Biomarkers of Venous Thromboembolism

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Disclosures
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 (Coagulation)
sP-Selectin (Adhesion)
Cytokines (Inflammation)
Galactin 3 and G3BP
DNA (NETs)

D-Dimer Assay
DVT
96%/40%/48%/95%
PE
Sensitivity 96%-98%, Specificity 39%-52%
Biomann K et al, Lancet 337:196-200, 1991

False Positive
Pregnancy, Malignancy, Recent Postoperative, Total Bilirubin >2mg/dl

Clinical Characteristic Score

Active cancer (patient receiving treatment for cancer within the previous 6 months or currently smoking palliative treatment)

1

Paralysis, paresis, or recent plaster immobilization of the lower extremities

1

Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia

1

Localized tenderness along the distribution of the deep venous system

1

Entire leg swollen

1

Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)

1

Pitting edema confined to the symptomatic leg

1

Previously documented deep-vein thrombosis

1

Collateral non varicose superficial veins

1

Alternative diagnosis at least as likely as deep-vein thrombosis

-2

Wells Criteria for Likelihood Estimation of Lower Extremity Deep Venous Thrombosis

High probability for DVT if score 3 or more (probability of DVT = approximately 53%)
Moderate probability for scores of 1 or 2 (probability of DVT = approximately 17%)
Low probability for scores of 0 (probability of DVT = approximately 5%)

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%


D-Dimer Testing to Determine the Duration of Anticoagulation Therapy

D-Dimer Abnormal 1 month after Stopping Coumadin

223/608 Patients

Remaining off Anticoagulation - 15% Recurrence (1.4y FU)

Resumed Anticoagulation - 2.9% Recurrence

OR 4.26 (p=0.02)

D-Dimer Normal 1 month after Stopping Coumadin

385 Patients

6.2% Recurrence


Selectins

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
- Arthritis
- Atherosclerosis
- Glomerulonephritis
- Lupus Erythematosus
- DVT

P-selectin/PSGL-1 Involvement in Thrombosis and Inflammation

Endothelium

Thrombosis

MAC-1 (αMβ2)

Fibrin Strands

P-selectin/PSGL-1 Involvement in Thrombosis and Inflammation

Fig 3. C-reactive protein, DVT, Deep venous thrombosis, LA, lower extremity, UF, upper extremity

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.

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

High Plasma Levels of Soluble P-Selectin are Predictive for VTE in Cancer Patients. Results from the Vienna Cancer and Thrombosis Study (CATS)


Associations between Elevated Levels and Future DVT In Cancer Patients

D-Dimer
Prothrombin 1+2
sP-Selectin
Factor VII
Thrombin Generation Potential
TF-bearing MPs – heterogeneous
(present for Pancreatic Cancer)


The relationship between inflammation and venous thrombosis

A systematic review of clinical studies

Fox EA & Kahn SR, Thromb Haemost 94:362-365, 2005
<table>
<thead>
<tr>
<th>Authors</th>
<th>Marker of Inflammation (cut-off for abnormal)</th>
<th>Number of Patients</th>
<th>Number of Controls</th>
<th>Odds Ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Fox et al. (2005)</td>
<td>CRP (&lt;90% cclt)</td>
<td>182</td>
<td>230</td>
<td>2.4 (1.5-3.9)</td>
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<tr>
<td>Fox et al. (2005)</td>
<td>MCP-1 (&gt;95% cclt)</td>
<td>182</td>
<td>234</td>
<td>1.9 (1.2-3.2)</td>
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<tr>
<td>Fox et al. (2005)</td>
<td>IL-6 (&lt;90% cclt)</td>
<td>466</td>
<td>462</td>
<td>6.0 (2.0-17)</td>
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<tr>
<td>Rautonen (2004)</td>
<td>TNF-alpha (&lt;90% cclt)</td>
<td>470</td>
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<td>IL-6 (&lt;90% cclt)</td>
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<td>Rautonen (2004)</td>
<td>IL-12p70 (&gt;95% cclt)</td>
<td>470</td>
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<td>1.0 (0.3-2.2)</td>
</tr>
</tbody>
</table>

Fox EA & Kahn SR, Thromb Haemost 94:362-365, 2005
Galectin3 (Gal3) and its binding partner, Galectin3 Binding Protein (Gal3BP), are secreted proteins that interact with each other in order to promote cell-to-cell adhesion and initiate signaling cascades.

Studies from our laboratory have shown that both the inhibition of Gal3BP in wild type (WT) mice and the absence of Gal3 in Gal3 knock-out mice decrease VT.

We measured circulating levels of Gal3 and Gal3BP in mouse and human plasma to study if those molecules could be considered biomarkers for VT.