

D-dimer

Intended use

The D-dimer test is intended as an aid in diagnosis of venous thromboembolism (deep vein thrombosis and pulmonary embolism).

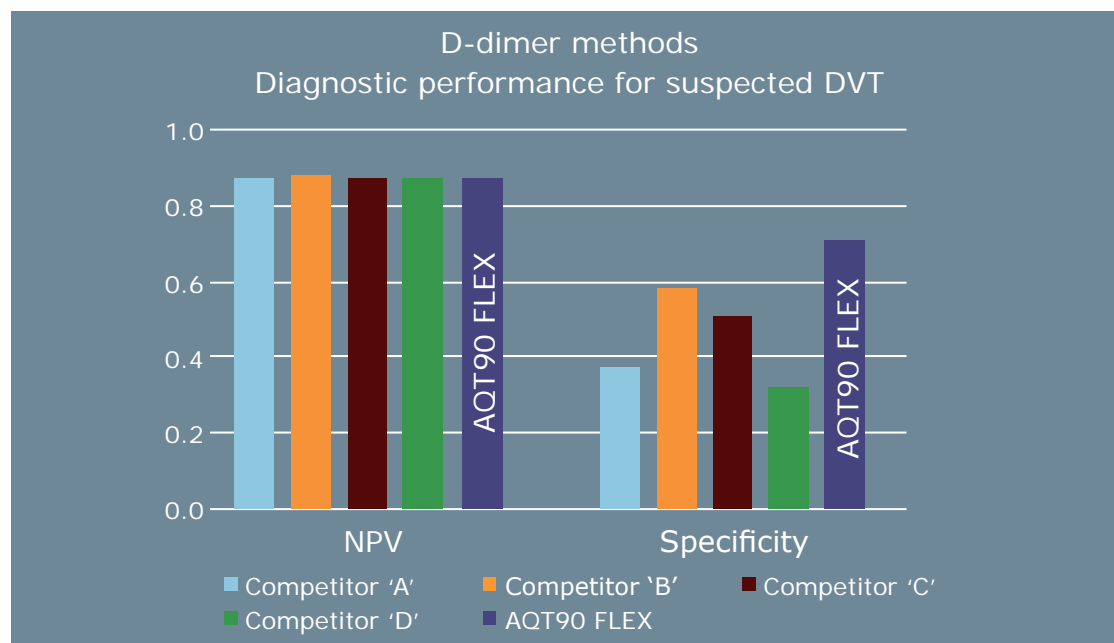
Summary

Under normal physiological conditions, the hemostatic system maintains the balance between two opposing processes:

- The coagulation process leads to the formation of thrombin, which converts fibrinogen to fibrin monomer molecules, with release of fibrinopeptides A and B. These fibrin monomer molecules polymerize forming an insoluble fibrin network stabilized by covalent cross-links introduced by the action of the enzyme factor XIIIa, causing the formation of a thrombus.
- The fibrinolytic process leads to the lysis of the cross-linked fibrin by plasmin into a heterogeneous population of fragments released into the blood. These end-stage fibrin degradation products are called D-dimer [1].

Under pathological conditions, a thrombus may escape the normal fibrinolytic system to grow and propagate. As D-dimer is a specific marker of the breakdown of a fibrin clot and an indirect marker of fibrin formation, its measurement may reflect a disturbance in this

The AQT90 FLEX assay combines high negative predictive value with very high specificity.



hemostatic balance. Indeed, D-dimer levels increase one hour after thrombus and have a half-life of 4 to 6 hours.

Therefore, the presence of D-dimer can be used as an early sensitive marker for thrombotic disorders such as deep vein thrombosis (DVT), pulmonary embolism (PE), disseminated intravascular coagulation (DIC) and for coronary artery diseases. However, as high levels of D-dimer are observed in a wide variety of conditions (for example, pregnancy, post-surgery state, in malignancy, trauma, cancer), it is not a specific marker.

The result of the D-dimer assay is used as an aid in ruling out the suspicion of DVT or PE [2, 3, 4], when D-dimer concentration is below the cut-off value, and should be clinically validated [11].

The clinical usefulness of a D-dimer assay is demonstrated by the decrease in the number of invasive and expensive investigations required to diagnose a condition. D-dimer assay can also be helpful in detecting DIC [5] and is a potential addition to clinical diagnosis models for the risk stratification of patients with ischemic heart disease [6, 7, 8, 9, 10]. Updated recommendations regarding the clinical use of D-dimer have been given recently [11, 12].

Product calibrator traceability

The D-dimer assay is calibrated with HyTest 8D70 material.

Samples

Blood samples are collected by venipuncture. Whole-blood or plasma samples with either citrate, EDTA or lithium heparin as anticoagulant can be used.

Performance characteristics

Analytical specificity

The analytical specificity of the AQT90 FLEX D-dimer assay was determined by studying the cross-reactivity with fragment D and fragment E at concentrations of 40,000 µg/L and 20,000 µg/L respectively. The cross reactivity of fragment D was estimated to be 3 % for patients with no fragment D elevations. For highly elevated fragment D levels the cross-reactivity was up to 28 %. Fragment E showed no cross-reactivity.

Analytical sensitivity and measuring range

The limit of detection has been determined to be 35 µg/L.

The reportable range of the assay is 80-100,000 µg/L.

Reference values

Whole blood (lithium-heparin, EDTA and citrate) and plasma (lithium-heparin, EDTA and citrate) were obtained from 272 apparently healthy individuals (54 men and 78 women < 50 years of age; 74 men and 66 women > 50 years of age) and analyzed using the AQT90 FLEX D-dimer assay. The 95th percentile for both whole-blood and plasma samples was

determined to be 583 µg/L for persons < 50 years of age and 654 µg/L for persons > 50 years of age.

NOTICE: These values should only be used as examples. Each laboratory should establish its own reference ranges.

Imprecision

Within-day and total imprecision were determined by analyzing spiked plasma pools over 20 days, two runs a day, four replicates per run.

D-dimer, Mean, µg/L	CV _{within-run} %	CV _{total} %
268	7.2 %	9.7 %
702	4.6 %	6.9 %
62,329	3.8 %	5.7 %

Clinical performance

Clinical performance of the AQT90 FLEX D-dimer assay was evaluated analyzing a clinically characterized panel consisting of citrate plasma specimens of 170 patients. Of this patient population, 64 were diagnosed as having deep venous thrombosis (DVT) based on phlebography according to Rabinov [15], performed without compression during injection of at least 100 mL iodine 240 mg/mL. The leg that was examined was not weight bearing. DVT restricted to the calf veins was classified as distal, whereas DVT in the popliteal, femoral, iliac or inferior caval veins was classified as proximal.

Cut-off:	DVT	Negative predictive value	Specificity
500 µg/L	Distal	0.88	0.71
	Proximal	0.99	0.71

These values should only be used as examples, and each laboratory should establish its own diagnostic cut-off values for venous thromboembolism.

The study was performed in cooperation with the University Hospital of Southern Denmark in Esbjerg, Denmark.

Hook effect

No hook effect was observed for concentrations up to 220,000 µg/L.

Carry over

Carry over from a sample with D-dimer value (297,726 µg/L) to an adjacent negative sample was determined to be <100 ppm.

Interfering substances

Haemolytic, lipaemic and icteric samples do not interfere with the assay.

Fibrinogen and immunoglobulin G, at concentrations of 8,000,000 µg/L and 16,000,000 µg/L respectively, were also tested. There was no interference of cross-reactivity from either fibrinogen or immunoglobulin G.

The following interfering substances were found to have no notable effect on the AQT90 FLEX D-dimer assay (interference < 20 %). The interference was tested by using a plasma pool with 465 µg/L of D-dimer and spiked with the interfering substance at the following concentration (about 5 times the upper therapeutic range): Abciximab, Acetaminophen, Acetylsalicylic acid, Allopurinol, Ambroxol, Ampicillin, Ascorbic acid, Atenolol, Caffeine, Captopril, Cefoxitin, Cinnarizine, Cocaine, Diclofenac, Digoxin, Dopamine, Erythromycin, Ethanol, Heparin low molecular weight, Heparin Sodium, Ibuprofen, Levodopa, Methylidopa, Metronidazole, Nicotine (±), Nifedipine, Nitrofurantoin, Nitroglycerin, Nystatin, Oxytetracycline, Phenylbutazone, Phenytoin, Propranolol, Quinidine, Rifampicin, Tetracycline, Theophylline, Trimethoprim, Verapamil, Warfarin.

References

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