HemosIL™ D-Dimer

Fully Automated Immunoturbidimetric Assay for the Measurement of D-Dimer in Citrated Plasma

Aids in the Diagnosis of
Deep Vein Thrombosis and Pulmonary Embolism
D-Dimer in Clinical Practice

In the Diagnosis of Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE)

DVT has an annual incidence of 0.5 - 1.2 per thousand. It is the primary cause of PE, a potentially fatal event, occurring with an incidence of 0.2 - 0.6 per thousand. The diagnostic strategy for Venous Thromboembolism (VTE), which includes DVT and PE, generally begins with a clinical evaluation, followed by D-Dimer testing. Confirmatory tests generally involve imaging techniques. For DVT, these are lower limb venous compression ultrasonography (CUS) and venography, which is invasive and considered the gold standard. For PE, imaging tests are helical computerized tomography (CT) scanning or ventilation/perfusion (VQ) lung scanning and angiography, which is also invasive.

A substantial number of publications in the past few years report the use of D-Dimer, together with pre-test probability (PTP) assessment, as a safe, cost-effective management strategy for the evaluation of patients presenting to emergency departments with clinically suspected VTE. This approach allows DVT and/or PE to be ruled out in outpatients with suspected VTE with low or low-moderate PTP and a negative D-Dimer, hence reducing the number of imaging tests required, particularly those invasive.

In the Diagnosis of Disseminated Intravascular Coagulation (DIC)

DIC is considered a systemic thrombohemorrhagic disorder, usually seen with well-defined clinical conditions. It is always a secondary manifestation to an underlying disorder, such as sepsis, trauma or malignancy. DIC has been described as low grade-compensated or fulminant, but when a patient presents with suspected DIC, such a clear differentiation of the disease is not apparent. The patient may be at any stage between these extremes with progressing severity. Therefore, early diagnosis and appropriate treatment are of primary importance in DIC diagnosis. Recent definitions of clinical laboratory criteria for the diagnosis of DIC include D-Dimer measurement as an important contributor to the algorithm for the DIC scoring system.

Other Clinical Applications

D-Dimer testing has been evaluated in a number of clinical applications such as, predictive factor for recurrences of VTE after discontinuation of oral anticoagulant therapy, and as an indicator of pregnancy complications due to abnormally increased fibrinolysis. Other studies suggest that D-Dimer levels in the normal population may indicate the risk for arterial thrombosis.
HemosIL D-Dimer

An automated latex immuno-assay for the quantitative determination of D-Dimer in human citrated plasma on IL Coagulation systems, as an aid in the diagnosis of DVT and PE.

- Fast, fully automated immunoturbidimetric assay
- Time to result: seven minutes
- Same VTE cut-off for the entire ACL instrument line*
- 100% Negative Predictive Value*
- Used in more than ten independently published studies on VTE

* from an internal evaluation and external management study

Traceability of Calibrators and Controls

Since a D-Dimer International Standard is not currently available, the House Standard has been assigned according to the harmonization criteria proposed by W. Niewenhuizen.

HemosIL D-Dimer

An automated latex immuno-assay for the quantitative determination of D-Dimer in human citrated plasma on IL Coagulation systems, as an aid in the diagnosis of DVT and PE.

- Fast, fully automated immunoturbidimetric assay
- Time to result: seven minutes
- Same VTE cut-off for the entire ACL instrument line*
- 100% Negative Predictive Value*
- Used in more than ten independently published studies on VTE

* from an internal evaluation and external management study

Traceability of Calibrators and Controls

Since a D-Dimer International Standard is not currently available, the House Standard has been assigned according to the harmonization criteria proposed by W. Niewenhuizen.

Analytical Characteristics

**Linearity**

<table>
<thead>
<tr>
<th>ACL Family</th>
<th>Mean (ng/mL)</th>
<th>CV% (Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low D-Dimer Control</td>
<td>310</td>
<td>7.18</td>
</tr>
<tr>
<td>High D-Dimer Control</td>
<td>732</td>
<td>2.99</td>
</tr>
</tbody>
</table>

**Imprecision**

<table>
<thead>
<tr>
<th>ACL Futura/Advance</th>
<th>Mean (ng/mL)</th>
<th>CV% (Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low D-Dimer Control</td>
<td>304</td>
<td>13.58</td>
</tr>
<tr>
<td>High D-Dimer Control</td>
<td>813</td>
<td>4.94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACL TOP</th>
<th>Mean (ng/mL)</th>
<th>CV% (Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low D-Dimer Control</td>
<td>340</td>
<td>7.7</td>
</tr>
<tr>
<td>High D-Dimer Control</td>
<td>729</td>
<td>4.5</td>
</tr>
</tbody>
</table>

**Detection Limit**

<table>
<thead>
<tr>
<th>ACL Family</th>
<th>140 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACL Futura/ACL Advance</td>
<td>156 ng/mL</td>
</tr>
<tr>
<td>ACL TOP</td>
<td>69 ng/mL</td>
</tr>
</tbody>
</table>

**Stability of Opened/Reconstituted Reagents**

- Latex Reagent: 1 month at 2-8°C
- Reaction Buffer: 1 month at 2-8°C
- Calibrator: 1 month at 2-8°C
Clinical Performance of D-Dimer Tests for VTE

The Negative Predictive Value (NPV) represents the percentage of patients with a negative D-Dimer (< the cut-off) who are VTE-negative. The Negative Predictive Value (NPV) is generally the most important feature in assessing the clinical performance of a D-Dimer assay. It is generally accepted that the NPV should be > 97%, equivalent to the current sensitivity of other gold standard techniques, such as venography.

The sensitivity and specificity are also important parameters for characterizing a D-Dimer assay. The sensitivity can be defined as the proportion of patients with proven VTE who are D-Dimer-positive. The sensitivity should be > 95%, or it is unlikely that the D-Dimer assay would reach an NPV > 97%.

Instead, the specificity, as well as the Positive Predictive Value (PPV), are recognized to be low for D-Dimer assays, in the range 25 – 50%. These numbers are low because fibrin is generated and degraded in a wide variety of clinical situations other than DVT or PE. Finally, although not widely used, a parameter worth calculating is exclusion rate, defined as the percentage of the total cohort of patients who are Negative for VTE and D-Dimer and would, therefore, be safely excluded without further testing.

Parameters in Use for the Clinical Performance Evaluation of D-Dimer Tests

\[
\text{Sensitivity} \% = \frac{TP}{TP + FN} \times 100
\]

\[
\text{Specificity} \% = \frac{TN}{TN + FP} \times 100
\]

\[
\text{NPV} \% = \frac{TN}{TN + FN} \times 100
\]

\[
\text{PPV} \% = \frac{TP}{TP + FP} \times 100
\]

\[
\text{Prevalence} \% = \frac{TP + FN}{TP + FN + FP + TN} \times 100
\]

\[
\text{Exclusion rate} \% = \frac{TN}{\text{Total \# of Samples}} \times 100
\]
HemosIL D-Dimer: Clinical Studies for the Diagnosis of DVT and PE

An internal study with 100 samples (32 confirmed PE and 68 Normal) was performed in blind mode on the ACL 7000, ACL 9000, ACL Futura/Advance and ACL TOP to define the optimal cut-off value on all instrument platforms. At a cut-off value of 230 ng/mL, the sensitivity and NPV of HemosIL D-Dimer was 100% on all ACL instruments.

An external management study was then performed to validate the cut-off. Three hundred samples from VTE-suspected patients admitted consecutively to an emergency department have been tested with HemosIL D-Dimer on the ACL TOP™ and the ACL™ 9000 at an external laboratory. Sequential, non-invasive tests were carried out in this order: D-Dimer testing, lower-limb compression ultrasonography and lung scan. Those patients with no conclusive diagnosis underwent phlebography or angiography. Patients diagnosed as DVT or PE were treated appropriately and those patients with a negative diagnosis (no VTE) were monitored for the risk of thromboembolic events during a three-months follow-up period.

At the end of this period, all patients were diagnosed as positive or negative for DVT or PE. Of the 300 samples, 78 were confirmed as VTE-positive (31 PE and 47 DVT) and the remaining 222 were confirmed as negative. ROC analysis was performed to assess the optimal cut-off value. At a cut-off value of 230 ng/mL on both ACL TOP and ACL 9000, sensitivity, specificity, negative predictive value and exclusion rate were calculated as summarized in the table below.

<table>
<thead>
<tr>
<th></th>
<th>HemosIL D-Dimer on ACL TOP</th>
<th>HemosIL D-Dimer on ACL 9000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # Samples</td>
<td>294</td>
<td>297</td>
</tr>
<tr>
<td>VTE Prevalence</td>
<td>25.2%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Cut-off</td>
<td>230 ng/mL</td>
<td>230 ng/mL</td>
</tr>
<tr>
<td>% Sensitivity (95% CI)</td>
<td>100.0% (95.1%-100%)</td>
<td>100.0% (95.2%-100%)</td>
</tr>
<tr>
<td>% Specificity (95% CI)</td>
<td>35.9% (29.6%-42.6%)</td>
<td>37.8% (31.4%-44.8%)</td>
</tr>
<tr>
<td>% NPV (95% CI)</td>
<td>100.0% (95.4%-100%)</td>
<td>100.0% (95.7%-100%)</td>
</tr>
</tbody>
</table>

This graph demonstrates the ROC analysis of the data from the management study reported above with HemosIL D-Dimer on the ACL TOP. The same analysis was performed for HemosIL D-Dimer on the ACL 9000 analyzer and very similar results were obtained.

ROC analysis is a plot of the Sensitivity (y axis, % of true positive samples) versus 1-Specificity (x axis, % of false positive samples) at various D-Dimer cut-off values. As the D-Dimer cut-off value decreases, the Sensitivity increases and the Specificity decreases. The optimal cut-off value is the D-Dimer concentration that produces a sensitivity of 100%; that is, all patient samples with confirmed DVT and/or PE have a plasma D-Dimer concentration above the cut-off value (no false negative samples). This corresponds to a NPV of 100%.

As shown in the graph, at a cut-off value of 230 ng/mL, the sensitivity was 100% and the specificity was 35.9% in the sample population tested.
### HemosIL D-Dimer

**Fully Automated Immunoturbidimetric Assay for the Measurement of D-Dimer in Citrated Plasma**

#### Kit Composition

<table>
<thead>
<tr>
<th>P/N 0020008500</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4 x 3 mL Latex Reagent</strong> (Lyo)</td>
</tr>
<tr>
<td><strong>3 x 9 mL Reaction Buffer</strong> (Liq)</td>
</tr>
<tr>
<td><strong>2 x 1 mL Calibrator</strong> (Lyo)</td>
</tr>
</tbody>
</table>

#### D-Dimer Controls

<table>
<thead>
<tr>
<th>P/N 0020008610</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 x 1 mL Low D-Dimer Control</strong></td>
</tr>
<tr>
<td><strong>5 x 1 mL High D-Dimer Control</strong></td>
</tr>
</tbody>
</table>

### References


### Worldwide Locations

**Instrumentation Laboratory**

**Corporate Headquarters**

Barcelona, Spain

Tel.: +34-93-4010101

**US, Canada, Latin America Headquarters**

Lexington, MA, U.S.A.

Tel.: +1-781-861-0710

Mexico

Colonia Juarez

Tel.: +52-5-525-8639

USA

Lexington, MA

Tel.: +1-781-861-0710

Pacific Headquarters

Minato-ku, Tokyo, Japan

Tel.: +81-3-3437-6350

Hong Kong

Hong Kong

Tel.: +852-2927773

Japan

Minato-ku, Tokyo

Tel.: +81-3-3437-6350

Europe, Middle East, Africa Headquarters

Milano, Italy

Tel.: +39-02-25221

Austria

Wien

Tel.: +43-1-2565800-0

Belgium

Zaventem

Tel.: +32-2-7252052

Czech

Prague

Tel.: +420-2-7816047

France

Paris

Tel.: +33-1-53338600

Germany

Kirchheim bei München

Tel.: +49-89-909070

Hungary

Budapest

Tel.: +36-1-4527810

Italy

Milano

Tel.: +39-02-25221

Lithuania

Kaunas

Tel.: +370-37-313157

Poland

Warszawa

Tel.: +48-22-3361800

The Netherlands

Breda

Tel.: +31-76-5480100

United Kingdom

Warrington, Cheshire

Tel.: +44-1925-81-0141

References