proximal versus distal DVT.¹
- In patients treated with VKA, sP-selectin returns to baseline within 1-month; it rises again with discontinuation of VKA.¹


Other Biomarkers of interest

- Inflammatory markers
  - CRP, Interleukins, TNF-alpha
- Microparticles
- Cellular adhesion molecules (ICAM, VCAM)
- Other selectins
- Galectins

Patients - newly diagnosed cancer, no chemotherapy, within the last three months; VTE confirmed by imaging.

687 patients (319 female/368 male, median age 62 yrs), median 415 days.

Hazard Ratio 1.2 for each 10ng/mL increase in sPsel

The cumulative probability of VTE after 6 months was 11.9% with sPsel plasma levels above, 3.7% below the 75th percentile.