Exdia 3-in-1 (Troponin I / CK-MB / Myoglobin)

One Step Immunoassay for 3-in-1 (Troponin I / CK-MB / Myoglobin)
For In Vitro Diagnostic Use

One–step quantitative time resolved fluorescence immuno-chromatography assay for the detection of Troponin I, CK-MB and Myoglobin in human whole blood, serum and plasma

Manufactured by Precision Biosensor Inc.

1. INTENDED USE

The Exdia 3-in-1 test is a time resolved fluorescence immuno-chromatography assay for the quantitative determination of Troponin I (TnI), Creatine Kinase MB (CK-MB), and Myoglobin in human whole blood, serum and plasma specimens at cutoff concentrations of 0.06ng/mL, 5.0 ng/mL, and 80 ng/mL respectively, as an aid in the diagnosis of Acute Myocardial Infarction (AMI). In conjunction with Exdia analyzer, the Exdia 3-in-1 test can monitor the rise and fall of Troponin I, CK-MB, and Myoglobin. Test results should be interpreted by the physician along with other test results and patient clinical symptoms findings.

2. SUMMARY AND EXPLANATION OF THE TEST

When a myocardial infarction (MI) occurs in the hypoperfused region of the myocardium, oxygen can no longer be supplied to the cells in the region. Cell death is inevitable if oxygen is not restored within 10-15 min. Cell death results in the release of certain proteins from cytoplasm into the blood stream. Some proteins are exclusive to and predominant in the cardiac muscle cells; they can function as cardiac makers and can be detected in the blood specimens of AMI patients by specialized immunoassays.[1-3] Unfortunately none of those cardiac markers can be detected within 2 hours after onset AMI with 100% specificity, and found a substantial life time in circulation. This situation has lead to a panel approach for the utilization of markers in patients with AMI. The constituents of this cardiac panel should include a marker that rapidly increases after cardiac injury and is highly cardiac tissue specific. The combination of Troponin I, CK-MB and Myoglobin are widely used in panel assays intended for the determination of AMI in chest pain patients.[4]

Troponin I
Troponin is a contractile regulatory protein complex found in skeletal and cardiac muscle. The Troponin complex consists of three distinctive polypeptide components, Troponin I (TnI), Troponin T (TnT), and Troponin C (TnC), and plays a fundamental role in the transmission of intracellular calcium signal actin-myosin interaction.[5] TnC of cardiac tissues is identical to that in skeletal tissues, but TnI and TnT of cardiac isoforms are distinctive to those of skeletal isoforms, which enables the development of cardiac specific antibodies.[6] Moreover, Troponin I level becomes elevated in the blood as a result of myocardial injury or necrosis. Therefore, Troponin I is used as an aid in the diagnosis of myocardial infarction.[7-8] Studies on the release kinetics indicate that Troponin I is not early marker of myocardial necrosis. It appears in serum within 3-6 hours after symptom onset, similar to the release of CK-MB. However, Troponin I remains elevated for 4-9 days post-AMI.[9-10] In addition to its utility in diagnosis, elevated troponin I levels convey prognostic information and has been shown to identify patients having an increased risk of death.[11]

CK-MB
Creatine Kinase (CK) is present in most tissues and is primarily concerned with ATP regeneration. This enzyme is dimeric and exists as three isozymes: MM (muscle), MB (hybrid), and BB (brain). [12] The MB isozyme has its highest concentration in the heart muscle, thus its level in the serum has diagnostic value. The CK-MB level in normal serum is less than 5 ng/mL. In cases of uncomplicated AMI, CK-MB level becomes elevated within 4-8 hours after the onset of chest pain, reaching a peak between 12-24 hours and then drops down to normal by 48 hours. The peak level of CK-MB is 21 ng/mL or higher.[13-14] CK-MB has been considered the Gold standard for the diagnosis of AMI because of its cardio-specificity. However, CK-MB is not an ideal marker to use alone because its level does not increase early enough to make a rapid diagnosis and may also be increased in other conditions. Although CK-MB is more concentrated in the myocardium (approximately 15% of the total CK), it is also present in skeletal muscle. False-positive elevations occur in a number of clinical settings, including trauma, heavy exertion, and myopathies.[15-16]

Myoglobin
Myoglobin, an oxygen binding heme protein present in muscle tissue including cardiac, skeletal and smooth muscle, has attracted considerable interest as an early marker of MI.[2,17] Following injury to any of these muscles, myoglobin appears in the blood more rapidly than any other marker4. Levels may be elevated as early as one hour following the onset of chest pain when CK-MB levels are still in the range of normal.[2,18,19] This rapid appearance is due to the location of myoglobin in the cell and its low molecular weight. Myoglobin typically rises 2-4 hours after the onset of infarction, peaks at 6-12 hours, and returns to normal within 24-36 hours. Normally the level of myoglobin in serum is 30-80 ng/mL. In patients with MI, the level could increase approximately 10 times above the upper limit of normal. Myoglobin exhibits high clinical sensitivity for AMI but poor specificity.[1, 3] Many studies suggest that myoglobin may be a good screening assay in Emergency Rooms for the early diagnosis of AMI. However, elevated myoglobin values should be cautiously interpreted if the patient has renal dysfunction or skeletal muscle injury. Because of these limitations, detection of myoglobin in a patient suspected of AMI may need to be supplemented by the presence of a more definitive cardiac maker. However, a negative result in a patient admitted within 2-9 hours after onset of chest pain may help in ruling out AMI.

3. PRINCIPLE

The Exdia 3-in-1 test is a time resolved fluorescence immuno-chromatography assay for the quantitative determination of three biochemical markers (Troponin I, CK-MB and Myoglobin) simultaneously in human whole blood, serum and plasma specimen. The membrane strip contains three test lines and one control line, printed with specific antibodies or receptor against each target molecules, monoclonal mouse antibody against CK-MB, monoclonal mouse antibody against Myoglobin, streptavidin for biotinylated Troponin I antibody, and goat anti-chicken IgY antibody for control line. A dye pad is placed at the end of the membrane containing biotinylated Troponin I antibody and europium particles coupled with CK-MM, Troponin I and Myoglobin antibodies. When a sample is applied into the sample well, the cardiac makers present in the sample bind to the specific antibodies coupled with Europium particles on the dried dye pad. Troponin I in a sample binds to both Troponin I specific dye coupled antibody and biotinylated antibody. These primary immune complexes move along the nitrocellulose membrane through the test lines and bind to their corresponding capture antibodies or receptor molecules immobilized on the test line. Unbound immune complexes pass through the test line and IgY coupled with europium particles are captured by goat anti-chicken IgY antibody in the control line. To measure the concentration of analyte, the tested cassette should be read by Exdia analyzer. The analyzer can analyze fluorescence intensity of the test line and convert it to concentration of the analyte in the specimen by the predetermined equation.

4. REAGENT

The Exdia 3-in-1 test contains all the reagents necessary for the detection of Troponin I, CK-MB and Myoglobin in human whole blood, serum, and plasma. The cassette contains a membrane strip coated with monoclonal mouse anti-CK-MB, anti- Myoglobin and streptavidin on the test line, and dye pad infused with biotinylated monoclonal mouse anti-Troponin I antibody and europium particles coupled with anti-CK-MM, anti-Troponin I and anti-Myoglobin antibodies. Stabilizer containing 0.05% sodium azide and BSA protein are deposited on the dye pad in dried form.

5. MATERIALS

Provided

- 20 Test cassette sealed in a pouch with disposable transfer pipette (80uL) and desiccant
- 1 QR card for calibration (lot specific)
- 1 Instructions for Use

Required but not provided

- Whole blood, serum or plasma collection container
- Positive and negative quality control materials
- Timer
- Exdia analyzer

6. STORAGE AND STABILITY

The test cassette should be stored at 2°C ~ 30°C in the original sealed pouch for the duration of shelf life.

7. PRECAUTIONS

- For *in-vitro* diagnostic and professional use only.
- Do not use hemolyzed specimens as hemolysis affect test results.
- Handle all specimens as potentially infectious. Proper handling and disposal methods should be established.
- To avoid cross contamination, use a fresh transfer cassette for each clinical sample tested.
- Do not use test cassette if the pouch is damaged or improperly sealed.
- Do not use test cassette beyond expiration date.

8. SPECIMEN COLLECTION AND PREPARATION

- This test can be used for whole blood, plasma, and serum samples. If serum samples are to be used, collect the blood in a tube without anticoagulant and allow clotting for at least 25 minutes before centrifugation. Whole blood or plasma samples using heparin or EDTA as the anticoagulant can be used for testing with this product. Other blood anticoagulants have not been evaluated. Each laboratory should determine the acceptability of its own blood collection tubes and serum separation products. Variation in these products may exist between manufacturers and, at times from lot-to-lot.
- The samples should be collected under standard laboratory conditions.
- Optimal results were obtained when patient samples were tested immediately after collection. Whole blood samples should be used within 4 hours after collection. Plasma or serum samples may be refrigerated for 24 hours at 2°C ~ 8°C. If testing cannot be performed within 24 hours, or for shipment of samples, freeze at -20°C or below.[20, 21]
- Sodium azide can be added as a preservative up to 0.1% without affecting the test results.
- Refrigerated or frozen serum or plasma specimen should reach room temperature and be homogeneous prior to testing

9. TEST PROCEDURE AND PROTOCOL

- Collect specimen according to instructions in **"Specimen Collection"**.
- Test cassette and sample should be brought to room temperature (20°C ~30°C) prior to testing.
- Remove the test cassette from the sealed pouch immediately before use. Label the cassette with patient or control identification.
- Using sample transfer pipette, deliver dropper contents (80 uL) of sample into the sample well.
- Read the results at 15 minutes. The tested cassette should be analyzed by the Exdia analyzer following the instruction manual.

10. INTERPRETATION OF RESULTS

The signal intensity of test line are analyzed by Exdia analyzer and the results are expressed as concentration of analytes using predetermined calibration curves specific for Exdia 3-in-1 cassettes.If the test result is valid and higher than the clinical cutoff value, 0.5 ng/mL for Tn I, 5ng/ml for CK-MB and 80ng/ml for Myoglobin, it can be interpreted as AMI suspicious specimen . For a test result of TnI level is below the upper limit reference, 0.06 ng/mL, or all three markers concentrations are lower than cutoff level it can be interpreted as AMI negative.

11. LIMITATIONS

- The test is for professional and in-vitro diagnostic use only.
- A positive test result may only be used as an indicator of myocardial damage and requires further confirmation. Serial sampling of patients suspected of AMI at multiple time points is also recommended due to the delay between onset of symptoms and the release of cardiac marker proteins into the blood stream.
- As with all diagnostic tests, a definitive clinical diagnosis should not be made based on the results of a single test. The test result should be used in conjunction with other clinical information such as clinical signs and symptoms and other test results to diagnose AMI. Confirmation of test results should only be made by a physician after all clinical and laboratory findings have been evaluated.
- Samples containing unusually high titers of certain antibodies such as human anti-mouse or human anti-goat antibodies have been known to affect the performance of these cassettes[22] However these studies using the Exdia 3-in-1 test have not been performed.

12. QUALITY CONTROL

The presence of fluorescence band in the Control area of the window acts as an internal control to ensure an adequate volume of sample has been added. In the absence of this Control band, the associated test result is invalid and must be retested. Good laboratory practice recommends quality control to ensure proper test performance. Quality control materials are available from commercial sources, and should be tested by following same procedures as running the patient sample tests. Good laboratory practice suggests that external controls should be tested with every new lot or in case of questionable test result in using the reagent cassette. If the quality control procedures in your laboratory require more frequent use of controls to verify the test results, follow your laboratory-specific procedures. The recommended requirement for testing the Exdia IQC provided with the instrument is for regular time period. When the test result is questionable for any reason, contact the customer support.

13. CLINICAL CUTOFF AND REFERENCE RANGE

The clinical cutoff value of the Exdia 3-in-1 test was determined by comparison with the Access® Accu TnI, CK-MB and Myoglobin Assay (Beckman Coulter). The clinical cutoff of 0.5 ng/mL for TnI, 5 ng/mL for CK-MB and 80 ng/mL for Myoglobin were determined in a feasibility study by ROC analysis. The cutoff level may be different if a quantitative assay system was compared to other than Beckman Coulter Access.
The upper reference limit of Exdia Troponin I test (0.06 ng/mL), was determined by ROC analysis with negative plasma samples below upper reference limit of Beckman Coulter Access Accu TnI assay (0.04ng/mL).

14. PERFORMANCE CHARACTERISTICS

14-1 Detection limits
Determination of limit of blank (LoB), limit of detection (LoD) and limit of quantification (LoQ) for Exdia 3-in-1 Test was performed according to CLSI guidance, EP17-A.

(a) Determination of LoB
Total 100 negative samples collected from cardiac asymptomatic individuals were tested on Exdia 3-in-1 Test, the distribution of test result was evaluated statistically, and then the number at 95th percentile of negative sample run was determined as LoB of the Test.

(b) Determination of LoD
Determination of LoD test was conducted 20 replicated using 5 different levels of low positive samples (Myo concentration ranges between 3.6 ng/mL to 10.8 ng/mL, CK-MB concentration ranges between 0.8 ng/mL to 2.4 ng/mL, Troponin I concentration ranges between 0.01 ng/mL to 0.03 ng/mL). The calculated LoB was verified in using tentative concentration over the calculated LoB level following to the procedure in CLSI guideline EP17-A.

(c) Determination of LoQ
The LoQ was determined by CLSI guideline EP17-A based on LoD verification study results. The determined tentative LoD was verified 100 replicates testing of LoD level samples for 10

consecutive days with 10 replicates each day. The data met the set up requirements for LoQ verification test, assay precision criteria of less than 20%.

Analyte	Replicate No	Target	Mean	Sw1	SDT	CV_T
Myo	100	10.0 ng/mL	10.22 ng/mL	1.82	2.0	19.2 %
CK-MB	100	2.0ng/mL	1.89ng/mL	0.36	0.36	19.1%
Troponin I	100	0.03ng/mL	0.029ng/mL	0.00	0.01	18.1%

14-2 Linearity / assay reportable range

Linear range of Exdia 3-in-1 Test was determined as instructed in CLSI guideline, EP6-A.
Testing samples were prepared by serial dilution of Myoglobin (Myo), creatine kinase-MB (CK-MB) and Troponin I (TnI) high stock material. Myo concentrations ranges from 10 ng/mL to 500 ng/mL. CK-MB concentrations ranges from 2 ng/mL to 200 ng/mL. Troponin I concentration ranges from 0.03 ng/mL to 30 ng/mL. Linearity in measuring of analytes were confirmed that the linear model was capable of interpolating between the experimental points. Exdia 3-in-1 test was demonstrated to be linear in measuring ranges as described in below table.

Analytes	Low Limit(ng/mL)	High Limit(ng/mL)	Correlation coefficient (R^2)	CV(%)
Troponin I	0.03	30	0.916	13.8
CK-MB	2.0	200	0.9257	13.1
Myo	10.0	500	0.9578	11.1

14-3 Interference & specificity test

Potentially interfering substances were spiked into normal serum and patient serum containing either Troponin I, CK-MB or Myoglobin, about 1.5 times of the cutoff concentration. The substances at the following level do not interfere with the performance of the Exdia 3-in-1 Test.

	Substances	Concentration
Endogenous substances	Bilirubin	50 mg/dl
	Hemoglobin	4,000mg/dl
	Human serum albumin	5,000mg /dl
	Triglycerides	1,250 mg/dl

The cassette was tested for interference by potentially cross-reacting endogenous proteins. Potentially cross-reacting proteins, added into normal human serum up to the following concentrations, do not interfere with test result.

	Substances	Concentration
Cross-reacting endogenous proteins	Cardiac myosin light chain	1,000 ng/mL
	Cardiac Troponin T	1,000 ng/mL
	Cardiac Troponin C	1,000 ng/mL
	Skeletal Troponin I	1,000 ng/mL
	CK-MB	5,000 ng/mL

The following medicines and chemicals were proven to be not interfering to Exdia 3-in-1 performance.

Acetaminophen	Diltiazem	Metoprolol	Probenecid
Acetylsalicylic Acid	Dipyridamole	Morphine	Procainamide
Allopurinol	Dopamine	Nicotine	Propranolol
Ampicillin	Erythromycin	Nitrofurantoin	Quinidine
Ascorbic Acid	Fluoxetine	Oxytetracycline	Sulfamethoxazole
Caffeine	Furosemide	PCP	Theophylline
Captopril	Hydrocodone	Phenobarbital	Verapamil
Chloramphenicol	Ibuprofen	Phenytoin	Warfarin
Digoxin	Indomethacin		

14-4 Precision Test

Precision of the Exdia 3-in-1 test with Exdia analyzer was determined following by CLSI guideline EP5-A. Three different levels of plasma samples including Myoglobin (Myo), creatine kinase-MB (CK-MB) and Troponin I (TnI) antigen were prepared by dilution of standard Myo, CK-MB, Troponin I stock material. and their concentrations in tested samples, listed in the below table, ten replicates of test per day at each concentration were ran for 20 consecutive days and the collected data were analyzed statistically as follows.

Precision Test Results of Myoglobin

	Level 1 (30ng/mL)	Level 2 (100ng/mL)	Level 3 (300ng/mL)
Mean (ng/mL)	31.26	101.77	302.77
Within Run CV	17.4%	17.1%	17.1%
Total Run CV	18.6%	18.2%	17.8%

Precision Test Results of CK-MB

	Level 1 (10ng/mL)	Level 2 (20ng/mL)	Level 3 (80ng/mL)
Mean (ng/mL)	9.93	22.63	77.05
Within Run CV	12.2%	12.2%	12.0%
Total Run CV	12.6%	12.4%	11.9%

Precision Test Results of Troponin I

	Level 1 (0.1ng/mL)	Level 2 (0.5ng/mL)	Level 3 (4.0ng/mL)
Mean (ng/mL)	0.13	0.54	4.03
Within Run CV	12.2%	8.8%	11.1%
Total Run CV	12.8%	9.9%	11.6%

14-5 Matrix Comparison Study

To perform matrix comparison study between plasma and whole blood in Exdia 3-in-1 quantitative test, ten different levels of analyte concentrations ranging from negative to upper detection limit were prepared by spiking analyte molecules into normal whole blood collected from 8 different healthy volunteers. Corresponding plasma specimens were prepared from each level of whole blood specimens by centrifugation. Each level of whole blood and plasma specimens were ran on the same lot of Exdia 3-in-1 cassette in 3 replicates. The concentrations were measured using the matrix specific analysis programs for whole blood, serum and plasma test on Exdia analyzer. Each sample of matched matrices was tested on Exdia 3-in-1 and the results were evaluated and analyzed with Heparinized Plasma sample by Passing-Bablok regression and Spearman's correlation method. The data of regression and correlation analysis demonstrated strong correlation between matrices (correlation coefficient between matrices as 0.919 to 0.97), which indicated that samples in different matrices, heparinized whole blood, heparinized plasma, EDTA treated whole blood, EDTA treated plasma and serum, perform equivalently for 3 different makers on Exdia 3-in-1 test Cassette.

Analytes			**Serum**	**EDTA treated Plasma**	**Heparinized Whole Blood**	**EDTA treated Whole Blood**
Troponin I	regression equation*	Intercept A	-0.0052	0.0004	0.0793	0.0317
		Slope B	1.0526	0.9654	1.0223	0.9629
	ranked correlation*	rho	0.979	0.997	0.999	0.988
CK-MB	regression equation*	Intercept A	0.7351	0.4043	1.0793	0.8173
		Slope B	0.9802	0.9654	1.0303	0.9529
	ranked correlation*	rho	0.963	0.965	0.981	0.968
Myo	regression equation*	Intercept A	-4.8045	2.0442	3.8731	2.0317
		Slope B	1.0526	0.9454	0.9803	0.9529
	ranked correlation*	rho	0.949	0.957	0.976	0.964

*Regression analysis and correlation analysis was conducted referring to heparinized plasma.

14-6 Method Comparison Study

Method comparison study was performed for Exdia 3-in-1 in conjunction with Exdia analyzer versus Access Accu TnI, CK-MB and Myo test (Beckman Coulter Inc). Plasma samples were collected from 145 emergency room patients who had a chest pain or any other symptoms to be suspected cardiac problems. The predicative test value is over the measuring range of Exdia 3-in-1 was eliminated this data. The comparison result was regressed using Passing-Bablok model and correlation was analyzed using Spearman's ranked correlation. Results were summarized below. The results showed the below table indicating a good correlation between two systems. Therefore, the reading value of Troponin I, CK-MB and Myo in Exdia 3-in-1 test measured by Exdia analyzer strongly correlated with Beckman Coulter Access Accu TnI, CK-MB and Myoglobin test.

Analyte	**n**	**Ranges of Observation (ng/mL)**	**Intercept (ng/mL)**	**Slope**	**Correlation Coefficient**
Troponin I	133	0.03 – 30	0.0149	0.9691	0.959
CK-MB	138	2.0 - 200	-0.3202	0.9733	0.921
Myoglobin	133	10 - 500	1.7265	1.0373	0.887

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