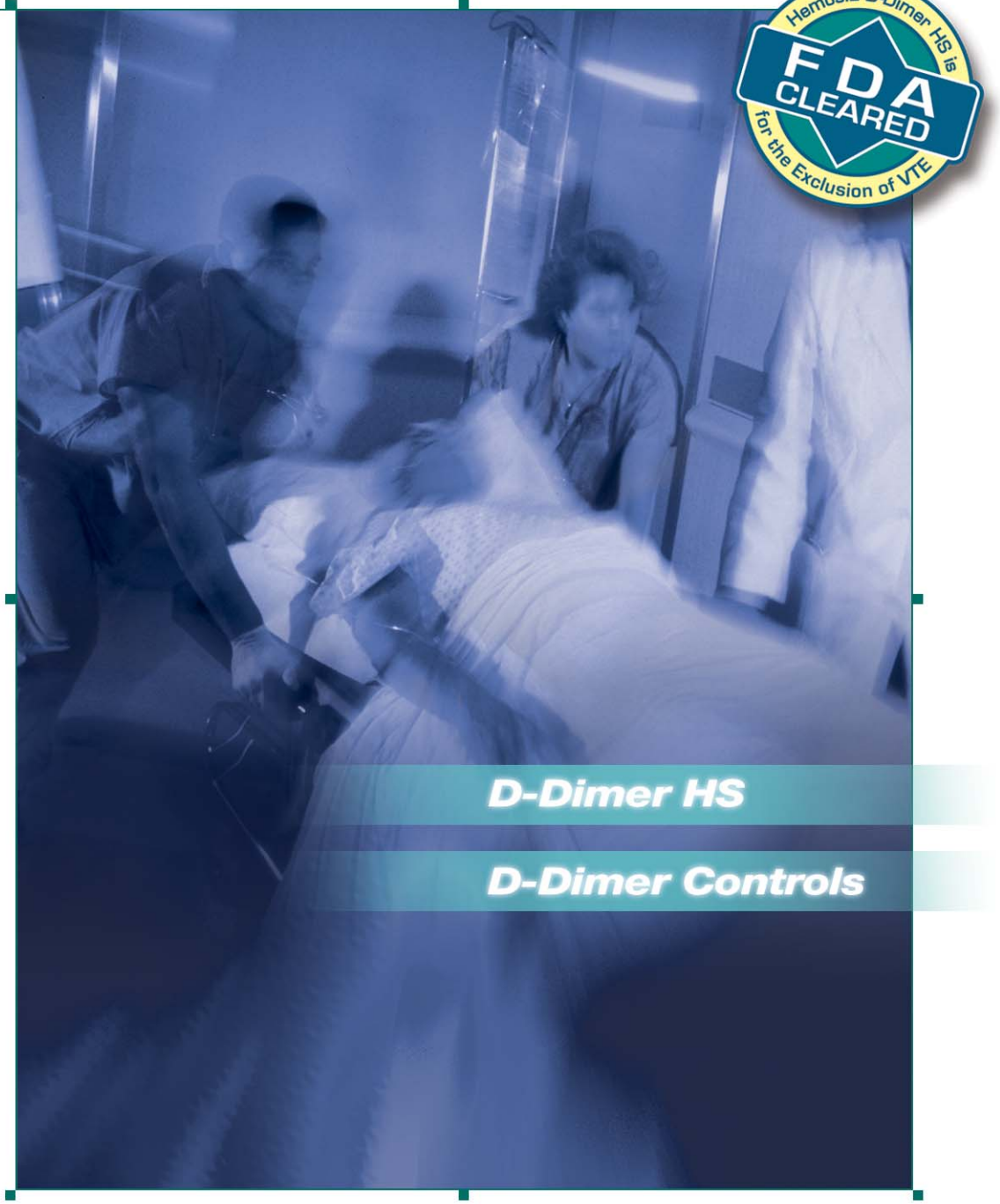
HemosIL® D-Dimer HS

DVT and PE Exclusion

Hemostasis



Rapid and
Cost-Effective for
Enhanced Patient Care

Werfen Group

Instrumentation Laboratory

D-Dimer in Clinical Practice

In the Diagnosis of DVT and PE

Deep Vein Thrombosis (DVT) has an annual incidence of 0.5 - 1.2 per thousand. It is the primary cause of Pulmonary Embolism (PE), a potentially fatal event, occurring with an incidence of 0.2 - 0.6 per thousand. One diagnostic strategy for Venous Thromboembolism (VTE), which includes DVT and PE, 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 (V/Q) 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.

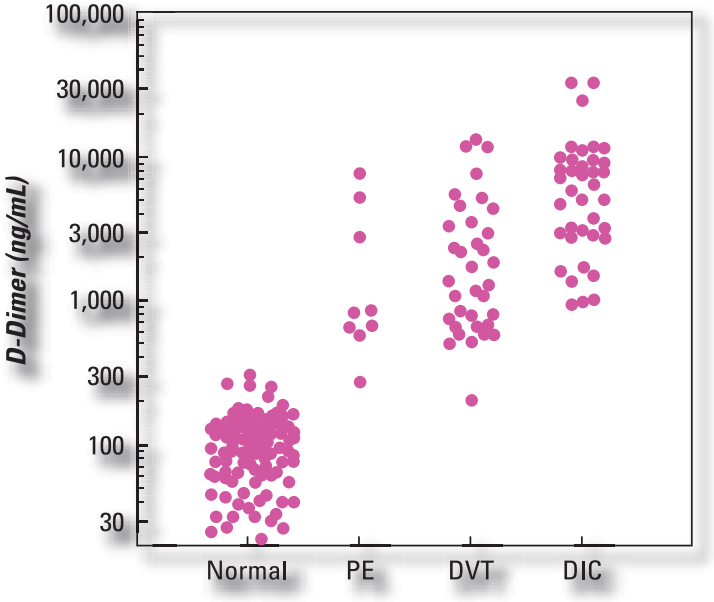
In the Diagnosis of DIC

Disseminated Intravascular Coagulation (DIC) is considered a systemic thrombohemorragic disorder. It is 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 and staging 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. Other studies suggest that D-Dimer levels in the normal population may indicate the risk for arterial thrombosis.

D-Dimer Levels in Patient Groups and Normal Subjects



An example of D-Dimer levels in different clinical conditions: normal patients, PE, DVT, DIC.

HemosIL D-Dimer HS

HemosIL D-Dimer HS is a fully automated, D-Dimer assay for the exclusion of DVT and PE, in conjunction with a clinical Pretest Probability (PTP) assessment model.

The latex reagent is a suspension of polystyrene latex particles of uniform size, coated with the $F(ab')_2$ fragment of a monoclonal antibody, highly specific for the D-Dimer domain included in fibrin soluble derivatives. The use of the $F(ab')_2$ fragment allows for a more specific D-Dimer detection, avoiding the interference from some endogenous factors like the Rheumatoid Factor.

The assay is optimized for a wavelength of 671 nm, providing very high analytical sensitivity, enhanced working range and minimized interferences from hemoglobin.

In multi-center management studies with over 800 samples from patients suspected of VTE, HemosIL D-Dimer HS demonstrated 100% Negative Predictive Value (NPV) and 100% Sensitivity at a cut-off value of 230 ng/mL.

- *FDA cleared for the exclusion of VTE*
- *100% NPV*
- *High specificity for VTE*
- *Results in less than 5 minutes*

Enhanced Patient Care
Excludes DVT and PE

Cost-Effective
Reduces the number of unecessary imaging techniques

Time-Effective
Optimizes the laboratory workload and provides rapid patient response

- *Minimized interference from Rheumatoid Factor and Hemoglobin*
- *Easy to use, fully automatic*
- *Enhanced working range*
- *Very high analytical specificity and sensitivity*

Analytical Characteristics on the ACL TOP® Hemostasis Testing System

The data were obtained according to Clinical Laboratory Standards Institute (CLSI) guidelines.

Linearity
Up to 3,680 ng/mL without rerun
Up to 69,000 ng/mL with automated rerun

Imprecision

	Mean (ng/mL)	CV (Total)
Low D-Dimer Control	314	7%
High D-Dimer Control	677	7%

Detection Limit
21 ng/mL

Interferences

Hemoglobin	none up to 500 mg/dL
Bilirubin	none up to 18 mg/dL
Triglycerides	none up to 1,327 mg/dL
Rheumatoid Factor	none up to 1,400 IU/mL

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

VTE Management Studies with HemosIL D-Dimer HS

Enhancing Diagnosis of DVT and PE

Three hundred frozen samples from patients admitted consecutively to the Emergency Department with suspected PE or DVT (frequency of venous thromboembolism 26%) were evaluated during the single center study. Seventy-eight were confirmed as VTE-positive (47 PE and 31 DVT) by standard objective tests and the remaining 222 were confirmed as negative. The optimal cut-off value on the ACL TOP Hemostasis Testing System was determined to be 230 ng/mL. Patient samples were also tested with a traditional automated, latex-based method and an ELISA assay. The cut-off values were those recommended by the manufacturer. The results are summarized in the table below.

	HemosIL D-Dimer HS	Traditional Automated Latex	ELISA Method
Sensitivity (95% CI)	*100% (95.4 - 100%)*	*100% (95.1 - 100%)*	*100% (95.4 - 100%)*
Specificity (95% CI)	*46.8% (40.1 - 53.6%)*	*35.9% (29.6 - 42.6%)*	*34.7% (28.4 - 41.3%)*
NPV (95% CI)	*100% (96.5 - 100%)*	*100% (95.4 - 100%)*	*100% (95.3 - 100%)*

Fewer False Positive Results Versus Traditional Latex and ELISA Methods

The management study comparing HemosIL D-Dimer HS to a traditional automated, latex-based assay and an ELISA assay demonstrated the following results in the sample population tested.

Distribution of Patient Samples from the Management Study

	HemosIL D-Dimer HS	Traditional Automated Latex	ELISA Method
Total number of patients with suspected VTE, tested with D-Dimer	*300*	*294**	*300*
Number of patients excluded for VTE (D-Dimer < cut-off)	*104*	*79*	*77*
Number of patients undergoing investigation with imaging techniques (D-Dimer > cut-off)	*196*	*215*	*223*
Outcome:			
Confirmed for DVT	*31*	*31*	*31*
Confirmed for PE	*47*	*43**	*47*
False Negative for DVT or PE	*0*	*0*	*0*
False Positives for VTE	*118*	*141*	*145*

** Six samples did not report any result due to instrument errors and were excluded from the analysis; four were PE and two were normal samples.*

HemosIL D-Dimer HS demonstrated fewer false positive patient samples (N=118) than the traditional automated, latex-based assay (N=141) and the ELISA method (N=145); thus, supporting the value of the assay as a cost-effective tool for the management of VTE patients.

Excluding DVT and PE

Multi-center Studies

To confirm the 230 ng/mL cut-off value, a multi-center study was performed at four hospitals on 668 samples from patients admitted consecutively to the Emergency Department with suspected PE or DVT. As part of the study, patients underwent a PTP assessment using the Wells model and were classified as having a high, moderate, or low probability of PE or DVT. Patients with a negative D-Dimer test result and a low PTP score underwent no further diagnostic testing and were followed-up after three months for development of PE or DVT. For patients with a negative D-Dimer test result and a moderate PTP, the physicians determined if a three-month follow-up or imaging techniques were required. Patients with a positive D-Dimer test result or a high PTP score underwent imaging techniques. The overall prevalence in the total population of samples was 16.1% (58/361) for PE and 20.2% (62/307) for DVT. The sensitivity, specificity and NPV of HemosIL D-Dimer HS, using the previously established clinical cut-off of 230 ng/mL, is summarized below for DVT and PE with the corresponding 95% confidence intervals (CI).

DVT Population	*All samples*	*High PTP*	*Low + Moderate PTP*
n	*307*	*54*	*253*
Sensitivity (95% CI)	*100% (62/62) (94.2 - 100%)*	*100% (28/28) (87.7 - 100%)*	*100% (62/62) (89.7 - 100%)*
Specificity (95% CI)	*38.4% (94/245) (32.2 - 44.8%)*	*34.6% (9/26) (17.2 - 55.7%)*	*38.8% (62/62) (32.3 - 45.6%)*
NPV (95% CI)	*100% (94/94) (96.2 - 100%)*	*100% (9/9) (66.4 - 100%)*	*100% (62/62) (95.8 - 100%)*

PE Population	*All samples*	*High PTP*	*Low + Moderate PTP*
n	*361*	*28*	*333*
Sensitivity (95% CI)	*100% (58/58) (93.8 - 100%)*	*100% (10/10) (62.2 - 100%)*	*100% (48/48) (92-6 - 100%)*
Specificity (95% CI)	*35.6% (108/303) (30.2 - 41.3%)*	*16.7% (3/18) (3.6 - 41.4%)*	*36.8% (105/285) (31.2 - 42.7%)*
NPV (95% CI)	*100% (108/108) (96.6 - 100%)*	*100% (3/3) (29.9 - 100%)*	*100% (105/105) (96.5 - 100%)*

HemosIL D-Dimer HS Safely Excludes DVT and PE when Used in Conjunction with a PTP Assessment Model

Using a 230 ng/mL cut-off, HemosIL D-Dimer HS successfully excluded DVT and PE in both studies' patient populations with an NPV of 100% and sensitivity of 100%.

Single Center Management Study

- *300 outpatients*
- *NPV = 100%*
- *Specificity = 46.8%*

Multi-Center Management Study

- *668 outpatients*
- *NPV = 100%*
- *Specificity for DVT = 38.4%*
- *Specificity for PE = 35.6%*

HemosIL D-Dimer HS

DVT and PE Exclusion

D-Dimer HS Kit Composition P/N 0020007700	3 x 2 mL Latex Reagent (Lyo)
	3 x 8 mL Reaction Buffer (Liq)
	2 x 1 mL Calibrator (Lyo)
D-Dimer Controls P/N 0020008610	5 x 1 mL Low D-Dimer Control
	5 x 1 mL High D-Dimer Control

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