Abbott

CARDIAC BIOMARKER CONSENSUS PAPERS

INFOGRAPHIC SUMMARIES OF SIX EXPERT CONSENSUS PAPERS ON THE USE OF CARDIAC BIOMARKERS IN REGULAR CLINICAL PRACTICE

INTRODUCTION

WHEN IT COMES TO PREVENTION OF CARDIOVASCULAR EVENTS, EARLY DETECTION OF PEOPLE WITH AN ELEVATED RISK OF DEVELOPING CARDIOVASCULAR DISEASE IS KEY[1]

The development of increasingly sensitive assessment methods, such as the use of cardiac biomarker assays, **could help to improve existing cardiovascular risk-stratification strategies** in the general population and allow clinicans to identify patients who are at a low-, intermediate- and high-risk of a future cardiac event.[2,3]

Abbott is committed to advancing cardiovascular risk stratification through the development of cardiac biomarker tests such as STAT High Sensitive Troponin-I (hsTnI) and B-type natriuretic peptide (BNP) and Alere N-terminal pro-B-type natriuretic peptide (NT-proBNP) assays. These biomarkers can support the stratification of cardiovascular risk in an asymptomatic population (STAT hsTnI), the risk stratification of patients with acute coronary syndrome and CHF, monitoring the treatment in patients with left ventricular dysfunction (Alere NT-proBNP), and the diagnosis and assessment of severity of heart failure (BNP). This document contains infographic summaries of six consensus papers written by **61 thought leaders across seven regions,** outlining their expert opinions on the use of cardiac biomarkers and how they can **support clinicians around the world to stratify cardiovascular risk.**

DISCOVER THE INTENDED USE FOR...

- hsTnI[4,5]
- BNP[6,7]
- NT-proBNP[8,9]

REFERENCES:

1. Mendis S. Global progress in prevention of cardiovascular disease. *Cardiovascular diagnosis and therapy*. 2017;7(1):32–38.
2. Farmakis D, Mueller C, Apple FS. High-sensitivity cardiac troponin assays for cardiovascular risk stratification in the general population, *European Heart Journal*. 2020;41:4050–4056
3. Muscente F, Caterina RD. New insights from the MESA study: increased high-sensitivity troponins as a cardiovascular risk factor, *European Heart Journal Supplements*. 2021;23:68–72
4. ARCHITECT STAT High Sensitive Troponin-I [package insert]. Lake Bluff, IL: Abbott Laboratories; 2018. G97079R01.
5. Alinity i High Sensitive Troponin-I [package insert]. Lake Bluff, IL: Abbott Laboratories; 2019. H05938R03.
6. BNP for Alinity i Reagent [package insert]. 704-326R02.
7. BNP for ARCHITECT Reagent [package insert] 616-001R02.
8. Alere NT-proBNP for Alinity i Reagent [Package insert]. ABBL535R03.
9. Alere NT-proBNP for ARCHITECT Reagent [Package insert]. ABBL458R03.

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NEW OPPORTUNITIES FOR BIOMARKERS IN CARDIOVASCULAR (CV) RISK STRATIFICATION[1]

Drapkina, O.M. and Kontsevaya A.V. *Russian Journal of Cardiology*. 2021;(26)9:4700.

Early detection of people with a high risk of developing cardiovascular diseases (CVD) is key to prevention.[2] Therefore, implementing **accurate and cost-effective methods** of risk stratification for the general population is vital to support efforts to reduce the global impact of CVD. Prevention is based on **two fundamentals:**

Accurate cardiovascular risk (CVR) stratification

Optimal interventions with established efficacy, including non-medical risk factor management and drug therapy

Biomarkers such as cardiac troponins (cTn), which are currently well established in the acute setting, have been shown to provide accurate assessment for risk stratification.

SEX-SPECIFIC DIFFERENCES IN THE PREDICTIVE ROLE OF TROPONIN I (TnI)

The Russian pilot study was conducted to assess the significance of biomarkers in predicting the risk of CV outcomes in men and women of reproductive age. The results demonstrated **differences between men and women** including:

Young men have higher cTn levels than women of the same age group

Women's cTn grows faster with age: 5.9% per year compared to 2.6% for men

SCORE* risk was low to moderate in 25% of men and 37% of women with elevated TnI levels.

*SCORE = Systemic Coronal Risk Evaluation

COST EFFECTIVENESS OF TnI ASSESSMENT

In a secondary analysis of BiomarCaRE, cost-effectiveness modelling of TnI was carried out to estimate cardiovascular risk (CVR) in the general population of Germany (low CVR) and Kazakhstan (high CVR).

Screening and prevention could reduce CV events by 5.1 and 5.0 per 1000 people over 10 years in both countries[1]

In Kazakhstan, **this strategy led to economic savings:** the increased cost of conducting TnI risk assessment was lower than the economic savings to the healthcare system from avoided deaths[1]

In Germany, **the cost of preserving quality of life,** per year, was $6,755, significantly **lower than the "willingness-to-pay" threshold** for this country.[1]

Facilitating the prevention of CVDs involves accurate risk stratification.
As existing risk stratification scales have limitations, enhancing them with **biomarkers that can help to predict CV risk, such as TnI, could improve the accuracy of risk stratification.**

REFERENCES:
1. Drapkina, O.M. and Kontsevaya A.V. New opportunities for biomarkers in cardiovascular risk stratification. *Russian Journal of Cardiology*. 2021;(26)9:4700.
2. Mendis S. Global progress in prevention of cardiovascular disease. *Cardiovascular diagnosis and therapy*. 2017;7(1):32–38.

HIGH SENSITIVE TROPONIN-I FOR CARDIOVASCULAR (CV) RISK STRATIFICATION IN THE GENERAL ASYMPTOMATIC POPULATION: PERSPECTIVES FROM ASIA-PACIFIC (APAC)[1]

Lam CSP, Castillo R, Ho DT, et al. *International Journal of Cardiology.* 2019;(282):93–98.

Concern is growing over the cardiovascular disease (CVD) epidemic in Asia, and there is a critical need to improve CVD risk stratification in the APAC region. **Cardiac troponin (cTn) is well established as a biomarker for acute myocardial injury** and has **emerged as a valuable tool** to support clinicians in **identifying asymptomatic patients with an elevated risk of a future cardiac event,** so that they can be treated proactively.

Research indicates that high-sensitivity Troponin I (hsTnI) is an **independent predictor of a future CV event** in the asmptomatic population

hsTnI can be **reliably identified in 80–90% of asymptomatic individuals** with research showing a connection between detectable levels of cTn and cardiac events

hsTnI has been found to outperform high sensitivity C reactive protein (hsCRP) in the risk stratification of future CV events

LIMITATIONS OF CURRENT CVD RISK STRATIFICATION STRATEGIES IN THE APAC REGION

Current risk scoring systems for CVD prevention are widely available, however, as they are mainly based on caucasian populations, they may inaccurately stratify CV risk in other ethic groups (through over- or under-estimation), leading to unnecessary treatment with preventative medication or delays in accessing suitable therapy.

The SCORE model has been found to be relatively accurate for Asian men, but underestimates CV risk in women.

The AHA-ACC-ASCVD and three Framingham based scores overestimated CV events by as much as 154% in men and 67% in women.

IN APAC POPULATIONS, hsTnI UTILIZATION FOR CV RISK STRATIFICATION REQUIRES FURTHER RESEARCH

An Australian study found that doubling of baseline hsTnI values was a significant predictor of CVD mortality, CV events and detecting high-risk asymptomatic individuals within the APAC population.

- The Asia Pacific Cohort Studies Collaboration assessed **the relationship between known CV risk factors and CV events in 34 population-based cohorts** in APAC
- The study discovered comparable associations between **risk factor clusters and risk of CV events** in Australia, New Zealand, and Asia
- The disparities in risk factor prevalence across sexes and regions led to **differences in the burden of CVD** attributable to risk factors

Several studies with hsTnI have not only **shown independent associations with adverse CV outcomes,** but also **increased net reclassification improvement** (NRI) – a quantitative measure of how appropriately a risk model reclassifies subjects in comparison to a previous model.

IN CONJUNTION WITH CLINICAL AND DIAGNOSTIC FINDINGS, hsTnI CAN IMPROVE CV RISK STRATIFICATION IN THE GENERAL POPULATION, BASED ON THE CURRENT PUBLISHED DATA

Further studies and real-world evidence will **help to establish biomarker thresholds for risk stratification** of the APAC population.

REFERENCES:

1. Lam CSP, Castillo R, Ho DT, et al. High-sensitivity troponin I for cardiovascular risk stratification in the general asymptomatic population: Perspectives from Asia-Pacific. *International Journal of Cardiology.* 2019;(282):93–98.

EXPERT CONSENSUS ON THE USE OF BIOMARKERS FOR CARDIOVASCULAR DISEASE (CVD) RISK ASSESSMENT IN PHYSICAL EXAMINATION POPULATION*[1]

Chinese Society of Health Management, Chinese Society of Laboratory Medicine and Chinese College of Cardiovascular Physicians.
***Chinese Journal of Health Management*. 2022; 16(8):505–519.**

Advancements in CVD risk stratification have been made by developing increasingly sensitive assessment methods such as biomarker assays to help ensure **accurate risk stratification to tackle the global disease burden.**

China currently carries the most significant burden of CVD in the world. Therefore, it is imperative to establish and assess CVD prediction models to help ensure **scalability** and **effectiveness.** CVD prediction models have been developed using data from long-term follow-up cohort studies of CVD in China, e.g. the China-PAR model.

THE CHINA-PAR MODEL MAKES A CALCULATION BASED ON RISK FACTORS SUCH AS:

- **Sex**
- **Age**
- **Current residence**
- **Waist circumference**
- **Total cholesterol**
- **High-density lipoprotein-cholesterol**
- **Current blood pressure level and blood pressure medication history**
- **History of smoking and/or diabetes**
- **Family history of CVD and cerebrovascular diseases.**

THE USE OF CARDIAC BIOMARKERS IN CVD RISK ASSESSMENT

In 2020, the European Society of Cardiology proposed that potential biomarkers for CVD risk stratification in the general population should fulfil the following requirements:

Cardiac specificity

The ability to predict future cardiovascular (CV) events

The ability to detect/respond to changes in biomarker levels following interventions such as the control of risk factor

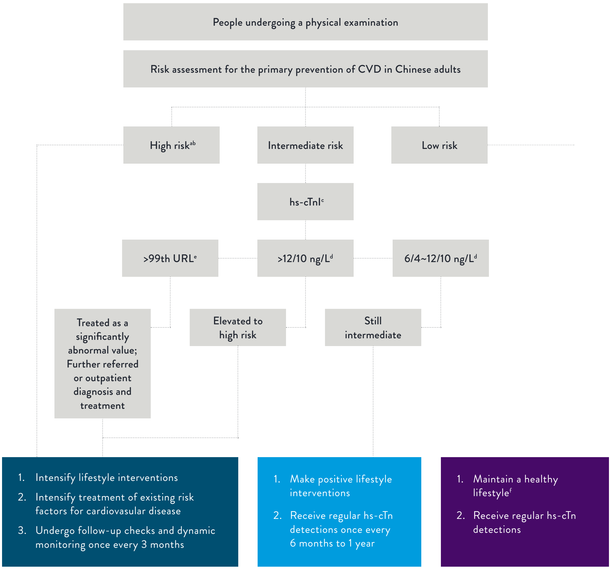
The ability to increase the value of existing risk assessment tools

Cost effectiveness

High sensitivity cardiac troponin (hs-cTn) can be used on the basis that the general population are first stratified for CVD risk using traditional assessment tools, the level of CVD risk should be based on **different cut off values of hs-cTn with specific reference values for sex** and different methodologies.

Biomarkers such as hs-cTn, BNP, or NT-proBNP should be evaluated in annual physical exams for people at risk of CVD.

CARDIAC TROPONINS CAN BE EASILY INCORPORATED INTO ANNUAL PHYSICAL EXAMINATIONS USING THE FOLLOWING DECISION TREE:



Note: Adapted from Chinese Society of Health Management et al, Figure 2.[1] [a]High risk: patients with diabetes (aged 40 or above), LDL-C levels ≥ 4.9 mmol/L (or TC ≥ 7.2 mmol/L), or with stage 3/4 CKD; [b]: people considered at high risk can also be screened for cTn for detection of people with > 99th URL and referred to the Department of Cardiovascular Medicine; [c]: the cut-off values of hs-cTnI levels are based on the Abbott chemiluminescence assay; [d]: the cut-off values are gender-specific cut-off values; [e]: the cut-off of the 99th URL may vary by assay; [f]healthy lifestyle: (1) maintain a reasonable diet; (2) engage in physical activity; (3) control body weight; (4) quit smoking; (5) control alcohol intake; (6) maintain sleep; and (7) keep a good state of mind.

CARDIAC TROPONIN, PARTICULARLY cTnI, AND cTnT ARE HIGHLY SPECIFIC MARKERS OF MYOCARDIAL TISSUE DAMAGE DUE TO HIGHER SENSITIVITY AND SPECIFICITY THAN CK-MB AND MYOGLOBIN

Numerous studies have established the predictive utility of hs-cTn elevation for future CV events in the general population, including WOSCOPS, BiomarCaRE, and HUNT

High Sensitive Troponin-I has been independently associated with the long-term risk of **CV mortality, CVD, and total mortality**

Very low concentrations of cTn can be **detected in 50–96% of asymptomatic individuals,** so is suitable for CVD risk assessment in the general population

*In this paper, the physical examination population is defined as an "apparently healthy population" (such as people undergoing a physical exam).

REFERENCES:
1. Chinese Society of Health Management, Chinese Society of Laboratory Medicine, Chinese College of Cardiovascular Physicians. Expert consensus on the use of biomarkers for cardiovascular disease risk assessment in physical examination population. *Chinese Journal of Health Management.* 2022;16(8):505–519.

HIGH SENSITIVITY TROPONINS: POTENTIAL BIOMARKERS OF CARDIOVASCULAR (CV) RISK FOR PRIMARY PREVENTION[1]

Leite L, Matos P, Leon-Justel A, et al. *Frontiers in Cardiovascular Medicine*. 2022;(9):1054959.

Biomarkers such as cardiac troponins (cTn) can be used as myocyte injury markers for use in assessing CV risk levels in the general, asymptomatic population. Troponin assays such as the High Sensitive Troponin-I (hsTnI) assay have been shown to have **good analytical performance**, the ability to **measure very low levels of circulating troponin** and **have low intra individual variation of below 10%.**

A biomarker, when used in combination with other measurable factors, can be applied to risk stratification charts and has a potential role in assisting with **calculating risk,** selecting appropriate treatment interventions, and potentially **precluding adverse patient outcomes.**

Several studies have shown that hsTnI can complement current CV risk charts, and that both cTns and cardiac natriuretic peptides (cNPs) are able to detect individuals in the general population who have an elevated level of CV risk.

CARDIOVASCULAR BIOMARKERS

Several studies have investigated cardiac-specific biomarkers for their role in risk stratification and screening of CV. Results from the STOP-HF study have indicated that cNP biomarkers could be used as a **screening tool to assess heart failure risk** in those who were >40 years of age and had at least one risk factor.[1,2] Additionally, cardiac troponins such as cTnI and cTnT have been the most successful cardiac specific circulating biomarkers in CV medicine because they have:[2]

Significantly **enhanced the diagnosis** of acute chest pain[3]

Shown pathological elevation in various conditions and are considered an **independent predicitve tool** in several CV conditions.[4]

Troponin levels increase with age and vary according to sex and ethnicity; consequently, cut-offs must be modified to account for these differences. Furthermore, renal function should also be considered since low glomerular filtration rate reduces troponin clearance.

A META-ANALYSIS OF 28 LONG-TERM PROSPECTIVE STUDIES SHOWED THAT INDIVIDUALS WITH CARDIAC TROPONIN VALUES IN THE TOP THIRD OF THE POPULATION DISTRIBUTION ARE AT:

- **A 43% increased risk of any CV disease**
- **A 59% increased risk of coronary heart disease**
- **A 67% increased risk of fatal CV disease outcomes**
- **A 35% increased risk of stroke**

In post-hoc study analyses, hsTnI improved mortality and CV risk stratification in older adults (>66 years) beyond traditional risk factors. Cardiac troponin I concentrations were also significantly associated with a first major CV event, and with a higher all-cause mortality.

CARDIAC TROPONINS CAN SUPPORT CLINICIANS TO MORE ACCURATELY ASSESS CV RISK LEVELS IN THE GENERAL POPULATION, IN CONJUNCTION WITH CLINICAL AND DIAGNOSTIC FINDINGS

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1. Leite L, Matos P, Leon-Justel A, et al. High sensitivity troponins: A potential biomarkers of cardiovascular risk for primary prevention. *Frontiers in Cardiovascular Medicine*. 2022;(9):1054959.
2. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *Journal of the American Medical Association*. 2013;310(1):66–74.
3. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*. 2021;42(36):3599–3726.
4. Chaulin AM. Elevation Mechanisms and Diagnostic Consideration of Cardiac Troponins under Conditions Not Associated with Myocardial Infarction. Part 1. *Life (Basel)*. 2021;11(9):914.

EVIDENCE ON CLINICAL RELEVANCE OF CARDIOVASCULAR (CV) RISK EVALUATION IN THE GENERAL POPULATION USING CARDIO-SPECIFIC BIOMARKERS[1]

Clerico A, Zaninotto M, Passino C, et al. *Clinical Chemistry and Laboratory Medicine*. 2020;59(1):79–90.

The role of cardiovascular (CV) prevention in the asymptomatic population is based on **two fundamental clinical actions:**

Accurate risk stratification

Optimal prevention methods

Early detection of individuals with an elevated CV risk should be the most important goal of primary prevention in the general population, and many studies have demonstrated that cardiac-specific biomarkers such as cardiac troponins (cTn) and natriuretic peptides (cNP) may help identify elevated CV risk in apparently healthy individuals.

> Measurement of cTnI and cTnT using high-sensitivity methods in multiple studies have demonstrated that combined mortality and cardiovascular risk increases even in the general population who have cTn values below the 99th percentile URL (i.e., the cut-off value recommended by international guidelines for the diagnosis of myocardial injury).

CARDIAC BIOMARKERS

Results from previous studies indicate that brain natriuretic peptide (BNP) and NT-proBNP assays are able to differentiate individuals who have structural heart disease (in an asymptomatic population), while cTns such as troponin I (cTnI) and troponin T (cTnT) are able to detect individuals in the general population who have an elevated CV risk.

Cardiac-specific biomarkers such as **cNP and cTn show different, but complementary, pathophysiological characteristics.** An increment in circulation of both biomarkers suggest that:

- **Powerful stressor mechanisms have already caused relevant alterations to cardiac function (i.e., increased cNP levels)**
- **There is evidence of damage to cellular structure (i.e. increased high sensitivity cTn [hs-cTn] levels).**

A NUMBER OF STUDIES REPORT THAT INDIVIDUALS WHO ARE SHOWN TO HAVE INCREASED CIRCULATING LEVELS OF BOTH OF THESE BIOMARKERS HAVE MORE SEVERE OUTCOMES THAN THOSE WITH ONLY ONE ALTERED BIOMARKER

- cTnI and cTnT show a **more favourable analytical and biological profile** for a cardiovascular risk marker than cNP
- A single measurement of cTn using high sensitivity methods can **support clinicians with the prediction of CV risk**
- hs-cTn methods could **identify individuals who are at the highest risk** of developing symptomatic heart failure, in turn, aiding in the prevention of poor prognoses

Individuals with confirmed higher hs-cTn and cNP values are at an elevated CV risk, and should be appropriately assessed for the presence of asymptomatic myocardial changes or extra-cardiac diseases capable of causing myocardial injury.

REFERENCES:
1. Clerico A, Zaninotto M, Passino C, et al. Evidence on clinical relevance of cardiovascular risk evaluation in the general population using cardio-specific biomarkers. *Clinical Chemistry and Laboratory Medicine*. 2020;59(1):79–90.

JAPANESE-WESTERN CONSENSUS MEETING ON BIOMARKERS: AN EXECUTIVE SUMMARY[1]

Maisel AS, Nakao K, Ponikowski P, et al. *International Heart Journal.* 2011;52(5):253–65.

Brain natriuretic peptide (BNP) shows clinical utility as a diagnostic marker for pathophysiological conditions of heart disease, including heart failure (HF), ventricular remodelling and pulmonary hypertension. **BNP values can be a useful tool in diagnosing cardiac failure** in clinical settings in the following areas:

Early diagnosis of HF in health screening

Determining the diagnosis, **severity, therapeutic effects, and prognosis** of patients with HF

Detecting cardiac dysfunction including in patients still in the asymptomatic stages (in conjunction with other clinical findings)

- **In an ER setting,** rapid BNP assays, in conjunction with other clinical information, can help to more easily diagnose suspected HF
- **In the ICU,** it is important to know the course of HF and the chronological changes in BNP values after admission as they are useful for assessing the therapeutic effects and prognosis of HF patients

BNP levels are strongly linked to mortality. In an analysis of over 45,000 patients, higher levels indicated a greater risk of acute mortality.[1,2]

STUDIES CLEARLY HIGHLIGHT THAT BOTH CIRCULATING BNP AND NT-PRO-BNP LEVELS OBTAINED IN THE ACUTE PHASE OR SUBACUTE PHASE ARE DIRECTLY LINKED WITH:

- Cardiovascular mortality in the short and long-term, independently of traditional risk factors
- HF and left ventricular dysfunction
- Extent of myocardial necrosis
- Coronary artery disease.[1,2]

BNP REFERENCE VALUES

- **When cardiac function declines, BNP values rise**
- **BNP values tend to slightly increase in the elderly or patients with renal failure, but tend to slightly decline in individuals with obesity**

This indicates that **BNP values not only reflect the severity of HF,** but also the **type of underlying disease,** the severity of **renal dysfunction** and the effects of **age and obesity.**

For patients presenting with dyspnea, physicians should assess clinical history, perform a physical examination, chest x-ray and ECG, along with laboratory measurements that include BNP.

REFERENCES:
1. Maisel AS, Nakao K, Ponikowski P, et al. Japanese-Western Consensus Meeting on Biomarkers. *International Heart Journal*. 2011;52(5):253–65.
2. Fonarow GC, Peacock WF, Phillips CO, et al; ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *Journal of the American College of Cardiology*. 2007;49(19):1943–50.

THANK YOU FOR READING

We hope that the wealth of information and expertise shared across these **consensus publications by 61 experts in the field,** has provided you with useful information about how cardiac biomarkers could be implemented in your clinical practices and laboratories to help reduce the impact of CVD on the population.

Together, we can **drive improved patient care and help patients receive appropriate treatment in a timely manner through accurate risk stratification.** Help us take steps towards reducing the burden of CVD around the world.

STAT High Sensitive Troponin-I

The **Alinity i STAT High Sensitive Troponin-I** assay is a chemiluminescent microparticle immunoassay (CMIA) used for the quantitative determination of cardiac troponin I (cTnI) in human plasma and serum on the Alinity i analyzer.

The Alinity i STAT High Sensitive Troponin-I assay is to be used as an **aid in the diagnosis of myocardial infarction (MI) and to aid in the assessment of 30-day and 90-day prognosis relative to all-cause mortality and major adverse cardiac events (MACE)** consisting of myocardial infarction, revascularization, and cardiac death in patients who present with symptoms suggestive of acute coronary syndrome (ACS).

The cTnI values may also be used, in conjunction with clinical and diagnostic findings, to **aid in stratifying the risk of cardiovascular disease,** including cardiovascular death, MI, coronary revascularization, heart failure, or ischemic stroke in asymptomatic individuals.

BNP:

The **Alinity i BNP** assay is a chemiluminescent microparticle immunoassay (CMIA) used for the quantitative **determination of human B-type natriuretic peptide (BNP)** in human EDTA plasma on the Alinity i analyzer.

The Alinity i BNP assay is to be used as an **aid in the diagnosis and assessment of severity of heart failure.**

Alere NT-proBNP:

The **Alere NT-proBNP** for Alinity i assay is a chemiluminescent microparticle immunoassay (CMIA) used for the in vitro quantitative **determination of N-terminal pro B-type natriuretic peptide (NTproBNP)** in human serum and plasma on the Alinity i analyzer.

The Alere NT-proBNP for Alinity i assay is to be used as an **aid in the diagnosis of individuals suspected of having congestive heart failure (CHF) and detection of mild forms of cardiac dysfunction.** The test also **aids in the assessment of heart failure severity in patients diagnosed with CHF.**

The Alere NT-proBNP for Alinity i assay is further **indicated for the risk stratification of patients with acute coronary syndrome (ACS) and CHF,** and it can also be used for **monitoring the treatment in patients with left ventricular dysfunction.**