QUIDEL

Triage®

Cardio3 PANEL | Cardio2 PANEL

Troponin I TEST

Triage Cardio Product Insert

Rapid quantitative tests for creatine kinase MB, troponin I and B-type natriuretic peptide

A symbols glossary can be found at quidel.com/glossary.

For Export Only. Not for sale in the United States.

INTENDED USE

The Quidel Triage Cardio3 Panel is a fluorescence immunoassay to be used with the Quidel Triage Meters for the rapid quantitative determination of creatine kinase MB, troponin I, and B-type natriuretic peptide in EDTA anticoagulated whole blood and plasma specimens. The Quidel Triage Cardio3 Panel is to be used as an aid in the diagnosis of myocardial infarction (injury), an aid in the diagnosis and assessment of severity of congestive heart failure (also referred to as heart failure), an aid in the risk stratification of patients with heart failure, and an aid in the risk stratification of patients with acute coronary syndromes.

The Quidel Triage Cardio2 Panel is a fluorescence immunoassay to be used with the Quidel Triage Meters for the rapid quantitative determination of troponin I and B-type natriuretic peptide in EDTA anticoagulated whole blood and plasma specimens. The Quidel Triage Cardio2 Panel is to be used as an aid in the diagnosis of myocardial infarction (injury), an aid in the diagnosis and assessment of severity of congestive heart failure (also referred to as heart failure), an aid in the risk stratification of patients with heart failure, and an aid in the risk stratification of patients with acute coronary syndromes.

The Quidel Triage Troponin I Test is a fluorescence immunoassay to be used with the Quidel Triage Meters for the quantitative determination of troponin I in EDTA anticoagulated whole blood and plasma specimens. The test is to be used as an aid in the diagnosis of myocardial infarction (injury).

SUMMARY AND EXPLANATION OF THE TEST

The diagnosis of acute myocardial infarction (AMI) in a patient presenting with chest pain is difficult in many cases. The three major criteria outlined by the World Health Organization for differentiating chest pain associated with AMI from chest pain due to other non-cardiac reasons are: (1) patient history in addition to physical examination, (2) electrocardiographic data, and (3) changes in serum protein markers associated with myocardial infarction. At least two of these criteria must be fulfilled to appropriately diagnose an AMI.

Frequently, physical examination cannot differentiate AMI from other cardiac abnormalities. The electrocardiogram is useful in diagnosing AMI but is limited because it is diagnostic in only approximately 50% of AMI patients. Typically, Q wave formation and changes in the ST segment, elevation or depression, are indicative of AMI. However, the results of the electrocardiogram must be considered with the physical examination and clinical history of the patient. The electrocardiogram may be normal initially even though the patient is truly presenting with AMI.

Blood protein markers play an important role in the differential diagnosis of AMI when other indicators may be negative or questionable. Markers used in the diagnosis of myocardial infarction include: creatine kinase (CK), the MB isoenzyme of creatine kinase (CK-MB), myoglobin, and the structural proteins of the troponin complex, i.e., troponin T and troponin I.

Creatine kinase MB (CK-MB) is an 82,000 Dalton cytosolic enzyme that is present in high concentrations in the myocardium. This isoenzyme of creatine kinase is frequently used in the diagnosis of acute myocardial infarction. Typically, CK-MB increases above normal within the first 4-8 hours following acute myocardial infarction, reaching maximum concentrations between 12 and 24 hours and returning to normal in approximately 3 days. CK-MB is not specifically localized in

cardiac muscle. Blood concentrations of CK-MB can be elevated as a result of acute or chronic muscle damage, including strenuous exercise and trauma. Nonetheless, measurements of blood CK-MB concentrations are widely relied on for the management of patients having an AMI.

The contractile proteins of the myofibril have gained increased popularity as cardiac specific markers for acute myocardial infarction and myocardial damage. These include two specific proteins of the contractile regulatory complex: troponin I and troponin T. Troponin I and troponin T isolated from cardiac muscle have unique amino acid sequences that enable the development of specific antibodies to these cardiac proteins. The amino terminal amino acid sequence of the cardiac isotype of troponin I has 31 amino acid residues that are not present in either of the two isotypes of troponin I found in skeletal muscle. Given its tissue specificity, cardiac troponin I is primarily elevated as a result of myocardial infarction. However, cardiac troponin I also may be elevated as a result of minor cardiac injury that includes: unstable angina, cardiac contusions, cardiac transplant, coronary artery bypass graft surgery, physical trauma to the heart, congestive heart failure and other conditions that may damage the myocardium. Despite this, cardiac troponin I does not appear to be elevated as a result of skeletal muscle injury. As a result, cardiac troponin I has become an important marker in the diagnosis and evaluation of patients suspected of having an AMI. More recently, the TACTICS-TIMI 18 study and several other clinical trials have demonstrated that elevated troponin levels in patients with suspected ACS are independently associated with a higher risk of recurrent cardiovascular events or complications. Therefore, in addition to being a diagnostic for AMI, cardiac troponin I has also become an important marker for risk stratification of patients with suspected acute coronary syndromes.

It is estimated that 5.8 million people in the United States have heart failure with approximately 670,000 new cases occurring each year. Congestive heart failure (CHF) occurs when the heart cannot deliver a sufficient amount of blood to the body. This condition can occur at any age but is most prevalent in an aged population. Symptoms of CHF include shortness of breath, fluid retention and respiratory distress. These symptoms are often vague and nonspecific for detecting early stages of CHF.

B-Type Natriuretic Peptide (BNP) is a member of a class of hormones that regulate blood pressure. The heart is the main source of circulating BNP in humans. The molecule is released into the blood in response to increased heart pressure. Various studies have demonstrated that increased levels of circulating BNP are found in early stages of CHF. The level of BNP in the blood continues to increase as the CHF disease advances. Furthermore, BNP has been demonstrated to have utility as a prognostic indicator in patients with acute coronary syndromes (ACS). The Quidel Triage Cardio3 Panel and the Quidel Triage Cardio2 Panel offer an objective, noninvasive measurement for assessing patients for CHF and risk stratification in patients with ACS.

PRINCIPLES OF THE TEST PROCEDURE

The Quidel Triage Cardio3 Panel is a single use fluorescence immunoassay device designed to determine the concentration of CK-MB, troponin I and BNP in EDTA anticoagulated whole blood or plasma specimens.

The Quidel Triage Cardio2 Panel is a single use fluorescence immunoassay device designed to determine the concentration of troponin I and BNP in EDTA anticoagulated whole blood or plasma specimens.

The Quidel Triage Troponin I Test is a single use fluorescence immunoassay device designed to determine the concentration of troponin I in EDTA anticoagulated whole blood or plasma specimens.

The test procedure involves the addition of several drops of an EDTA anticoagulated whole blood or plasma specimen to the sample port on the Test Device. After addition of the specimen, the whole blood cells are separated from the plasma using a filter contained in the Test Device. The specimen reacts with fluorescent antibody conjugates and flows through the Test Device by capillary action. Complexes of each fluorescent antibody conjugate are captured on discrete zones specific for each analyte.

The Test Device is inserted into the Quidel Triage Meter (hereafter referred to as Meter). The Meter is programmed to perform the analysis after the specimen has reacted with the reagents within the Test Device. The analysis is based on the amount of fluorescence the Meter detects within a measurement zone on the Test Device. The concentration of the analyte(s) in the specimen is directly proportional to the fluorescence detected. The results are displayed on the Meter screen in approximately 20 minutes from the addition of specimen. All results are stored in the Meter memory to display or print when needed. If connected, the Meter can transmit results to the lab or hospital information system.

REAGENTS AND MATERIALS PROVIDED

The Quidel Triage Cardio3 Panel contains all the reagents necessary for the simultaneous quantification of CK-MB, troponin I, and BNP in EDTA anticoagulated whole blood or plasma specimens.

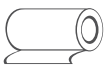
The Quidel Triage Cardio2 Panel contains all the reagents necessary for the simultaneous quantification of troponin I and BNP in EDTA anticoagulated whole blood or plasma specimens.

The Quidel Triage Troponin I Test contains all the reagents necessary for the quantification of troponin I in EDTA anticoagulated whole blood or plasma specimens.

The Test Device Contains:

- Murine monoclonal and polyclonal antibodies against CK-MB and BNP
- Murine monoclonal antibodies against troponin I
- Fluorescent dye
- Stabilizers

Kit contains:

Component	Quantity	Description
	25	Test Devices
	25	Transfer Pipettes
	1	Reagent CODE CHIP™ Module
	1	Printer Paper Roll

MATERIALS REQUIRED BUT NOT PROVIDED

- Quidel Triage MeterPro Cat. # 55071
- Triage MeterPlus Cat. # 55041
- Quidel Triage Total 3 Control 1 Cat. # 88733
- Quidel Triage Total 3 Control 2 Cat. # 88734

WARNINGS AND PRECAUTIONS

- For *In Vitro* Diagnostic Use.
- For use by healthcare professionals.
- Do not use the kit beyond the expiration date printed on the outside of the box.
- Carefully follow the instructions and procedures described in this insert.
- Optimal results will be achieved by performing testing at temperatures between 20°C to 24°C (68°F to 75°F).
- If results from multiple specimens from the same patient will be compared, it is recommended to maintain a consistent sample type (whole blood or plasma).
- Sample dilution is not recommended.
- The use of non-Quidel Controls and Calibration Verification materials is not recommended.
- Keep the Test Device in the sealed pouch until ready for immediate use. Discard after single use.
- The Transfer Pipette should be used for one patient specimen only. Discard after single use.
- Patient specimens, used Test Devices, and used Transfer Pipettes may be potentially infectious. Proper handling and disposal methods should be established by the laboratory in accordance with local, state and federal regulations.
- Proper laboratory safety techniques should be followed at all times when working with patient specimens because they are potentially infectious.

STORAGE AND HANDLING REQUIREMENTS

- Store the Test Devices in a refrigerator at 2°C to 8°C (35°F to 46°F).
- Once removed from refrigeration, the pouched Test Device is stable for up to 10 days at room temperature, but not beyond the expiration date printed on the pouch. With a soft, felt tip marker, gently write the date and time of removal from the refrigerator on the pouch and cross out the manufacturer expiration date printed on the pouch. Care must be taken to document the time the product is at room temperature. Once equilibrated to room temperature, do not return the Test Device to refrigeration.
- Before using refrigerated Test Devices, allow individual foil pouches to reach the operating temperature (20°C to 24°C or 68°F to 75°F). This will take a minimum of 15 minutes. If a kit containing multiple Test Devices is removed from refrigeration, allow the kit to reach room temperature before use. This will take a minimum of 60 minutes.
- Do not remove the test Device from the pouch until prepared for immediate use.

SPECIMEN COLLECTION AND PREPARATION

- A venous whole blood or plasma specimen using EDTA as the anticoagulant is required for testing with this product. Other blood specimen types have not been evaluated. Plastic K2 EDTA tubes are recommended for sample collection to ensure optimal product performance.
- For specimen collection, follow the sample tube manufacturer's recommended procedure.
- Test blood specimens immediately or within 1 hour of sample collection. If testing cannot be completed within 1 hour, the plasma should be separated and tested within 2 hours from the time of collection or frozen at ≤ −20°C until it can be tested.
- No more than a single freeze / thaw cycle is recommended.
- Transport specimens at room temperature or chilled and avoid extreme temperatures.
- Avoid using severely hemolyzed specimens whenever possible. If specimen appears to be severely hemolyzed, another specimen should be obtained and tested.

TEST PROCEDURE

Lot Calibration Using the Reagent CODE CHIP Module

When a new lot of Test Devices is opened, the calibration and expiration data for that lot of Test Devices must be transferred to the Meter before patient testing. Use the Reagent CODE CHIP module supplied with the new lot of Test Devices to transfer the data to the Meter.

REAGENT CODE CHIP MODULE

Perform one time for each new lot of Test Devices

1. From the main screen, select **Install New Code Chip**. Press **Enter**.
2. Place the Reagent CODE CHIP module into the lower left front corner of the Meter and follow the prompts on the screen.

3. Remove the Reagent CODE CHIP module from the Meter when data transfer is complete.
4. Place the Reagent CODE CHIP module back into its original container for storage.

Testing Patient Specimens

Procedural Notes

- For each day of patient testing, perform QC Device testing. Refer to the Quality Control Considerations section.
- Frozen plasma and refrigerated whole blood or plasma specimens must be allowed to reach room temperature and be mixed thoroughly before testing.
  - ► Mix whole blood specimens by gently inverting the tube several times.
  - ► Mix plasma specimens by vortexing or inverting the tube several times.

Step 1 – Patient Specimen

1. Open the pouch and label the Test Device with the patient identification number.

   NOTE: Do not use fluorescent or brightly colored ink, or write outside of the blank area as this may interfere with the test.
2. Place the Test Device on a level, horizontal surface.
3. Using the Transfer Pipette, squeeze the larger (top) bulb completely and insert the tip into the specimen.
4. Release the bulb slowly. The Transfer Pipette barrel should fill completely with some fluid flowing into the smaller (lower) bulb.

   NOTE: Ensure that the pipette is not under filled or over filled. An under filled pipette is one where the barrel is not filled completely with specimen and there is no specimen in the lower bulb. An over filled pipette is one where there is some specimen in the top bulb. Ideally the lower bulb should contain a small amount of specimen (less than one quarter the volume of the lower bulb).
5. Place the tip of the Transfer Pipette into the sample port of the Test Device and squeeze the larger bulb completely. The entire volume of fluid in the Transfer Pipette barrel must flow into the sample port. The specimen in the smaller (lower) bulb should not be expelled.

   NOTE: Too much specimen has been added to the device if the specimen has migrated outside of the sample port and on to the label.
6. Remove the Transfer Pipette tip from the sample port and then release the larger (top) bulb.
7. Discard the Transfer Pipette.
8. Allow specimen to absorb completely before moving the Test Device. At a minimum the sample should be below the sample port opening to be considered fully absorbed.

Step 2 – Run Test

1. From the main screen, select **Run Test** and press **Enter**.
2. Select **Patient Sample** and press **Enter**.
3. Enter the patient identification number and press **Enter**.
4. Confirm that the number was entered correctly by selecting **Confirm Patient ID** and pressing **Enter**. If the number was not entered correctly, select **Correct Patient ID**, press **Enter** and repeat the previous step.
5. Holding the Test Device by the edges, insert the Test Device into the Meter and press **Enter**. The results will be displayed when the analysis is complete.

NOTE: The Test Device must be inserted into the Meter within 30 minutes from the time the patient specimen was added. A delay longer than 30 minutes may cause the results to be invalid and blocked out on the printout.

Step 3 – Read the Results

1. Results may be printed by pressing the **Print** button.
2. Discard the Test Device after release from the Meter.
3. A blocked-out result indicates the result was invalid and the test should be repeated.

Results

The Meter measures the target analyte(s) automatically. The results are displayed on the screen. The operator has the option to print the results.

For additional information, refer to the Quidel Triage Meter User Manual.

STANDARDIZATION

The Quidel Triage Cardio3 Panel, Quidel Triage Cardio2 Panel and Quidel Triage Troponin I Test have been standardized using purified protein preparations of CK-MB, BNP and / or troponin I based on the mass (concentration) of analyte present in EDTA anticoagulated plasma. In particular, the troponin I is standardized to the mass (concentration) of NIST standard reference material for cardiac troponin I (SRM 2921) in EDTA anticoagulated plasma.

QUALITY CONTROL CONSIDERATIONS

Every Quidel Triage Cardio3 Panel, Quidel Triage Cardio2 Panel and Quidel Triage Troponin I Test is a quantitative test that includes two control materials of different concentrations that are run automatically with every patient specimen, external liquid control solution, or proficiency testing sample. If the automatic check of these built-in controls shows that the control value results are within the limits set during manufacturing, the Meter will report a result for the specimen or sample being tested. If the automatic check of these built-in controls shows that the control value results are not within the limits set during manufacturing, a test result will not be reported. Instead, the Meter will display a warning or error message that is described in the Quidel Triage Meter User Manual.

Good Laboratory Practice suggests that external controls should be tested with each new lot or shipment of test materials, or every 30 days, and as otherwise required by your laboratory's standard quality control procedures. Controls should be tested in the same manner as if testing patient specimens. When running patient specimens or external controls, if an analyte fails for any reason (built-in control failure or an external control out of range) no patient results will be reported.

Users should follow government guidelines (for example, federal, state or local) and/or accreditation requirements for quality control.

Performing Quidel Triage System Quality Control – QC Device

Use the QC Device to ensure proper function of the Meter. Perform QC Device testing for the following conditions:

- Upon initial setup of the Meter.
- Each day of patient testing.
- When the Meter has been transported or moved.
- Whenever there is uncertainty about the performance of the Meter.
- Whenever required by your laboratory's quality control requirements.

Do not discard the Quidel Triage QC Device and associated CODE CHIP module. Store them in the QC Device Box.

Refer to the Quidel Triage User Manual for complete instructions for use of the QC Device.

1. The first time a new QC Device is run in the Meter, install the QC Device CODE CHIP module. The QC Device CODE CHIP module data is stored in the Meter memory. The QC Device CODE CHIP module does not need to be reinstalled after the first time.

QC DEVICE CODE CHIP MODULE

   a. From the main screen, select **Install New Code Chip** and press **Enter**.
   b. Place the QC Device CODE CHIP module into the lower left front corner of the Meter. Follow the prompts on the screen.

   c. Remove the QC Device CODE CHIP module from the Meter when data transfer is complete.
   d. Place the QC Device CODE CHIP module back into the QC Device Box for storage.
2. From the main screen, select **Run Test** and press **Enter**.
3. If User ID is enabled enter your User ID number and press **Enter**.
4. Select **QC Device** and press **Enter**.
5. Insert QC Device into the Meter and press **Enter**.
6. A Pass or Fail result will be displayed when complete. Each parameter should pass before patient testing is performed.
7. Remove the QC Device from the Meter and place in the QC Device Box. **DO NOT DISCARD THE QC DEVICE.**

NOTE: If the QC Device or external controls do not perform as expected, review the above instructions to see if the test was performed correctly, repeat the test, or contact Quidel or your local Quidel representative (refer to the Assistance section). Refer to the Quidel Triage User Manual for a complete description of the quality control system.

LIMITATIONS OF THE PROCEDURE

- Test results should be evaluated in the context of all the clinical and laboratory data available. In those instances where test results do not agree with the clinical evaluation, additional tests should be performed accordingly.
- Severely hemolyzed specimens should be avoided. When a sample appears to be severely hemolyzed, another specimen should be obtained and tested.
- This test has been evaluated with venous whole blood and plasma using EDTA as the anticoagulant. Other specimen types, draw methods, or anticoagulants have not been evaluated. Use standard veni-puncture techniques. Follow the sample collection recommendations of the sample tube manufacturer.
- There is the possibility that factors such as technical or procedural errors, as well as interfering or cross-reacting substances in patient specimens, may impact test results and cause erroneous results.
- As with any assay employing mouse antibodies, the possibility exists for interference by human anti-mouse antibodies (HAMA) in the sample. The test has been formulated to minimize this interference; however, specimens from patients who have been routinely exposed to animals or to animal serum products may contain heterophile antibodies which may cause erroneous results.
- These assays are fluorescence immunoassays, and may be affected by environmental conditions. Therefore, it is important for each laboratory to establish its own reference range, based on the laboratory conditions and procedures.
- Patients with skeletal muscle injury may have elevated CK-MB. Patients with renal failure may have elevated CK-MB.
- Failure to display or report troponin I results invalidates the use of the test as an aid in the diagnosis of myocardial infarction (injury).
- Failure to display or report CK-MB results invalidates the use of the test as an aid in the diagnosis of myocardial infarction (injury).
- Failure to display or report BNP results invalidates the use of the test as an aid in the diagnosis and assessment of severity of heart failure, as well as the risk stratification of patients with heart failure and acute coronary syndromes.
- Troponin I results are not interchangeable with other Quidel Triage product lines.

PERFORMANCE CHARACTERISTICS

Representative Data: results in individual laboratories may vary from these data. Individual laboratory results may differ from these studies due to differences in the testing protocol, and between instruments, calibrations, reagents and replicates.

Analytical Sensitivity

The lowest detectable concentration that is distinguishable from zero with 95% confidence was determined for BNP, CK-MB, and TnI using the methods provided in CLSI EP17-A. Twenty replicates per day of a whole blood blank sample and twenty replicates of a plasma blank sample were each tested for 5 days on three lots of test devices. The analytical sensitivity is the 95th percentile of the measured results. The analytical sensitivity of each assay is presented below:

Troponin I: 0.01 ng/mL
CK-MB: 1.0 ng/mL
BNP: 5 pg/mL

In addition, the limit of quantitation for TnI and CK-MB was established using the methods provided in CLSI EP17-A. Whole blood and plasma samples containing low levels of TnI and CK-MB were tested with three lots of test devices across multiple replicates and test runs. Test results were analyzed to determine the lowest analyte concentration yielding a total CV less than 20%. These concentrations were defined as the limit-of-quantitation and are reported below.

Troponin I: 0.02 ng/mL
CK-MB: 1.5 ng/mL

Measurable Ranges

Troponin I: 0.01 - 10 ng/mL
CK-MB: 1.0 - 80 ng/mL
BNP: 5 - 5,000 pg/mL

Hook Effect

A sample containing elevated concentrations of BNP, CK-MB and TnI was assayed with multiple lots of Quidel Triage Cardio3 panel Test Devices. No high dose hook effect was observed with the Quidel Triage Cardio3 panel assays up to the following concentrations:

TnI: 2,870 ng/mL
CK-MB: 1,500 ng/mL
BNP: 152,000 pg/mL

Reproducibility

Within-run and total imprecision was evaluated by testing low and high plasma control samples using the methods described in CLSI document EP5-A2. The low control sample contained BNP, CK-MB, and TnI at concentrations near each analytes clinical decision point. The high control sample contained the same analytes at concentrations near the midpoint of each analytes measurable range. Both samples were tested in a single laboratory by a single operator. Furthermore, the study was completed with one lot of reagents, one Quidel Triage meter, and a single test device calibration. A total of 80 replicates were tested for each control sample. These data were collected over 40 separate test runs conducted over 20 days of testing. Each day, two test runs were completed. In each run, each control sample was tested in duplicate with two separate test devices. Data were analyzed using the methods described in CLSI document EP5-A2. Results of this analysis are presented below.

Plasma Precision

Analyte	Control Sample	Mean Concentration	Within-Run Precision		Total Precision	
			SD	%CV	SD	%CV
CK-MB	Low	7.6 ng/mL	0.6 ng/mL	7.9	0.8 ng/mL	10.8
	High	47 ng/mL	5 ng/mL	10.3	6 ng/mL	13.0
Troponin I	Low	0.06 ng/mL	0.01 ng/mL	16.0	0.01 ng/mL	16.7
	High	5.0 ng/mL	0.5 ng/mL	9.9	0.6 ng/mL	11.0
BNP	Low	116 pg/mL	7 pg/mL	6.0	8 pg/mL	6.7
	High	2461 pg/mL	293 pg/mL	11.9	330 pg/mL	13.4

An additional study was performed with whole blood samples following the same CLSI guideline. In this study, the whole blood was tested over 1 hour (stability of the analyte in whole blood) instead of multiple days.

Whole Blood Precision: Troponin

Device Lot	Lot 1		Lot 2		Lot 3	
Sample	Conc.	CV	Conc.	CV	Conc.	CV
Low	0.048	13.6	0.063	13.3	0.053	12.9
Med	0.47	15.2	0.38	12.2	0.45	12.5
High	7.28	12.9	6.06	11.4	4.52	16.4

Whole Blood Precision: CK-MB

Device Lot	Lot 1		Lot 2		Lot 3	
Sample	Conc.	CV	Conc.	CV	Conc.	CV
Low	6.5	12.3	9.6	12.0	8.6	11.3
Med	23.6	14.7	19.2	11.9	21.2	11.0
High	49.4	11.6	44.3	13.3	44.8	15.0

Quality Control specifications allow release of product that has the following range of precision (%CV):

Troponin I	CK-MB	BNP
8.4 – 19.4	5.5 – 17.4	5.4 – 19.4

Whole Blood / Plasma Method Comparison

Results in whole blood and plasma were compared by testing matching whole blood and plasma specimens in duplicate with a single lot of test devices. Study data were analyzed with Passing-Bablok regression analysis and Bland-Altman bias plots. The results of these analyses are presented below.

Analyte	Slope (95% CI)	Intercept (95% CI)	r	Mean Bias (%)
Troponin I	0.85 (0.82 to 0.89)	0.01 (−0.01 to 0.02)	0.976	−9.30%
CK-MB	1.13 (1.08 to 1.16)	0.00 (−0.15 to 0.14)	0.992	12.80%
BNP	1.06 (1.02 to 1.10)	-12.6 (−20.2 to −4.3)	0.973	0.20%

A bias can exist between whole blood and plasma specimen. It is recommended to use a consistent sample type when comparing results from multiple tests.

Interfering Substances

Samples containing up to 100 mg/dL hemoglobin, 280 mg/dL cholesterol, 500 mg/dL triglycerides, or 2 mg/dL bilirubin (conjugated) were evaluated for potential cross-reactivity and interference using the methods provided in CLSI EP7-A. These substances did not impact BNP, CK-MB, or troponin I results.

Pharmaceuticals

The following drugs were evaluated for potential cross-reactivity and interference using the methods provided in CLSI EP7-A. Each drug was added to a plasma pool containing approximately 100 pg/mL BNP, 5 ng/mL CK-MB, and 0.05 ng/mL troponin I. Each drug was tested at the concentration recommended by CLSI EP7-A or at a concentration at least equivalent to the maximum therapeutic level. None of the drugs impacted CK-MB, troponin I, or BNP results.

Acetaminophen	Dextromethorphan	Lisinopril
Activase	Digoxin	Loratadine
Albuterol	Diphenhydramine	Metoprolol
Alprazolam	Dopamine	Nicotine
Amiodipine	Doxycycline	Nicotinic acid
Amoxicillin	Erythromycin	Nitroglycerin
Ascorbic acid	Furosemide	Prednisone
Aspirin	Heparin	Prochlorperazine
Atenolol	Hydrochlorothiazide	Sertraline
Atorvastatin	Hydrocodone	Verapamil
Caffeine	Ibuprofen	Warfarin
Cephalexin	Levothyroxine	Zolpidem

Proteins

The BNP, CK-MB, and troponin I assays were evaluated for cross-reactivity with the following related proteins using the methods provided in CLSI EP7-A. Each protein was added to a plasma pool containing approximately 100 pg/mL BNP, 5 ng/mL CK-MB, and 0.05 ng/mL troponin I.

Cross-Reactivity with Related Protein				
Protein	**ng/mL**	**CK-MB**	**Troponin I**	**BNP**
		% Cross-reactivity	% Cross-reactivity	% Cross-reactivity
CK-BB	500	2.0	--	--
CK-MM	5000	0.0	--	--
cTnC	2000	--	0.0	--
cTnT	2000	--	0.0	--
sTnI	1000	--	0.0	--
sTnT	1000	--	0.0	--
ANP	1	--	--	0.2
NT-proANP	1	--	--	0.0
proBNP	0.5	--	--	2.6
NT-proBNP	1	--	--	0.1
CNP	1	--	--	0.0

EXPECTED VALUES - DIAGNOSIS OF MYOCARDIAL INFARCTION (INJURY)

Healthy Volunteers

CK-MB concentrations were determined using specimens obtained from 452 apparently healthy individuals (264 women and 188 men). The 95th percentile upper reference limit as determined with these specimens is shown below.

Analyte	95th Percentile
CK-MB	4.3 ng/mL

Troponin I concentrations were determined using specimens obtained from 989 apparently healthy individuals. The TnI values seen in this study ranged from <0.01 ng/mL to 0.065 ng/mL with a 90% confidence interval of 0.02 ng/mL to 0.03 ng/mL for the 99th percentile.

Analyte	95th Percentile	97.5th Percentile	99th Percentile
Troponin I	0.01 ng/mL	0.01 ng/mL	0.02 ng/mL

The above values are representative. In an external clinical study performed by Quidel Cardiovascular Inc., a negative bias was shown when using whole blood. A correlation between whole blood and plasma suggests that the proportional bias is approximately 0.95 at the cut-off. Therefore, the 99th percentile cut-off when using whole blood is approximately 0.019 ng/mL. Each laboratory should establish a reference range that is representative of its specific patient population, sample type, and environmental conditions. Additionally, each laboratory should consider the current practice in the evaluation of patients experiencing chest pain and AMI at their respective institution.

Clinical Performance in the Evaluation of Chest Pain

Plasma samples were collected in a prospective, multi-center study from 363 chest pain patients who presented to the hospital emergency department shortly after the onset of chest discomfort. These samples were tested to determine the sensitivity and specificity of troponin I and CK-MB in diagnosing myocardial infarction (MI). Patients meeting the following criteria were included in this study.

- 18 years of age or older
- Experiencing chest discomfort lasting at least 30 minutes in duration
- Presenting to the hospital emergency department within 6 hours of onset of chest discomfort

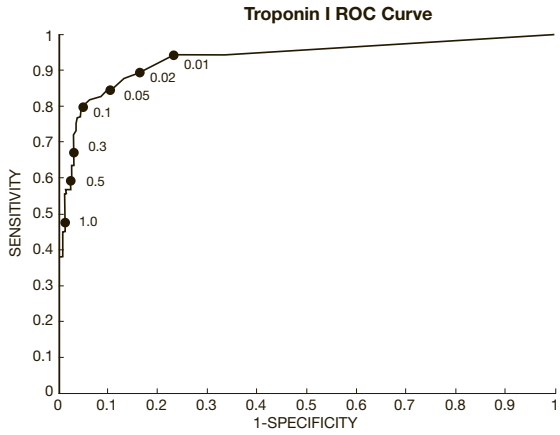
Among the 363 patients that were evaluated, 104 were assigned a final diagnosis of MI by the physician at each study site. The remaining 259 patients were assigned a final diagnosis other than MI. This included unstable angina, coronary artery disease, and other causes of chest pain where MI was ruled out.

Up to four serial blood samples were collected and tested for each patient. The sensitivity and specificity for the troponin I assay along with the median time from symptom onset for each of these serial samples are shown below.

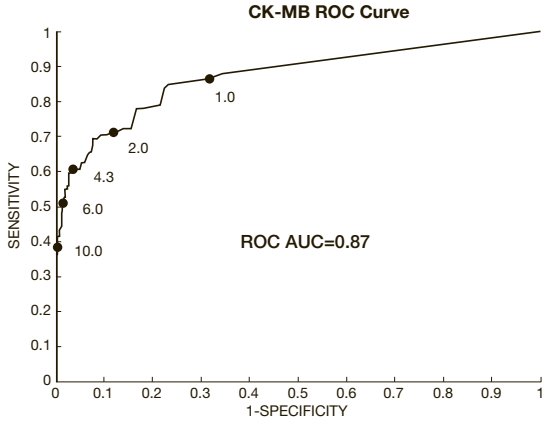
	Serial Sample Median Time From Symptom Onset			
	1st sample 4.00 hours	2nd sample 5.50 hours	3rd sample 7.08 hours	4th sample 10.00 hours
Cardio3 TnI > 0.02 ng/mL				
Number of Samples (MI, non-MI)	358 (103, 255)	351 (96, 255)	346 (90, 256)	344 (85, 259)
Sensitivity (95%CI)	0.78 (0.68, 0.85)	0.79 (0.70, 0.87)	0.87 (0.78, 0.93)	0.87 (0.78, 0.93)
Specificity (95%CI)	0.86 (0.81, 0.90)	0.89 (0.85, 0.93)	0.87 (0.82, 0.91)	0.89 (0.84, 0.92)

The sample that yielded the peak troponin I result for each patient was also evaluated to determine clinical performance. In particular, the receiver operating characteristics (ROC) analysis was conducted to assess the clinical sensitivity and specificity of troponin I and CK-MB. ROC curves constructed from the samples with peak troponin I values are provided below. Several potential cut-off concentrations are labeled along each curve.

Troponin I ROC Curve



CK-MB ROC Curve



The ROC curves graphically present the clinical sensitivity and specificity of troponin I and CK-MB across all potential cut-off concentrations. The clinical sensitivities and specificities at several defined cut-off concentrations, including the upper end of the normal reference range for each assay (i.e. troponin I >0.02 ng/mL and CK-MB >4.3 ng/mL), are tabulated below.

The above data were performed using plasma, not whole blood samples, and are representative. Each laboratory should establish reference ranges and diagnostic cut-off concentrations that are representative of the patient population to be evaluated, sample type, and environmental conditions. Additionally, each laboratory should consider current practice in the evaluation of patients experiencing chest pain and MI at their respective institution.

Interpretation of Results

Temporal elevations of CK-MB and troponin I are observed in patients diagnosed with myocardial infarction. However, CK-MB may be elevated in renal disease and skeletal muscle injury. In addition, while cardiac troponin I appears to be elevated only in those diseases that directly involve the heart, it may be elevated in conditions other than myocardial infarction. Other conditions that may result in elevated cardiac proteins are: cardiac contusions, myocarditis, invasive examination of the heart, coronary artery bypass surgery, congestive heart failure, and unstable angina. Collectively, the diagnosis of myocardial infarction should include measurement of troponin I and / or CK-MB as well as other clinical information, including patient history and electrocardiographic data.

EXPECTED VALUES – DIAGNOSIS AND ASSESSMENT OF SEVERITY OF CHF

Individuals Without CHF

The circulating BNP concentration was determined from 1286 individuals without CHF (676 women and 610 men). This population included individuals with hypertension, diabetes, renal insufficiency, and chronic obstructive pulmonary disease. There are no statistically significant changes in BNP concentration associated with hypertension, diabetes, renal insufficiency, and chronic obstructive pulmonary disease. The descriptive statistics for BNP concentrations in individuals without CHF are shown in the table below. The values are representative of the values obtained from clinical studies. The decision threshold was determined by the 95% confidence limit of BNP concentration in the non-CHF population age 55 and older. The most appropriate decision threshold apparent from these distributions is 100 pg/mL. This value translates into a general specificity of the test of 98%, i.e. less than 2% expected false positives in individuals without CHF. Each laboratory should establish a reference range that represents the patient population that is to be evaluated.

Descriptive Statistics - BNP Concentration (pg/mL)

Non-CHF Population

All

	All	Age < 45	Age 45-54	Age 55-64	Age 65-74	Age 75+
Median	12.3	7.7	11.1	17.9	19.8	53.9
95th Percentile	73.5	39.6	64.5	76.1	84.7	179.4
Percent < 100 pg/mL	98.0%	99.5%	99.2%	97.4%	96.9%	84.2%
Minimum	5.0	5.0	5.0	5.0	5.0	5.0
Maximum	252.0	251.3	252.0	207.7	197.9	218.5
N	1286	423	385	229	192	57

Males

	All	Age < 45	Age 45-54	Age 55-64	Age 65-74	Age 75+
Median	7.1	5.0	7.2	9.0	15.7	39.0
95th Percentile	56.9	23.8	39.0	72.4	62.7	77.9
Percent < 100 pg/mL	98.9%	98.9%	99.5%	98.3%	98.9%	95.8%
Minimum	5.0	5.0	5.0	5.0	5.0	5.0
Maximum	252.0	251.3	252.0	207.7	127.3	218.5
N	610	183	196	118	89	24

Females

	All	Age < 45	Age 45-54	Age 55-64	Age 65-74	Age 75+
Median	18.5	11.6	17.7	28.2	27.6	67.1
95th Percentile	84.2	47.4	71.7	80.5	95.4	179.5
Percent < 100 pg/mL	97.2%	100.0%	98.9%	96.4%	95.1%	75.8%
Minimum	5.0	5.0	5.0	5.0	5.0	5.0
Maximum	197.9	92.6	142.8	143.2	197.9	194.1
N	676	240	189	111	103	33

Individuals With CHF

Blood samples were obtained from 804 patients diagnosed with CHF (246 women and 558 men). The descriptive statistics for BNP concentrations in patients with CHF are presented in the table below. These values are representative of the values obtained from clinical studies. Each laboratory should establish a reference range that represents the patient population that is to be evaluated. In addition, laboratories should be aware of their respective institutions' current practice for the evaluation of patients with CHF.

CHF Population – All

NYHA Functional Class

	All CHF*	I	II	III	IV
Median	359.5	95.4	221.5	459.1	1006.3
5th Percentile	22.3	14.8	9.9	37.6	147.2
Percent> 100 pg/mL	80.6%	48.3%	76.6%	86.0%	96.3%
Minimum	5.0	5.0	5.0	5.2	5.0
Maximum	>5000	904.6	4435.8	>5000	>5000
N	804	118	197	300	187

CHF Population – Males

NYHA Functional Class

	All CHF*	I	II	III	IV
Median	317.8	87.8	232.6	458.9	1060.3
5th Percentile	21.9	16.8	10.7	25.0	196.5
Percent> 100 pg/mL	78.9%	46.5%	78.8%	85.2%	97.2%
Minimum	5.0	5.0	5.0	5.2	5.0
Maximum	>5000	904.6	2710.6	>5000	>5000
N	558	101	146	203	106

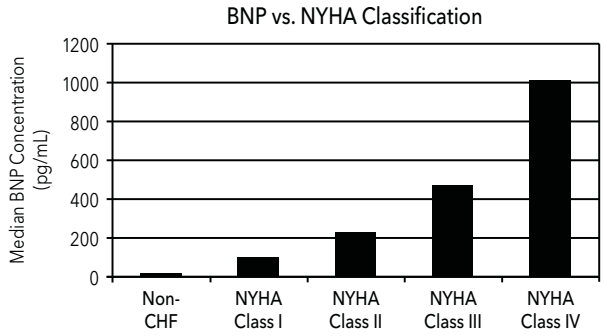
CHF Population – Females

NYHA Functional Class

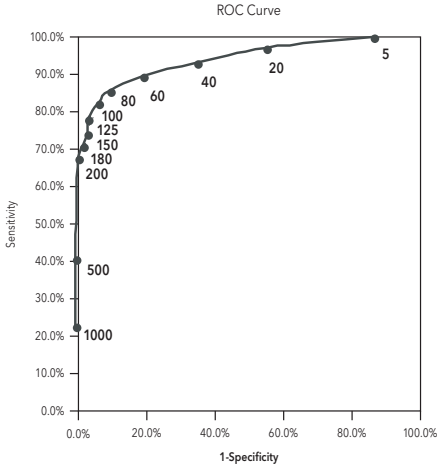
	All CHF*	I	II	III	IV
Median	499.7	114.7	191.2	469.2	966.5
5th Percentile	30.7	6.8	9.7	45.6	121.0
Percent> 100 pg/mL	84.6%	58.8%	70.6%	87.6%	95.1%
Minimum	5.0	5.0	5.0	11.7	15.5
Maximum	>5000	519.6	4435.8	4582.0	4706.5
N	246	17	51	97	81

***** 2 CHF with unknown NYHA class (male)

The New York Heart Association (NYHA) developed a four-stage functional classification system for CHF that is based on a subjective interpretation of the severity of a patient's clinical signs and symptoms. Class I patients have no limitations of physical activity and have no symptoms with ordinary physical activity. Class II patients have a slight limitation of physical activity and have symptoms with ordinary physical activity. Class III patients have a marked limitation of physical activity and have symptoms with less than ordinary physical activity, but not at rest. Class IV patients are unable to perform any physical activity without discomfort. Reports in the scientific literature have indicated that there is a relationship between BNP and the severity of CHF. An analysis of NYHA classification and BNP concentrations from the clinical study data indicate that there is a relationship between the severity of the clinical signs and symptoms of CHF and BNP concentration. These data are consistent with the previous reports in the literature, and further demonstrate that BNP measurements, along with NYHA classification, can provide additional objective information to the physician about the patient's CHF severity.



Various studies have demonstrated that circulating BNP concentrations increase with the severity of CHF based on the NYHA classification. BNP concentrations are much lower than ANP concentrations normally, but as the severity of CHF advances according to the NYHA classification, plasma BNP increases progressively more than respective ANP values. Therefore, BNP is a more useful marker than ANP to distinguish between normal subjects and patients in the earlier stages of CHF. BNP is more sensitive and specific than ANP for detecting decreases in LVEF. Additionally, there is a positive correlation between blood BNP concentrations and left ventricular end diastolic pressure and inverse correlation to left ventricular function following acute myocardial infarction. Blood BNP concentrations represent an independent assessment of ventricular function without the use of other invasive or expensive diagnostic tests. There is an association with elevated BNP concentrations and alterations in hemodynamic parameters including raised atrial and pulmonary wedge pressures, reduced ventricular systolic and diastolic function, left ventricular hypertrophy, and myocardial infarction. Numerous reports in the scientific literature have described the utility of BNP as a diagnostic marker for CHF and left ventricular dysfunction. These observations are supported by an analysis of the clinical study data. The Receiver Operating Characteristic (ROC) Curve of BNP cut-offs versus clinical sensitivity and specificity from the clinical study data is provided below. The area under the curve is 0.955 ± 0.005. The clinical utility of BNP also has been confirmed and described in detail in the scientific literature.



The clinical sensitivity and specificity of BNP using a cutoff of 100 pg/mL for various age groups within each gender is described in the table below.

Males	**Age < 45**	**Age 45-54**	**Age 55-64**	**Age 65-74**	**Age 75+**
Sensitivity	81.6%	76.0%	75.6%	79.3%	82.4%
95% Confidence Interval	70.8%-92.5%	67.5%-84.6%	68.2%-82.9%	72.6%-86%	76.1%-88.7%
Specificity	98.9%	99.5%	98.3%	98.9%	95.8%
95% Confidence Interval	97.4%-100.0%	98.5%-100.0%	97.7%-98.9%	98.4%-99.4%	94.7%-96.9%

Females	**Age < 45**	**Age 45-54**	**Age 55-64**	**Age 65-74**	**Age 75+**
Sensitivity	82.1%	69.0%	82.4%	97.9%	91.9%
95% Confidence Interval	68.0%-96.3%	57.1%-80.9%	71.9%-92.8%	93.7%-100.0%	85.2%-98.7%
Specificity	100.0%	98.9%	96.4%	95.0%	75.7%
95% Confidence Interval	100.0%-100.0%	97.5%-100.0%	95.5%-97.4%	93.4%-96.7%	72.2%-79.2%

It has been reported that BNP has excellent utility as an aid in the diagnosis of patients with CHF and preserved systolic function (CHF-PSF), generally referred to as diastolic dysfunction. The diagnostic utility of BNP in CHF-PSF patients was determined from the clinical study data by determining the area under the ROC curve for individuals without CHF versus 155 individuals with CHF that had ejection fractions ≥50%. The area under the curve is 0.934 ± 0.012, which indicates that the test is effective as an aid in the diagnosis of CHF in patients with preserved systolic function.

An age-matched analysis of the clinical data was performed with the following common age distribution in the groups of individuals with and without CHF: individuals less than 35 years old comprise 3% of the total number of observations, individuals age 35-44 comprise 6% of the total, individuals age 45-54 comprise 11% of the total, individuals 55-64 years old comprise 22% of the total, individuals 65-74 years old comprise 26% of the total, and individuals 75 years and older comprise 32% of the total. This age distribution reflects the prevalence of CHF within the age groups and genders, according to data published by the American Heart Association in the 2000 Heart and Stroke Statistical Update, and also reflects the age structure of the United States population, according to data published by the National Center for Health Statistics in Health, United States, 2000. The resulting area under the ROC curve is 0.930 with a 95% confidence interval of 0.902-0.958.

EXPECTED VALUES – RISK STRATIFICATION OF PATIENTS WITH ACS

BNP concentrations measured in patients with acute coronary syndromes (ACS) or cardiovascular disease provide prognostic information about the patient's risk for death and the development of CHF. Statistically significant increases in death, future myocardial infarction, and CHF have been associated with higher BNP concentrations measured within the first 72 hours after the onset of ACS symptoms. In a recent clinical study, BNP concentrations were evaluated in an observational, retrospective manner in patients with ACS (consisting of unstable angina, myocardial infarction with ST-segment elevation, or myocardial infarction without ST-segment elevation). BNP measurements were performed on specimens obtained within 72 hours after the onset of ischemic discomfort from a population of 2525 high-risk ACS patients that met standard diagnostic criteria for ACS. Patients whose BNP concentration was at least 80 pg/mL had higher rates of death, myocardial infarction, and CHF both at 30 days and at 10 months after presentation than patients whose BNP concentration was below 80 pg/mL. In this population of patients with ACS, BNP measurements within the first 72 hours after the onset of symptoms provide useful predictive information to aid in the risk stratification of patients with ACS.

Troponin I concentrations also have been described in the scientific literature to provide prognostic information related to the risk of future cardiac events and mortality in patients with acute coronary syndromes. More recently, it has been demonstrated that a multimarker analysis including troponin I, and CK-MB, provides better risk stratification than a single-marker approach.

Prognostic Utility in Patients with Heart Failure

BNP concentrations measured at admission and/or discharge in patients with heart failure provide prognostic information about the patient's risk for death or rehospitalization. A systematic review of studies investigating BNP for prognostic utility in patients with heart failure concluded that every 100 pg/mL increase in BNP concentration was associated with a 35% increase in the relative risk of death, and that admitted heart failure patients whose BNP values did not decrease over the course of their treatment are at a particularly high risk of death or a cardiovascular event. Doust et al also found that higher BNP concentrations in asymptomatic patients were prognostic for future death or cardiovascular events. Vrtovec et al and Harrison et al studied heart failure patients at the time of presentation and found that patients with higher BNP concentrations (> 1,000 pg/mL and > 480 pg/mL, respectively) had a significantly higher risk of all-cause, cardiac, and pump-failure death and cardiac-related readmissions. Cheng et al and Bettencourt et al studied admitted heart failure patients receiving treatment and found that patients who did not experience death or readmission within 30 days or 6 months exhibited a decrease in BNP concentrations from admission to discharge, while patients whose BNP concentration did not decrease from admission to discharge were at significantly higher risk for adverse events. Logeart et al found that admitted heart failure patients

with pre-discharge BNP concentrations of 350-700 pg/mL had a hazard ratio of 5.1 for death or readmission for heart failure within 6 months and patients with a pre-discharge BNP concentration greater than 700 pg/mL had a hazard ratio of 15.2 for the same endpoint compared to patients with a pre-discharge BNP concentration less than 350 pg/mL. Taken together, these studies indicate that higher BNP concentrations or the lack of a decrease in the BNP concentration from hospital admission to discharge indicate an increased risk of hospitalization or death in patients with heart failure.

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REFERENCES

1. AHA Medical/Scientific Statement, ACC/AHA Guidelines for the Early Management of Patients with Acute Myocardial Infarction. *Circulation* **82**: 664-707, 1990.
2. Bodor, G.S., Porter S., Landt, Y. and Ladenson, J.H. Development of Monoclonal Antibodies Specific for Troponin I and Preliminary Results in Suspected Cases of Myocardial Infarction. *Clin. Chem.* **38**: 2203-2214, 1992.
3. Puleo, P.R., Guadagno P.A., Roberts, R., Scheel, M.V., Marian, A.J., Churchill, D., and Perryman, M.B. Early Diagnosis of Myocardial Infarction for Subforms of Creatine Kinase-MB. *Circulation* **82**: 759-764, 1990.
4. Marin, M.M., and Teichman, S.L. Use of Rapid Serial Sampling of Creatine Kinase MB for Very Early Detection of Myocardial Infarction in Patients with Acute Chest Pain. *Am. Heart J.* **123**: 354-361, 1992.
5. Gerhardt, W., Waldenstrom, J., Horder, M., Hofvendahl, S., Billstrom, R., Ljungdahl, R., Berning, H., and Bagger, P. Creatine Kinase and Creatine Kinase B-Subunit Activity in Serum in Cases of Suspected Myocardial Infarction. *Clin. Chem.* **26**: 277-283, 1982.
6. Lee, T.H. and Goldman, L. Serum Enzyme Assays in the Diagnosis of Acute Myocardial Infarction: Recommendations Based on Quantitative Analysis. *Ann. Int. Med.* **105**: 221-233, 1986.
7. Vaidya, H.C., Maynard, Y., Dietzler, D.N., and Ladenson, J.H. Direct Measurement of Creatine Kinase-MB Activity in Serum after Extraction with a Monoclonal Antibody Specific to the MB isoenzyme. *Clin. Chem.* **32**: 657-663, 1986.
8. Hedges, J.R., Rouan, G.W., Tolzis, R., Goldstein-Wayne, B., and Stein, E.A. Use of Cardiac Enzymes Identifies Patients with Acute Myocardial Infarction Otherwise Unrecognized in the Emergency Department. *Ann. Emerg. Med.* **16**: 248-252, 1987.
9. Apple, F.S. Diagnostic Use of CK-MM and CK-MB Isoforms for Detecting Myocardial Infarction. *Clin. Lab. Med.* **9**: 643-655, 1989.
10. Hedges, J.R., Swanson, J.R., and Heeter, C. Prospective Assessment of Presenting Serum Markers for Cardiac Risk Stratification. *Ac. Emerg. Med.* **3**: 27-33, 1996.
11. Willerson, J.T., Clinical Diagnosis of Acute Myocardial Infarction. *Hosp. Prac.* **24**: 65-77, 1989.
12. Cummins, B., Auckland, M.S. and Cummins, P. Cardiac-Specific Troponin I Radioimmunoassay in the Diagnosis of Acute Myocardial Infarction. *Am. Heart J.* **113**: 1333-1344, 1987.
13. Apple, F.S. Acute Myocardial Infarction and Coronary Reprofusion: Serum Cardiac Markers for the 1990s. *Am. J. Clin. Path.* **97**: 217-226, 1992.
14. Laure, C., Calzolari, C., Bertinchant, J-P., Leclercq, F., Grolleau, R., and Pau, B. Cardiac Specific Immunoenzymometric Assay for Troponin I in the Early Phase of Acute Myocardial Infarction. *Clin. Chem.* **39**: 972-979, 1993.
15. Adams, J.E., Schechtman, K.D., Landt, Y., Ladenson, J.H., and Jaffe, A.S. Comparable Detection of Acute Myocardial Infarction by Creatine Kinase MB Isoenzyme and Cardiac Troponin I. *Clin. Chem.* **40**: 1291-1295, 1994.
16. Adams, J.E., Sicard, G.A., Allen, B.T., Bridwell, K.H., Lenke, L.G., Davila-Roman, V.G., Bodor, G.S., Ladenson, L.H., and Jaffe, A.S. Diagnosis of Perioperative Myocardial Infarction with Measurement of Cardiac Troponin I. *N. Eng. J. Med.* **330**: 670-674, 1994.

17. Brogan, G.X., Hollander, J.E., McCuskey, C.F., Thode, Jr., H.C., Sama, A., Bock, J.L., and the Biochemical Markers for Acute Myocardial Ischemia Study Group. Evaluation of a New Assay for Cardiac Troponin I vs Creatine Kinase-MB for the Diagnosis of Acute Myocardial Infarction. *Acad. Emerg. Med.* **4**: 6-12, 1997.

18. Adams, J.E., Bodor, G., D-Roman, V.G., Delmez, J.A., Apple, F.S., Ladenson J.H., and Jaffe, A.S. Cardiac Troponin I: A Marker with High Specificity for Cardiac Injury. *Circulation* **88**: 101-106, 1993.

19. Buechler, K.F., and McPherson, P.H. Novel Methods for the Assay of Troponin I and T and Complexes of Troponin I and T and Selections of Antibodies for Use in Immunoassays. International Patent WO 96/33415, 18 April, 1995.

20. Katrukha, A.G., Bereznikova, A.V., Esakova, T.V., Pettersson, K., Lövgren, T., Severina, M.E., Pulkki, K., Vuopio-Pulkki, L.-M., and Gusev, N.B. Troponin I is released in bloodstream of patients with acute myocardial infaction not in free form but as complex. *Clin. Chem.* **43**: 1379-1385, 1997.

21. Wu, A., B-Type natriuretic peptide and its clinical utility in patients with heart failure. *Med. Lab. Ob.* **10**: 10-14, 2001.

22. Wu, A., Analytical and clinical evaluation of new diagnostic tests for myocardial damage. *Clin. Chim. Acta* **272**: 11-21, 1998.

23. Bonow, R. O., New insights into the cardiac natriuretic peptides. *Circulation,* **93**: 1946-1950, 1996.

24. McDowell, G., Shaw, C., Buchanan, K., and Nicholls, D., The natriuretic peptide family. Eur. *J. Clin. Invest.* **25**: 291-298, 1995.

25. Yandle, T., Biochemistry of natriuretic peptides. *J. Internal Med.* **235**: 561-576, 1994.

26. Mukoyama, M., Nakao, K., Hosoda, K., Hosoda, K., Suga, S., Saito, Y., Ogawa, Y., Shirakami, G., Jougaski, M., Obata, K., Yasue, H., Kambayashi, Y., Inouye, K., and Imura, H., Brain natriuretic peptide as a novel cardiac hormone in humans: Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J. Clin Invest.* **87**: 1402-1412, 1991.

27. Clerico, A., Iervasi, G., Del Chicca, M.G., Emdin, M., Maffei, S., Nannipieri, M., Sabatino, L.,Forini, F., Manfredi, C., and Donato, L., Circulating levels of cardiac natriuretic peptides (ANP and BNP) measured by highly sensitive and specific immunoradiometric assays in normal subjects and in patients with different degrees of heart failure. *J. Endocrinol. Invest.* **21**: 170-179, 1998.

28. deLemos, J.A., Morrow, D.A., Bentley, J.H., Omland, T., Sabatine, M.S., McCabe, C.H., Hall, C., Cannon, C.P., and Braunwald, E., The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N. Eng. J. Med.* **345**: 1014-1021, 2001.

29. Maeda, K., Tsutamoto, T., Wada, A., Hisanaga, T. and Kinoshita, M., Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am. Heart J.* **135**: 825-832, 1998.

30. Dao, Q., Krishnaswamy, P., Kazanegra, R., Harrison, A., Amirnovin, R., Lenert, L., Clopton, P., Alberto, J., Hlavin, P., and Maisel, A., Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J. Am. Coll. Cardiol.* **37**: 379-385, 2001.

31. Mukoyama, M., Nakao, K., Saito, Y., Ogawa, Y., Hosoda, K., Suga, S., Shirakami, G., Jougasaki, M., and Imura, H., Increased human brain natriuretic peptide in congestive heart failure. *N. Engl. J. Med.* **323**: 757-758, 1990.

32. Sagnella, G.A., Measurement and significance of circulating natriuretic peptides in cardiovascular disease. *Clin. Science* **95**: 519-529, 1998.

33. McDonagh, T.A., Robb, S.D., Murdoch, D.R., Morton, J.J., Ford, I., Morrison, C.E., Tunstall-Pedoe, H., McMurray, J.J.V., and Dargie, H.J., Biochemical detection of left-ventricular systolic dysfunction. *Lancet* **351**: 9-13, 1998.

34. Mair, J., Friedl, W., Thomas, S., and Puschendorf, B., Natriuretic Peptides in assessment of left-ventricular dysfunction. Scand. *J. Clin. Lab. Invest.* **59**: 132-142, 1999.

35. Muders, F., Kromer, E.P., Griese, D.P., Pfeifer, M., Hense, H.-W., Riegger, G.A.J., and Elsner, D., Evaluation of plasma natriuretic peptides as markers for left ventricular dysfunction. *Am. Heart J.* **134**: 442-449, 1997.

36. Cowie, M.R., Struthers, A.D., Wood, D.A., Coats, A.J.S., Thompson, S.G., Poole-Wilson, P.A., and Sutton, G.C., Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* **350**: 1347-1351, 1997.

37. Maisel, A.S., Krishnaswamy, P, Nowak, R.M., McCord, J., Hollander, J.E., Duc, P., Omland, T., Storrow, A.B., Abraham, W.T., Wu, A.H., Clopton, P., Steg, P.G., Westheim, A., Knudsen, C.W., Perez, A., Kazanegra, R., Herrmann, H.C., McCullough, P.A; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N. Engl. J. Med.* **347**: 161-167, 2002.

38. McCullough, P.A., Nowak, R.M., McCord, J., Hollander, J.E., Herrmann, H.C., Steg, P.G., Duc, P., Westheim, A., Omland, T., Knudsen, C.W., Storrow, A.B., Abraham, W.T., Lamba, S., Wu, A.H., Perez, A., Clopton, P., Krishnaswamy, P., Kazanegra, R., and Maisel, A.S. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* **106**: 416-422, 2002.

39. Maisel, A.S., Koon, J., Krishnaswamy, P., Kazanegra, R., Clopton, P., Gardetto, N., Morrisey, R., Garcia, A., Chiu, A., and De Maria, A., Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. *Am. Heart J.* **141**: 367-374, 2001.

40. Lubien, E., DeMaria, A., Krishnaswamy, P., Clopton, P., Koon, J., Kazanegra, R., Gardetto, N., Wanner, E., and Maisel, A.S., Utility of B-natriuretic peptide in detecting diastolic dysfunction. *Circulation* **105**: 595-601, 2002.

41. Krishnaswamy, P., Lubien, E., Clopton, P., Koon, J., Kazanegra, R., Wanner, E., Gardetto, N., Garcia, A., DeMaria, A., and Maisel, A.S., Utility of B-natriuretic peptide in identifying patients with left ventricular systolic or diastolic dysfunction. *Am. J. Med.* **111**: 274-279, 2001.

42. Omland, T., Aakvaag, A., Bonarjee, V.V.S., Caidahl, K., Lie, R.T., Nilsen, D.W.T., Sundsfjord, J.A., and Dickstein, K., Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction. *Circulation* **93**: 1963-1969, 1996.

43. Richards, A.M., Nicholls, M.G., Yandle, T.G., Ikram, H., Espiner, E.A., Turner, J.G., Buttimore, R.C., Lainchbury, J.G., Elliott, J.M., Frampton, C., Crozier, I.G., and Smyth, D.W., Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. *Heart* **81**: 114-120, 1999.

44. Stein, B.C. and Levin, R.I., Natriuretic peptides: physiology, therapeutic potential, and risk stratification in ischemic heart disease. *Am. Heart J.* **135**: 914-923, 1998.

45. Wallen, T., Landahl, S., Hedner, T., Nakao, K., and Saito, Y., Brain natriuretic peptide predicts mortality in the elderly. *Heart* **77**: 264-267, 1997.

46. Darbar, D., Davidson, N.C., Gillespie, N., Choy, A.M.J., Lang, C.C., Shyr, Y., McNeill, G.P., Pringle, T.H., and Struthers, A.D., Diagnostic value of B-type natriuretic peptide concentrations in patients with acute myocardial infarction. *Am. J. Cardiol.* **78**: 284-287, 1996.

47. Galvani, M., Ferrini, D., Ghezzi, F., and Ottani, F., Cardiac markers and risk stratification: an integrated approach. *Clin Chim Acta* **311**: 9-17, 2001.

48. Meyer, T., Binder, L., Graeber, T., Luthe, H., Kreuzer, H., Oellerich, M., Buchwald, A.B., Superiority of combined CK-MB and troponin I measurements for the early risk stratification of unselected patients presenting with acute chest pain. *Cardiology* **90**: 286-294, 1998.

49. de Winter, R.J., Risk stratification with cardiac troponin I in acute coronary syndromes. J. *Am. Coll. Cardiol.* **36**: 1824-1826, 2000.

REF

97400EU – Quidel Triage Cardio3 Panel
97500EU – Quidel Triage Cardio2 Panel
98600EU – Quidel Triage Troponin I Test

IVD

CE

EC REP

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Revision Changes:

Initial release for Quidel Cardiovascular Inc.

GLOSSARY

REF Catalogue number	CE CE mark	EC REP Authorized representative in the European Community
LOT Batch code	Use-by date	Manufacturer
Date of manufacture	Temperature limit	Intended use
Consult instructions for use	IVD *In vitro* diagnostic medical device	TEST DEVICE Test device
Do not re-use	CONT Contents/Contains	# Patient number
Transfer pipette	CODE CHIP module	Printer paper
Peel open here	Add sample immediately after opening foil pouch	EDTA EDTA Use EDTA whole blood or plasma sample only
Add sample here		