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USE OF BIOMARKERS IN CARDIAC EMERGENCIES

Acute Coronary Syndromes
Acute Heart Failure

PIONEERING DIAGNOSTICS

CARDIOVASCULAR DISEASE,
A MAJOR PUBLIC HEALTH ISSUE

Acute Coronary Syndromes (ACS)

- First cause of death worldwide, [1]
- Leading cause of disease burden in high-income countries, [1]
- Over 5 million annual hospital discharges in Europe and the USA, [2, 3]
- Total annual cost of USD 215 billion in Europe and the USA. [2, 4]

Heart Failure (HF)

- High proportion (1 in 3) of individuals aged 55 will develop HF during their remaining lifespan, [5]
- Total annual cost of USD 100 billion in Europe and the USA, 70% of which is due to hospitalization. [6]

Rapid exclusion is particularly useful in ED patients with chest pain and/or acute dyspnea, because the majority will not have ACS or acute HF:

- Ischemic cardiac disease is present in less than 25% of patients with suspected ACS, [7]
- Acute HF is present in 35% of patients with acute dyspnea. [8]

INTRODUCTION

Chest pain and shortness of breath (SOB)/dyspnea often occur together and are among the most frequent complaints in patients visiting an emergency department (ED) [8, 9].

The evaluation of patients with these symptoms is a challenge for the ED physician because of the variety of potential causes and comorbid medical conditions.

It is particularly important to rapidly and accurately diagnose life-threatening cardiac emergencies such as acute coronary syndromes (ACS) [10] and acute heart failure (HF) [11]. However, diagnostic difficulties may lead to "over-admission" to in-hospital patient care for patients with suspected ACS with a negative effect on costs and resource utilization [12].

Biomarker tests have been shown to contribute to efficient triage and improved patient management of acute cardiac conditions [13].

Cardiac biomarkers with a high negative predictive value (NPV) allow rapid discharge from the ED, whereas biomarkers with a high positive predictive value (PPV) are useful for risk stratification and therapy guidance.

This booklet describes the use of cardiac markers in the diagnosis and risk stratification of ED patients with signs and symptoms of cardiac emergencies such as ACS and acute HF.

Emphasis is placed on cardiac troponin and B-type natriuretic peptides with reference to the most recent evidence-based professional recommendations [6, 14].

OUR SPECIAL THANKS GO TO

Dr Pierre-Frédéric Keller

Cardiology Department / Intensive Care Unit University Hospitals, Geneva, Switzerland

for his comprehensive review of this booklet.

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ACUTE CORONARY SYNDROMES

1 Definition and classification

Acute coronary syndromes (ACS) refer to a constellation of clinical symptoms as a result of acute myocardial ischemia. It may range from a potentially reversible phase (**unstable angina**) to irreversible cell death (**myocardial infarction**).

The diagnosis and risk stratification of ACS is based on the integration of:

- the patient's presenting **symptoms**,
- ECG abnormalities,
- measurement of a **biomarker** of cardiac necrosis (**cardiac troponin**).

This results in the distinction of **three categories** (Table 1):

- unstable angina (**UA**),
- non-ST-segment elevation myocardial infarction (**NSTEMI**),
- ST-segment elevation myocardial infarction (**STEMI**).

The distinction between ACS categories is clinically important and drives the decision for type and intensity of therapeutic intervention.

- **ECG**: identifies approximately 1/3rd of ACS patients with persistent ST-segment elevation **(STEMI)** who require immediate reperfusion.
- **Cardiac troponin**: distinguishes the 2/3rd of ACS patients without ST-segment elevation (**NSTEACS**; non-ST-segment elevation ACS) who require either a conservative (**UA**) or early-invasive approach (**NSTEMI**).

Table 1: Distinguishing features of acute coronary syndromes[14,15]

	Myocardial Infarction		
	NSTEACS		
	Unstable Angina	NSTEMI	STEMI
Pathophysiology	Ischemia without necrosis	Ischemia with necrosis	
	Partially or transiently obstructive thrombus		Complete obstruction by intracoronary thrombus
Clinical features ■ Physical examination and history	Chest pain (angina and associated features) presence of risk factors		
■ Typical presenting symptoms	Severe angina (new onset, crescendo or rest angina)	Prolonged "crushing" chest pain, more severe and wider radiation than usual angina	
12-lead ECG	No abnormalities, transient ST-elevation, ST-depression or T-wave inversion		Persistent ST-elevation, newleft bundle branch block (LBBB)
Cardiac troponin Measurement on arrival and at 6 h	Negative (2x)	Positive	Positive**
Therapeutic intervention	Non-invasive (conservative)	Early-invasive	Immediate reperfusion

* Observation of dynamic profiles is more informative (repeat or continuous monitoring).
** Useful for confirmation, but availability of cTn test result should not delay therapeutic intervention.

2 Pathophysiology

UA, NSTEMI and STEMI have a common pathophysiological origin related to **atherosclerotic coronary artery disease** (CAD) [15,16]. Progression of the atherosclerotic plaque may result in its erosion or rupture with subsequent activation of blood platelets and coagulation factors leading to the formation of

an intracoronary thrombus. Intracoronary obstruction results in loss of blood flow to the myocardium, causing **ischemia** (imbalance between oxygen supply and demand) and ultimately myocardial death (**necrosis**).
In rare cases, ACS may occur due to ischemia in the absence of occlusive atherosclerosis (e.g. coronary spasm such as Prinzmetal's angina, cocaine abuse, or coronary artery inflammation such as Kawasaki disease) [15, 16].

3 Signs and symptoms

The chief complaint in ACS is **angina**, defined as central chest pain or discomfort that occurs due to inadequate delivery of oxygen to the heart muscle. The pain may radiate to the neck, jaw or (left) arm. "Typical stable angina" is provoked by exertion or emotional stress and is relieved by rest or sublingual nitrates, but not in the case of unstable angina or myocardial infarction.

Often, the discomfort is diffuse (not localized, not positional) and may be accompanied by sweating, dyspnea, nausea, syncope. Chest pain is not specific for ACS and may also occur in other cardiac and non-cardiac conditions (Table 2). Among the cardiac conditions, aortic dissection and pericarditis must be excluded before initiation of therapy for myocardial infarction.

Table 2: Causes of chest pain or discomfort

CARDIAC	NON-CARDIAC
■ **Acute coronary syndrome** ■ **Aortic dissection** ■ **Pericarditis** ■ **Myocarditis** ■ **Valvular disease**	■ **Gastrointestinal** Esophageal spasm or reflux Peptic ulcer ■ **Pulmonary** Pneumonia Pulmonary embolism Pneumothorax ■ **Neurological** (nerve root pain, herpes zoster) ■ **Musculoskeletal** (e.g. osteochondritis)

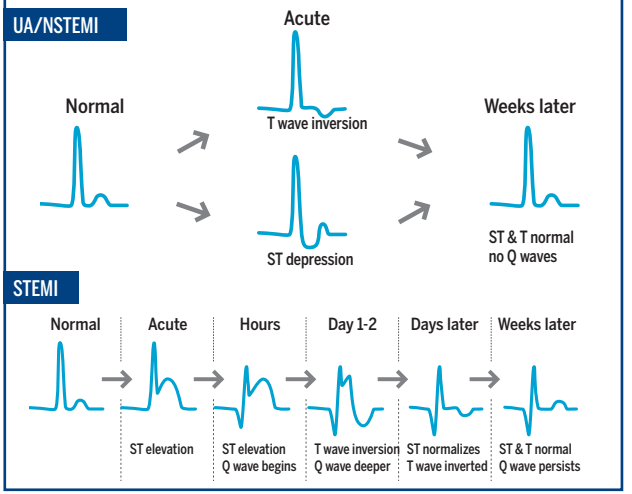
Atypical presentations of ACS (e.g. epigastric pain, upper back pain or dizziness) are frequent in younger (25-40 years) and older (>75 years) patients and in women. Asymptomatic myocardial ischemia (**silent ischemia**) is particularly common among diabetics.

4 Electrocardiogram

A number of typical ECG abnormalities are often observed during ACS, including **ST-segment depression** or **T-wave inversion** in UA/NSTEMI and **ST-segment elevation** in the early phase of STEMI (Figure 1).

The ECG may also provide information on the anatomic location, extent and severity of the coronary lesion as well as the presence of complications of acute MI with a poor prognosis (e.g. arrhythmias and conduction abnormalities such as bundle branch block and heart block) [17].

Figure 1: ECG evolution in ACS [18]



ST-segment elevation is the hallmark finding in **STEMI**, but may also be observed in other conditions (e.g. acute pericarditis and left ventricular hypertrophy). Abnormal Q-waves are less frequently observed nowadays due to earlier interventions.

5 Diagnosis and risk stratification

Decision-making algorithm

The objective of the initial evaluation of patients with chest pain and suspected ACS is to address the following two questions [14, 15]:

1 Differential diagnosis:
What is the likelihood that the patient's symptoms represent ACS due to underlying coronary artery disease?

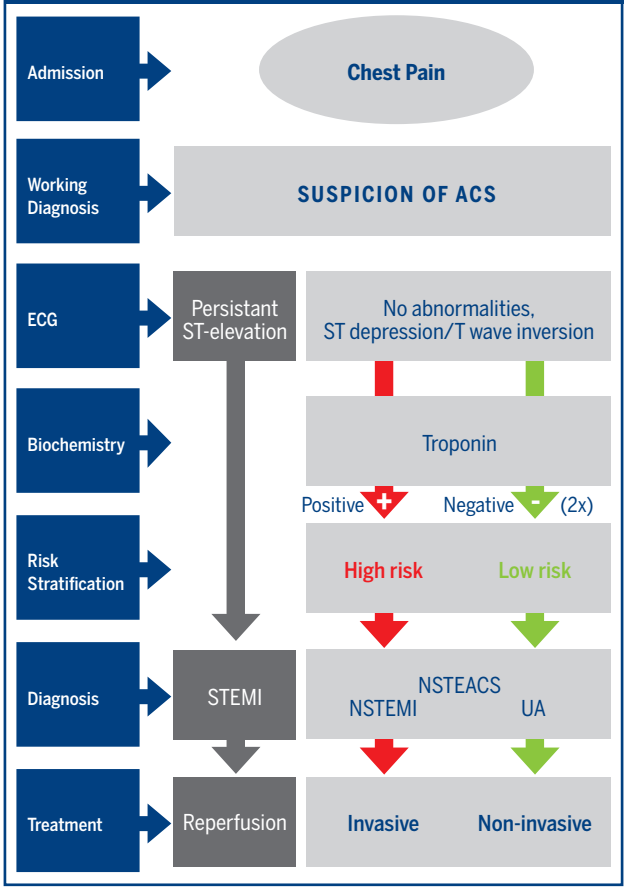
2 Risk stratification:
What is the likelihood that the patient will experience an adverse cardiovascular outcome (e.g. death, myocardial infarction, recurrent ischemia, stroke, heart failure)?

The outcome of this assessment (Figure 2) provides information that guides decision-making in terms of **selection, timing and intensity of therapeutic intervention, patient disposition** (coronary care unit, high dependency unit, etc.) and further investigations (**stress testing, angiography, etc.**).

Risk stratification can be refined by integration of cardiac necrosis markers and clinical factors into a **risk score**. Examples of validated risk scores are the **TIMI** and **GRACE** risk scores [19].

Calculators for these scores are available on-line:
www.timi.org
www.outcomes.org/grace

Figure 2: Approach to diagnosis and risk stratification
(ESC Guidelines) [15]



Serial measurement of cTn (on arrival and after 6 hours) is required in patients without ST-elevation on ECG.

ACUTE CORONARY SYNDROMES

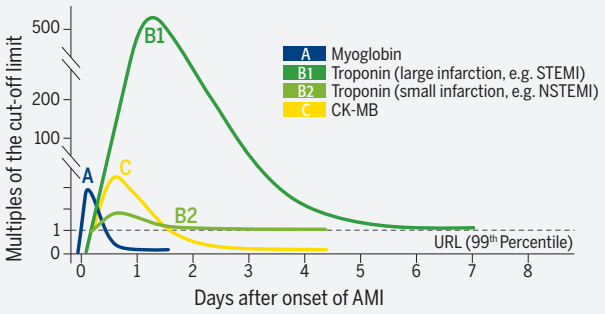
6 Cardiac necrosis markers

Myocardial infarction is defined as myocardial cell death (**necrosis**) due to prolonged ischemia. Myocardial necrosis is recognized by the appearance in blood of different proteins that are released from the damaged myocytes. The best described and most widely available biomarkers of myocardial necrosis include cardiac troponin I and T (**cTnI, cTnT**), the MB fraction of creatine kinase (**CK-MB**) and **myoglobin**. These cardiac necrosis markers show important differences in key properties such as diagnostic performance (Table 3) and kinetic profile (Figure 3).

Because recognition of acute MI is important for prognosis and therapy selection, measurement of cardiac necrosis markers is indicated in all patients with suspected ACS [14,15,16]:

- **Cardiac troponin is the preferred cardiac necrosis biomarker.**
- CK-MB is an acceptable alternative when cTn is not available.

Figure 3: Temporal profile of cardiac necrosis markers after acute myocardial infarction [13]



Biomarker concentrations are plotted as multiples of the cut-off for AMI, i.e. any measurement exceeding the 99th percentile of a normal reference population (URL = upper reference limit). Troponin shows small elevations above the URL in small infarctions (typically in NSTEMI) but may rise to 20 to 50 times the URL with large infarctions (typically in STEMI).

Table 3: Properties of cardiac necrosis markers [14]

	CARDIAC SPECIFICITY	TEMPORAL PROFILE			CLINICAL UTILITY	
		TIME TO FIRST DETECTION	MEAN TIME TO PEAK ELEVATION	DURATION OF ELEVATION	ADVANTAGE	DISADVANTAGE
Myoglobin	+	1-3 h	6-7 h	12-24 h	High sensitivity and NPV. **Early detection of MI** (early rule-out) and detection of **reperfusion**.	Low specificity in presence of skeletal muscle injury and renal insufficiency. Rapid clearance.
CK-MB	+++	3-4 h	24 h	24-36 h	Detection of **reinfarction**. Large clinical experience, previous "gold standard" for myocardial necrosis (best alternative if cTn assays are not available).	Reduced specificity in presence of skeletal muscle injury. Gender-specific cut-off values. Not an early marker of myocardial necrosis; serial testing needed when first result is normal.
cTnI	++++	3-6 h	24 h	5-10 days	Superior **sensitivity** and **specificity**. **Current biomarker of choice for detection of myocardial injury**.	Not an early marker of myocardial necrosis; serial testing needed when first result is normal.
cTnT	++++	3-6 h	24 h	5-14 days	Powerful tool for risk stratification and therapy selection. Detection of recent MI up to 2 weeks.	Reduced ability to discriminate reinfarction (serial testing needed).

CK-MB: creatine kinase MB fraction; cTn: cardiac troponin

7 Cardiac troponin

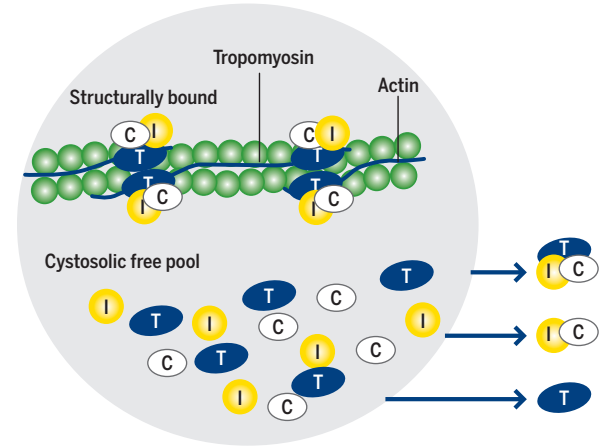
Biomarker of choice for detecting cardiac injury

The troponin complex consists of 3 subunits (**I, T and C**) and is essential for the regulation of skeletal and cardiac muscle contraction (Figure 4). In contrast to troponin C, **cardiac-specific isoforms of troponin T and I exist**. Specific antibodies have been raised against these cardiac isoforms, and form the basis of widely available quantitative and reliable cardiac troponin (cTn) assays.

Due to its high sensitivity and nearly absolute myocardial tissue specificity, cTn assays have become the cornerstone in the diagnosis and risk stratification of ACS [14,15,16].

Figure 4: Troponin is a marker of cardiac damage [20]

The troponin complex is essential for the calcium-mediated regulation of muscle contraction. It consists of 3 subunits (troponin I, T and C) structurally bound on the actin filament. The cytosol of the cardiac myocyte contains unbound troponins which are released into the circulation upon damage.



Elevated cTn is only diagnostic for acute MI when there is evidence of myocardial ischemia (i.e. clinical symptoms and/or ECG abnormalities or imaging evidence) [16].

The utility of cTn in the diagnosis of acute MI is contingent on the use of the proper cut-off value and the timing of measurement (Table 4).

Table 4: Diagnosis of acute MI: considerations for use of cTn [14,16]

CRITERION	RECOMMENDATION
Decision level for MI	The 99th percentile* of a normal reference population (URL=upper reference limit)**
Assay precision	The optimal precision at the URL should be ≤ 10% (total CV)*
Timing of measurement	Admission and 6 h later At 12-24 h (if earlier measurements are normal and clinical suspicion of MI is high)

* See "Frequently Asked Questions" section, page 24, for further information.

** The actual value of the URL depends on the particular assay that is being used. The 1xURL cut-off applies to MI due to a primary coronary event, the most common form. Higher cut-off levels are indicated for MI associated with percutaneous coronary intervention (PCI; cut-off is 3xURL) and coronary artery bypass grafting (CABG; cut-off is 5xURL).

Elevated cTn is specific for cardiac damage, but not for coronary disease and can also be elevated in the absence of ACS (Table 5).

Table 5: Causes of elevated cTn in absence of ACS [16,20]

Demand ischemia	■ Critically ill patients (respiratory failure, sepsis) ■ Arrhythmias ■ Aortic dissection
Myocardial ischemia	■ Hemorrhagic or ischemic stroke
Direct myocardial damage	■ Trauma including cardiac surgery, ablation, pacing, etc. ■ Rhabdomyolysis ■ Drug toxicity (e.g. chemotherapy) ■ Cardiac infiltrative diseases ■ Inflammatory diseases (myocarditis, pericarditis)
Myocardial strain	■ Heart failure ■ Pulmonary embolism ■ Severe pulmonary hypertension ■ Extreme exertion
Renal failure	

ACUTE HEART FAILURE

1 Definition and classification

Heart failure (HF) is a complex clinical syndrome in which the pumping function of the heart becomes insufficient (**ventricular dysfunction**) to meet the needs of the vital systems and tissues of the body. A unified and practical definition of HF has recently been put forward by the ESC (Table 6).

Many **descriptive terms** are used to characterize and classify patients with HF:

- TEMPORAL PRESENTATION
  Acute or stable **chronic** HF.
- **LEFT VENTRICULAR EJECTION FRACTION (LVEF)**
  Systolic (LVEF < 40%) or **diastolic** HF (i.e. HF with normal ejection fraction, LVEF > 40-50%). These are not strict distinct entities and most HF patients have evidence of both.
  Diastolic HF is more common in female and the elderly.
- **LOCATION**
  Right HF (congestion of systemic veins causing peripheral edema or hepatomegaly) or **left** HF (most common, congestion of pulmonary veins causing pulmonary edema).

The **severity** of HF is commonly described by the **NYHA functional classification system**, based on symptoms and exercise capacity (Table 7).

Table 6: ESC definition of heart failure [21]

Heart failure is a clinical syndrome in which patients have the following features:	
Symptoms typical of heart failure	Breathlessness at rest or on exercise Fatigue Tiredness Ankle swelling
AND	
Signs typical of heart failure	Tachycardia Tachypnea Pulmonary rales Pleural effusion Raised jugular venous pressure Peripheral edema Hepatomegaly
AND	
Objective evidence of a structural or functional abnormality of the heart at rest	Cardiomegaly Third heart sound Cardiac murmurs Abnormality on the echocardiogram Raised natriuretic peptide concentration

Table 7: Severity of heart failure: the NYHA classification [21]

NYHA CLASS	DESCRIPTION
Class I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
Class II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III	Marked limitation of physical activity; comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV	Unable to carry on any physical activity without discomfort; symptoms at rest, if any physical activity is undertaken, discomfort is increased.

NYHA: New York Heart Association

2 Pathophysiology

HF is a progressive and chronic disease, worsening over time. HF is caused by progressive **remodeling** of the heart, a process that changes its size and shape and subsequently **impairs the function of the ventricles**:

- **Systolic HF**: thinning and weakening of the ventricle walls results in dilation and a reduced capacity to eject blood (reduced ejection fraction).
- **Diastolic HF**: thickening and stiffening of the ventricles due to hypertrophy results in impaired relaxation (preserved ejection fraction).

Any structural or functional disorder that leads to deterioration of heart muscle function may lead to HF. Coronary heart disease is the initiating cause in about 70% of patients with HF [21].

Acute HF is either due to **acute decompensation** of previously stable chronic HF (ADCHF, 63%) or new onset HF (37%) [22]. The causes and **precipitating factors** are listed in Table 8. ACS is the most frequent precipitating factor of new onset acute HF, whereas non-compliance with therapy is the major cause of ADCHF [22].

Table 8: Causes and precipitating factors of acute heart failure [21]

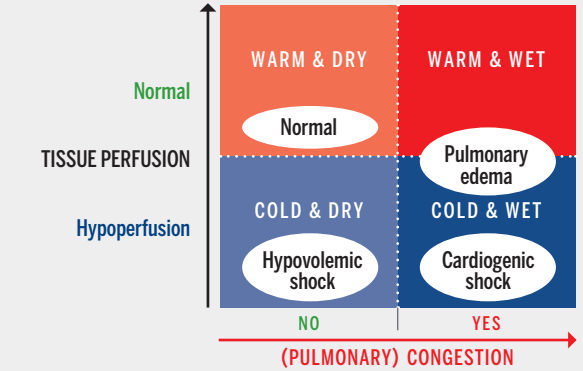
Ischemic heart disease	ACS Complications of acute MI
Valvular diseases	Valve stenosis Regurgitation Endocarditis Aortic dissection
Myopathies	Post-partum cardiomyopathy Acute myocarditis
Hypertension/arrhythmia	
Circulatory failure	Sepsis Anemia Pulmonary embolism
Decompensation of pre-existing chronic HF	Lack of compliance with treatment Volume overload Infections (especially pneumonia) Cerebrovascular insult Surgery Renal dysfunction Asthma, COPD Drug abuse, alcohol abuse

3 Signs and symptoms

- Patients with acute HF have an **altered hemodynamic profile** manifested by signs of congestion ("wet") and **hypoperfusion** ("cold") (Figure 5).
- **Dyspnea** is the most common presenting symptom, but this is not unique for acute HF (Table 9).
- Frequent **co-morbidities** in acute HF include coronary heart disease, hypertension, atrial fibrillation, diabetes, valvular disease, anemia, COPD and renal failure [22].

Figure 5: Hemodynamic profile in acute HF [21]

Clinical classification according to the hemodynamic profile (modified Forrester classification).



Signs of hypoperfusion (low cardiac output)	Signs of congestion (fluid overload)
■ Low blood pressure, narrow pulse pressure	■ Severe dyspnea
■ Pulsus alternans	■ Jugular venous pressure i
■ Tachycardia	■ Gallop rhythm
■ Cool extremities	■ Rales
■ Confusion, agitation, drowsiness	■ Pulmonary edema (chest X-ray)
■ Oliguria	■ Ascites
■ Low serum sodium	■ Hepatic distension

Table 9: Causes of dyspnea

CARDIOVASCULAR	NON-CARDIOVASCULAR
CARDIAC ■ Heart failure ■ ACS ■ Significant valvular disease ■ Arrhythmias (especially atrial fibrillation) ■ Constrictive pericarditis/cardiac tamponade ■ Restrictive cardiomyopathy	**RESPIRATORY** ■ Pneumonia ■ Asthma ■ COPD ■ Pneumothorax ■ Pleural effusion ■ Upper airway obstruction ■ Pneumonitis/pulmonary fibrosis
NON-CARDIAC Pulmonary embolism Pulmonary hypertension	**OTHERS** ■ Anemia ■ Thyrotoxicosis ■ Metabolic, e.g. acidosis ■ Chest wall pain (pleuritic/musculoskeletal) ■ Skeletal abnormalities ■ Neuromuscular (diaphragmatic weakness) ■ Anxiety/psychogenic

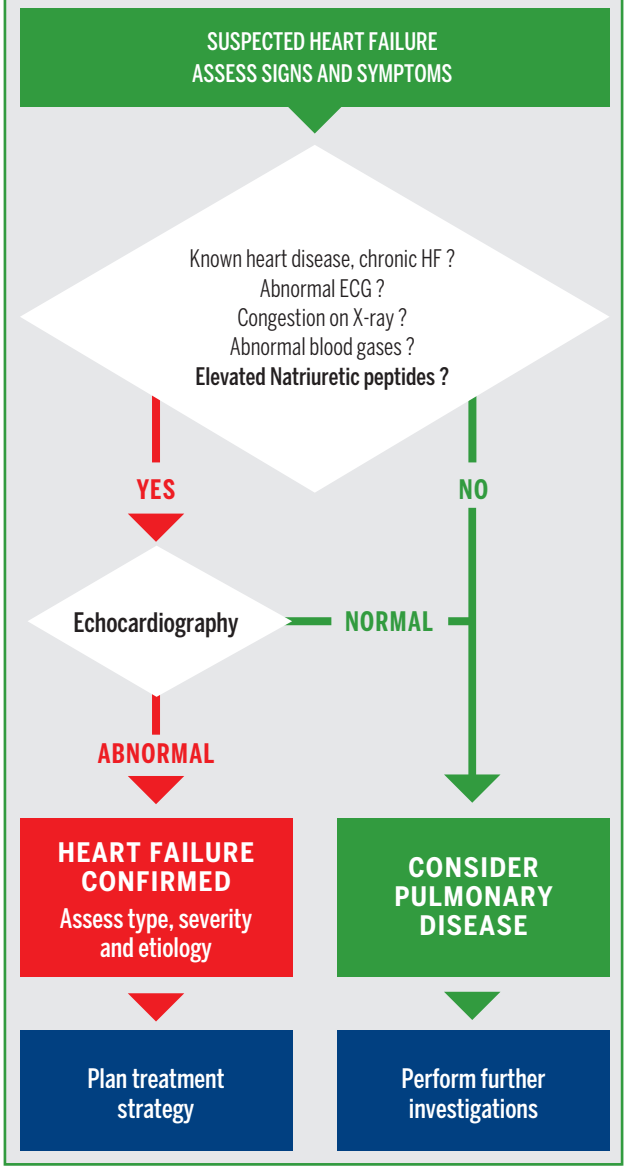
4 Diagnosis and risk stratification

Diagnosing acute heart failure is difficult because there are many varied and often **non-specific clinical symptoms** (dyspnea, chest pain, fatigue, cough). The diagnosis, therefore, is based on the combined use of patient history and physical examination, ECG, chest X-ray, echocardiography and laboratory tests, including **natriuretic peptides** (Figure 6) [21].

An **accurate** and **early diagnosis** is essential to target appropriate therapy and improve patient outcome. Apart from determining the presence and type of HF, the medical decision-making process (risk stratification and therapy selection) is further based on a complete understanding of underlying etiology, hemodynamic profile and stage/severity [21]. Causes and **precipitating factors** are listed in Table 8. ACS is the most frequent precipitating factor of new onset acute HF, whereas non-compliance with therapy is the major cause of ADCHF [22].

Decision-making algorithm

Figure 6: Evaluation of suspected acute HF (ESC Guidelines) [21]



5 Natriuretic peptides

Biomarkers of myocyte stress

The natriuretic peptide family consists of 3 peptides: atrial natriuretic peptide (ANP), brain (or B-type) natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). These neurohormones are released in response to hemodynamic stress and are involved in the regulation of intravascular volume homeostasis [23,24].

BNP is secreted by the ventricles, and to a lesser extent by the atria, and appears in blood after cleavage of the precursor molecule proBNP. This cleavage also results in the release of **NT-proBNP**, the N-terminal counterpart (Figure 7). Therefore, the blood levels of both molecules are increased in HF.

BNP and NT-proBNP assays show similar clinical performance characteristics and their levels are well correlated [25].

- Different cut-off values of BNP and NT-proBNP are in use.
- Absolute levels of BNP and NT-proBNP are not interchangeable.

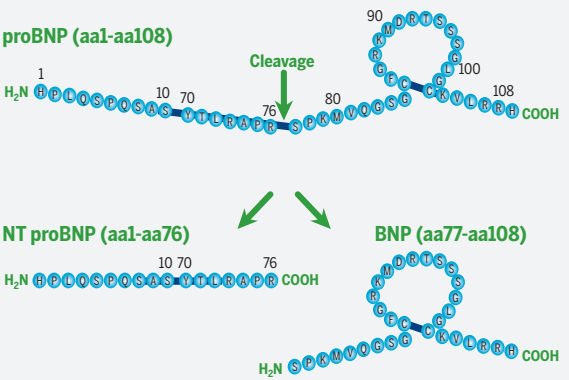
Table 10: Properties of B-type natriuretic peptides [24]

CHARACTERISTIC	BNP	NT-proBNP
Biologically active	Yes	No
Prohormone fragment	C-terminal (proBNP 77-108) 32 amino acids	N-terminal (proBNP 1-76) 76 amino acids
Half-life (min)	20	60-120
In vitro sample stability (room temperature)	4 hours	> 3 days
Sample type	Whole blood, plasma (EDTA)	Plasma (heparin) or serum
Assay measuring range (pg/mL)	5 – 5,000	20 – 25,000 *

* VIDAS® NT-proBNP (bioMérieux)

Figure 7: Release of BNP and NT-proBNP [24]

BNP and NT-proBNP are quantitative markers of cardiac stress that are released into blood after cleavage of the precursor protein proBNP.



ACUTE HEART FAILURE

6 NT-proBNP

for evaluation of HF in patients with acute dyspnea

The measurement of B-type natriuretic peptides is recommended in many guidelines as an integral part in the HF diagnostic work-up[6,21,25]. This is particularly useful in the assessment of patients with acute dyspnea in the **ED setting**, where NT-proBNP has utility as both a **rule-out** and a **rule-in** test for HF (Figure 8).

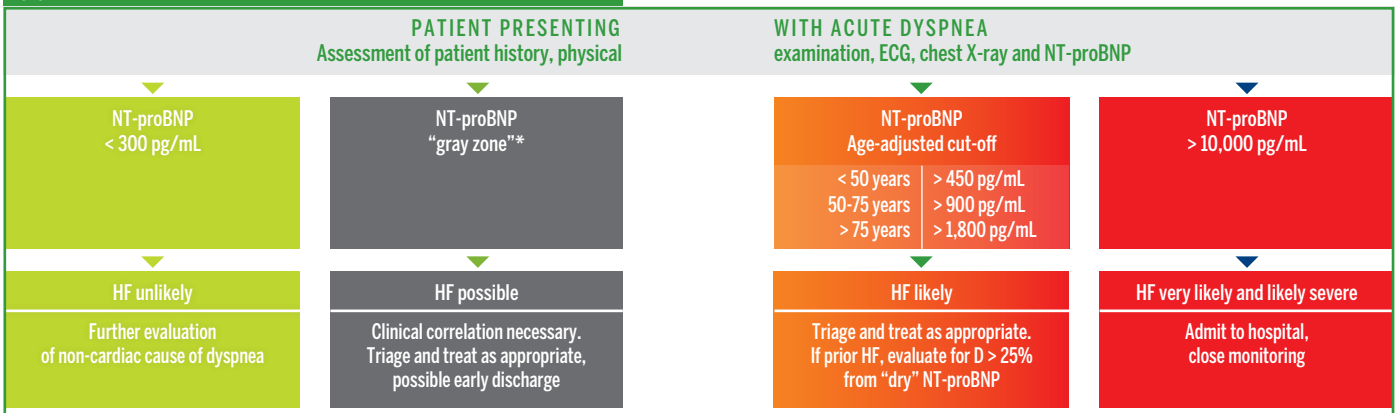
NT-proBNP is highly sensitive and specific for the diagnosis or exclusion of acute HF and is a powerful and cost-effective adjunctive tool for the clinician in the diagnosis and triage of patients with acute dyspnea [26].

The NT-proBNP level must be interpreted in conjunction with a thorough history and physical examination of the patient, as it can also be elevated in the absence of HF (Table 11).

Table 11: Elevated NT-proBNP in absence of HF [27]

- **Heart muscle disease** (e.g. myocarditis, cardiomyopathies, amyloidosis)
- **Heart valvular disease** (e.g. aortic/mitral stenosis and regurgitation)
- **Arrhythmia** (atrial fibrillation)
- **Acute coronary syndrome**
- **Stroke**
- **Pulmonary embolism**
- **Chronic pulmonary disease** (e.g. COPD, pulmonary artery hypertension)
- **Anemia**
- **Renal failure**
- **Diabetes mellitus**
- **Critical illness** (e.g. sepsis, burns, ARDS)

Figure 8: NT-proBNP in the evaluation and triage of ED patients with acute dyspnea [26]



* The area between the rule-out (< 300 pg/mL) and the rule-in (age-adjusted) cut-off values is designated as the "gray zone".

In this cost-effective and clinically validated algorithm (International NT-proBNP Consensus Panel), **a single cut-off value of 300 pg/mL** is used for **exclusion**, whereas age-adjusted cut-off values are used to rule-in HF.

A "gray zone" NT-proBNP value **should not be ignored** because it is associated with **worse outcomes** compared with NT-proBNP values below the rule-out cut-off [28].

See Frequently Asked Questions section, page 24, for further information.

FREQUENTLY ASKED QUESTIONS

1 Cardiac troponin and ACS

WHAT IS THE OPTIMAL cTn DECISION LIMIT FOR MYOCARDIAL INFARCTION (i.e. what is the difference between the 99th percentile of a normal reference population and the 10% CV limit) ?

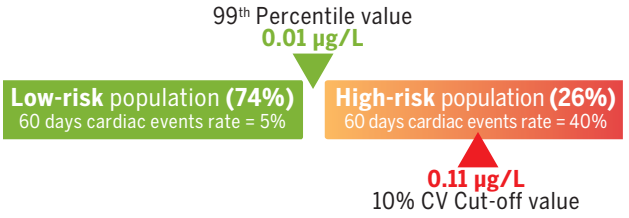
According to the universal definition of myocardial infarction, the **99th percentile of a normal reference population** is recommended as the **decision limit** [16]. Furthermore, the optimal precision (total coefficient of variation) at this level should be ≤ **10%** [16].

For most cTn assays, however, the lowest concentration with a total CV of 10% is above the 99th percentile reference. Therefore, experts have in the past proposed to use the higher 10% CV value as an acceptable alternative decision limit [29]. This view is being abandoned and, irrespective of the total CV at the 99th percentile value, only the 99th percentile value is recommended as the MI decision limit [30].

Intermediate cTn values (i.e. above the 99th percentile but below the 10% CV limit) have **prognostic value** and it is not appropriate to disregard them (Figure 9) [31, 32].

Figure 9: VIDAS® Troponin I Ultra (bioMérieux) 99th percentile and prediction of cardiac events [32]

In a cohort of suspected ACS patients (n=302), cTnI values were measured on admission on the VIDAS system. Patients with cTnI above the 99th percentile (26%) had a 9-fold increased risk for adverse cardiac events (MI or death) at 60 days [32].



WHAT IS THE CLINICAL IMPACT OF THE NEW GENERATION OF ULTRA-SENSITIVE cTn ASSAYS?

The new generation of cTn assays allows the detection of lower **concentrations with higher precision** [33]. With the newer assays, cTn elevations are detected **within about 2 hours from the onset of symptoms**. The **earlier detection** of myocardial necrosis by the newer cTn assays could result in **decreased costs** and **better patient care** because of earlier triage to an invasive strategy or earlier discharge [34].

On the other hand, assays with improved sensitivity will also lead to an increase in the number of patients with slightly elevated cTn concentrations due to "minor" myocardial damage, not always related to an ischemic cause. Yet, there is increasing evidence that these minor previously undetectable elevations of cTn are prognostic in a variety of populations, including the general community, and patients with heart failure and/or stable coronary artery disease [34].

CAN A FALSE-NEGATIVE cTn RESULT BE EXPECTED?

To diagnose myocardial infarction, it is important to perform **serial measurement** of cTn because the first measurement on admission may still be negative when the **patient presents early after the onset of symptoms** [14, 16]. Analytical false-negatives may occur in the presence of **circulating troponin autoantibodies** [35].

CAN A FALSE-POSITIVE cTn RESULT BE EXPECTED?

Analytical false-positives may occur due to the presence of potentially interfering factors such as **heterophilic antibodies** or **rheumatoid factor** [20]. Medical false-positives in the absence of ACS may occur with many **underlying diseases** (Table 5). However, the term "false-positives" is misleading because, even **without cardiac ischemia, elevated cTn correlates with a worse prognosis** [36].

Serial cTn testing is necessary to distinguish an acute coronary event, characterized by a typical rising and falling pattern, from other more chronic conditions [33]. Changes of ≥ 20% in cTn are considered significant [14, 16].

WHAT IS THE DIFFERENCE BETWEEN cTnI AND cTnT?

Both cTnI and cTnT are equally effective in the **diagnosis and prognosis of ACS** [14, 16]. There is only one manufacturer of cTnT assays, whereas cTnI assays are available from many sources with differences in standards and antibodies. Consequently, comparability of cTnI test results between methods is not optimal [37]. There is a different clearance pattern and the duration of cTnT elevation is longer (2 weeks) than cTnI (1 week) [14]. Renal failure leads more frequently to elevations in cTnT than cTnI [38].

IS cTn MEASUREMENT USEFUL IN ICU PATIENTS?

Cardiac conditions are common in the ICU and cardiac biomarkers may play a role in providing **additional information in critically ill patients** [39]. Elevated cTn is frequently observed in such patients and is associated with **increased mortality** and **ICU length of stay** [40]. Elevated cTn alone, however, is not diagnostic of MI in critically ill patients, because it is also elevated in conditions such as renal failure, sepsis, trauma, heart failure and inflammatory disorders (see Table 5, page 13).

WHAT IS THE VALUE OF COMBINED MEASUREMENT OF cTn AND NT-proBNP IN ACS?

Risk stratification is less accurate in patients with suspected ACS and normal cTn levels, because it relies only on clinical and ECG variables. Because NT-proBNP provides **independent prognostic information** irrespective of cTn status, its measurement has been recommended in ACS patients [14, 41]. This is particularly important in patients with **suspected ACS and normal cTn**, where **NT-proBNP > 474 pg/mL** was able to discriminate individuals at higher risk [42].

2 NT-proBNP and HF

WHAT IS THE DIFFERENCE BETWEEN BNP AND NT-proBNP?

BNP and NT-proBNP refer to the C-terminal and N-terminal cleavage products of proBNP, respectively. Due to differences in clearance, NT-proBNP has a longer half-life [23].

Although numerically different values are reported, BNP and NT-proBNP generally **have equivalent diagnostic and prognostic properties** [25]. In direct comparison studies, however, **NT-proBNP** was reported to have **better accuracy for mild HF** [43] and **HF with preserved ejection fraction** [44].

The main difference resides in their (pre)analytical properties which may favor NT-proBNP as a more convenient molecule to work with in clinical laboratories [45]:

- **Good harmony of results**, because the various NT-proBNP assays on the market are based on the same antibodies.
- **Better sample stability** at different temperatures and wider dynamic range, owing to its longer half-life.
- **Excellent precision** on automated instruments.

HOW IMPORTANT IS NT-proBNP IN THE "GRAY ZONE"?

NT-proBNP values **between the rule-out and rule-in cut-off values** for HF in the ED are referred to as **intermediate or gray zone** values (see Figure 8). In the **ICON study**, the gray zone was observed in **17% of dyspneic patients**, 54% of whom had HF as the ultimate diagnosis [28]. Gray zone patients usually have **mild HF with fairly good short-term outcome**. Nevertheless, a gray zone NT-proBNP value should not be ignored because it is associated with worse outcomes compared with NT-proBNP values below the rule-out cut-off [28].

ARE THERE CONFOUNDERS THAT MAY AFFECT THE USEFULNESS OF NT-proBNP FOR HF DIAGNOSIS IN ED PATIENTS?

Co-morbid conditions such as **COPD, renal disease, obesity, diabetes mellitus** and **atrial fibrillation** are frequently observed in ED patients with dyspnea. In the absence of HF, these conditions may result in elevated or decreased (in case of obesity) NT-proBNP levels. The influence of these conditions on the diagnostic accuracy of NT-proBNP for HF has been investigated in the PRIDE and ICON studies [46, 47, 48, 49, 50].

With the exception of atrial fibrillation, these conditions do not influence the diagnostic accuracy of NT-proBNP and no changes are required to the recommended age-adjusted cut-off values.

CAN FALSE-NEGATIVE OR FALSE-POSITIVE NT-proBNP RESULTS BE EXPECTED?

Despite severe symptoms, NT-proBNP may not **be very high** when HF is due to a cause upstream from the left ventricle such as in **mitral stenosis or acute mitral regurgitation** [25]. NT-proBNP also remains relatively low in patients presenting with HF symptoms that develop abruptly (< 1 hour), a rare condition referred to as **"flash" pulmonary edema** [25].

Although NT-proBNP is elevated in many other conditions (see Table 11, page 23), the term "false-positives" is misleading because, **even without HF, elevated NT-proBNP is linked to an adverse outcome** [27].

WHAT IS THE OPTIMAL TIMING OF NT-proBNP MEASUREMENT?

Timing of the initial NT-proBNP measurement in ED patients with suspected HF is critical because delayed measurement has been reported to be associated with delays in treatment and an increase in hospital mortality [51]. Subsequent **serial measurement at 4, 12 and 24 hours from admission** is useful in confirming the diagnosis of acute HF [52]. Variations in NT-proBNP levels are also predictive of outcome after hospital discharge [53].

CAN NT-proBNP BE USED TO GUIDE THERAPY?

Natriuretic peptide levels are **commonly reduced by treatment** with diuretics, ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists and cardiac resynchronization therapy [25]. Also, changes of NT-proBNP over months are predictive of outcome of HF [54]. This suggests that NT-proBNP could be **useful to guide therapy in selected cases**. However, there is no consensus among experts (mixed results of small controlled trials) and tailoring therapy to achieve a target NT-proBNP level is not warranted at this time [6, 25].

IS THERE A VALUE FOR NT-proBNP MEASUREMENT IN THE ICU?

Since increased NT-proBNP is not specific for HF and may be influenced by a variety of cardiac and non-cardiac conditions commonly seen in the ICU, the diagnostic accuracy for left ventricular failure is reduced [55]. In the ICU, NT-proBNP may be useful as a **general marker for cardiac dysfunction**, in distinguishing cardiogenic and non-cardiogenic pulmonary edema, and as an **aid in the timing of extubation** [25, 56].

IS THERE A VALUE FOR NT-proBNP MEASUREMENT IN PRIMARY CARE?

Detection of patients with **early stage HF** may allow the **initiation of preventive therapies**. However, these patients are difficult to diagnose because of the very insidious signs and symptoms. Although NT-proBNP holds promise for the detection of these largely asymptomatic patients, it is not recommended yet for wide-scale population screening [57]. Nevertheless, **screening of targeted symptomatic patient populations** (e.g. diabetes, high blood pressure,...) is valuable.

Compared with NT-proBNP values in ED patients with acute HF, lower values are expected in chronic HF patients in the community.

Therefore, the following cut-off values are recommended in primary care [58]:

AGE (years)	NT-proBNP (pg/mL)	INTERPRETATION
< 75 ≥ 75	< 125 < 450	**HF unlikely** Further investigation of non-cardiac causes
< 75 **≥ 75**	**≥ 125** **≥ 450**	**Left ventricular dysfunction possible** Further investigations needed

Consequently, in primary care patients, NT-proBNP is only a **rule-out test to exclude significant cardiac disease**.

IS THERE A VALUE FOR COMBINED MEASUREMENT OF cTn AND NT-proBNP IN HF?

Both NT-proBNP and cTn can identify patients with HF at increased risk for an adverse outcome [6]. Elevated cTn is not uncommon in HF and provides **prognostic information in patients hospitalized with acute decompensated heart failure** [59]. The combination of NT-proBNP and cTn is even more powerful, and, in ED patients with acute HF, the highest mortality rate was observed when both markers were elevated [60]. The therapeutic approach to such patients has not been established at this time.

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GLOSSARY

ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndromes
ADCHF	Acute decompensation of chronic HF
ANP	Atrial natriuretic peptide
ARDS	Acute respiratory distress syndrome
BNP	Brain (or B-type) natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CK-MB	Creatine kinase MB fraction
CNP	C-type natriuretic peptide
COPD	Chronic obstructive pulmonary disease
cTn	Cardiac troponin
CV	Coefficient of variation
ECG	Electrocardiogram
ED	Emergency department
ESC	European Society of Cardiology
GRACE	Global Registry of Acute Coronary Events
HF	Heart failure
ICU	Intensive care unit
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NPV	Negative predictive value
NSTEACS	Non-ST-segment elevation acute coronary syndromes
NSTEMI	Non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PPV	Positive predictive value
SOB	Shortness of breath
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
UA	Unstable angina
URL	Upper reference limit