

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 COBAS INTEGRA 400 plus COBAS INTEGRA 800
05050901 190	D-Dimer Gen.2 Calibrator Set (6 × 0.5 mL)	System-ID 07 6994 0
05050936 190	D-Dimer Gen.2 Control I/II Control I (2 × 1 mL) Control II (2 × 1 mL)	System-ID 07 6995 9 System-ID 07 6996 7
20756350 322	NaCl Diluent 9 % (6 × 22 mL)	System-ID 07 5635 0

English

System information

Test D-DI2 (citratated plasma), test ID 0-458

Test DDI2H (Heparin or EDTA plasma), test ID 0-558

Intended use

In vitro test for the quantitative immunological determination of fibrin degradation products (D-Dimer and X-oligomers)^{1,2} in human plasma on COBAS INTEGRA systems.

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 formed accordingly during the degradation of a fibrin clot by plasmin.

A large proportion of the fibrin degradation products consists of high molecular weight X-oligomers. The Tina-quant D-Dimer Gen.2 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 %.⁷ This rule-out strategy was found to be 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, Leclercq 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 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 %, an 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 intravascular 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

R2 Latex particles coated with monoclonal anti-human D-Dimer antibodies (mouse) 0.12 %; preservative

R1 is in position A and R2 is in position B.

Precautions and warnings

Pay attention to all precautions and warnings listed in Section 1 / Introduction of this Method Manual.

For USA: For prescription use only.

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



Warning

H317 May cause an allergic skin reaction.

Prevention:

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

P272 Contaminated work clothing should not be allowed out of the workplace.

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 primarily follows EU GHS guidance.

Contact phone: all countries: +49-621-7590, USA: 1-800-428-2336

Reagent handling

COBAS INTEGRA 400 plus systems

All new (not punctured) **cobas c** packs must be mixed for 10 minutes using the off-board mixing station before placing on-board the analyzer. All in-use **cobas c** packs have to be mixed daily before use for one (1) minute on the cassette mixer.

COBAS INTEGRA 800 systems

The reagent is automatically mixed for 10 minutes after **cobas c** packs puncture and for half a minute during Begin of Day.

Storage and stability

Shelf life at 2-8 °C	See expiration date on cobas c pack label
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COBAS INTEGRA 400 plus system

On-board in use at 10-15 °C	12 weeks
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COBAS INTEGRA 800 system

On-board in use at 8 °C	12 weeks
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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-heparin²⁶ and K₂- or K₃-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)

NaCl Diluent 9 %, Cat. No. 20756350 322, system-ID 07 5635 0 for automatic postdilution. NaCl Diluent 9 % is placed in its predefined rack position and is stable for 4 weeks on-board COBAS INTEGRA 400 plus/800 analyzers.

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.

Application for plasma**COBASINTEGRA 400 plus test definition**

Measuring mode	Absorbance
Abs. calculation mode	Endpoint
Reaction mode	R1/R2-S
Reaction direction	Increase
Wavelength A	659 nm
Calc. first/last	T ₀ /38
Unit	µg FEU/mL*

Pipetting parameters

		Diluent (H ₂ O)
R1	90 µL	
R2	90 µL	
Sample	5 µL	10 µL
Total volume	195 µL	

COBAS INTEGRA 800 test definition

Measuring mode	Absorbance
Abs. calculation mode	Endpoint
Reaction mode	R1/R2-S
Reaction direction	Increase
Wavelength A	659 nm
Calc. first/last	T ₀ /53
Unit	µg FEU/mL*

Pipetting parameters

		Diluent (H ₂ O)
R1	90 µL	
R2	90 µL	
Sample	5 µL	10 µL
Total volume	195 µL	

*The addition "FEU" is not displayed by the analyzer.

Calibration

Calibrator	D-Dimer Gen.2 Calibrator Set
Calibration mode	Logit/log 4
Calibration replicate	Duplicate recommended
Calibration interval	Each lot, every 6 months when using a single lot of reagent, and as required following quality control procedures.

Calibrators must be placed from the highest concentration first, to the lowest last, on the CAL/QC rack.

Traceability: This method has been standardized against the Asserachrom D-Dimer method.²⁸

Quality control

Reference range	D-Dimer Gen. 2 Control I/II
Control interval	24 hours recommended
Control sequence	User defined

Control after calibration Recommended

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

COBAS INTEGRA analyzers automatically calculate the analyte concentration of each sample. For more details, please refer to Data Analysis in the Online Help (COBAS INTEGRA 400 plus/800 analyzers).

Conversion factors: $\mu\text{g FEU/mL} = \text{mg FEU/L}$
 $\mu\text{g FEU/mL} \times 1000 = \text{ng FEU/mL}$

Limitations - interference

Results just below the cutoff normal/pathological (0.5 $\mu\text{g FEU/mL}$) should be considered pathological if the sample is either highly turbid or has an intense red color.

Criterion: Recovery within $\pm 10\%$ of initial value.

Icterus:²⁹ No significant interference up to an I index of 60 for conjugated bilirubin and 30 for unconjugated bilirubin (approximate conjugated bilirubin concentration: 1026 $\mu\text{mol/L}$ or 60 mg/dL ; approximate unconjugated bilirubin concentration: 513 $\mu\text{mol/L}$ or 30 mg/dL).

Hemolysis:²⁹ No significant interference up to an H index of 500 (approximate hemoglobin concentration: 310 $\mu\text{mol/L}$ or 500 mg/dL).

Lipemia:²⁹ No significant interference up to an L index of 600. There is a poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors: No significant interference up to 100 IU/mL.

Heparin: No significant interference up to 100 IU/mL.

High-dose hook effect: No high-dose hook effect is seen up to a D-Dimer concentration of 220 $\mu\text{g FEU/mL}$.

Drugs: No interference was found at therapeutic concentrations using common drug panels.^{30,31}

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

In rare cases (less than 1 reported case per 10000 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.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on COBAS INTEGRA analyzers. Refer to the CLEAN Method Sheet for further instructions and for the latest version of the Extra wash cycle list.

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

Limits and ranges**Measuring range**

0.15-9.0 $\mu\text{g FEU/mL}$

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:3 dilution (postdilution 1) or a 1:6 dilution (postdilution 2). Results from samples diluted by the rerun function are automatically multiplied by a factor of 3 (postdilution 1) or by a factor of 6 (postdilution 2).

Lower limits of measurement

Limit of Blank and Limit of Detection:

Limit of Blank = 0.08 $\mu\text{g FEU/mL}$

Limit of Detection = 0.15 $\mu\text{g FEU/mL}$

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 $n \geq 60$ 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 values³³

< 0.5 μg fibrinogen equivalent units/mL ($\mu\text{g FEU/mL}$) 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 COBAS INTEGRA 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 ($n = 3$ aliquots per run, 1 run per day, 21 days). The following results were obtained:

	Repeatability		Intermediate precision	
	Mean $\mu\text{g FEU/mL}$	CV %	Mean $\mu\text{g FEU/mL}$	CV %
Plasma 1	0.54	2.1	0.47	3.4
Plasma 2	1.05	1.3	1.50	2.8
Plasma 3	2.66	1.5	5.44	3.4
Low control	1.01	1.2	0.93	3.3
High control	4.40	1.2	3.85	3.6

Method comparison

D-Dimer values for human plasma samples obtained on a COBAS INTEGRA 400 analyzer using the Tina-quant D-Dimer Gen.2 test (y) were compared with those determined using the previous Tina-quant D-Dimer test on the same analyzer (x).

COBAS INTEGRA 400 analyzer	Sample size (n) = 60
Passing/Bablok ³⁴	Linear regression
$y = 1.038x + 0.013 \text{ mg FEU/L}$	$y = 1.005x + 0.056 \text{ mg FEU/L}$
$\tau = 0.953$	$r = 0.997$
$\text{SD (md 95)} = 0.398$	$\text{Sy.x} = 0.147$

The sample concentrations were between 0.286 and 8.61 $\mu\text{g FEU/mL}$.

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 $\mu\text{g FEU/mL}$. 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, three developed non-fatal PE and one 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 %)

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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.

	Contents of kit
	Volume after reconstitution or mixing
	Global Trade Item Number

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Roche Diagnostics warrants that this product will meet the specifications stated in the labeling when used in accordance with such labeling and will be free from defects in material and workmanship until the expiration date printed on the label. THIS LIMITED WARRANTY IS IN LIEU OF ANY OTHER WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR PARTICULAR PURPOSE. IN NO EVENT SHALL ROCHE DIAGNOSTICS BE LIABLE FOR INCIDENTAL, INDIRECT, SPECIAL OR CONSEQUENTIAL DAMAGES.

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