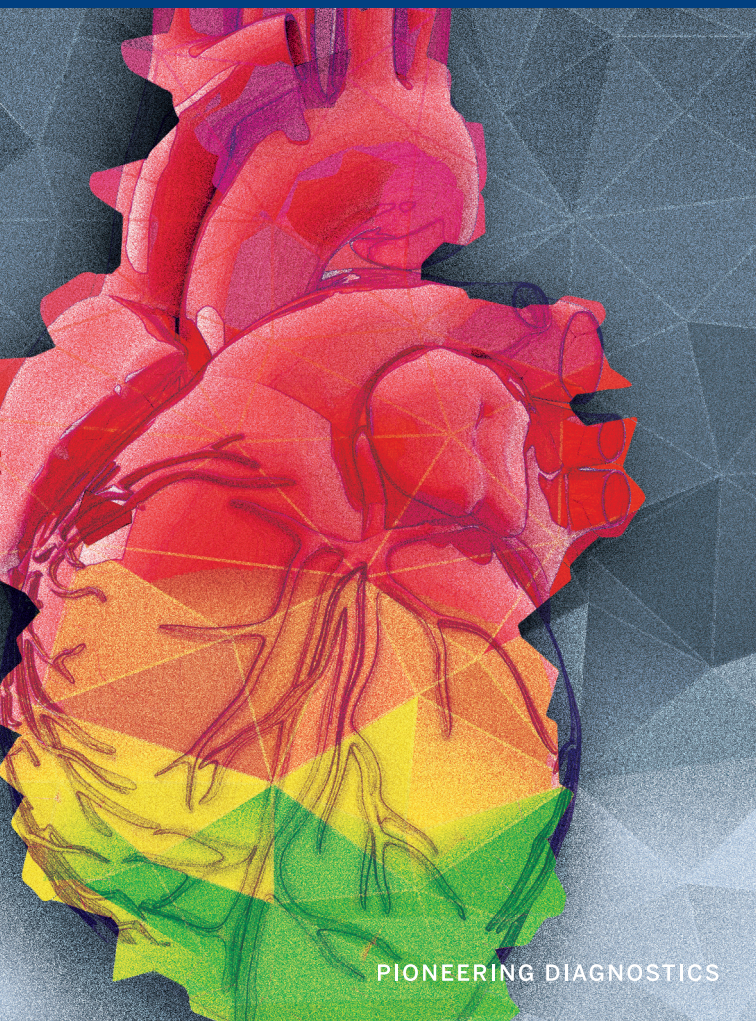# HEART FAILURE MANAGEMENT
Clinical Utility of NT-proBNP

OUR SPECIAL THANKS GO TO

Professor Christophe Meune

for providing expert advice and for his comprehensive review of this booklet.

PREFACE

Heart failure (HF) is one of the most prevalent diseases worldwide. It is also one of the most severe medical conditions, by far more severe than many cancers.

Furthermore, the management of HF patients has considerably changed in recent years:

- A new, more precise classification of chronic HF has been defined.
- HF with preserved or moderate alteration of ejection fraction is now well-defined based on left ventricular ejection fraction (LVEF), natriuretic peptides (NPs), and diastolic function using echocardiography.
- Natriuretic peptides (NPs) are considered as first line tools for the diagnosis of chronic and acute HF.
- A new drug class has emerged (ARNI: angiotensin receptor-neprilysin inhibitor) and has proven to be more effective than angiotensin-converting enzyme inhibitors.
- Some drugs (ARNI) may increase B-type natriuretic peptides (BNP) and decrease N-terminal pro-B-type natriuretic peptides (NT-proBNP) while the patient is improving. Measurement/monitoring of these changes is crucial in the management of HF patients.

This booklet provides clinicians and laboratory managers with concise, up-to-date information on the pathophysiology and diagnosis of heart failure, with special emphasis on the role of NT-proBNP measurements for the risk stratification and management of patients. Some aspects of heart failure prognosis and treatment are also discussed.

I trust you will find it to be a useful and practical guide to the management of heart failure using NT-proBNP.

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HEART FAILURE: A COMMON, COSTLY AND DEADLY DISORDER[1, 2]

High prevalence

- In developed countries, up to 1 in 5 persons are expected to develop heart failure (HF) at some point in their life.
- The prevalence of HF is about 1-2% of the total population in developed countries corresponding to 26 million people worldwide.
- HF prevalence is increasing with age averaging 10% in the elderly (>70 years).
- HF prevalence is expected to increase because of ageing of the population and improvements in treatment (e.g. improved survival from heart attack), as well as the development of new diseases (diabetes, obesity...).

- Worldwide: **26 million**
- General population: **2-3%**
- Elderly (70-80 years): **10-20%**

Poor survival and high morbidity

- In-hospital mortality of 4-10% following admission for acute HF.
- One-year mortality is 10-50%, depending on the type (preserved versus reduced ejection fraction) and severity. Majority of patients (up to 70%) die within 5 years.
- Each hospitalization for decompensated heart failure is associated with a further 20% increase in re-hospitalization.

High economic burden

- HF accounts for 1-2% of total direct healthcare expenditures.
- Hospitalization is the major cost driver.
- Acute HF accounts for up to 5% of all emergency hospital admissions and HF is the most common cause of hospitalization in patients > 65 years.
- HF is associated with long (5-10 days) and repeated hospital stays; 25% are readmitted within 1 month and up to 66% - within 1 year.

CONTENTS

For easy reading and reference, look for the colored boxes highlighting the key points in each chapter.

HEART FAILURE (HF)

1 Definition and classification

**European Society of Cardiology (ESC) definition[3]:**

HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intra-cardiac pressures at rest or during stress.

Time course: acute *vs*. chronic HF (Figure 1)

HF is a progressive and chronic disease, worsening over time. Chronic stable HF patients frequently deteriorate and become **decompensated**. Acute heart failure (AHF) is an acute event that requires hospitalization. Acute decompensation of previously stable chronic HF accounts for about 2/3rd of hospitalized acute HF patients, whereas approximately 1/3rd present for the first time (new onset or de novo).[4] New-onset HF may present acutely (e.g. after myocardial infarction (MI)) or gradually (e.g. with dilated cardiomyopathy).

Figure 1. Time course (progression) of HF.[5]

Adapted from Gheorghiade M, et al. *Am J Cardiol.* 2005;96:11G-17G
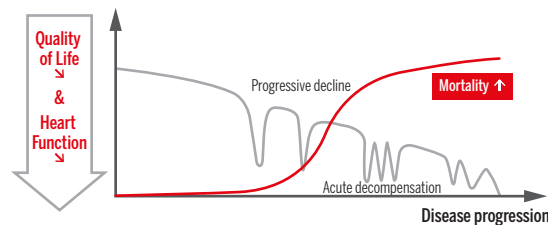
HF is a chronic disorder where acute events contribute to progression and deterioration. Acute HF refers to rapid onset or worsening of symptoms and/or signs of HF. It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospital admission. With each admission for acute HF there is a short-term improvement, but the patient leaves the hospital with a further decrease in cardiac function ultimately leading to end-stage HF and death.

The following terminology is used to describe and classify HF[3]:

Ejection fraction (EF) (Table 1)

Ejection fraction reflects the pumping function of the left ventricle (LV) and is also called **left ventricular ejection fraction (LVEF)**. It describes the proportion of left ventricle blood volume pumped out compared to the whole volume in this heart's chamber. **Echocardiography** is the most common test used to measure ejection fraction.

Ejection fraction is considered as normal if >50-55%.

Table 1. Classification of chronic HF according to ejection fraction.[3]

Adapted from Ponikowski P, et al. Eur Heart J. 2016;37:2129-200

Type of HF	Mandatory criteria for diagnosis of HF			
	HF signs and/or symptoms	LVEF (*)	Elevated NP (**)	Echocardiograpic evidence of structural heart disease and/or diastolic dysfunction
HFrEF HF with reduced EF	Yes	< 40%	Yes***	-
HFmrEF HF with mid-range EF	Yes	40 – 49%	Yes	Yes
HFpEF HF with preserved EF	Yes	≥ 50%	Yes	Yes

(*) LVEF: left ventricular ejection fraction = [SV/EDV] x 100%
(**) BNP > 35 pg/mL; NT-proBNP > 125 pg/mL
(***) not mandatory to confirm the diagnosis

The rationale to separate different forms of HF based on EF is that these categories may correspond to different demographic characteristics, etiologies of HF, comorbidities and ultimately responses to available therapies.

Based on LVEF, HF is classified as:

- **HFrEF- HF** with reduced ejection fraction. (LVEF < 40%; formerly systolic HF)
- **HFmrEF- HF** with mid-range ejection fraction. (LVEF 40-49%)
- **HFpEF - HF** with preserved ejection fraction. (LVEF ≥ 50%; formerly diastolic HF)

About half of HF patients have HFpEF and these patients are more likely to be older, female, with more comorbidities; whereas coronary artery disease is the main determinant of HFrEF.[6] HFmrEF may account for 10-20% of HF patients with characteristics that are intermediate between HFpEF and HFrEF.[7] Of note, up to 20-30% of patients with HFmrEF will have LVEF evolution over time and therefore their classification may change during follow-up.

The distinction between these phenotypes of heart failure is associated with different pathophysiological mechanisms, prognosis and treatment options.

Clinical severity (Table 2)

Two classifications are in use: the **NYHA functional classification** describes the functional status of the patient based on symptom severity and exercise capacity, whereas the **ACCF/AHA classification** describes stages of HF based on the course of the disease. Progression in HF stages is associated with reduced survival and increased plasma natriuretic peptide concentrations.[8]

The main difference between these two classifications is the consideration of a patient at risk without structural myocardial deterioration as the first stage of HF according to the ACCF/AHA classification.

> The **NYHA functional classification** predicts mortality and can be applied in stages with structural heart disease: B (Class I), C (Class I, II, III, IV) and D (Class IV).[9]

Table 2. Clinical classifications of HF severity.[9]

Adapted from Yancy CW. et al. *J Am Coll Cardiol.* 2013;62:e147-239

NYHA functional classification		ACCF/AHA stages of HF	
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations	Stage A	At risk for HF but without structural heart disease or symptoms of HF.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations	Stage B	Structural heart disease, but without signs or symptoms for HF.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations	Stage C	Structural heart disease with prior or current symptoms of HF
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased	Stage D	Refractory HF requiring special interventions

■ NYHA: New York Heart Association ■ ACCF/AHA: American College of Cardiology Foundation / American Heart Association
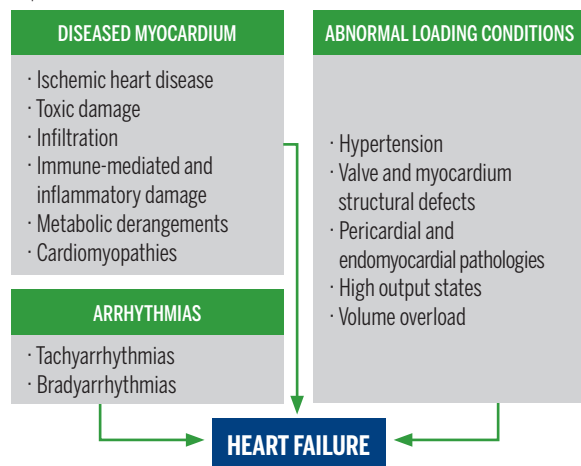
Comparison of ACCF/AHA and NYHA classifications [9]:

Stage A	None	Stage C	Class I, II, III, IV
Stage B	Class I	Stage D	Class IV

2 Etiology and pathophysiology

HF is a complex clinical syndrome with many possible causes of ventricular dysfunction and reduced cardiac output. These may include **etiologies** associated with **diseased myocardium, abnormal loading conditions** or **arrhythmias (Figure 2)**.[3] Many HF patients will have several different underlying pathologies, cardiovascular and non-cardiovascular. **Coronary artery disease (CAD)** is the cause of approximately 2/3rd of cases of HFrEF[10], whereas **comorbidities** such as **obesity, diabetes, chronic obstructive pulmonary disease (COPD) and hypertension** are highly prevalent in (and possibly directly responsible for) HFpEF.[11]

Figure 2. Causes of HF.[3]

Adapted from Ponikowski P, et al. *Eur Heart J.* 2016;37:2129-200

DISEASED MYOCARDIUM
· Ischemic heart disease
· Toxic damage
· Infiltration
· Immune-mediated and inflammatory damage
· Metabolic derangements
· Cardiomyopathies

ABNORMAL LOADING CONDITIONS
· Hypertension
· Valve and myocardium structural defects
· Pericardial and endomyocardial pathologies
· High output states
· Volume overload

ARRHYTHMIAS
· Tachyarrhythmias
· Bradyarrhythmias

HEART FAILURE

Toxic damage: alcohol or drug misuse, heavy metals, medications (e.g. cytostatic drugs), radiation.

Infiltration: malignancy, non-malignant (e.g. amyloidosis, sarcoidosis, hemochromatosis).

Immune-mediated and inflammatory damage: infection (bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV/AIDS)) and other (e.g. myocarditis, auto-immune disorders).

Metabolic derangements: hormonal (e.g. thyroid diseases, diabetes), nutritional (e.g. obesity).

Valve and myocardium structural defects: mitral, aortic, tricuspid and pulmonary valve diseases; atrial and ventricular septum defects.

Pericardial and endomyocardial pathologies: constrictive pericarditis, pericardial effusion, endomyocardial fibrosis, hypereosinophylic syndrome, endocardial fibroelastosis.

High output states: severe anemia, sepsis, thyrotoxicosis, Paget's disease, arteriovenous fistula, pregnancy.

Volume overload: renal failure, iatrogenic fluid overload.

■ **Main HF etiologies are associated with:**
  - **diseased myocardium**
    (i.e. coronary artery disease; toxic damage)
  - **abnormal loading conditions**
    (i.e. hypertension; valvular disease; renal failure)
  - **arrhythmias**

■ **Many HF patients have several different underlying pathologies**

Cardiac damage and increased wall stress (pressure and/or volume overload) leads to changes in the size, shape, and function of the left ventricle, a process termed remodeling. These changes lead to electrical instability and systemic processes resulting in many effects on other organs and tissues, and further damage to the heart. This cycle causes progressive worsening of HF over time.

Ventricular remodeling and increased neuro-humoral activity are key in the development and progression of HF **(Figure 3)**.[10] Remodeling, that develops in response to myocardial injury and increased wall stress, refers to changes in size and shape of the ventricles.[12] In the long run, however, remodeling may become maladaptive leading to **concentric/eccentric** hypertrophy (HFpEF) **and/or dilatation** (HFrEF) which impairs the function of the left ventricle (Figure 4).[13]

Volume overload plays an important role in heart dilatation (eccentric hypertrophy). Dilatation will progressively lead to decrease in LVEF. On the other hand, concentric hypertrophy will progressively alter the filling capacity of the heart.

■ **Changes in size and shape of the ventricles, that develop in response to myocardial injury, are known as ventricular remodeling.**

■ **This process leads to changes in LV cavity volume and/ or walls thickness and causes progressive worsening of HF over time.**

Figure 3. Pathophysiology of HF.[10]

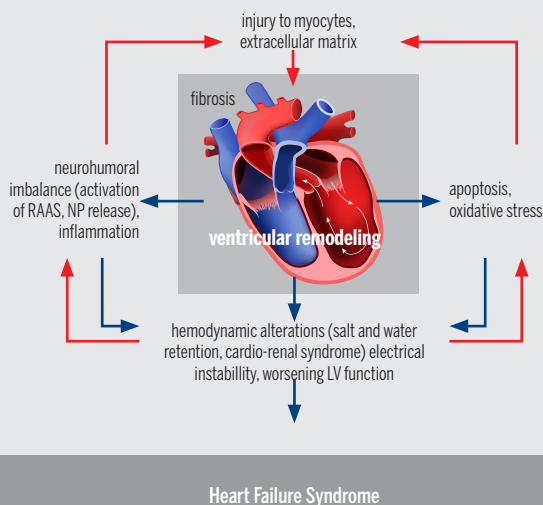Adapted from McMurray JJ. *N Engl J Med*. 2010;362:228-38

injury to myocytes, extracellular matrix

fibrosis

neurohumoral imbalance (activation of RAAS, NP release), inflammation

ventricular remodeling

apoptosis, oxidative stress

hemodynamic alterations (salt and water retention, cardio-renal syndrome) electrical instabillity, worsening LV function

Heart Failure Syndrome

Figure 4. Patterns of ventricular remodeling.[13]

Adapted from Jessup M, Brozena S. *N Engl J Med*. 2003;348:2007-18

Normal heart | Hypertrophied heart (HFpEF) | Dilated heart (HFrEF)
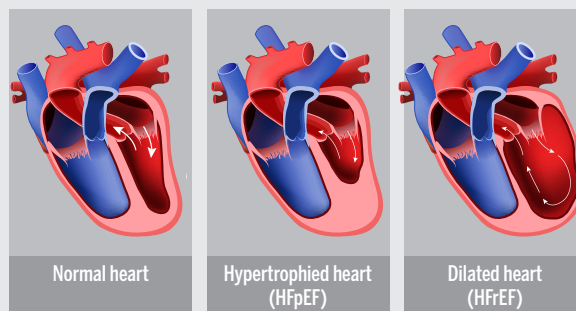
Middle: concentric hypertrophic growth results in a normal sized LV cavity with thickening and stiffening of the LV walls and preserved systolic function.

Right: eccentric hypertrophy results in an enlarged globular shape of the heart (enlarged LV volume) with thinning and weakening of the LV walls and an overall decrease in systolic function.

Neurohumoral imbalance plays an important role in maladaptive remodeling and progression of HF. Activation of the adrenergic system and the **renin-angiotensin-aldosterone system** (RAAS) stimulates the depressed contractility of the failing heart and raises blood pressure (vasoconstriction) which aids in the perfusion of vital organs.[14] However, prolonged activation of these systems causes maladaptive remodeling, increases oxygen demand, promotes ischemia and apoptosis, and can lead to arrhythmias.

Secretion of **natriuretic peptides** (NPs) is a physiologic response to counterbalance the action of RAAS and reduce symptoms and progression of HF.[15]

As HF advances, the **RAAS becomes the predominantly activated neurohumoral system (Figure 5)**. Targeting the RAAS, therefore, has become the cornerstone in pharmacological therapy of chronic systolic HF.[16] Other hormones are also involved such as endothelials and arginine vasopressin.
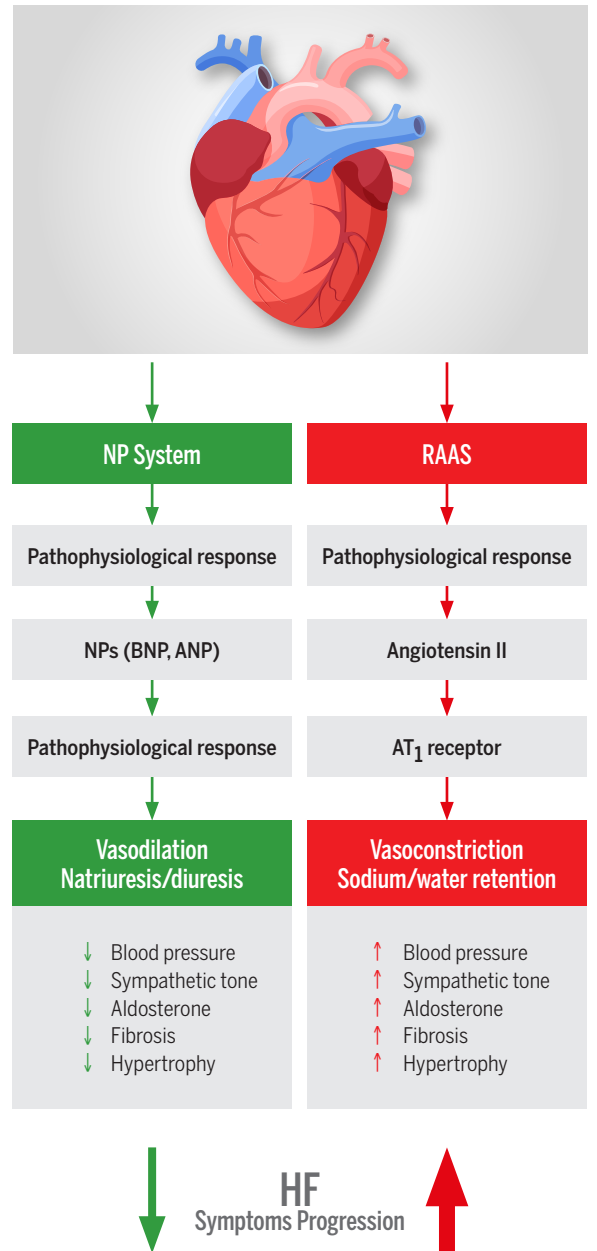
Activation of all these systems will lead to increased afterload, water and sodium retention, further reducing EF, which in turns leads to enhanced neurohumoral activation and remodeling – this is the vicious circle of CHF **(Figure 3)**.

The pathophysiology of neurohumoral imbalance is highly complex:

- The fall in cardiac output experienced in heart failure is detected by stretch and pressure receptors at various sites within the arteries, great veins and cardiac chambers.

- The under-activation of these receptors leads to a physiological response mediated through the sympathetic nervous system, the renin-angiotensin-aldosterone system and via vasopressin release from the hypothalamus.[17]

- Release of vasopressin and other vasoconstrictors, such as endothelins, lead to systemic vasoconstriction, which effectively maintains cardiac output.

Figure 5. Neurohumoral imbalance in HF.[15]

Adapted from Levin ER, et al. *N Engl J Med*. 1998;339:321-8

NP System	RAAS
Pathophysiological response	Pathophysiological response
NPs (BNP, ANP)	Angiotensin II
Pathophysiological response	AT_1 receptor
Vasodilation Natriuresis/diuresis	Vasoconstriction Sodium/water retention
↓ Blood pressure ↓ Sympathetic tone ↓ Aldosterone ↓ Fibrosis ↓ Hypertrophy	↑ Blood pressure ↑ Sympathetic tone ↑ Aldosterone ↑ Fibrosis ↑ Hypertrophy

HF
Symptoms Progression

3 Diagnosis

> It is important to distinguish between **non-acute** and **acute onset** of symptoms and signs.

In the acute setting, symptoms can be **life-threatening** and diagnosis and treatment are carried out together **(Figure 6)**. In this setting, the primary goal is to relieve symptoms and stabilize the patient (stabilize blood pressure, maintain blood oxygen levels and prevent organ damage).

In the non-acute setting (e.g. primary care, outpatient clinic), the goal is to establish the need for referral to echocardiography.

Acute dyspnea is the most frequent symptom of AHF[18], although not specific of HF.[19] Among all patients presenting to the ED with dyspnea, HF is the final diagnosis in about 1/3rd of patients.[20, 21]

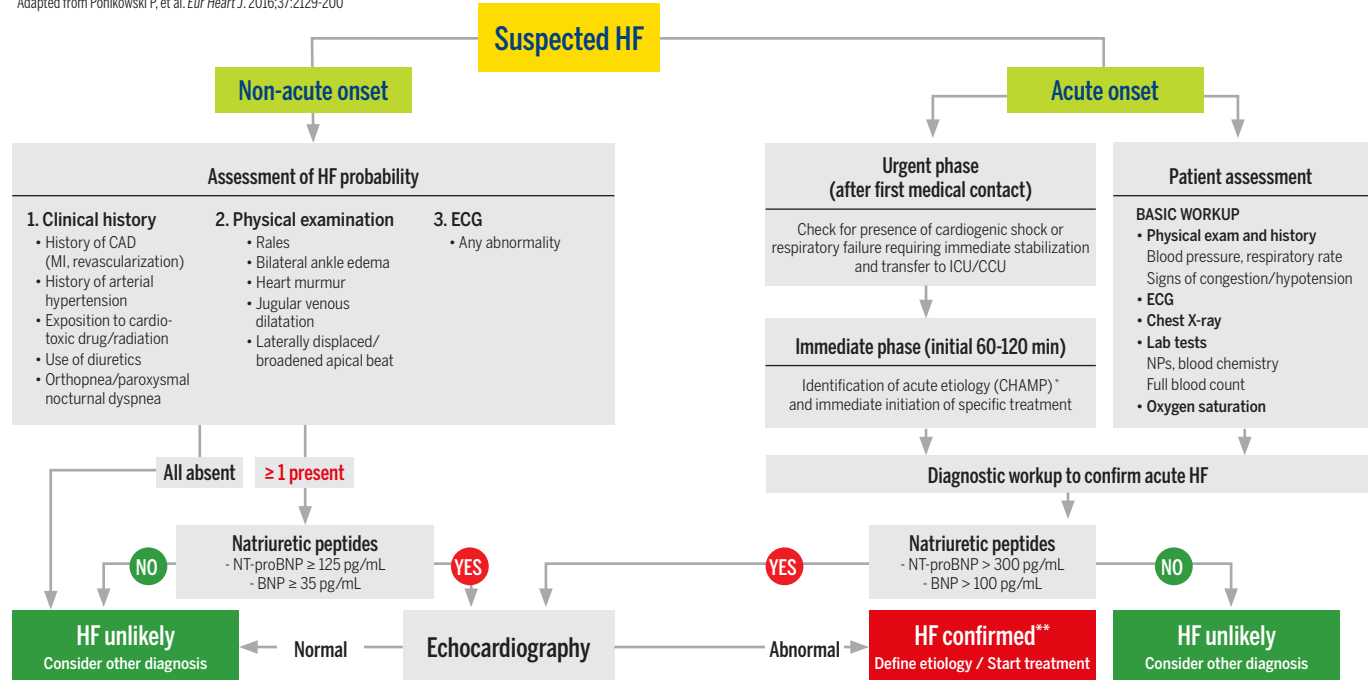Other common causes of acute dyspnea include:
- exacerbation of COPD or asthma (20%),
- pneumonia or bronchitis (15%),
- pulmonary embolism (PE) (5–10%),
- anxiety disorders (5%),
- other causes (malignancy, interstitial lung disease, upper airway obstruction, or anemia in 5–10%).[19]

The prompt and adequate diagnosis of HF is a clinical challenge. The diagnosis is based on detailed history analysis, physical examination and the use of several diagnostic tools.

> The latest ESC guidelines recommend ECG, chest x-ray, NP measurements and echocardiography (see pages 15-16).[3]

Figure 6. Diagnostic workup of patients with suspected HF.[3]

Adapted from Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-200

Suspected HF

Non-acute onset

Acute onset

Assessment of HF probability

1. Clinical history
- History of CAD (MI, revascularization)
- History of arterial hypertension
- Exposition to cardio-toxic drug/radiation
- Use of diuretics
- Orthopnea/paroxysmal nocturnal dyspnea

2. Physical examination
- Rales
- Bilateral ankle edema
- Heart murmur
- Jugular venous dilatation
- Laterally displaced/ broadened apical beat

3. ECG
- Any abnormality

Urgent phase (after first medical contact)

Check for presence of cardiogenic shock or respiratory failure requiring immediate stabilization and transfer to ICU/CCU

Immediate phase (initial 60-120 min)

Identification of acute etiology (CHAMP)* and immediate initiation of specific treatment

Patient assessment

BASIC WORKUP
- **Physical exam and history** Blood pressure, respiratory rate Signs of congestion/hypotension
- **ECG**
- **Chest X-ray**
- **Lab tests** NPs, blood chemistry Full blood count
- **Oxygen saturation**

All absent | **≥ 1 present**

Diagnostic workup to confirm acute HF

Natriuretic peptides
- NT-proBNP ≥ 125 pg/mL
- BNP ≥ 35 pg/mL

NO | YES | YES | **Natriuretic peptides**
- NT-proBNP > 300 pg/mL
- BNP > 100 pg/mL | NO

HF unlikely Consider other diagnosis

Normal | **Echocardiography** | Abnormal

HF confirmed** Define etiology / Start treatment

HF unlikely Consider other diagnosis

* CHAMP: acute Coronary syndrome, Hypertension emergency, Arrhythmia, acute Mechanical cause, Pulmonary embolism (see also Table 5, page 17). ** Based on all available data.

ESSENTIAL INITIAL INVESTIGATIONS

> Making an accurate diagnosis requires clinical judgement and expert knowledge, in conjunction with a series of diagnostic tools.[3]

◾ Patient history and physical examination

Symptoms and signs (Table 3) are often non-specific and, taken alone, do not discriminate between HF and other problems.[3]

Table 3. Symptoms and signs of HF.[3]

Adapted from Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-200

SYMPTOMS	SIGNS
Typical	**More specific**
Breathlessness Orthopnea Paroxysmal nocturnal dyspnea Reduced exercise tolerance Fatigue, tiredness Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse
Less typical	**Less specific**
Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in elderly) Depression Palpitations Dizziness Syncope Bendopnea	Weight gain (> 2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral edema (ankle, sacral, scrotal) Pulmonary crepitations Pleural effusion Tachycardia Irregular pulse Tachypnea Cheyne Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

◾ Electrocardiogram (ECG)

An abnormal ECG increases the likelihood of HF but has poor specificity, whereas HF is unlikely with a completely normal ECG. The ECG is not only useful to rule-out HF but also to identify underlying cardiac disease and potential triggers of acute HF such as myocardial infarction and arrhythmias.

◾ Chest X-ray

Chest radiography (X-ray) is particularly useful in the acute setting to identify pulmonary congestion/edema and detect/exclude other diseases which may contribute to dyspnea.

◾ Natriuretic peptides (NP)

In patients presenting with acute dyspnea and suspected acute HF measurement of the plasma NP level (BNP, NT-proBNP) is helpful in the **differentiation of acute HF from non-cardiac causes of acute dyspnea**.[19]

NPs play a key role in the diagnostic process, particularly to exclude HF. Cut-offs for HF exclusion have been chosen to minimize false-negatives while reducing unnecessary echocardiographic investigations. Cut-offs are different for BNP and NT-proBNP and are also different between non-acute and acute settings **(Table 4)**.

Table 4. Natriuretic peptide cut-offs for HF exclusion.[3]

Adapted from Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-200

	Non-acute onset (pg/mL)	Acute onset (pg/mL)
NT-proBNP	125	300
BNP	35	100

> **Natriuretic peptides are mainly recommended for ruling-out HF** because their negative predictive value (NPV) is very high (>95%), allowing HF to be ruled out when the concentration is below a predefined cut-off value.

If the NP concentration is above the cut-off value, physicians should be cautious, since there are numerous cardiovascular and non-cardiovascular causes of elevated NPs (see **Table 7**, page 22). The higher the concentration of NP above cut-off value, the higher the positive predictive value (PPV) for heart failure will be (rule-in). Nevertheless, for a **final diagnosis of HF, confirmation by echocardiography is required.**[3] The NP concentrations between the rule-out and rule-in cut-off values are referred to as the "grey zone" (see page 24) and in this case, echocardiography and/or other tools are needed to establish the diagnosis.

■ Echocardiography

This imaging technology provides crucial information on cardiac structure and function and is recommended to establish the diagnosis in suspected HF patients. Immediate echocardiography is only mandatory in patients with hemodynamic instability (e.g. cardiogenic shock) or suspected acute life-threatening cardiac abnormalities (e.g. aortic dissection).

When the diagnosis of HF is confirmed, other exams should be performed (biological tests as well as imaging).[3]

■ Work-up of Acute Heart Failure

In **the acute setting**, it is important to be aware of factors triggering acute HF **(Table 5)** particularly those that are life-threatening and require specific immediate intervention. It is crucial to check for presence of cardiogenic shock or respiratory failure requiring immediate stabilization and transfer to ICU/CCU. The most common precipitating factors include ACS, arrhythmia, valvular dysfunction, infection and non-compliance with medication.[6]

> Acute heart failure requires immediate treatment, since any delay in initiation of treatment may increase mortality.[22]

Table 5. Factors triggering acute HF.[3]

Adapted from Ponikowski P, et al. *Eur Heart J.* 2016;37:2129-200

Acute etiology requiring immediate initiation of specific treatment

C — acute **C**oronary syndrome
H — **H**ypertension emergency (excessive rise in blood pressure)
A — **A**rrhythmia (tachyarrhythmia, bradyarrhythmia)
M — acute **M**echanical cause*
P — **P**ulmonary embolism

* Myocardial rupture complicating ACS (free wall rupture, ventricular septal defect, acute mitral regurgitation), chest trauma or cardiac intervention, acute native or prosthetic valve incompetence secondary to endocarditis, aortic dissection or thrombosis.

■ Work-up of Chronic Heart Failure

In the **non-acute setting** (e.g. primary care, outpatient clinic), initial clinical examination with ECG and natriuretic peptides measurement are the initial steps.

Unless HF is ruled-out by natriuretic peptides measurement, an echocardiography should be performed. This technology will allow to distinguish between HFrEF, HFpEF and HFmrEF. Once the final diagnosis and etiology are established, the goal is to initiate the most appropriate treatment.

KEY STEPS OF DIAGNOSTIC WORK-UP

1 Assessment of clinical probability
This involves clinical history, physical examination and ECG.

2 Measurement of natriuretic peptides for exclusion of HF
Patients with NP levels below the appropriate cut-off are unlikely to have HF and do not require echocardiography.

3 Confirmation by echocardiography
Echocardiography allows to measure left ventricular ejection fraction, and many other well-known prognostic parameters.

NT-proBNP

1 Biochemistry and pathophysiology

The heart acts as an endocrine organ with the release of several structurally related **natriuretic peptides** in response to cardiac hemodynamic stress, as is the case in HF: A-type, B-type, C-type, D-type NP. All these peptides have a similar ring structure with di-Cysteine amino-acid. Among these, two have been proposed as markers of HF and seem to be particularly involved in the pathophysiology of HF: **atrial natriuretic peptide** (ANP) and **B-type natriuretic peptide** (BNP).[23, 24] ANP is produced predominantly in the atrium whereas BNP is produced predominantly in the ventricular myocardium. BNP is also secreted in atrium, arterial fibroblasts, brain and muscle cells.[25]

> ■ Natriuretic peptides are markers of cardiac stress and HF, and are therefore related to the extent of atrial, ventricular, and valvular dysfunction.[23]
>
> ■ BNP has an increased *in vitro* stability and superior diagnostic performance compared to ANP. BNP and its related peptide NT-proBNP have been extensively studied and have demonstrated clinical value in diagnosis, risk stratification and follow-up of patients with HF.[24]
>
> ■ BNP is the physiologically active hormone while NT-proBNP lacks biological activity.

The molar plasma concentration of NT-proBNP is higher than BNP due its **longer biological half-life**: 90-120 min for NT-proBNP vs. 20 min for BNP.[26] The differences in half-life and circulating concentrations can be explained by differences in clearance mechanisms.[26] BNP and NT-proBNP are equally cleared by the kidneys but there are **additional clearance mechanisms active for BNP** involving specific peripheral clearance receptors and enzymatic degradation.

Figure 7. Release of BNP and NT-proBNP.[26]
Adapted from Motiwala SR, Januzzi JL Jr. *Clin Pharmacol Ther*. 2013;93:57-67
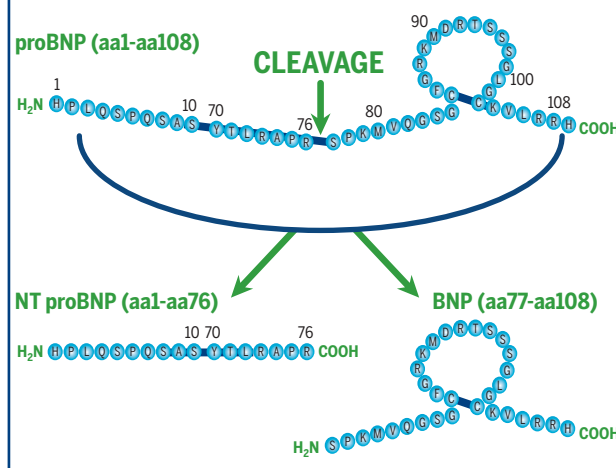
When the BNP gene is activated in response to ventricular stretch or ischemia, cardiomyocytes first produce a 134 amino acid **pre-proBNP precursor** which is rapidly cleaved to the 108 amino acid **proBNP** by removal of a 26 amino acid signal peptide. The biologically inactive proBNP is proteolytically cleaved to form the 32 amino acid C-terminal fragment **BNP** (amino acids 77-108) and the 76 amino acid N-terminal fragment **NT-proBNP** (amino acids 1-76) **(Figure 7)**. The precursor pre-proBNP is only present in myocardium whereas proBNP, BNP and NT-proBNP are present in both myocardium and plasma.[26]

2 Guide to interpretation of NT-proBNP

Pre-analytical and analytical considerations

➡ **Sample type**

> ■ Serum or heparinized plasma are recommended for testing of NT-proBNP on automated immunoassay analyzers.[27]
>
> ■ EDTA-plasma should not be used because it consistently produces 10-13% lower values.[27]

➡ **Sample stability**

NT-proBNP assay is stable during storage in serum or heparinized plasma when stored at room temperature or 4 °C for at least 72 h or for up to 1 year when stored at -80 °C.[24]

➔ Analytical variation

> All NT-proBNP assays use the same antibodies and calibrators. Consequently, there are only minor differences between commercial NT-proBNP assays with <10% variation across methods.[24]

A total imprecision of <15% is recommended for NT-proBNP concentrations within the reference interval and <10% for monitoring changes over time.[28] With typical total imprecision below 6.5%, automated methods clearly meet these precision requirements.[27]

➔ Biological variation

The biological variability of NT-proBNP is 25-40% in patients with stable HF and this should be taken into account when evaluating the significance of any change.[27]

> A practical approach is to consider only changes of >30% as clinically relevant.[23]

Table 6. BNP and NT-proBNP analytical and clinical comparison.[35, 36, 54]

Adapted from Januzzi et al. *Eur Heart J.* 2006; Maisel et al. NEJM, 2002; van Kimmenade et al. ACC, 2006

| FEATURES	NT-proBNP	BNP
Analytical		
Hormone activity	No	Yes
Half-life	60-120 mins	20 mins
In vitro stability (room temperature	>72 hours	4 hours
ARNI interference	No	Yes
Agreement between methods	High	Moderate
Clinical		
Study	ICON	BNP
Patients (n)	1,256	1,586
Rule-OUT cut-off	300 pg/mL	100 pg/mL
NPV/PPV (%)	98/77	89/79
Rule-IN cut-off	450/900/1,800 (age-adjusted)	400
Patients in grey zone	215 (17.1%)	428 (27.0%)
HF patients in grey zone	116 (54.0%)	263 (61.2%)

Expected values

➔ Impact of age, gender and ethnicity

NT-proBNP values are about **50% higher in normal women than in men (Figure 8)**. Age is another predictor of increased NT-proBNP levels, particularly **in the elderly >65 years (Figure 8)**. Ethnicity has been reported to influence NT-proBNP levels with **lower values in black and Chinese** compared with white individuals and **intermediate concentrations in Hispanic individuals**.[29]

Figure 8. Influence of age and gender on NT-proBNP.[30]

Adapted from Costello-Boerrigter LC, et al. *J Am Coll Cardiol*. 2006;47:345-53
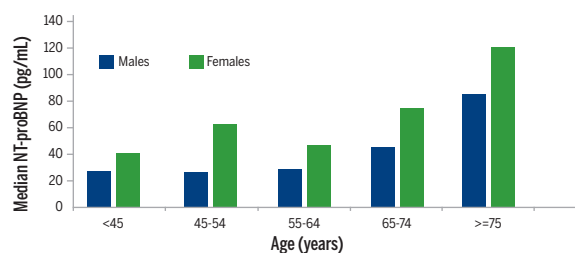
Median NT-proBNP values in a normal population (344 males and 402 females).

➔ Causes of elevated NT-proBNP

NT-proBNP is a marker of cardiac stress and related to the extent of cardiac dysfunction. As such, NT-proBNP is elevated in HF with concentrations related to disease severity **(Figure 9)**.

Figure 9. NT-proBNP in HF.[31]

Adapted from Emdin M, et al. *Clin Chem*. 2007;53:1289-97.
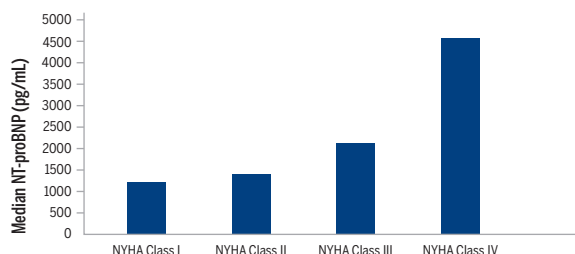
Median NT-proBNP values in a population of 479 HF patients stages C and D grouped according to NYHA class. NT-proBNP is highly elevated compared to normal healthy individuals and increasing with severity of HF.

> However, NT-proBNP is not specific for HF and can be elevated in numerous other clinical conditions, both cardiac and non-cardiac **(Table 7)**.

Table 7. Causes of elevated NT-proBNP.[3]

Adapted from Ponikowski P, et al. *Eur Heart J*. 2016;37:2129-200

Cardiac	Heart failure Acute coronary syndromes Pulmonary embolism Myocarditis Left ventricular hypertrophy Hypertrophic or restrictive cardiomyopathy Valvular heart disease Congenital heart disease Atrial and ventricular tachyarrhythmias Heart contusion Cardioversion, ICD shock Surgical procedures involving the heart Pulmonary hypertension
Non-cardiac	Advanced age Ischemic stroke Subarachnoid hemorrhage Renal dysfunction Liver dysfunction (mainly liver cirrhosis with ascites) Paraneoplastic syndrome Chronic obstructive pulmonary disease Severe infections (including pneumonia and sepsis) Severe burns Anemia Severe metabolic and hormone abnormalities (e.g. thyrotoxicosis, diabetic ketosis)

3 Clinical utility of NT-proBNP

Diagnosis of HF

> ■ Measurement of NT-proBNP is an integral part of the diagnostic workup to reliably rule-out HF and prevent unnecessary echocardiographic investigations.
>
> ■ In the subgroup of patients with acute dyspnea, measurement of NT-proBNP is associated with reduced time spent in the ED, and reduced re-hospitalizations and medical costs.[32]

→ Rule-out of HF

Irrespective of age, gender and ethnicity, a single NT-proBNP cut-off is recommended for HF exclusion[3]:

■ 125 pg/mL in the case of non-acute onset of symptoms
■ 300 pg/mL in patients presenting with acute onset of symptoms.

In the **non–acute setting**, a higher rule-out cut-off value of **450 pg/mL for patients >75 years** has been previously reported as the ideal cut-off value[33] but is not mentioned in the latest ESC guidelines.[3]

In meta-analyses, these cut-off values have shown to provide a high sensitivity, but only moderate specificity for the diagnosis of HF **(Table 8)**. Consequently, the rule-out cut-off values provide a high negative predictive value (NPV), but only moderate positive predictive value (PPV).

Table 8. NT-proBNP for HF rule-out: meta-analysis of diagnostic performance.[33, 55]

Adapted from Hildebrandt P, et al. *Eur Heart J*. 2010;31:1881-9; Roberts E, et al. BMJ. 2015;350:h910

Clinical setting	Rule-out cut-off (pg/mL)	N	Sensitivity (%)	Specificity (%)	Prevalence (%)	NPV (%)	PPV (%)
Non-acute onset	125	4,096 6 studies (33)	93	58	18 (a)	97	33
Acute onset	300	3,349 10 studies (55)	99	43	35 (b)	99	48

a) Systolic dysfunction (EF < 40%) in primary care.[33]
b) HF in acute dyspnea.[20]

Impact of ejection fraction (EF): an inverse relationship exists between EF and NT-proBNP and, on average, NT-proBNP levels are lower in HFpEF than in HFrEF.[34] This can be explained by the greater wall stress in HFrEF due to larger ventricular chamber radius. However, the cut-off values defined to rule-out HF apply similarly to HFpEF and HFrEF, with no risk for more false negatives when EF is preserved.[3, 34]

➔ Rule-in of HF

In the non-acute setting, no rule-in cut-off value has been validated and a patient with a positive NT-proBNP result (≥ 125 pg/mL) should be referred for specialist care including echocardiography.[33]

In the acute setting, the following **age-related cut-off values for rule-in of HF** have been validated in the ICON study.[35]

< 50 years	450 pg/mL
50 – 75 years	900 pg/mL
> 75 years	1,800 pg/mL

Although this makes it likely that a patient with a positive NT-proBNP result has HF, confirmation with echocardiography will still be required.[23]

In patients with advanced renal failure, higher cut-off values are to be recommended for rule-in.

➔ Grey zone

Patients with acute symptoms who present with NT-proBNP values between the rule-out and rule-in cut-offs are in the 'grey zone'. In the ICON study, the grey zone was observed in 17% of dyspneic patients, 54% of whom were ultimately diagnosed with HF.[35]

> For patients with NT-proBNP values in the grey zone, confirmation by echocardiography is required.[23]

In "grey zone" patients, HF is often mild to moderate with fairly good medium-term prognosis.[37] Nevertheless, these patients have worse outcomes compared to patients with NT-proBNP values below the rule-out cut-off.[36] In the grey zone it is particularly important to consider other causes of a modest rise in NT-proBNP such as pulmonary hypertension, PE, ACS, AF, COPD or pneumonia.[37]

Prognostic value

Guidelines indicate that measurement of NT-proBNP has the following prognostic utility[38]:

> - Establishing prognosis or disease severity in chronic HF.
> - Measurement of baseline levels on admission to the hospital is useful to establish a prognosis in acutely decompensated HF.
> - During a HF hospitalization, a pre-discharge level can be useful to establish a post-discharge prognosis.

In hospitalized patients, it is reasonable to collect a baseline sample and a second sample prior to discharge for risk assessment and identification of those in need for more aggressive management.[23] Patients with >30% decrease in NT-proBNP between admission and discharge have a favorable prognosis.[39]

➔ Follow-up and guided therapy

Treatment with guideline-directed therapies in chronic HF has been shown to reduce NP levels[26] and may reduce the rate of re-admissions. Furthermore, trends in NP concentrations over a period of several months add considerably to prognostic utility as compared with the value from a single measurement.[26]

This suggests that **NT-proBNP or BNP could be useful to guide therapy in the outpatient setting** with the goal of reducing NP levels by intensifying drug therapy. This has been tested in several randomized controlled trials with mixed results considering the impact on improving outcomes, although a significant reduction in risk for morbidity and mortality has been reported in the majority of studies and in 2 meta-analyses.[26, 52] In addition, the benefit seems to be only observed in patients < 75 years.[52]

However, no specific recommendations related to NP–guided therapy are given in recent HF guidelines.[38]

The **GUIDE-IT study** was designed to definitively assess the effects of an **NP-guided strategy in high-risk HFrEF patients** on clinically relevant endpoints. In this study, a strategy of adjusting therapy with the goal of achieving a target NT-proBNP level of <1,000 pg/mL was compared with usual care. The data and safety monitoring board recommended stopping enrollment after the inclusion of 894 of the planned 1,100 patients, since the strategy of NT-proBNP-guided therapy was not more effective than the usual care strategy in improving outcomes.[40]

This study has several important limitations: 1) unblinded design, 2) no formal restriction to measurement of NT-proBNP in usual care group existed (just discouraged), and some patients may have had NT-proBNP levels assessed. Finally, most patients were already receiving the best available treatment at baseline (difficult to do better) and there was no difference between groups in treatment up-titration. This is demonstrated by the observation of similar NT-proBNP decrease in both groups.[40]

Since the recent publication of **PARADIGM-HF** study results[41], a new drug class has been introduced in updated ESC and ACC/AHA 2016 Guidelines for CHF treatment, **ARNI (angiotensin receptor-neprilysin inhibitor)**.[3,38] When compared to ACE inhibitors, sacubitril-valsartan was associated with a significant (20%) reduction in the primary endpoint of mortality or hospitalization for acute decompensation of HF, as well as a significant reduction in re-hospitalization rate, cardiovasc mortality and even overall mortality.[41]

Sacubitril is a pro-drug that will inhibit neprilysin, an enzyme involved in the clearance of ANP and BNP. As a consequence, BNP is expected to increase during treatment with sacubitril-valsartan, especially during the first weeks after its introduction contrasting with clinical improvement.

Conversely, NT-proBNP is not affected by the direct mechanism of action of sacubitril-valsartan and its trends correspond to clinical status.

Interpretation of NT—proBNP in the presence of comorbidities

Renal function

The umbrella term cardio-renal syndromes is used to describe the **bidirectional relationship between cardiac and renal dysfunction**.[42] Patients with cardiac dysfunction develop renal dysfunction and, conversely, patients with renal dysfunction develop cardiac dysfunction. Over 50% of HF patients have renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.[43] These patients have a two-fold higher risk of dying than HF patients without renal dysfunction.

An inverse relationship exists between renal function (eGFR) and NT-proBNP values.[44] Consequently, NT-proBNP values are higher in patients with kidney disease than in those without. However, the diagnostic value of NT-proBNP is maintained in the presence of renal dysfunction and elevated levels do not necessarily reflect reduced clearance of NT-proBNP.[44] Highly elevated NT-proBNP should not be ignored in patients with renal dysfunction, as this suggests that cardiac disease is present.[37]

- The NT-proBNP rule-out cut-off value does not need to be adjusted for renal dysfunction.[44]
- However, for the age-related rule-in cut-points a lower specificity for HF diagnosis is observed for eGFR < 60 mL/min/1.73 m^2 and a higher cut-off value of 1200 pg/mL has been suggested.[44]

Atrial fibrillation (AF)

AF is a common comorbidity in patients hospitalized with HF.[4] In the BACH study of acute dyspneic patients, 39% were diagnosed with HF and 17% with AF.[45] Concurrent AF was present in 28% of HF patients whereas concurrent HF was present in 63% of AF patients.

NT-proBNP is elevated in patients with AF, both in the presence and absence of HF.[44]

NT-proBNP levels in AF patients without HF approach levels observed in HF patients. Consequently, in AF patients, the previously defined cut-off levels for HF diagnosis will not affect sensitivity but will result in reduced specificity.

Obesity

NT-proBNP levels are lower in obese people, both with and without HF.[37]

In the ICON study of patients with acute dyspnea, overweight (BMI 25-30 kg/m^2) and obesity (BMI ≥30 kg/m^2) were observed in 34% and 29%, respectively.[46] In this cohort, compared to lean patients (BMI <25 kg/m^2), NT-proBNP levels were lower in overweight and obese patients both with and without HF. Nevertheless, the sensitivity of the previously defined rule-out cut-off (300 p/mL) was retained across all BMI categories and no adjustment is needed for BMI.[46]

FREQUENTLY ASKED QUESTIONS

1 What is the difference between BNP and NT-proBNP?

BNP is the C-terminal and NT-proBNP the N-terminal cleavage product of proBNP **(Figure 7)**. Both are markers of cardiac stress with essentially equivalent clinical performance as biomarkers for HF.[3, 23]

Important differences reside in the **mechanisms for clearance from the circulation**, resulting in up to 6-fold longer half-life of NT-proBNP compared to BNP.[26] However, both BNP and NT-proBNP are equally cleared by the kidneys and show a parallel inverse relationship with declining eGFR.[47]

Considering their half-life differences, concentrations of NT-proBNP are higher than BNP and each marker has its own cut-off values for rule-out and rule-in of HF.[3, 23]

NT-proBNP offers a wider dynamic measuring range of 15 to 25,000 pg/mL compared with 5 to 5,000 pg/mL for BNP. This may explain the reportedly better accuracy of NT-proBNP in detecting mild HF[31] and HFpEF.[34]

Both BNP and NT-proBNP values decrease with increasing BMI.[37] In the acute setting, a lower cut-off is recommended for BNP to rule-out HF in obese patients, whereas no adjustment is needed for NT-proBNP.[23, 37]

BNP, but not NT-proBNP, is a substrate for neprilysin and the differential effect of neprilysin is important in the interpretation of NP levels in patients on an angiotensin receptor-neprilysin inhibitor (ARNI).[48] Treatment with the ARNI valsartan/sacubitril results in increased BNP compared with baseline levels, whereas a rapid and sustained reduction in NT-proBNP is observed.[48]

Important differences exist in **(pre)analytical properties** which may favor NT-proBNP as a more convenient molecule to work with in clinical laboratories[27]:

- Better *in vitro* sample stability at different temperatures.
- Lower variation across detection platforms.

2 Can false-negative or false-positive NT-proBNP results be expected?

There are a few situations where **NT-proBNP is not elevated**, or only marginally elevated, despite symptoms suggestive of HF.[37] This may occur in situations where there is not a significant risk in LV wall stress, such as in mitral stenosis or acute mitral regurgitation and constrictive pericarditis. 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.

The term 'false-positive' is a misnomer since NT-proBNP is known to be elevated in many conditions besides HF **(Table 7)**. In patients presenting with acute dyspnea, an elevated NT-proBNP is predictive of a future adverse outcome, both in patients with and without HF.[49]

3 Can NT-proBNP distinguish HFrEF from HFpEF?

An **inverse relationship** exists between NT-proBNP and EF and NT-proBNP levels are generally lower in HFrEF than in HFpEF.[34] However, **NT-proBNP alone cannot be used to distinguish HFrEF from HFpEF**. The diagnosis of HFpEF is based on the presence of the following criteria **(Table 1)**: HF signs and/or symptoms, LVEF ≥50%, elevated NT-proBNP (>125 pg/mL) and echocardiographic evidence of structural heart disease and/or diastolic dysfunction.

4 What is the difference between 'wet' and 'dry' NT-proBNP?

Figure 10. Hemodynamic profile in acute HF.[3]

Clinical classification according to the hemodynamic profile (modified Forrester classification). Adapted from Ponikowski P, et al. Eur Heart J. 2016;37:2129-200
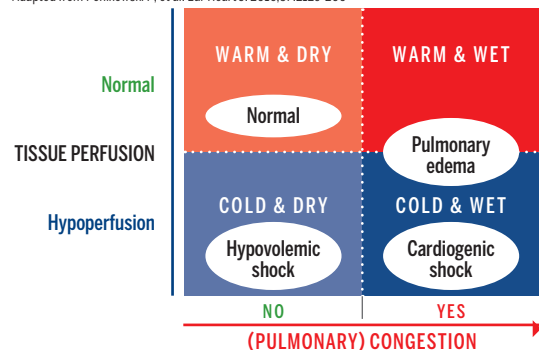
In a patient with decompensated HF, the NT-proBNP level is the sum of the baseline level plus the volume overload.[37] The baseline level is the level that occurs once optimum fluid status is reached; this is referred to as the optivolemic or 'dry' level. The additional level, occurring from acute pressure or volume overload, is referred to as the 'wet' level. In patients presenting to the ED with a history of HF, knowledge of a patient's baseline (dry) NT-proBNP level is helpful in the clinical management process. Any NT-proBNP level 25-50% over the baseline optivolemic level usually reflects volume overload. The wet NT-proBNP level falls rapidly with treatment, whereas the optivolemic dry NT-proBNP level falls slowly with treatment.[37]

5 What is the cost-effectiveness of using NT-proBNP in the ED?

In patients attending the ED with acute dyspnea, the combination of NT-proBNP with clinical judgment improves the diagnostic process compared with clinical judgment alone.[20] The impact of NT-proBNP testing on clinical management has been investigated in randomized controlled trials. The Canadian multi-center IMPROVE-CHF study showed that the improved diagnostic process with use of NT-proBNP testing resulted in shorter duration of ED visits, less readmissions and a reduction in medical costs.[32] A single center study in The Netherlands showed that the introduction of NT-proBNP testing in the ED setting reduced time to discharge and medical costs.[50]

6 What is the utility of NT-proBNP in other critically ill conditions besides acute dyspnea?

NT-proBNP has prognostic utility in the following acute clinical conditions[23]:

→ Acute coronary syndromes

NT-proBNP is released upon myocardial ischemia and several diastolic and systolic abnormalities. NT-proBNP is a powerful prognostic marker in ACS that **improves risk stratification** in combination with cardiac troponin and existing clinical risk scores. Patients with acute myocardial infarction and NT-proBNP concentrations <1,000 pg/mL have a high probability for recovery of LV function.

→ Acute pulmonary embolism

Measurement of NT-proBNP is a useful aid in the risk stratification of patients with acute PE which **guides decisions on clinical management**.[51]

Plasma levels of NT-proBNP reflect the severity of hemodynamic compromise and RV dysfunction in acute PE. Patients with elevated NT-proBNP have a high risk of an adverse clinical outcome, whereas hemodynamically stable patients with low NT-proBNP (<500 pg/mL) may be candidates for early discharge and outpatient treatment. Inversely, patients with >1,000pg/ml have more frequent severe PE and specific treatment might be considered if confirmed.

→ Intensive care

Severe dyspnea due to respiratory failure is common in patients in intensive care units (ICUs). However, the high rate of cardiac and renal dysfunction in ICU patients limits the discriminative role of NT-proBNP. Patients with acute respiratory problems have elevated NT-proBNP concentrations due to right heart dysfunction. Patients with sepsis and septic shock have elevated NT-proBNP associated with organ and myocardial dysfunction. An NT-pro-BNP concentration on admission has prognostic value and might facilitate the triage of ICU patients. The absence of rapid reduction in NT-proBNP over 24-48h has **strong prognostic significance in critically-ill patients and in patients with sepsis**.

7 Can NT-proBNP be used in an ambulatory heart failure evaluation and/or in screening for asymptomatic left ventricular dysfunction?

In the outpatient setting, both peptides (BNP and NT-proBNP) remain sensitive, though perhaps less specific for the diagnosis of HF due to overlap of concentrations between those with and without the diagnosis of clinical HF.[53] Nonetheless, use of BNP and NT-proBNP may be of clinical utility to support evaluation for HF in the outpatient environment. Data show that in the ambulatory setting, the **optimal use of natriuretic peptide testing is to exclude HF with a lower cut-off value**, optimizing sensitivity and negative predictive value (e.g. BNP <35 pg/mL; NT-proBNP <125 pg/mL).[53]

Use of BNP or NT-proBNP in the asymptomatic general population for detection of left ventricular dysfunction has less utility. Data suggests that a modestly elevated BNP or NT-proBNP in patients without a diagnosis of HF identifies those at high risk for developing HF events, and that such events could be prevented.[53]

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LIST OF ABBREVIATIONS & ACRONYMS

ACCF/AHA	American College of Cardiology Foundation/American Heart Association
ACS	acute coronary syndromes
AF	atrial fibrillation
AHF	acute heart failure
ANP	A-type natriuretic peptide
ARNI	angiotensin receptor-neprilysin inhibitor
AT$_1$	angiotensin II receptor type 1
BMI	body mass index
BNP	B-type natriuretic peptide
CAD	coronary artery disease
CCU	Coronary Care Unit
CHAMP	acronym for acute etiology requiring immediate specific treatment: acute **C**oronary syndrome, **H**ypertension emergency, **A**rrhythmia, acute **M**echanical cause, **P**ulmonary embolism
CHF	chronic heart failure
COPD	chronic obstructive pulmonary disease
ECG	electrocardiogram
ED	emergency department
EDTA	ethylenediaminetetraacetic acid
EDV	end diastolic volume
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
GUIDE-IT	Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (US multicenter randomized controlled trial)
HF	heart failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICON	International Collaborative of NT-proBNP Study
ICU	intensive care unit
IMPROVE-CHF	Improved Management of Patients With Congestive Heart Failure (Canadian multicenter randomized controlled trial)
LV	left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NP	natriuretic peptide
NPV	negative predictive value
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PARADIGM-HF	Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial
PE	pulmonary embolism
PPV	positive predictive value
proBNP	pro-B-type natriuretic peptide
RAAS	renin angiotensin aldosterone system
RV	right ventricular
SBP	systolic blood pressure
SV	stroke volume

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