D-DI2

cobas®

Tina-quant D-Dimer Gen.2

REF	CONTENT		SYSTEM
07429410190	Σ 100	System-ID 07 2006 1	**cobas t** 511 **cobas t** 711

English

System information

Short name	ACN (application code number)
D-DI2	28320

Intended use

In vitro assay for the quantitative immunological determination of fibrin degradation products (D-dimer and X-oligomers) in human citrated plasma on the indicated **cobas t** analyzers.

In conjunction with a non-high clinical probability assessment, a normal D-dimer result (< 0.5 µg FEU[a)]/mL) is intended as an aid in the exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE).

a) Fibrinogen Equivalent Unit

Summary

Thrombin converts fibrinogen to soluble fibrin by cleaving the fibrinopeptides A and B. The fibrin monomers polymerize spontaneously. Active factor XIII links two D-domains and generates a solid fibrin clot. A new plasmin-resistant antigenic determinant ("D-dimer") is produced. Fragments containing D-dimer are accordingly formed during the degradation of a fibrin clot by plasmin. A large proportion of the fibrin degradation products consist of high molecular weight X-oligomers.[1,2,3]The D-DI2 assay has a strong affinity for these high molecular weight degradation products. Only in vitro or during lysis therapy complete degradation to D-dimer molecules takes place. D-dimer is a very sensitive marker for the activation of coagulation.[3,4,5,6,7,8,9]

In disseminated intravascular coagulation (DIC) / consumptive coagulopathy, fibrin degradation products are a sensitive marker.[10,11,12]

Monitoring the fibrin-specific degradation products can be used as an aid to

- confirm or refute a tentative diagnosis
- estimate the potential risk for patients with existing DIC
- monitor an initiated therapy

Apart from DVT,[12,13,14] PE,[15,10] and DIC,[11,12] D-dimer may reflect other causes associated with fibrin formation such as trauma, pregnancy complications, malignant disease or vascular abnormalities. Elevated D-dimer levels therefore have to be interpreted in the context of possible underlying diseases and clinical symptoms.[16,17,18]

Test principle

Particle-enhanced immunoturbidimetric assay. Latex particles are coated with monoclonal antibodies ($F(ab')_2$ fragments) to the D-dimer epitope. The antigen/antibody complexes produced by the addition of samples containing D-dimer lead to an increase in the turbidity of the test reactants. The change of absorbance with time is dependent on the concentration of D-dimer epitopes in the sample. The aggregate is determined turbidimetrically.

Reagents - working solutions

cobas t pack

R1 TRIS/HCl buffer: 250 mmol/L, pH 8.2; preservatives (liquid).

SR[b)] Latex particles coated with monoclonal anti-human D-dimer antibodies (mouse): 0.12 %; preservative (liquid).

b) Start reagent

R1 is in position A and SR is in position B.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317 May cause an allergic skin reaction.

H412 Harmful to aquatic life with long lasting effects.

Prevention:

P261 Avoid breathing dust/fume/gas/mist/vapours/spray.

P273 Avoid release to the environment.

P280 Wear protective gloves.

Response:

P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the cassette have been assembled into a ready-for-use unit (**cobas t** pack).

All information required for correct operation is available via the **cobas** link.

Storage and Stability

Store at 2-8 °C.

Store the **cobas t** pack **upright**.

The unopened **cobas t** pack is stable up to the stated expiration date.

Stability of the opened **cobas t** pack:	
on the **cobas t** analyzer	12 weeks after piercing

Do not freeze.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable:
3.2 % citrated human plasma.

Use standard sampling tubes made of plastic or siliconized glass. Strictly observe the ratio of blood (9 parts) to sodium citrate solution 0.11 M (1 part).[19,20]

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge 15 minutes at 2500 g or such that the platelet count is < 10000 platelets/µL and assay samples within the given stability period.

Stability:	
at 15-25 °C	8 hours
at 2-8 °C	4 days
at -20 °C (± 5 °C)	28 days

Frozen plasma aliquots should be thawed within 5 minutes at 37 °C in a waterbath, homogenized by carefully mixing without foam formation. Assay thawed samples within 2 hours. Do not refreeze samples.

Materials provided

See "Reagents – working solutions" section.

Materials required (but not provided)

- REF 07683456190, D-DI2 Cal Set, 6 x 0.5 mL
- REF 07571933190, D-DI2 Con, 2 x 2 x 1 mL
- General laboratory equipment
- Distilled or deionized water
- **cobas t** coagulation analyzer. See User Assistance of the analyzer concerned for additionally required materials.

Assay

For optimum performance of the assays follow the directions given in this document. Refer to the appropriate User Assistance for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Calibration

For calibration, use calibrator as listed in the "Materials required (but not provided)" section.

Calibration frequency: full calibration must be performed

- once per reagent lot change
- every 6 months when using a single reagent lot
- as required following quality control procedures.

Traceability: This method has been standardized against the Asserachrom D-Dimer method.[21]

Quality control

Controls are required for checking the accuracy and reproducibility of the results.

For quality control, use control kits as listed in the "Materials required (but not provided)" section.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. No impact on results was observed up to the listed concentrations.

Endogenous substances

Compound	Concentration
Conjugated bilirubin	60 mg/dL
Unconjugated bilirubin	60 mg/dL
Hemoglobin	200 mg/dL
Intralipid	1000 mg/dL

Criterion: Recovery within ± 10 % of initial values at a D-dimer concentration of > 0.5 µg FEU/mL or ± 0.05 µg FEU/mL at a D-dimer concentration of ≤ 0.5 µg FEU/mL.

The impact of lipemia, hemoglobin and bilirubin was tested according to Glick.[22]

Rheumatoid factors up to 100 IU/mL do not interfere.

Heparin concentrations up to 5 IU/mL do not interfere.

The presence of oritavancin (Orbactiv) in the sample influences the assay results of D-Dimer.

No high-dose hook effect is seen up to a D-dimer concentration of 150 µg FEU/mL.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[23,24]

High concentrations of D-fragments, as can occur during lysis therapy, or other cases[25,26] lead to depressed measurements.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[27]

In rare cases (less than 1 reported case per 100000 tests) certain immunoglobulins can cause a non-specific agglutination leading to falsely high results.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Extra wash cycle: The use of special wash steps is mandatory when certain test combinations are run together on **cobas** t analyzers. Refer to the latest version of the carry over evasion list found with the CLEAN and Deproteinizer Method Sheet and the User Assistance for further instructions. Where required, special wash/carry over evasion cycles must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.20-9 µg FEU/mL

Determine samples having higher concentrations via the rerun function. For samples with higher concentration, the rerun function decreases the sample volume by a factor of 2.34. The results are automatically multiplied with this factor.

Lower limits of measurement

Limit of Blank = 0.08 µg FEU/mL

Limit of Detection = 0.15 µg FEU/mL

Limit of Quantitation = 0.20 µg FEU/mL

The Limit of Blank, the Limit of Detection and the Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.[28]

The Limit of Blank is the 95th percentile value from n = 60 measurements of analyte free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples.

The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is defined as the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of 17 %.

Expected values

< 0.5 µg fibrinogen equivalent units/mL (µg FEU/mL).[29]

The stated fibrinogen equivalent is based on the quantity of fibrinogen used in the preparation of the original Asserachrom standard.

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

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Repeatability and intermediate precision were determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05 requirements (2 aliquots per run, 2 runs per day, 21 days)[30]. The following results were obtained:

		Repeatability		Intermediate precision	
Sample	**Mean** (µg FEU/mL)	**SD** (µg FEU/mL)	**CV** (%)	**SD** (µg FEU/mL)	**CV** (%)
Control 1	0.862	0.0108	1.3	0.0127	1.5
Control 2	3.76	0.0225	0.6	0.0338	0.9
Plasma 1	0.266	0.0148	5.6	0.0148	5.6
Plasma 2	0.494	0.0195	4.0	0.0219	4.4
Plasma 3	0.674	0.0129	1.9	0.0132	2.0
Plasma 4	3.76	0.0361	1.0	0.0398	1.1
Plasma 5	8.56	0.0375	0.4	0.0495	0.6

Method comparison

D-DI2 activity values for human plasma samples obtained on a **cobas t** 711 (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi **cobas c** 501 analyzer (x).

Number of samples measured: 136

Deming[31]

y = 0.976x - 0.0225 µg FEU/mL

r = 1.000

The sample concentrations using D-DI2 reagent were between 0.200 and 8.71 µg FEU/mL.

References

1 Ariëns RAS. Novel mechanisms that regulate clot structure/function. Thromb Res 2016;141S2:25-27.

2 Doolittle RF. The conversion of fibrinogen to fibrin: a brief history of some key events. Matrix Biol 2016;9:945-953.

3 Stang LJ. D-dimer and fibrinogen/fibrin degradation products. Haemostasis: methods and protocols (ed. Monagle P). Methods in molecular biology 2013;992:415-427.

4 Deng Y, He L, Yang J, et al. Serum D-dimer as an indicator of immediate mortality in patients with in-hospital cardiac arrest. Thromb Res 2016;143:161-165.

5 Hollenhorst MA, Battinelli EM. Thrombosis, hypercoagulable states, and anticoagulants. Prim Care 2016;43(4):619-635.

6 Bruinstroop E, van de Ree MA, Huismann MV. The use of D-dimer in specific clinical conditions: a narrative review. Eur J Intern Med 2009;20:441-446.

7 Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. Blood 2009;113(13):2878-2887.

8 Djurabi RK, Klok FA, Nijkeuter M, et al. Comparison of the clinical usefulness of two quantitative D-dimer tests in patients with a low clinical probability of pulmonary embolism. Thromb Res 2009;123:771-774.

9 Huisman MV et al. for the Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006;295:2, 172-179.

10 Boral BM, Williams DJ, Boral LI. Disseminated Intravascular Coagulation. Am J Clin Path 2016;146:670-680.

11 Kolev K, Longstaff C. Bleeding related to disturbed fibrinolysis. Br J Haematol 2016;175:12-23.

12 Thachil J, Fitzmaurice DA, Toh CH. Appropriate use of D-dimer in hospital patients. Am J Med. 2010;123(1):17-19.

13 Kafeza M, Shalhoub J, Salooja N, et al. A systematic review of clinical prediction scores for deep vein thrombosis. Phlebology 2016; 24:1-16.

14 Jacobs B, Obi A, Wakefield T. Diagnostic biomarkers in venous thromboembolic disease. J Vasc Surg Venous Lymphat Disord 2016; 4(4):508-517.

15 Righini M, Robert-Ebadi H, Le Gal G. Diagnosis of pulmonary embolism. Presse Med 2015; 44(12 Pt 2):385-391.

16 Angstwurm MW, Reininger AJ, Spannagl M. D-Dimer as marker for microcirculatory failure: correlation with LOD and APACHE II scores. Thromb Res 2004;113(6):353-359.

17 Wakai A, Gleeson A, Winter D. Role of fibrin D-Dimer testing in emergency medicine. Emerg Med J 2003 Jul;20:319-325.

18 Levi M, van der Poll T. Coagulation and Sepsis. Thromb Res 2017; 149:38-44.

19 CLSI Document H21-A5, Vol.28, No.5, 2008. Collection, transport, and processing of blood specimens for testing plasma-based coagulation assays and molecular hemostasis assays; approved guideline, 5th edition.

20 CLSI Document H3-A6. Procedures for the collection of diagnostic blood specimens by venipuncture; approved standard - Sixth Edition, vol. 27, No. 26, 2007.

21 Adema E, Gebert U. Pooled patient samples as reference material for D-Dimer. Thromb Res 1995;80:85-88.

22 Glick MR, Ryder KW, Jackson SA. Graphical Comparisons of Interferences in Clinical Chemistry Instrumentation. Clin Chem 1986;32:470-475.

23 Breuer J. Report on the Symposium "Drug Effects in Clinical Chemistry Methods". Eur J Clin Biochem 1996;34:385-386.

24 Sonntag O, Scholer A. Drug interference in clinical chemistry: recommendation of drugs and their concentrations to be used in drug interference studies.

25 Nugroho J, Wardhana A, Mulia EP et al. Elevated fibrinogen and fibrin degradation product are associated with poor outcome in COVID-19 patients: A meta-analysis. Clin Hemorheol Microcirc. 2021;77(2):221-231.

26 Han H, Yang L, Liu R et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020 Jun 25;58(7):1116-1120.

27 Bakker AJ, Mücke M. Gammopathy interference in clinical chemistry assays: mechanisms, detection and prevention. Clin Chem Lab Med. 2007;45(9):1240-1243.

28 CLSI Document EP17-A2. Evaluation of Detection Capability for Clinical. Laboratory Measurement Procedures. Vol. 32, No. 8, 2012. Approved standard, 2nd Edition.

29 Dempfle CE, Hafner G, Lestin HG, et al. Multizentrische Evaluierung von Tina-quant [a] D-Dimer. J Lab Med 1996, 20: 31-37.

30 CLSI Document EP05-A3. Evaluation of Precision of Quantitative Measurement Procedures. Vol. 24, No. 25, 2014. Approved guideline, 3rd Edition.

31 Martin RF. General Deming Regression for Estimating Systematic Bias and its Confidence Interval in Method Comparison Studies. Clinical Chemistry 2000;46(1):100-104.

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

For further information, please refer to the appropriate User Assistance for the relevant analyzer and Method Sheets of all necessary components.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution

ms_07429410190V4.0

D-DI2

Tina-quant D-Dimer Gen.2

GTIN Global Trade Item Number

CE 0123

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