CLIABook

Safeguarding your cardiac health

BNP

CK-MB

NT-proBNP

hs-cTnI

TnI

MYO

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healthcare within reach

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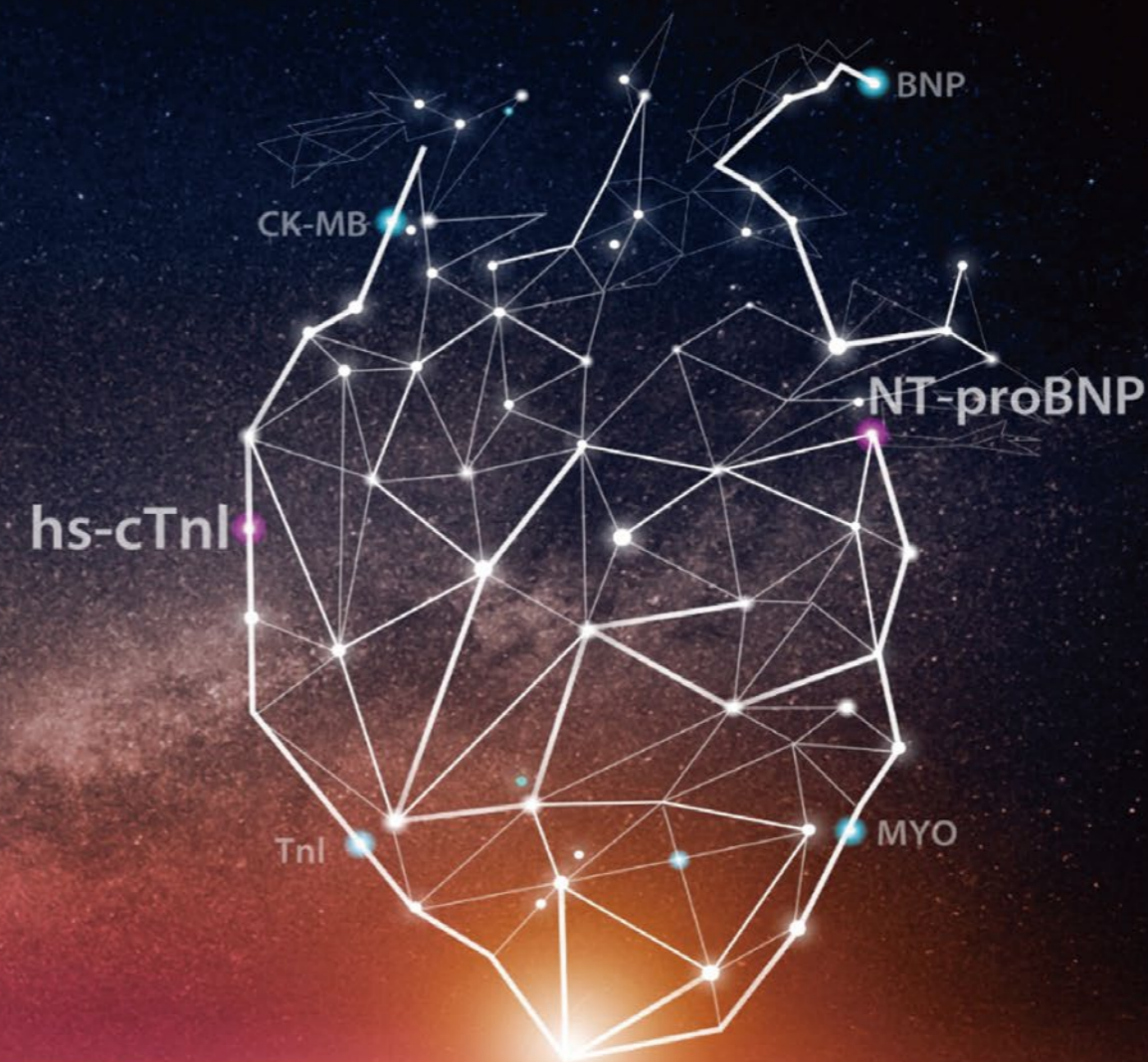
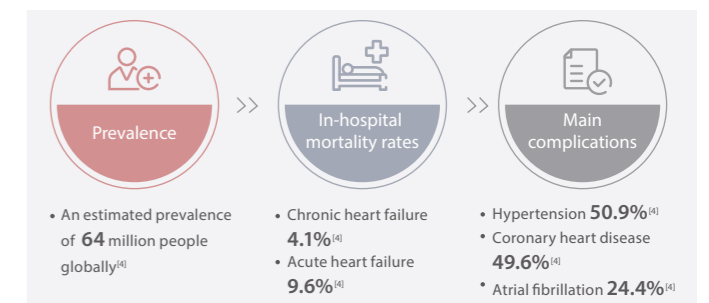# Content

Preface

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Cardiovascular diseases (CVDs) are the leading cause of death globally. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attack and stroke. Over three quarters of CVD deaths take place in low- and middle-income countries. Out of the 17 million premature deaths (under the age of 70) due to noncommunicable diseases in 2019, 38% were caused by CVDs. Most cardiovascular diseases can be prevented by addressing behavioral risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcoho[1].

It is important to detect cardiovascular disease as early as possible so that management with counselling and medicines can begin[1].

Acute myocardial infarction

Acute myocardial infarction is myocardial necrosis resulting from acute obstruction of a coronary artery. Symptoms include chest discomfort with or without dyspnea, nausea, and/or diaphoresis. Diagnosis is by electrocardiography (ECG) and the presence or absence of serologic markers [2].

Prevalence
- An estimated prevalence people of 3 million people globally[3]

Heart failure

Heart failure, also known as congestive heart failure, is a condition characterized by the heart's difficulty in pumping sufficient blood to meet the body's blood and oxygen requirements. This can be attributed to problems with the heart itself or other organs that hinder its normal functionality.

Prevalence
- An estimated prevalence of 64 million people globally[4]

In-hospital mortality rates
- Chronic heart failure 4.1%[4]
- Acute heart failure 9.6%[4]

Main complications
- Hypertension 50.9%[4]
- Coronary heart disease 49.6%[4]
- Atrial fibrillation 24.4%[4]

This book describes the values and functions of cardiac biomarkers for different cardiovascular diseases and clinical applications. It provides a full picture of how these biomarkers play significant roles in the occurrence, development, treatment and prognosis of diseases.

hs-cTnI: Empowering Heart Risk Assessment
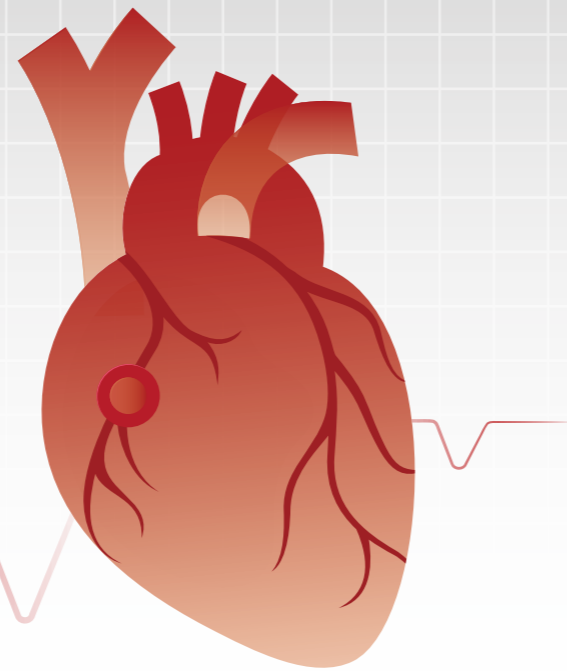
Mindray has reinforced its capacity for independent development and production of IVD raw materials with the acquisition of HyTest, a leading global provider of antibodies and antigens situated in Finland. The strategic acquisition has significantly bolstered Mindray's capability to provide cutting-edge immunoassay solutions in various domains, with a particular focus on cardiac disease management.

Strengthened Scientific Research Capabilities in Cardiac Biomarkers

With nearly 30 years of experience, HyTest specializes in developing and supplying world-class antibodies and antigens, particularly in the field of cardiac biomarkers for myocardial infarction and heart failure. Since its foundation in 1994, HyTest has been at the forefront of cardiac biomarker research. In the same year, HyTest introduced its first-generation cardiac troponin I monoclonal antibody, gaining recognition for its exceptional performance.[5-6]

Pioneering Troponin Research:
HyTest's Quest for Enhanced Cardiac Diagnostics

| 1994	2001	2004	2007	2016	2020
Founded in Finland	Its myoglobin preparation was selected by the IFCC as an international standard material	Its troponin I-T-C complex was selected by the AACC as a raw material for the international standard	HyTest obtained "patents for method and kit for the diagnosis of troponin I"	Fred Apple, a world-renowned expert on troponin, joined the HyTest Board of Directors to help promote the international standardization of the troponin project	HyTest published 50+ academic articles, with 1800+ citations

Fred S Apple, PhD

- Chair, IFCC Committee on Clinical Application of Cardiac Biomarkers (C-CB)
- Member, AACC Academy Laboratory Medicine Practice Guidelines on Cardiac Markers
- Chief Scientific Advisor, HyTest

We've been trying to do educational products since the last several years. It's a combination of industry, academic, and hospital-based people. It really works when you put industry together. And one of our focuses is to understand what's going on with troponin, especially high-sensitivity troponin.

By harnessing the scientific expertise of HyTest alongside Mindray's innovative prowess, we have successfully developed the state-of-the-art cardiac assay, hs-cTnI (high-sensitivity troponin I). This achievement allows us to provide a wide range of cardiac tests in the immunoassay field, catering to the diverse needs of clinical settings.

hs-cTnI: Empowering Heart Risk Assessment

hs-cTnI, an exceptional assay, earns the "high-sensitivity" label for its ability to detect troponin I in over 50% of seemingly healthy individuals while maintaining a coefficient of variation below 10% at the 99th percentile upper-reference limit (URL). This remarkable sensitivity makes hs-cTnI an essential tool for diagnosing, stratifying risk, and managing acute coronary syndrome (ACS), a subset of cardiovascular diseases (CVDs). CVDs are a leading cause of death worldwide and impose a significant burden on many countries. As per WHO data,[7] CVDs accounted for 32% of global fatalities in 2019.
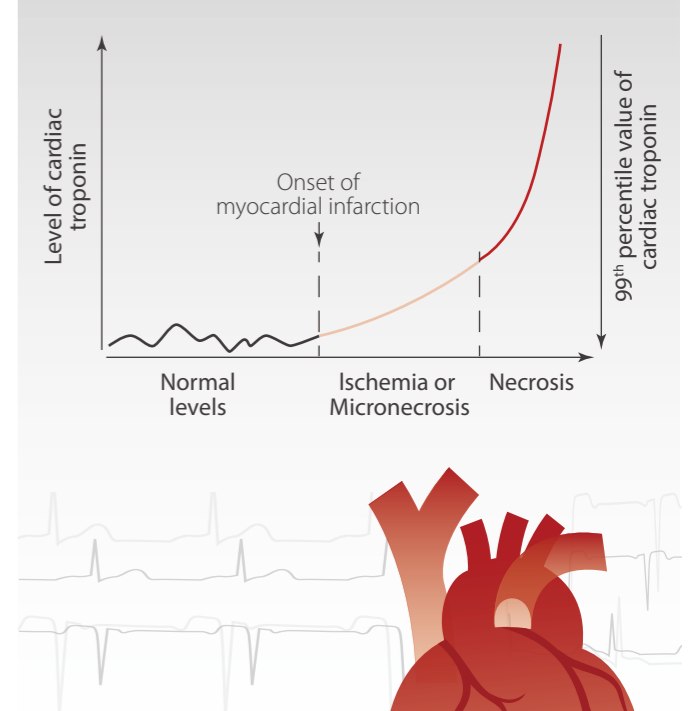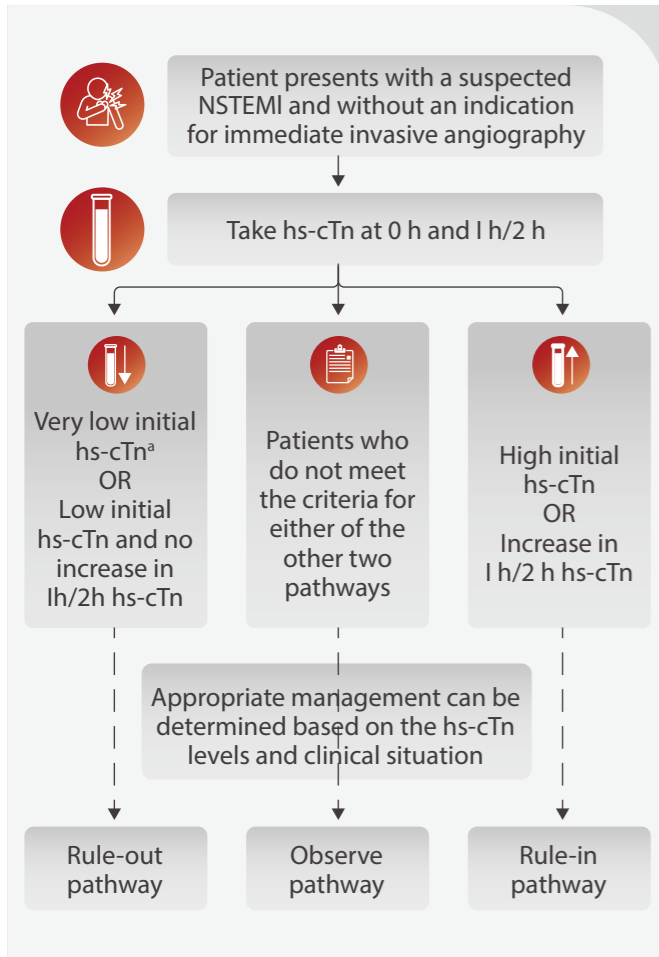

Identification of patients with AMI

Acute Myocardial Infarction (AMI) is a significant clinical manifestation of ACS. Per AMI guidelines,[8] the identification of individuals with AMI involves continuous monitoring of hs-cTnI values. This includes observing fluctuations in the values, with at least one measurement surpassing the 99th percentile URL. Moreover, clinical evidence indicating myocardial ischemia is essential for accurate identification.

Early diagnosis and rule-out/rule-in of NSTEMI

hs-cTnI testing not only aids in identifying individuals with a high likelihood of AMI but also facilitates the early diagnosis and rapid exclusion of AMI in a significant proportion of patients.

Since 2015, the European Society of Cardiology (ESC) has recommended employing the 0/1h algorithm (preferred) or the 0/2h algorithm (alternative) for swift rule-out and rule-in of Non-ST-segment-elevation myocardial infarction (NSTEMI) type of AMI. Numerous studies conducted in recent years have consistently demonstrated that hs-cTnI values falling below the level of detection yield a negative predictive value (NPV) for AMI exceeding 99%.[9-10]

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ESC algorithms for 0 h/1 h or 0 h/2 h rule-out and rule-in [11]

Patient presents with a suspected NSTEMI and without an indication for immediate invasive angiography

Take hs-cTn at 0 h and I h/2 h

Very low initial hs-cTnª OR Low initial hs-cTn and no increase in Ih/2h hs-cTn

Patients who do not meet the criteria for either of the other two pathways

High initial hs-cTn OR Increase in I h/2 h hs-cTn

Appropriate management can be determined based on the hs-cTn levels and clinical situation

Rule-out pathway

Observe pathway

Rule-in pathway

Differential diagnosis of myocardial injury

Elevated levels of hs-cTnI can also be detected in various other clinical conditions, including acute myocardial injury and chronic myocardial injury.

Similar to the diagnostic interpretation for AMI, acute myocardial injury may require at least one hs-cTnI concentration exceeding the 99th percentile URL, accompanied by a significant dynamic rise or fall pattern.[12] The critical clinical distinction between these two conditions is the absence of myocardial ischemia symptoms in acute myocardial injury.

Risk stratification and prognosis of patients with ACS

In addition to its diagnostic value in cases of AMI and myocardial injury, serial measurement of hs-cTnI levels, when combined with existing risk score systems, proves helpful in risk stratification for patients with suspected ACS who are receiving in-hospital care. It also provides valuable prognosis information in terms of short- and long-term mortality. An individual may be considered at intermediate risk based solely on a risk score even if hs-cTnI concentrations are below the 99th percentile. In contrast, the low-risk group can be characterized by hs-cTnI levels that are close to or below the limit of detection (LOD).[13]

Combining HyTest's advancements in cardiac biomarker research with Mindray's robust R&D capabilities in IVD, we are poised to introduce more cutting-edge products that provide reliable test results for clinical diagnosis. Mindray remains committed to aligning our research with clinical needs and translating scientific breakthroughs into practical applications in the management of cardiac and other diseases.

Exploring the Clinical Power of NT-proBNP for Heart Failure Patient Care
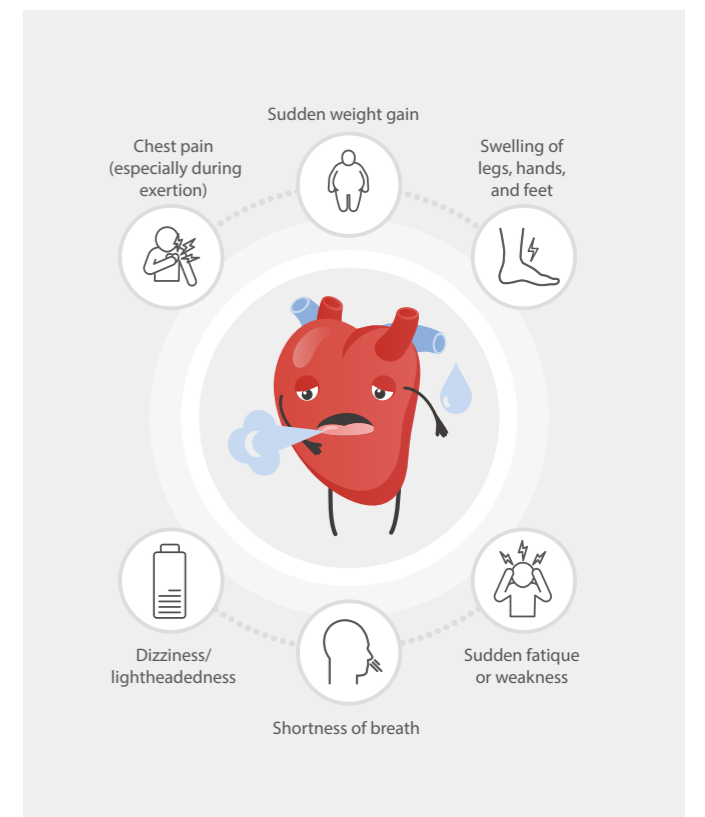

The heart is known to be one of the most important organs in humans due to its vital role in maintaining human health. Despite being only slightly larger than a fist, the heart is a powerful, muscular pump responsible for circulating oxygenated blood throughout the entire body. During contraction, the heart expels blood and transports it to every part of the body. If you compare a human being to a machine, then the heart can be regarded as the central component of that machine. Only when the heart operates in a stable condition can the body maintain good overall function.

What is heart failure?

The term "heart failure" may lead one to believe that the heart ceases to function altogether. In fact, heart failure, also known as congestive heart failure, is a condition characterized by the heart's difficulty in pumping sufficient blood to meet the body's blood and oxygen requirements. This can be attributed to problems with the heart itself or other organs that hinder its normal functionality. Basically, the heart becomes unable to keep up with the workload it is expected to handle.

As such, heart failure is a syndrome that manifests as a combination of signs and symptoms caused by the heart's impaired ability to pump an adequate amount of blood.

Typically, the symptoms of heart failure include shortness of breath, excessive fatigue, and leg swelling. The severity of heart failure is primarily evaluated based on ejection fraction, as well as the intensity of its accompanying symptoms.[14]

Chest pain (especially during exertion)

Sudden weight gain

Swelling of legs, hands, and feet

Dizziness/ lightheadedness

Sudden fatique or weakness

Shortness of breath

The role of NT-proBNP in diagnosing heart failure

In 1956, researchers began studies aimed at identifying effective markers of heart failure. B-type natriuretic peptide (BNP) was found to indicate the myocardial function and degree of injury. Compared to BNP, NT-proBNP exhibits a longer half-life, lower biological variability, stability in both serum and plasma, reduced susceptibility to specimen collection, compatibility with a more diverse range of sample types, and improved ease of measurement by laboratory departments[15]. Therefore, NT-proBNP serves as a ideal marker for heart failure in clinical settings. Its utilization allows for a more accurate reference point in clinical diagnosis and treatment decisions.
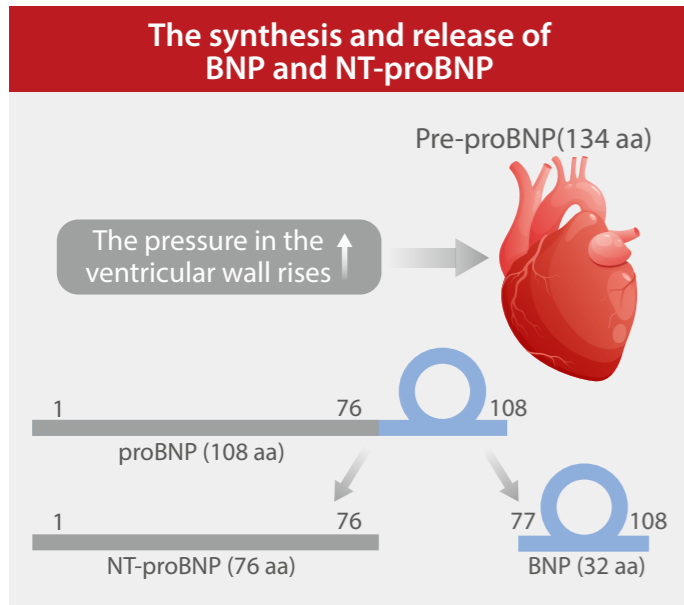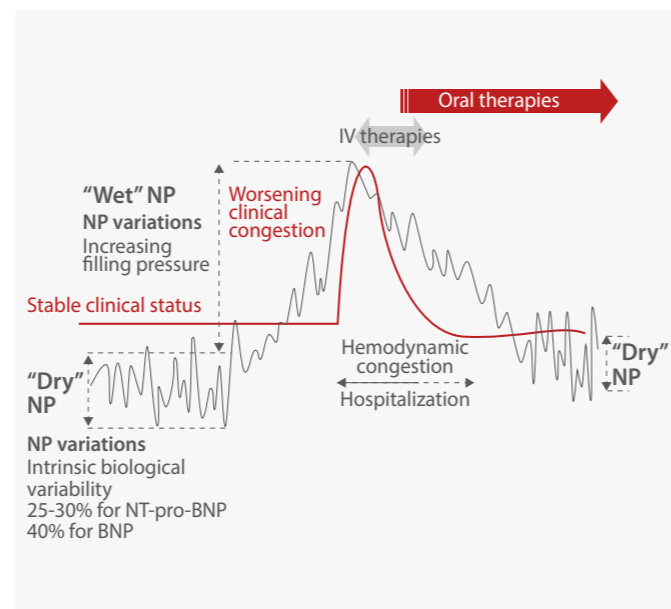
The synthesis and release of BNP and NT-proBNP

	4 h at room temperature (degrades shortly after sample collection)	72 h at room temperature, over 6 days at 4℃
In vitro stability at room temperature		
Specimen	EDTA plasma	Heparin and EDTA plasma and serum
Susceptible to drugs such as rhBNP	Yes	No

Characteristics	BNP	NT-proBNP
Number of amino acids	32aa	76aa
Molecular weight	4 kD	8.5 kD
Bioactive	Yes	No
Half-life	20 min	120 min
Concentration in blood	Low	High
Clearance mechanism	Through enkephalinase, natriuretic peptide receptor, and the kidney	Mainly through the kidney

Diagnostic and prognostic implications in acute heart failure

Acute heart failure (AHF) can occur across various disease conditions and its symptoms may resemble those of many other life-threatening conditions. This introduces a high level of uncertainty to the diagnostic process, especially in emergency situations. NT-proBNP testing can help physicians make more informed decisions in the management of AHF.

The figure below illustrates the trajectory of natriuretic peptide changes throughout the treatment of AHF.[16]

In the diagnostic work-up of newly presented acute heart failure, an NT-proBNP level greater than 300 pg/mL serves as an appropriate clinical threshold to indicate congestion consistent with AHF.[17]
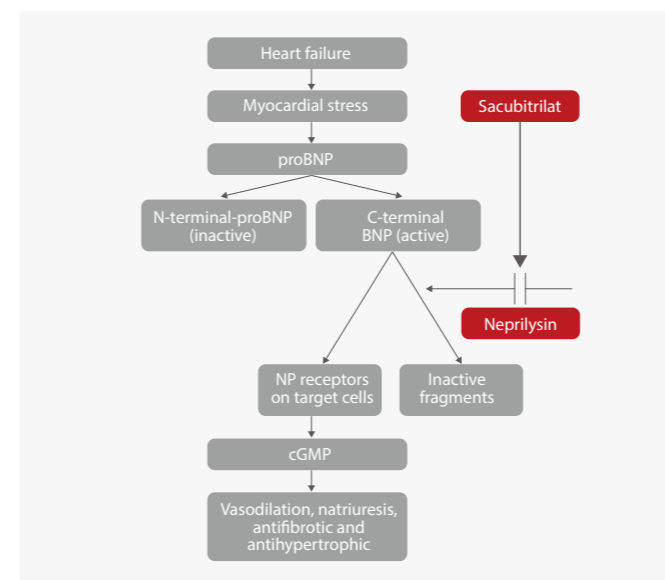

Diagnostic and prognostic implications in chronic heart failure

Chronic heart failure (CHF) is a progressive syndrome that leads to a decreased quality of life for patients and imposes significant financial strain on the healthcare system. Therefore, establishing a prognosis plays a critical role in the optimal management of heart failure. The 2021 ESC guidelines suggest that an NT-proBNP plasma concentration below 125 pg/mL is unlikely to be diagnostic of heart failure. Conversely, higher NT-proBNP levels are associated with a poorer prognosis.[8]

Accurately evaluating the efficacy of ARNi drugs

Angiotensin receptor neprilysin inhibitors (ARNi) have attracted considerable attention in the field of heart failure treatment. ARNi drugs can inhibit renin enzyme (NEP) and block angiotensin type II receptors, thereby hindering the development of heart failure. The natriuretic peptides (NPs) system and the renin angiotensin aldosterone system (RAAS) contribute to improved cardiovascular and renal function in patients with heart failure.

ARNi therapy is found to be feasible and well tolerated when initiated immediately after the onset of acute decompensated heart failure (ADHF). Patients exhibit significantly lower levels of NT-proBNP at discharge compared to the baseline group. Furthermore, ARNi therapy reduces the degradation of BNP, while NT-proBNP levels remain unaffected. As more drugs that target NPs systems are developed and gain popularity, the clinical applications will expand from BNP to include NT-proBNP in the future.[18]


Conclusion

In summary, NT-proBNP holds important diagnostic and prognostic implications in both AHF and CHF, while also being instrumental in advancing the diagnosis and treatment of heart failure.

By harnessing HyTest's proven expertise in cardiac marker antibody production and Mindray's innovative capabilities, we have successfully developed a state-of-the-art cardiac assay, NT-proBNP. With the introduction of this assay, Mindray is now equipped to offer a full menu of cardiac assays including hs-cTnI, NT-proBNP, BNP, TnI, CK-MB, and MYO, catering to diverse clinical settings in the immunoassay field.

Cardiac biomarker assay menu
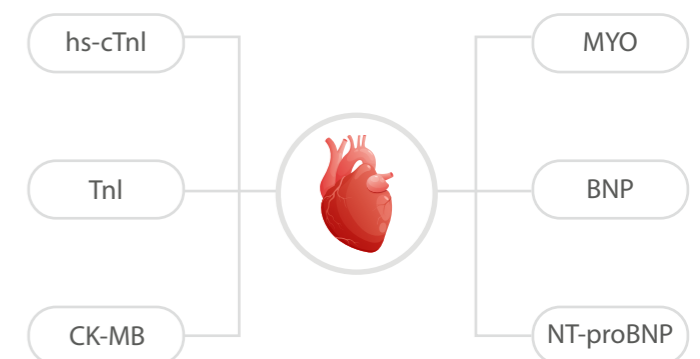
Mindray Expands Its Cardiac Biomarker Portfolio with Reliable hs-cTnI and NT-proBNP Assays

Cardiovascular diseases (CVDs) are the leading cause of death globally. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. Many guidelines recommend cTn and NT-proBNP as important biomarkers for suspected acute coronary syndrome (ACS) and heart failure patients, respectively. These biomarkers can be used for early disease screening, risk stratification, rapid diagnosis, and therapeutic monitoring, enabling physicians to make clinical decisions quickly.
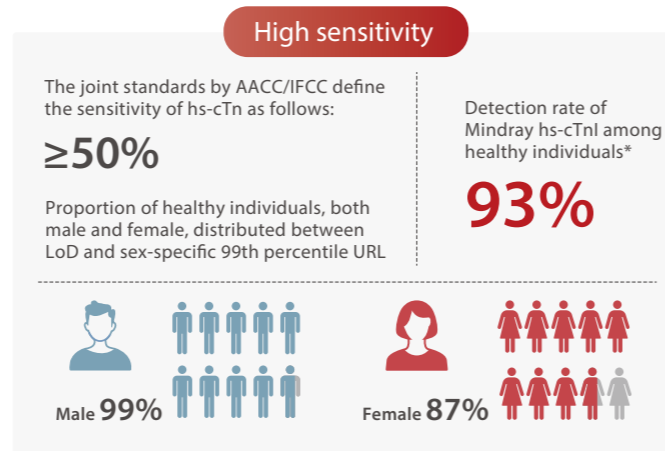
Mindray's hs-cTnI and NT-proBNP assays, jointly developed by Mindray and HyTest, have been validated by Wuhan Asian Heart Hospital and the Hennepin Healthcare Research Institute, demonstrating outstanding performance.
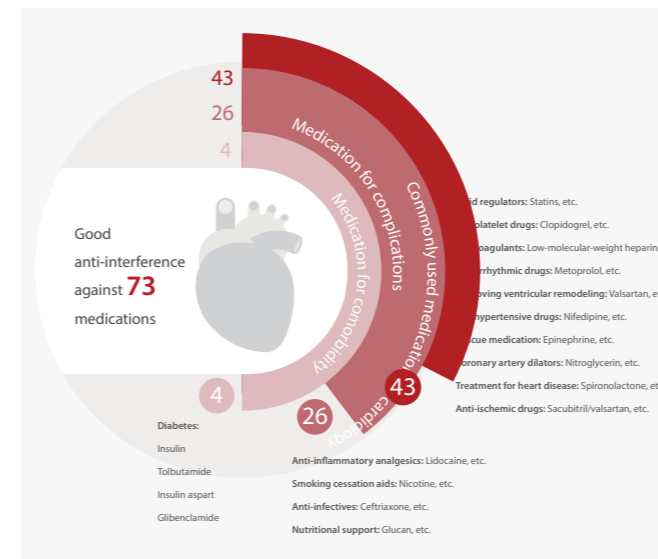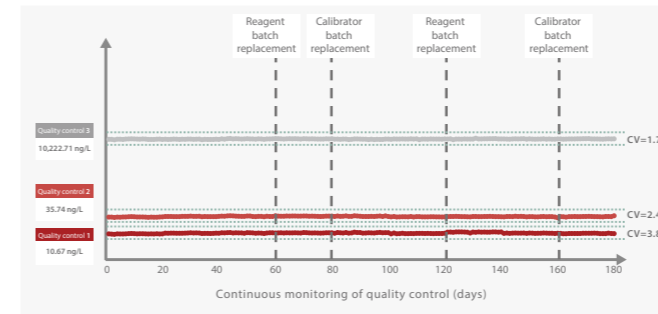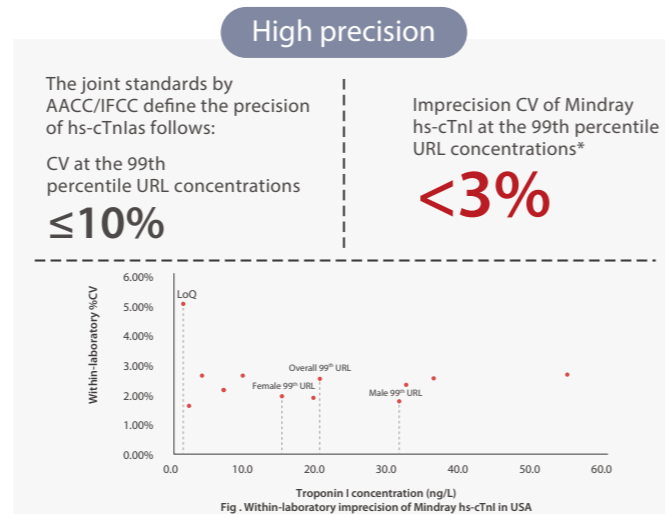
Mindray hs-cTnI Assay
An ideal biomarker for myocardial injury

Scientific detection system:
Mindray hs-cTnI assay is unsusceptible to proteases and can avoid cTnI terminal hydrolysis. The absence of endogenous antibodies interference improves the accuracy of test results, and Mindray hs-cTnI assay achieves a 93% detection rate in healthy individuals.
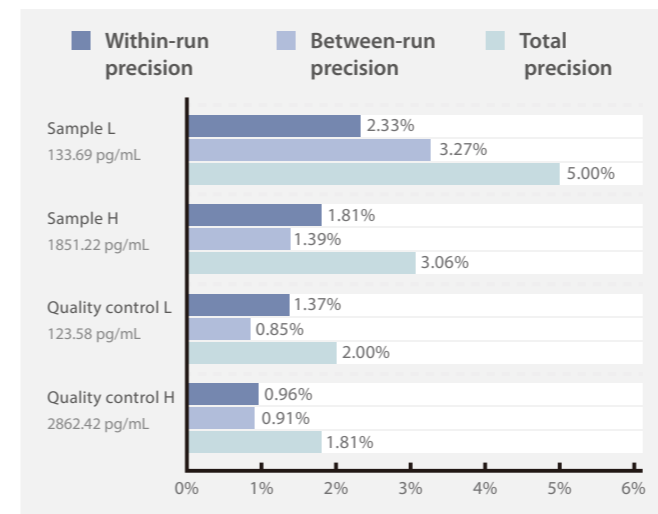
High sensitivity

The joint standards by AACC/IFCC define the sensitivity of hs-cTn as follows:

≥50%

Proportion of healthy individuals, both male and female, distributed between LoD and sex-specific 99th percentile URL

Detection rate of Mindray hs-cTnI among healthy individuals*

93%

Male 99%

Female 87%

Excellent assay performance:
Mindray hs-cTnI assay with high sensitivity, precision, and specificity meets the requirements of laboratory quality management and clinical guidelines.
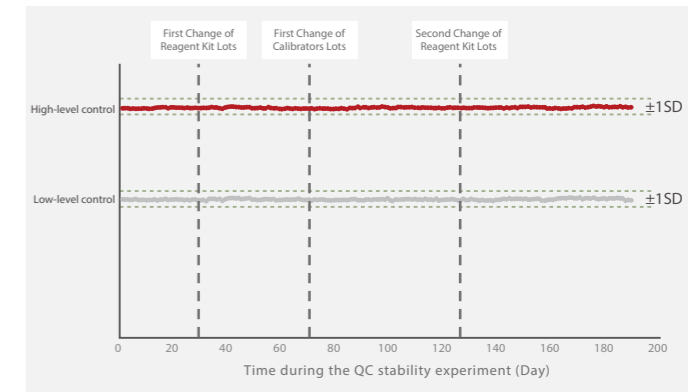
High precision

The joint standards by AACC/IFCC define the precision of hs-cTnIas follows:

CV at the 99th percentile URL concentrations

≤10%

Imprecision CV of Mindray hs-cTnI at the 99th percentile URL concentrations*

<3%

Fig . Within-laboratory imprecision of Mindray hs-cTnI in USA

Continuous monitoring of quality control (days)

Mindray NT-proBNP Assay
An ideal biomarker for heart failure

High precision:
The total imprecision (CV) of Mindray NT-proBNP ≤5%.


Good quality control stability:

Time during the QC stability experiment (Day)

Strong anti-interference capacity:

10 foundational heart failure medications
ACEI: Captopril
ARB: Valsartan
ARNI: Entresto
Beta-blocker: Atenolol
Aldosterone receptor antagonist: Spironolactone

14 cardiovascular medications
Antihypertensive: Nifedipine
Antiplatelet drug: Clopidogrel
Lipid-lowering drugs: Simvastatin, etc.
Antiarrhythmic drugs: Lidocaine, etc.

Good anti-interference against **55** medications

8 commonly used heart failure medications
Diuretic: Furosemide, etc.
Cardiac glycosides: Digitoxin, etc.
Vasodilator: Nitroglycerin, etc.
Vasoconstrictor: Norepinephrine
Beta-adrenergic agonist: Dopamine, etc.

23 clinically common medications
Paracetamol
Aspirin
Ceftriaxone
Cyclosporine
Theophylline, etc.

Note: Two basic serum samples with NT-proBNP concentration levels of 150±30 pg/mL and 2000±400 pg/mL were tested. The medication concentrations were set as recommended in EP037. The test results were biased within a range of ±10%.

Empowering Cardiovascular Diseases Care with Reliable Solutions

The introduction of hs-cTnI and NT-proBNP assays has enabled Mindray to provide a comprehensive menu of cardiac tests, covering six parameters, for reliable diagnosis and management of cardiovascular diseases (CVDs).
Leveraging the collaborative strengths of HyTest and Mindray, we remain committed to prioritizing fundamental research and utilizing advanced engineering techniques to modify raw materials. This dedication allows us to deliver even more dependable solutions, leading to improved patient outcomes in the realm of cardiovascular diseases and beyond.

Mindray Cardiac Total Solution
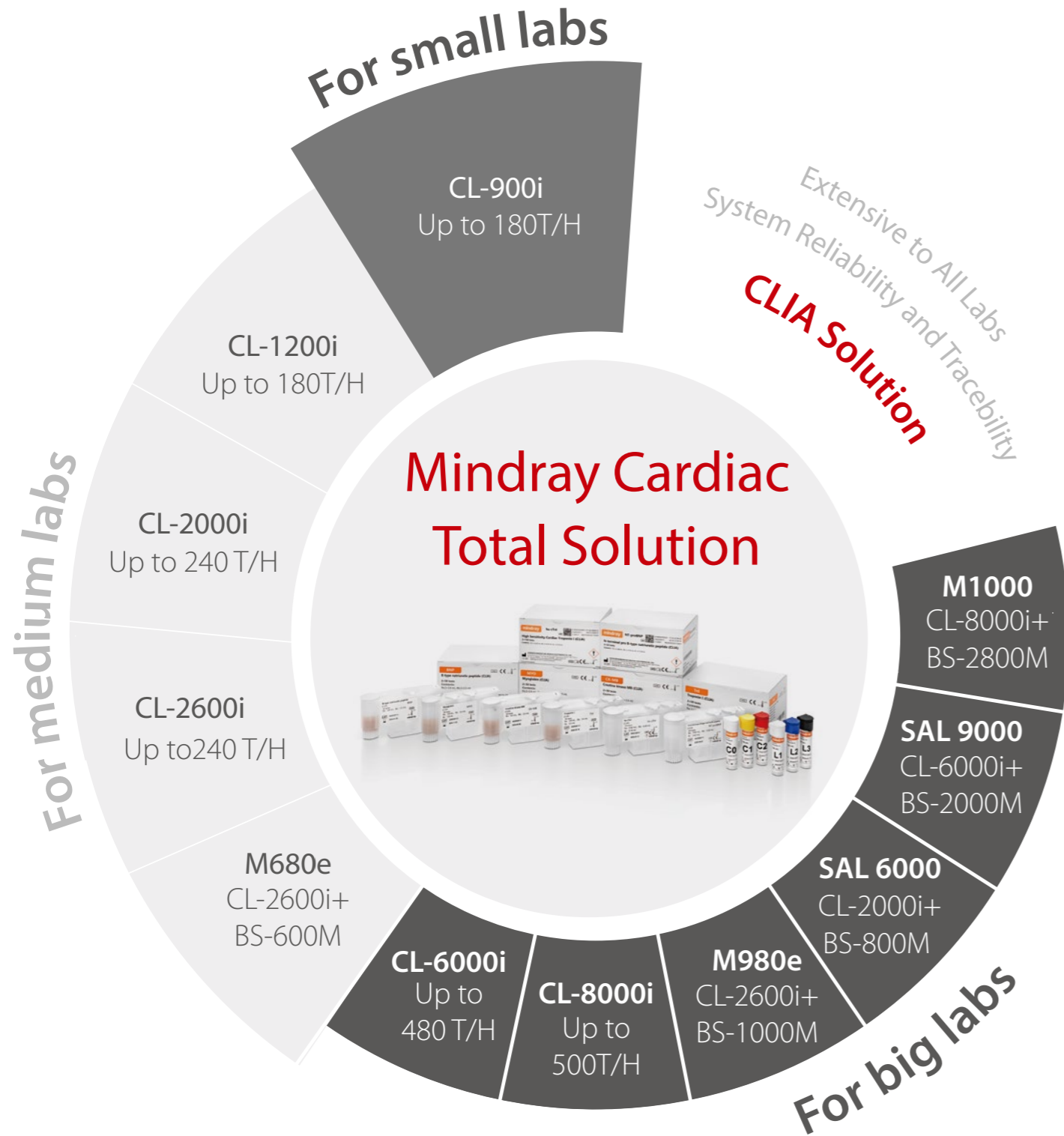
References

[1] https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

[2] https://www.msdmanuals.com/professional/cardiovascular-disorders/coronary-artery-disease/acute-myocardial-infarction-mi

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8636759/

[4] Global Public Health Burden of Heart Failure: An Updated Review.

[5] Hytest cardiac markers brochure

[6] Hytest troponin booklet

[7] https://www.who.int/news-room/fact-sheets/detail/ cardiovascular-diseases-(cvds)

[8] Holzmann M J. Clinical implications of high-sensitivity cardiac troponins [J]. Journal of internal medicine, 2018, 284(1): 50–60.

[9] Thygesen K, Alpert J S, Jaffe A S, et al. Fourth Universal Definition of Myocardial Infarction (2018) [J]. Circulation, 2018, 138(20): e618-e651.

[10] McCord J, Hana A, Cook B, et al. The role of cardiac testing with the 0/1-hour high-sensitivity cardiac troponin algorithm evaluating for acute myocardial infarction [J]. American Heart Journal, 2021, 233: 68-77.

[11] Byrne R A, Rossello X, Coughlan J J, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC) [J], European Heart Journal, 2023, 00: 1–107.

[12] Sandoval Y, Apple F S, Mahler S A, et al. High-sensitivity cardiac troponin and the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guidelines for the evaluation and diagnosis of acute chest pain [J]. Circulation, 2022, 146(7): 569-581.

[13] Jia X M, Sun W S, Hoogeveen R C, et al. High-sensitivity troponin I and incident coronary events, stroke, heart failure hospitalization, and mortality in the ARIC study

[14] Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update. National Clinical Guideline Centre.

[15] Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. Handbook of Experimental Pharmacology.

[16] NT-ProBNP in acute heart failure: correlation with invasively measured hemodynamic parameters during recompensation. J

[17] 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure.

[18] Natriuretic Peptides: Role in the Diagnosis and Management of Heart Failure: A Scientific Statement From the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society.[19] https://www.who.int/news-room/-fact-sheets/detail/cardiovascular-diseases-(cvds)

[20] Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018)[J]. Circulation, 2018,138(20): e618-e651. DOI: 10.1161/CIR. 0000000000000617.

[21] Byrne R A, Rossello X, Coughlan J J, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC)[J]. European heart journal, 2023, 44(38): 3720-3826.

[22] Jun Min.The National Health and Family Planning Commission issues "Guidelines for the construction and management of chest pain centers (trial)"[N]. Chinese Medical News, 2017-11-12(6).

[23] Heart Failure Group of Chinese Society of Cardiology of Chinese Medical Association, Heart Failure Professional Committee of Chinese Medical Doctor Association, Editorial Board of Chinese Journal of Cardiovascular Diseases. Chinese guidelines for the diagnosis and treatment of heart failure 2018 J]. Chinese Journal of Heart Failure and Cardiomyopathy, 2018,(4):196-225. DOI: 10.3760/cma.j.issn.2096-3076.2018.12.02.

[24] Natl Med J China, September 20, 2022, Vol.102, No.35