D-DIMER

Diagnostic reagent for determination of D-Dimer concentration.
Liquid. Dual reagents *(Ratio: R1/R2: 3/1)*. Store at +2/+8°C. For in Vitro Diagnostic Use (IVD). **Do not freeze.**

Ref No	Pack
MH-162	80 mL
MH-163	48 mL

Changes made in the instructions for use are marked as grey.

INTENDED USE

The test is applied for the quantitative determination of D-Dimer.

GENERAL INFORMATION

D-Dimer is a soluble fibrin degradation product resulting from plasmin-mediated degradation of cross-linked fibrin.[1] During hemostasis, the formation of fibrin clots by the coagulation system in response to vascular injury is balanced by the breakdown of the clot by the fibrinolytic system. D-Dimers are one of several fragments produced by plasmin, an enzyme activated by the fibrinolytic pathway, as a result of the breakdown of fibrin to degrade clots. The D-Dimer is formed from two covalently linked fibrin D domains that cross-link with factor XIII when the clot develops. This fragment forms unique epitopes that can be targeted by monoclonal antibodies in D-Dimer assays to confirm that the clotting cascade produces thrombin.[2]

D-Dimer is routinely used as part of a diagnostic algorithm to exclude the diagnosis of thrombosis in the lower extremities (deep vein thrombosis; DVT) or lungs (pulmonary embolism; PE). More recently, it has been used to predict which patients are more likely to experience recurrent thrombosis when anticoagulants are stopped.[2]

D-Dimer levels are increased in almost all cases of acute venous thromboembolism (VTE). However, any process that increases fibrin production or breakdown also increases D-Dimer levels.

Examples include pregnancy, infection, cancer, chronic inflammation, aging, trauma and post-surgery. A large retrospective study of 1647 patients showed that the most common causes of positive D-Dimer results were associated with infections, followed by VTE, syncope, heart failure, trauma and cancer.[3] This is of particular concern for hospitalized patients because D-Dimer can increase for reasons other than VTE and DIC. In one study, Brotman et al. found that only 22% of hospitalized patients had normal D-Dimer levels.[4] The D-Dimer test should therefore not be considered specific for VTE[5-8] and should mainly be used to exclude VTE, because low D-Dimer values reflect a lack of significant (sustained) activation of blood coagulation.[5,9]

D-Dimer levels in patients with VTE vary according to clot load, timing of measurement and time of initiation of therapy. Among patients with confirmed PE, higher D-Dimer levels are observed in patients with larger emboli, such as those involving more than 50% of lung volume, compared to patients with smaller thrombi.[10] Similarly, in patients with DVT, higher D-Dimer levels are observed in patients with thrombosis extending above knee level compared to patients with thrombosis located in the calf region (proximal and distal DVT).[11]

D-Dimer levels decrease with longer duration of VTE symptoms. Patients who have symptoms for more than 7 days with confirmed DVT have lower D-Dimer concentrations and shorter duration of symptoms compared to patients with DVT.[11] D-Dimer levels also fall rapidly after initiation of treatment (e.g. heparin, low molecular weight heparin, vitamin K antagonists). Within 24 hours of the start of heparin treatment, D levels fall by approximately 25%.[12] Therefore, D-Dimer testing is most accurate in patients with a high clot burden, with symptoms lasting less than one week and before the start of treatment.[2]

In fact, the term D-Dimer includes a broad mixture of degradation products of cross-linked fibrin, probably with molecular weights ranging from 190 to 10,000 kDa.[13] D-Dimer fragments are eliminated mainly through renal clearance and reticuloendothelial system catabolism. The plasma half-life of D-Dimer is 8 hours.[14] This is much longer than that of the thrombin-antithrombin complex (10-15 minutes) or prothrombin fragments 1+2 (F 1+2; 90 minutes).[1] Under normal physiologic conditions, approximately 2-3% of fibrinogen is converted to fibrin and enters the fibrinolytic pathway immediately. Therefore, D-Dimer can be measured in small amounts in healthy individuals and tends to increase with aging.[7,15]

It is also suggested that the D-Dimer test can be used as a biomarker to predict the prognosis and disease outcomes of COVID-19 patients at the time of hospital admission, more effective clinical management of patients, significantly reduce the mortality rate of such patients and enable faster recovery.[16]

TEST PRINCIPLE

Immunoturbidimetric measurement

These assays use latex particles coated with D-Dimer antibodies. If D-Dimer antigen is present in the plasma, the antibody-coated latex particles agglutinate around the D-Dimer molecules and form a large aggregate complex. The turbidity produced by the formation of the antibody-antigen complex and the change in absorbance with time is proportional to the concentration of D-Dimer epitopes in the sample and is measured at a wavelength of 600 nm.

REAGENT COMPONENTS

Reagent 1:
Tris buffer : 100 mmol/L

Reagent 2:
Latex coated with anti D-Dimer monoclonal antibody: %0.15

REAGENT PREPARATION

Reagents are ready for use.

REAGENT STABILITY AND STORAGE

Reagents are stable at +2/+8°C till the expiration date stated on the label which is only for closed vials.

Once opened vials are stable for 30 days at +2/+8°C in optimum conditions. On board stability is strongly related to auto analyzers' cooling specification and carry-over values.

Reagent stability and storage data have been verified by using Clinical and Laboratory Standards Institute (CLSI) EP25-A protocol.[17]

SAMPLE REQUIREMENTS

Plasma samples collected by standard procedure can be used. Sample tubes with trisodium citrate are used for plasma.

D-Dimer activity stability in plasma:

8 hours at +20/+25ºC
4 days at +2/+8°C
6 months at -20ºC

Annotation:

- There are also opinions recommending that samples should be kept at room temperature (15-25 C) for up to 4 hours before testing.[18] However, several studies have shown that D-Dimer can remain stable for a longer period of time.[1,19-21]
- There are also studies showing that frozen samples can be stored for years, especially when longer storage times are needed for research purposes.[21-24]
- A single freeze-thaw cycle does not affect the assay response. Plasma is separated by centrifugally separated collector tube as soon as possible after collection, and FDP-containing thrombin and aprotinin can have the same stability as citration plasma.

CALIBRATION AND QUALITY CONTROL

Calibration: The assay requires the use of a D Dimer Calibrator Set.

D Dimer Calibrator Set
Ref.No: VT-036

Calibration stability is 30 days. Calibration stability depends on the application characteristics and cooling capacity of the autoanalyzer used.

Control: Commercially available control material with established values determined by this method can be used. We recommend:

D Dimer Control Set
Ref No: VT-037

At least two level controls must be run once in every 24 hours. Each laboratory should determine its own quality control scheme and procedures. If quality control results are not within acceptable limits, calibration is required.

REFERENCE INTERVALS / MEDICAL DECISION LEVELS

Plasma : < 0.5 µg FEU/mL*

FEU: Fibrinojen Equivalent Unit

Annotation:

- If the prevalence of the disease of interest in a given population is low, the negative predictive value (NPV) of the test will increase because a negative result is more likely to be a true negative. Conversely, the positive predictive value (PPV) will decrease because a positive result is more likely to be a false positive. In other words, if the prevalence of DVT is low in a population, high D-Dimer levels are more likely to be due to causes other than DVT; therefore, PPV is low and NPV is high.[2]
- **Clinical Decision Levels Varying with Clinical Pretest Probability:** It is important that critical decision levels in DVT vary according to clinical pretest probability (C-PTP). For example, the "Wells score" is a validated clinical decision rule[25] that categorizes DVT patients into "low" (5% VTE prevalence), "moderate" (25%) or "high" (60%) pretest probability categories based on certain risk factors, physical signs and symptoms. Patients with a low Wells score have a low prevalence of VTE; therefore, a high D-Dimer threshold can be used to exclude VTE within this subgroup. Conversely, patients with a high Wells score have a high prevalence of VTE, which will decrease the NPV of the D-Dimer test, and a lower D-Dimer threshold should be used to increase the reliability and usability of the D-Dimer test in this subgroup. Furthermore, there are other reasons why hospitalized patients often have high D-Dimer levels (e.g. malignancy, infection, surgery); therefore, a negative D-Dimer result in this subgroup is both

unlikely and useless. Consequently, changing the D-Dimer threshold according to C-PTP and patient admission status may be more effective than using a single threshold approach.[2,26]

- **Varying Clinical Decision Levels by Age:** Another strategy to increase the clinical utility of D-Dimer testing is to vary the threshold according to the age of the patient. As is known, D-Dimer levels naturally increase with age; therefore, older patients are less likely to have a negative result even in the absence of VTE.[27]

  For example, one study suggested that the D-Dimer threshold for patients over 50 years of age could be safely increased by multiplying their age by 10 (e.g. for a 60-year-old patient, the D-Dimer threshold would be 600 µg/L instead of the manufacturer's 500 µg/L).[28]

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary, determine its own reference range.

Reference interval has been verified by using CLSI EP28-A3c protocol.[29]

Unit Conversion:
µg FEU/mL= mg FEU/L

µg FEU/mL x 1000 = ng FEU/mL

PERFORMANCE CHARACTERISTICS

Measuring Interval

According to CLSI EP34-ED1:2018, "Measuring Interval" refers to the interval where the analyte concentration is measured with intended accuracy in terms of medical and laboratory requirements without dilution, concentrating or any kind of pre-treatment that is between the analyte's lower limit of quantitation (LLoQ) and upper limit of quantitation (ULoQ).[30]

The determined analytic measuring interval for D-Dimer is 0.15 – 10 µg FEU/mL.

Detection Capability

Limit of Detection (LoD): 0.08 µg FEU/mL

Limit of Quantitation (LoQ): 0.15 µg FEU/mL

Note: LoQ values are based on Coefficient of Variation Percentage (CV) ≤ 20%.

LoD and LoQ values have been verified by using CLSI EP17-A2:2012 protocol.[31]

Linearity

This method shows measurement linearity in the activities up to 10 µg FEU/mL. Autoanaylzer's auto-dilution system can be used if the concentrations have higher values. See device manual for further information.

For the manual dilution procedure, dilute the sample 1:5 using 0.90% isotonic. After this process, multiply the result of the reworked sample by the dilution factor. Do not report the sample result after dilution if it is marked as lower than the linear lower limit. Rerun with a suitable dilution.

Linearity Studies data have been verified by using CLSI EP06-A:2003 protocol.[32]

Precision

Running system has been developed according to 20x2x2 "The Single Site" protocol. Repeatability and Within-Laboratory Precision/Within-Device values have been obtained according to the running results.

According to the protocol in use, 2 separate runs per day have been made for 20 days (no obligation for being consecutive days). This protocol has been applied to each low and high samples separately and 80 results have been obtained for each one. Statistically, the results have been obtained using 2-factor Nested-ANOVA model.[33]

Repeatability (Within Run) and Repeatability (Day to Day) SD (standard deviation) and CV% values of D-Dimer have been given in the table 1 and 2 respectively.

Table 1. D-Dimer Repeatability (Within Run) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
0.53 µg FEU/mL	0.01	1.88	80
2.94 µg FEU/mL	0.03	1.02	80

Note: This working system has been named "Within-Run Precision" in the previous CLSI - EP05-A2 manual.[34]

Table 2. D-Dimer Repeatability (Day to Day) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
0.53 µg FEU/mL	0.02	3.77	80
2.94 µg FEU/mL	0.06	2.04	80

Note: This working system has been named "Total Precision" in the previous CLSI - EP05-A2 manual.[34]

Method Comparison

As a result of the statistical evaluation of the method comparison data:

Passing-Bablok equation:[35]
y= 0.99x + 0.06 µg FEU/mL
r=0.993 (Interval: 0.16 – 8.55 µg FEU/mL)

Interference

Endogenous interferant and analyte concentrations that have been used in the D-Dimer scanning tests has been determined according to "CLSI EP37-ED1:2018" and "CLSI EP07-ED3:2018" manuals.[36,37]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from D-Dimer interference scanning test is appropriate, is determined as ±10%.[38]

In D-Dimer test results, no significant interaction has been observed in the determined endogenous interferant and analyte concentrations or between interferants and analyte.

Bilirubin	: 15 mg/dL
Triglycerides	: 700 mg/dL
Hemoglobin	: 350 mg/dL

Annotation:

- In addition to these 3 main reasons for interference, disease-associated monoclonal gammopathy was identified as the source of a false positive D-Dimer result in a Castleman patient with paraproteinemia interference associated with an elevated D-Dimer level.[39] Similar results have also been obtained in other studies.[40-42]

It should be noted that endogenous interferants, as well as various medicines and metabolites, anticoagulants (e.g. Heparin, EDTA, citrate, oxalate) and preservatives (e.g. sodium floride, iodoacetate, hydrochloride acide) such as additives, materials that may contact with samples during collection and processing (serum separator devices, sample collection containers and contents, catheters, catheter wash solutions, skin disinfectants, hand cleaners and lotions, glass washing detergents, powder gloves), dietary substances known to affect some specific tests (caffeine, beta-carotene, poppy seeds, etc.), or some substances present in a sample that cause foreign proteins (heterophilic antibodies, etc.), autoimmune response (autoantibodies, etc.), or due to malignancy (for example, interference by paraproteins with phosphate testing and indirect ion selective electrode methods) may show some negative effects that will cause various attempts and some misjudgements.[37]

These performance characteristics have been obtained using an autoanalyzer. Results may vary slightly when using different equipment or manual procedures.

WARNINGS AND PRECAUTIONS

IVD: For in Vitro Diagnostic use only.
Do not use expired reagents.
Reagents with two different lot numbers should not be interchanged.
For professional use.
Follow Good Laboratory Practice (GLP) guidelines.
Contains sodium azide.

CAUTION: Human source samples are processed with this product. All human source samples must be treated as potentially infectious materials and must be handled in accordance with OSHA (Occupational Safety and Health Administration) standards.

Danger

EUH032	:Releases a very toxic gas if contacts with acid.
H317	:May cause allergic skin reaction.

Precaution

P280	:Use protective gloves / clothes / glasses / mask.
P264	:Wash your hands properly after using.
P272	:Contaminated work clothes should not be allowed to be used outside of the workplace.

Intervention

P302+P352	:Wash with plenty of water and soap if it contacts with skin.
P333+P313	:Seek medical help if it irritates your skin or develops rash.
P362+P364	:Remove contaminated clothes and wash properly before using.

Disposal

P501	:Dispose the vials and contents according to the local regulations.

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SYMBOLS

IVD	In Vitro Diagnostic Medical Device
LOT	Lot Number
R1	Reagent 1
R2	Reagent 2
GTIN	Global Trade Item Number
REF	Reference Number
GLP	Good Laboratory Practices
FOR USE WITH	Identifies Products to Be Used Together
PRODUCT OF TURKEY	Product of Turkey
	Manufacturer
	Expiration Date
	Temperature Limits
	Consult Instructions for Use
	Caution
	Number of Tests

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