D-DI2

cobas®

Tina-quant D-Dimer Gen.2

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
04912551 190	Tina-quant D-Dimer Gen.2 100 tests	System-ID 07 6932 0	Roche/Hitachi **cobas c** 311, **cobas c** 501/502
05050901 190	D-Dimer Gen.2 Calibrator Set (6 × 0.5 mL)	Codes 764-769	
05050936 190	D-Dimer Gen.2 Control I/II (2 × 2 × 1 mL)	Code 242 Control I Code 243 Control II	

English

System information

For **cobas c** 311/501 analyzers:

D-DI2: ACN 102 (Citrated plasma)

DDI2H: ACN 403 (Heparin/EDTA plasma)

For **cobas c** 502 analyzer:

D-DI2: ACN 8102 (Citrated plasma)

DDI2H: ACN 8403 (Heparin/EDTA plasma)

Intended use

In vitro test for the quantitative immunological determination of fibrin degradation products (D-Dimer and X-oligomers) in human plasma on Roche/Hitachi **cobas c** systems.[1,2]

In conjunction with a non-high clinical probability assessment, a normal (< 0.5 µg FEU[a)]/mL) result excludes deep vein thrombosis (DVT) and pulmonary embolism (PE) with high sensitivity.

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. The Tina-quant D-Dimer assay has a strong affinity for these high molecular weight degradation products. Only in vitro or during lysis therapy does complete degradation to D-Dimer molecules take place.

D-Dimer is a very sensitive marker for the activation of coagulation. When D-Dimer values below the cutoff are obtained, deep venous thrombosis (DVT) of the lower limb and pulmonary embolism (PE) can be excluded with high sensitivity.[3,4,5,6]

The evidence for the use of Tina-quant D-Dimer in exclusion diagnosis comes from prospective management studies.[7,8,9,10,11]

In one such study of 812 outpatients with symptoms of DVT, Schutgens et al. found that the combination of a non-high clinical probability score and a normal Tina-quant D-Dimer concentration allowed rule-out of DVT with a sensitivity of 99.3 % and a Negative Predictive Value (NPV) of 99.4 %. This rule-out strategy was found to be very safe, with a failure rate of only 0.6 %. Only 1 of 176 patients with a non-high pretest probability and a normal D-Dimer developed thrombosis during the three month follow-up. In a study involving 202 patients with suspected PE, Leclerq et al. found that PE could be ruled out by a normal Tina-quant D-Dimer result combined with a nonhigh clinical probability score, with a sensitivity of 100 %, an NPV of 100 % and a failure rate of 0 %.[9]

In a similar study of 1238 patients, Huisman et al. found that PE could be ruled out by a normal Tina-quant D-Dimer result combined with a non-high clinical probability score with a sensitivity of 97.3 %, a NPV of 99.4 %, and a failure rate of 0.62 %.[10,11]

Further supporting evidence comes from numerous other clinical studies.[12, 13,14,15,16,17,18,19,20,21]

The D-Dimer result should not be used in isolation but in combination with a clinical probability assessment like the Wells score. DVT/PE should only be excluded on the basis of a low or moderate (non-high) clinical probability and a normal (< 0.5 µg FEU/mL) Tina-quant D-Dimer result.

It has been reported that patients with a distal DVT or a subsegmental/ peripheral PE may have a normal Tina-quant D-Dimer result.[22] The clinical relevance of such small(er) thrombi is unclear. The good results obtained in the management studies where patients were treated based on the Tina-quant D-Dimer result and then followed-up for 3 months suggest that these smaller thrombi do not result in adverse patient outcomes.[22]

In disseminated intravasal coagulation (DIC)/consumptive coagulopathy, fibrin degradation products are a sensitive marker. Monitoring the fibrin-specific degradation products can be used to
- confirm or refute a tentative diagnosis
- estimate the potential risk for patients with existing DIC
- monitor an initiated therapy

Apart from DVT, PE, and DIC, 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.[23,24,25]

Test principle

Particle-enhanced immunoturbidimetric assay.

Latex particles of uniform size 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 precipitate is determined turbidimetrically.

Reagents - working solutions

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

R3 Latex particles coated with monoclonal anti-human D-Dimer antibodies (mouse): 0.12 %; preservative (liquid)

R1 is in position A and R3 is in position B.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

Reagent handling

Ready for use

Mix **cobas c** pack well before placing on the analyzer.

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	12 weeks

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Citrated plasma

Collect venous blood using standard sampling tubes for clotting tests; employ sterile 0.11 molar sodium citrate solution. Maintain a precise mixture of 1 + 9 for sodium citrate and blood.

If necessary, pipette off the supernatant and store in a stoppered plastic tube.

Li-heparin[26] and K_2- or K_3-EDTA plasma may also be used. Unlike when using citrated tubes, there is no sample dilution with heparin or EDTA tubes. Therefore D-Dimer values in heparin or EDTA plasma are on average 19 % higher over the entire measuring range. However, by using

adjusted calibrator and control values, identical values are measured in patient specimens with all sample materials.

CAUTION. To avoid erroneous patient values, we recommend that all D-Dimer measurements are performed uniformly in the laboratory from either citrated plasma or heparin/EDTA plasma.

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.

Thaw frozen samples completely at 37 °C and then mix thoroughly. Leave to stand for 15 minutes at room temperature before use; then assay immediately. Once thawed, a sample may not be refrozen for coagulation analysis.

Use the samples undiluted.

Centrifuge samples containing precipitates before performing the assay.

Stability:[27]	8 hours at 15-25 °C
	4 days at 2-8 °C
	6 months at (-15)-(-25) °C

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- See "Order information" section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

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

Application for plasma

cobas c 311 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 27-57		
Wavelength (sub/main)	-/800 nm		
Reaction direction	Increase		
Units	µg/mL (mg/L, ng/mL)		
Reagent pipetting		Diluent (H_2O)	
R1	90 µL	–	
R3	90 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	5.0 µL	–	–
Decreased	2.1 µL	–	–
Increased	5.0 µL	–	–

cobas c 501 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 41-70		
Wavelength (sub/main)	-/800 nm		
Reaction direction	Increase		
Units	µg/mL (mg/L, ng/mL)		
Reagent pipetting		Diluent (H_2O)	
R1	90 µL	–	
R3	90 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	5.0 µL	–	–
Decreased	2.1 µL	–	–
Increased	5.0 µL	–	–

cobas c 502 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 41-70		
Wavelength (sub/main)	-/800 nm		
Reaction direction	Increase		
Units	µg/mL (mg/L, ng/mL)		
Reagent pipetting		Diluent (H_2O)	
R1	90 µL	–	
R3	90 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	5.0 µL	–	–
Decreased	2.1 µL	–	–
Increased	10.0 µL	–	–

Calibration

Calibrators	S1-S6: D-Dimer Gen.2 Calibrator Set
Calibration mode	Spline
Calibration frequency	Full calibration • after 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.[28]

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

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.

Calculation

Roche/Hitachi **cobas c** systems automatically calculate the analyte concentration of each sample.

Conversion factors:	µg FEU/mL = mg FEU/L
	µg FEU/mL x 1000 = ng FEU/mL

Limitations - interference

Criterion: Recovery within ± 10 % of initial values at a D-Dimer concentration of 0.5 µg FEU/mL.

Icterus:[29] No significant interference up to an I index of 60 for conjugated and 30 for unconjugated bilirubin (approximate conjugated bilirubin concentration 1026 µmol/L or 60 mg/dL and approximate unconjugated bilirubin concentration: 513 µmol/L or 30 mg/dL).

Hemolysis:[29] No significant interference up to an H index of 500 (approximate hemoglobin concentration: 310 µmol/L or 500 mg/dL).

Lipemia (Intralipid):[29] No significant interference up to an L index of 1000. There is a poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

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

Heparin concentrations up to 100 IU/mL do not interfere.

High dose hook-effect: No false result occurs up to a D-Dimer concentration of 220 µg FEU/mL.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[30,31]

Others: High concentrations of D-fragments, as can occur during lysis therapy, lead to depressed measurements.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[32]

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

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on Roche/Hitachi **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/Multiclean/SCCS or the NaOHD/SMS/SmpCln1+2/SCCS Method Sheets. For further instructions refer to the operator's manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is not required.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.15-9.00 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 2.4. The results are automatically multiplied by this factor.

Lower limits of measurement

Limit of Blank (LoB) and Limit of Detection (LoD):

Limit of Blank	= 0.08 µg FEU/mL
Limit of Detection	= 0.15 µg FEU/mL

The Limit of Blank and Limit of Detection were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A requirements.

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 %).

Expected values[33]

< 0.5 µg fibrinogen equivalent/mL (µg FEU/mL).

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

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 10 days).

The following results were obtained:

Repeatability	*Mean*	*SD*	*CV*
	µg FEU/mL	*µg FEU/mL*	*%*
Control 1	0.977	0.014	1.4
Control 2	3.75	0.03	0.7
Human plasma 1	0.414	0.012	2.9
Human plasma 2	1.00	0.01	1.3
Human plasma 3	2.55	0.01	0.3
Intermediate precision	*Mean*	*SD*	*CV*
	µg FEU/mL	*µg FEU/mL*	*%*
Control 1	0.869	0.03	3.8
Control 2	3.48	0.04	1.3
Human plasma 4	0.423	0.02	4.7
Human plasma 5	0.985	0.02	1.7
Human plasma 6	2.65	0.03	1.3

Method comparison

D-Dimer values for human citrated plasma samples obtained on a Roche/Hitachi **cobas c** 501 analyzer (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi 917 analyzer (x).

Sample size (n) =60

Passing/Bablok[34]	Linear regression
y = 0.971x + 0.018 µg FEU/mL	y = 0.964x + 0.031 µg FEU/mL
τ = 0.983	r = 0.999
SD(md95) = 0.110	Sy.x = 0.147

The sample concentrations were between 0.220 and 7.90 µg FEU/mL.

Clinical performance in the exclusion of DVT

Tina-quant D-Dimer was used in a multicenter management study involving 812 outpatients with suspected DVT.[7] Using the Wells probability assessment score, patients were classified as having a high (> 3) or non-high (≤ 3) pretest probability of DVT. The Tina-quant D-Dimer test was then performed using a cutoff of 0.5 µg FEU/mL. Those patients having a normal (negative) D-Dimer test result and a non-high pretest probability had no further diagnostic testing and were followed up for 3 months for development of DVT. Only one of 176 such patients developed DVT during the follow-up period. The performance characteristics of the Tina-quant D-Dimer assay in conjunction with a non-high pretest probability is summarized below:

Sensitivity:	99.3 %	(95 % CI: 96.4-100 %)
Negative Predictive Value:	99.4 %	(95 % CI: 96.9-100 %)
Specificity:	45.8 %	(95 % CI: 40.7-51 %)
Positive Predictive Value:	42.0 %	(95 % CI: 36.8-47.3 %)
Failure Rate:	0.6 %	(95 % CI: 0.02-3.1 %)

Clinical performance in the exclusion of PE

Tina-quant D-Dimer was used in a management study involving 202 patients with suspected PE.[9] Using the Wells clinical model for PE probability,[35] patients were classified as having a low, moderate, or high pretest probability of PE. The Tina-quant D-Dimer test was then performed using a cutoff of 0.5 µg FEU/mL. Those patients having a normal (negative) D-Dimer test result and a non-high (low or moderate) pretest probability had no further diagnostic testing and were followed up for 3 months for development of PE. No patients developed PE during the follow-up period. The performance characteristics of the Tina-quant D-Dimer assay in conjunction with a non-high pretest probability is summarized below:

Sensitivity:	100 %	(95 % CI: 91.8-100 %)
Negative Predictive Value:	100 %	(95 % CI: 94.4-100 %)
Specificity:	50.4 %	(95 % CI: 41.4-59.4 %)
Positive Predictive Value:	40.5 %	(95 % CI: 31.1-50.5 %)
Failure Rate:	0 %	(95 % CI: 0.0-5.6 %)

Tina-quant D-Dimer was studied in another management study involving 1238 patients with suspected PE.[10,11] Using the Wells probability assessment, patients were classified as having a likely (> 4) or unlikely (< 4) pretest probability of PE. The Tina-quant D-Dimer test was then performed using a cutoff of 0.5 µg FEU/mL. Those patients having a normal (negative) D-Dimer test result and a non-high (unlikely) pretest probability had no further diagnostic testing and were followed up for 3 months for development of PE. Of the 647 patients, 3 developed non-fatal PE and 1 developed DVT during the follow-up period. The performance characteristics of the Tina-quant D-Dimer assay in conjunction with a non-high probability assessment is summarized below:

Sensitivity:	97.3 %	(95 % CI: 93-99 %)
Negative Predictive Value:	99.4 %	(95 % CI: 98-99.8 %)
Specificity:	60.7 %	(95 % CI: 58-64 %)
Positive Predictive Value:	24.9 %	(95 % CI: 21-29 %)
Failure Rate:	0.62 %	(95 % CI: 0.17-1.6 %)

References

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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.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard.

CONTENT	Contents of kit
→	Volume after reconstitution or mixing

CE

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