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Guideline for the Use of Natriuretic Peptides in the Early Diagnosis and Management of Heart Failure in Primary Care *(Joint Consensus Report by the Eurasian Society of Heart Failure and the Turkish Association of Family Medicine)*

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ABSTRACT

Heart failure (HF) is a complex clinical condition associated with significant morbidity and mortality. Early diagnosis and effective management at the primary care level are essential for improving patient outcomes and reducing the burden on the healthcare systems. The Eurasian Society of HF and the Turkish Association of Family Medicine developed a guideline that underscores the critical role of natriuretic peptides (NPs) in the early detection, diagnosis, and management of HF. NPs, particularly the N-terminal pro-B-type NP, are a reliable biomarker for identifying HF, guiding treatment decisions, and monitoring disease progression. This guideline emphasizes the importance of measuring the levels of these peptides in primary care so as to detect individuals at risk, confirm the diagnosis of HF in symptomatic patients, and evaluate the treatment response. The recommended thresholds for NP levels account for variations arising from factors such as age, gender, and the presence of other health conditions. B-type natriuretic peptides (BNP) levels ≥ 35 pg/ml or N-terminus-proBNP levels ≥ 125 pg/ml are used to confirm the likelihood of HF in symptomatic patients, enabling timely diagnosis and appropriate intervention. Incorporating NP testing into routine clinical practice enables timely referrals and ensures appropriate management at all stages of HF. Beyond diagnosis, the measurement of NPs provides valuable information about treatment effectiveness and prognosis, allowing clinicians to individualize the treatment. By integrating NP testing into primary care, healthcare providers can facilitate early detection, optimize treatment strategies, and improve the quality of life for patients with or at risk of HF. Thus, this guideline highlights the essential role of primary care physicians in addressing the growing challenges of HF through the effective and evidence-based use of NPs.

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1. DEFINITION AND CLASSIFICATION OF HEART FAILURE

Heart failure (HF) is a complex clinical syndrome characterized by symptoms and signs resulting from pulmonary and/or systemic congestion, neurohormonal activation, and/or hypoperfusion. These conditions arise due to structural and/or functional abnormalities of the heart, which increase intracardiac pressures and/or reduced cardiac output at rest or during exertion.

In the universal definition of HF, the diagnosis requires the manifestation of symptoms and/or signs attributable to structural and/or functional cardiac abnormalities, along with elevated natriuretic peptide (NP) levels or findings that are consistent with cardiogenic pulmonary or systemic congestion (Figure 1).[1] Patients meeting this definition are classified into four categories based on their ejection fraction (EF):

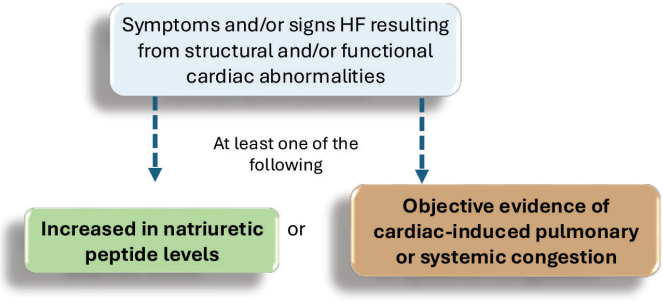

FIG. 1. Criteria for the heart failure diagnosis according to the universal definition of heart failure.

- **Heart failure with reduced ejection fraction:** EF ≤ 40%.
- **Heart failure with mildly reduced ejection fraction:** EF 41-49%.
- **Heart failure with preserved ejection fraction:** EF ≥ 50%.
- **Heart failure with improved ejection fraction:** Initially EF ≤ 40%, with an improvement of ≥ 10 points to EF > 40% over time.

The 2022 AHA/ACC/HFSA HF Guidelines classify HF into three groups: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF), and consider heart failure with improved ejection fraction (HFimpEF) as a subgroup of HFrEF.[2] In a 2022 Expert Consensus Report published in Türkiye, all HF cases with EF > 40% were collectively classified as HF with non-reduced EF, encompassing HFmrEF, HFpEF, and HFimpEF.[3]

HF develops through a continuum that begins with structural and/or functional alterations in the heart, progresses with the emergence of HF signs and symptoms, and worsens over time when these conditions persist. This continuum can be categorized into the following four stages (Figure 2):

- **Stage A:** At-risk individuals without structural or functional cardiac abnormalities.
- **Stage B:** Pre-HF patients with structural and/or functional cardiac abnormalities, but without HF signs or symptoms.
- **Stage C:** Patients with the onset of HF signs and symptoms.

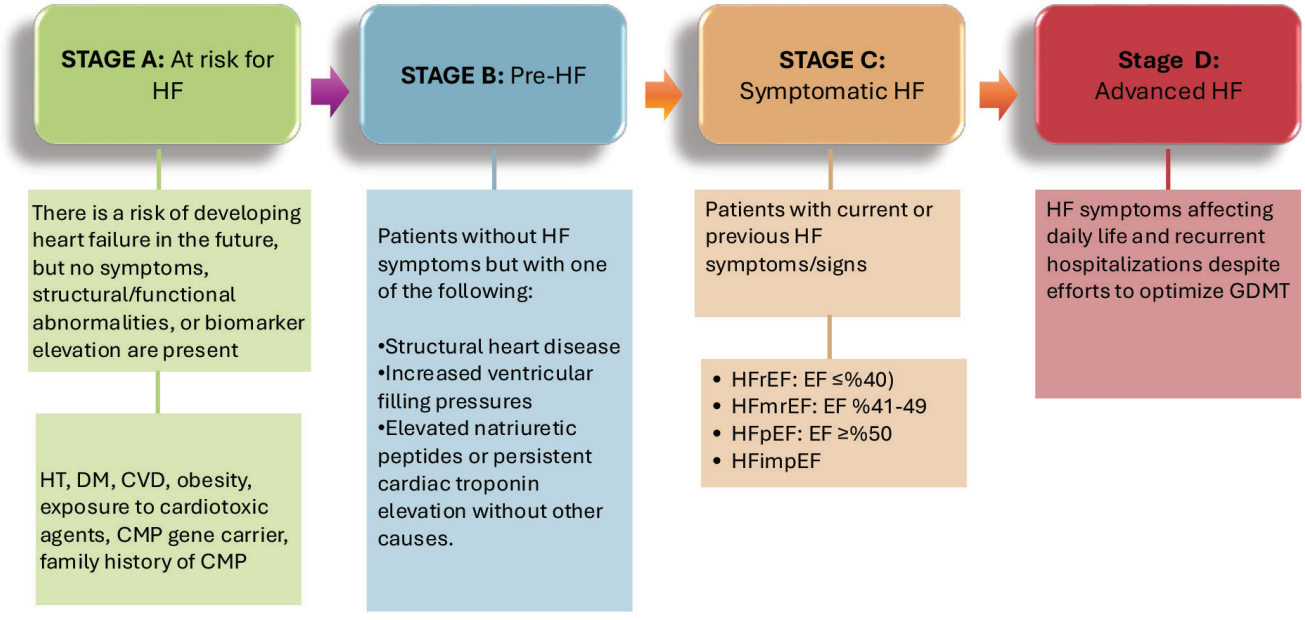

FIG. 2. Stages of heart failure.

HF, heart failure; HT, hypertension; DM, diabetes mellitus; CVD, cardio-cerebrovascular diseases; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFimpEF, heart failure with improved ejection fraction; EF, ejection fraction.

- **Stage D:** Patients with worsening HF symptoms and disease progression.

1.1. Epidemiology and prognosis of heart failure

The increasing life expectancy of populations, the growth of the elderly demographic, and the improved treatment of conditions such as ischemic heart disease, cardiomyopathies, and valvular diseases are the primary contributors to the rising prevalence of HF. Globally, HF prevalence in the adult population is reported to be 1-3%, with an incidence of 1-20 per 1,000 person-years.[4]

The ATLAS study, encompassing European countries, reported that, while the HF prevalence and incidence varied across nations, the median HF prevalence was 1.72%, and the median annual HF incidence was 3.2 per 1,000 patient-years.[5] In Türkiye, the TRends-HF study, which included the entire population of 85 million, reported that, by the end of 2022, HF prevalence would be 2.1% across all age groups and 2.9% in the adult population, corresponding to 1.8 million individuals diagnosed with HF.[6,7] The HF incidence in Türkiye is estimated to be 3-6 per 1,000 patient-years.[6]

In the United States, the 2022 Heart Disease Statistics reported the prevalence of HFpEF as 46%, HFmrEF as 8%, and HFrEF as 46%. Over the past two decades, the HFrEF incidence has declined, while the HFpEF incidence has risen.[8] The SELFIE-TR study revealed that, among the hospitalized HF patients in Türkiye, HFpEF accounted for 7.3%, HFmrEF 16.7%, and HFrEF 76%.[9] The relatively low proportion of HFpEF cases may be attributed to the high number of undiagnosed cases in this group, which requires greater evaluation and differential diagnosis. Notably, past studies have suggested that one in six patients presenting to primary care with exertional dyspnea has undiagnosed HF, predominantly HFpEF.[10]

Despite the advancements in medical diagnosis and treatment, the prognosis of HF remains worse than that of several other cancers. The 1-year mortality rate in HF patients is reportedly 15-30%, and the 5-year mortality rate is 50-75%.[4] In Türkiye, the 1-year mortality rate for HF patients is 17%, while the 5-year rate is 40%.[6]

Hospitalizations due to HF are of significant concern, as admission to the hospital usually indicates a worsened prognosis and hence reduced chances of survival. HF patients are hospitalized on average once a year after the first diagnosis. The EURObservational Research Program data indicated a 1-year rehospitalization rate of 43.9% following acute HF and 31.9% in chronic HF.[11] Mortality rates are higher during the second and third hospitalizations compared with the first one. In Türkiye, the 1-year hospitalization rate is 36.7%, with a median hospital stay of 6 days per year. Recent data suggest that HF imposes a financial burden of approximately $1 billion annually on the Turkish healthcare system.[12]

1.2. Natriuretic peptides

There are three main types of NPs: atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).[13] ANP is released from the atria, whereas BNP is secreted from the ventricles in response to myocardial stretch caused by volume or pressure overload.[14] Both are initially synthesized as precursor proteins (pre-proANP and pre-proBNP), which are then cleaved by proteases into active (ANP and BNP, respectively) and inactive [N-terminal proatrial natriuretic peptide (NT-proANP) and N-terminus pro-B-type natriuretic peptide (NT-proBNP), respectively] forms.

In HF patients, BNP/NT-proBNP is more commonly preferred compared to ANP due to its rapid release, specific expression, and significantly higher concentrations. NT-proBNP and BNP are released into circulation in a 1:1 ratio, but the NT-proBNP levels are higher in the blood because of its slower clearance rate (half-life of 60-120 min). Both BNP and NT-proBNP can be used for the diagnosis, treatment monitoring, and prognosis assessment of HF. The biological properties of the different NPs are summarized in **Table 1**.

2. APPROACH TO STAGES A AND B (ASYMPTOMATIC) HEART FAILURE

The management of clinical conditions constituting stages A and B of HF is crucial for preventing the development of structural and functional abnormalities that result in HF, and, in patients with structural abnormalities, the progression to symptomatic HF.

TABLE 1. Natriuretic Peptides.

Peptide	Site of secretion	Biological activity	Half-life*
BNP	Ventricular myocardium	Vasodilation, natriuresis, diuresis; reduction of fibrosis and necrosis	20 min
ANP	Atrial myocardium	Blood pressure reduction; the inhibition of the renin-angiotensin-aldosterone system	2.5 min
CNP	Endothelial cells (the heart, brain, kidneys, vessels)	Vasodilation; inhibition of fibrosis, platelet aggregation, and tissue plasminogen activation	2.6 min

*The clinical significance of half-lives lies in their influence on diagnostic and therapeutic applications. BNP's longer half-life compared with ANP and CNP makes it particularly suitable for monitoring heart failure progression and treatment response; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide.

Stage A encompasses patients without HF signs or symptoms, but with risk factors that could lead to HF in the future. The effective management of modifiable risk factors such as hypertension, diabetes, dyslipidemia, or obesity during this stage can prevent or slow the development of conditions such as coronary artery disease, left ventricular hypertrophy, or diastolic dysfunction. Primary treatment strategies include lifestyle modifications and pharmacotherapy for selected patients. Lifestyle interventions focus on smoking and alcohol cessation, a healthy diet, and increased physical activity.

Stage B represents the phase wherein structural cardiac changes are present, but HF-related symptoms have not yet appeared. To preserve cardiac functions and prevent HF progression, pharmacological treatments, and non-pharmacological interventions, when needed, are added to the lifestyle changes recommended at stage A. Most patients should be considered for angiotensin-converting enzyme inhibitors (ACEi) and beta-blockers. For diabetic patients, sodium-glucose cotransporter-2 inhibitors (SGLT-2i), eplerenone, or glucagon-like peptide-1 receptor agonists may be appropriate. Revascularization, valve repair, or replacement can be considered for eligible patients requiring interventional approaches.

3. USE OF NATRIURETIC PEPTIDES AT STAGES A AND B HEART FAILURE IN PRIMARY CARE

In primary care, identifying patients at high-risk of HF is critical for early diagnosis and management. People aged > 45 years and those with specific risk factors such as hypertension, diabetes mellitus (DM), obesity, coronary artery disease, exposure to cardiotoxic agents, or a family history of cardiomyopathy should be considered to be at high-risk.[15] These individuals should undergo regular evaluations to detect HF early, which includes checking for symptoms and, when necessary, performing NP measurements.

3.1. Patient assessment

For at-risk patients, symptoms like dyspnea (shortness of breath), fatigue, and swelling (edema) should be regularly evaluated. Signs such as weight gain, jugular venous distention, or the presence of a third heart sound are also important to monitor. Patients who develop these symptoms gradually or persistently require further diagnostic evaluations.[15,16]

3.2. Natriuretic peptides measurement

- Asymptomatic patients

Elevated NT-proBNP levels can indicate early cardiac stress or organ damage even before HF symptoms appear. Such findings are useful for adjusting treatments and identifying patients at a higher risk of developing HF.[15,16]

- NT-proBNP levels ≤ 50 pg/ml are normal.
- Levels ≥ 75 pg/ml (< 50 years), ≥ 150 pg/ml (50-75 years), or ≥ 300 pg/ml (≥ 75 years) may indicate cardiovascular disease and require further evaluation.[18]

- Symptomatic patients

Patients with HF symptoms should have their BNP or NT-proBNP levels measured to confirm the likelihood of HF.

- BNP levels > 35 pg/ml or NT-proBNP levels ≥ 125 pg/ml suggest HF.[15]
- If BNP is < 35 pg/ml or NT-proBNP is < 125 pg/ml, HF is unlikely, and other possible causes of symptoms should be considered. Elevated values warrant referral to a cardiologist and additional testing, such as echocardiography.[15,16]

4. APPROACH TO SYMPTOMATIC HEART FAILURE (STAGE C)

Patients at stage C, who present with symptoms and signs of HF or have a history of such symptoms require careful management to control the symptoms and improve the quality of life. In a primary care setting, the early recognition and management of HF can have a significant impact on the patient's overall health.

4.1. Symptoms and signs

Several clinical symptoms are similar across all HF patients, regardless of the EF. However, there exist demographic differences between patients with HFrEF and HFpEF. When compared with HFrEF, patients with HFpEF tend to be older, more often female and have a higher incidence of hypertension and atrial fibrillation (AF). In contrast, myocardial infarction and coronary artery disease are less common in HFpEF patients, whereas left ventricular hypertrophy is more prevalent. Patients with HFmrEF are considered an intermediate group presenting with clinical features of both HFrEF and HFpEF. When compared with HFrEF, the overall mortality is lower in HFpEF, although non-cardiovascular hospital admissions and deaths are more common in HFpEF patients.[19]

4.2. Functional capacity assessment

To determine the treatment approach and prognosis, functional capacity classification based on the New York Heart Association (NYHA) is essential for all HF patients. Although objective assessment methods such as exercise tests, 6 minute walk tests, and cardiopulmonary exercise tests can be used to evaluate the

functional capacity, the NYHA classification, which relies on detailed history taking, remains the most widely applied, as detailed below:

- **NYHA I:** No symptoms or limitations with ordinary physical activity.
- **NYHA II:** Mild symptoms or limitations with ordinary physical activities; can climb two flights of stairs.
- **NYHA III:** Marked limitation with even mild activity; can walk short distances (20-100 m), but are comfortable at rest.
- **NYHA IV:** Severe limitations; symptoms occur even at rest.

Patients with functional capacity classified as NYHA III or IV should be referred to specialized centers for considering advanced treatment options.

4.3. Physical examination

For stage C HF patients, a physical examination should assess the blood pressure, heart rate, and rhythm, as well as the signs of pulmonary and systemic congestion, including the following:

- Rales at the lung bases,
- Jugular venous distention,
- Hepatomegaly,
- Ascites,
- Pretibial edema.

Patients exhibiting increased congestion should be referred to secondary and tertiary healthcare centers for further management and evaluation.

5. DIAGNOSTIC APPROACH TO HEART FAILURE

All patients with HF should undergo a thorough diagnostic workup that includes a 12-lead electrocardiogram (ECG), chest X-ray, echocardiography, and biochemical tests. Below is a summary of the tests that can be used in primary care settings and the information these tests provide for managing HF patients:

5.1. Electrocardiogram

An ECG provides information about potential underlying conditions that may worsen the HF condition and guide treatment. Common ECG abnormalities seen in HF patients include:

- Atrial fibrillation,
- Arrhythmias,
- Previous myocardial infarction (pathological Q waves),
- Left ventricular hypertrophy,
- Widened QRS complexes and bundle branch blocks.

In patients with HFrEF, ECG abnormalities are almost always present, whereas in patients with HFpEF, some may have a normal ECG.

5.2. Chest X-ray

Chest X-rays are used to rule out other potential causes of shortness of breath and provide supportive evidence for HF (e.g., pulmonary congestion or cardiomegaly).

5.3. Biochemical tests

Biochemical tests help distinguish HF from other conditions that may mimic it, provide prognostic information, and guide potential treatment. Routine tests for all HF patients should include the following:

- Hemogram,
- Urea, creatinine, and estimated glomerular filtration rate,
- Electrolytes,
- Fasting glucose, hemoglobin A1c,
- Lipid profile,
- Ferritin and transferrin saturation,
- Thyroid function tests.

5.4. Measurement of the natriuretic peptides

NPs are used primarily to exclude HF rather than directly diagnose it. In primary care, if laboratory facilities are available, measurement of NPs is recommended. For ruling out chronic HF, low cut-off values of NP levels are preferred:

- BNP < 35 pg/ml,
- NT-proBNP < 125 pg/ml,

If NP levels are above these thresholds, the diagnosis should be confirmed, and further investigation should be performed. Patients should be referred to secondary or tertiary healthcare centers for advanced diagnostics.

The European Society of Cardiology (ESC) recommends an NT-proBNP level of ≥ 125 pg/ml for patient referral, with a sensitivity of 94.6% and specificity of 50%. Although ESC thresholds are good for exclusion, they have low specificity, necessitating further tests.[20] The UK NICE guidelines, which use higher cut-off values (NT-proBNP ≥ 400 pg/ml), may miss one out of five patients with HF.[21]

According to the NICE Guidelines:

- Patients with NT-proBNP levels between 400 and 2000 pg/ml should be referred for specialist assessment and echocardiographic evaluation within 6 weeks.

- Patients with NT-proBNP > 2000 pg/ml should be referred within 2 weeks.
- For those with NT-proBNP < 400 pg/ml (likely ≥ 125 pg/ml), alternative diagnoses should be considered, and if concerns persist, a cardiology specialist consultation is advised.

6. DIAGNOSTIC USE OF NATRIURETIC PEPTIDES

6.1. "Rule-out" and "rule-in" levels of NPs in HF diagnosis

Globally, NT-proBNP is the most widely accepted and used NP in the diagnosis of HF. The approach to HF management and the use of NPs have been defined by cardiology associations in Europe and North America.[2,15] Both the guidelines primarily establish exclusion (rule-out) criteria. These values differ for acute and chronic HF. In acute HF, if NT-proBNP < 300 pg/ml and BNP < 100 pg/ml are measured, the diagnosis of HF is excluded.[14] In chronic HF, for patients without a prior HF diagnosis and not receiving treatment, NT-proBNP < 125 pg/ml and BNP < 35 pg/ml are considered values that exclude the diagnosis (Figure 3). The diagnostic (rule-in) criteria for HF were defined in a recent update.[18]

It is not recommended to use NPs alone for diagnosis. This test should be performed when the patient shows symptoms consistent with HF and when physical examination findings, ECG, or chest radiography raise suspicion. The diagnostic NT-proBNP levels for acute HF patients presenting with congestion in the emergency department and for chronic HF patients presenting with dyspnea and exercise intolerance in outpatient clinics are summarized in Figure 4. The diagnostic BNP levels are not available.

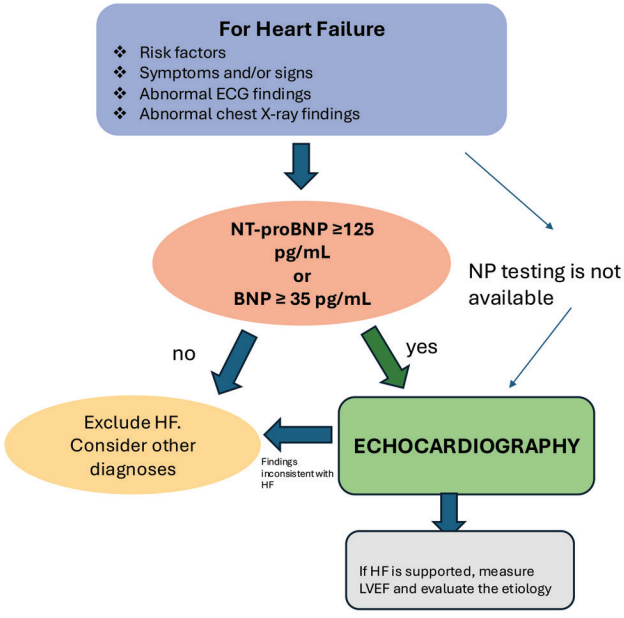

FIG. 3. Heart failure diagnostic algorithm.
ECG, electrocardiogram; NT-proBNP, N-terminal pro-B-type natriuretic peptide; BNP, B-type natriuretic peptide; NP, natriuretic peptide; EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction.

6.2. Interpretation of NP levels in clinical conditions affecting them

Comorbidities or clinical conditions can influence the NP levels to be higher or lower than expected, which may affect the ultimate clinical interpretation (Table 2). Medications used in HF treatment can also affect the secretion or clearance of NPs, thereby altering their levels in circulation.[22]

Age is one of the primary determinants of NP levels. In older individuals, the NP levels are significantly higher than those in younger people, and the difference becomes more pronounced after the age of 50 years. This effect can be explained by an increase in subclinical heart disease with age, an increase in the NP gene expression, and a reduction in the renal clearance of circulating NPs.

Women have higher NP levels than men. Although the physiological basis for the gender difference remains unclear, the possible mechanisms include the stimulatory effects of female sex hormones on the NP gene expression, extra-cardiac NP sources in the female reproductive system, and lower renin levels in women than in men. However, gender-specific NP cut-off levels have not been defined, as NPs perform similarly in both sexes for the diagnosis and prognostic evaluation of HF.

A significant factor that raises the NP levels is kidney failure. Increased water-sodium retention by the kidneys, reduced renal clearance, and associated risk factors such as hypertension and diabetes are the major contributors to elevated NP levels. In chronic kidney diseases, NT-proBNP cut-off values, which are based on age, can help diagnose acute HF without requiring further adjustments for kidney function. BNP may be a more reliable biomarker in cases of kidney dysfunction because it is less dependent on renal clearance compared with NT-proBNP.[23] It is therefore not recommended to check the NP levels in dialysis patients.

The body mass index has a nearly linear relationship with circulating NP levels. This negative relationship, which is relatively independent of HF, can be explained by factors such as the suppression of NP production by androgens produced by adipose tissues, "BNP deficiency" specific to obese patients, increased NP clearance, and a reduction in NP concentration due to greater binding of BNP to NP receptors in fat cells.[24] In approximately one-fifth of the overweight/obese, acute decompensated HF patients, BNP concentrations are < 100 pg/ml at the time of presentation. Therefore, 50% lower cut-off values (BNP < 50 pg/ml) should be used when diagnosing HF. Because NP levels are relatively lower in

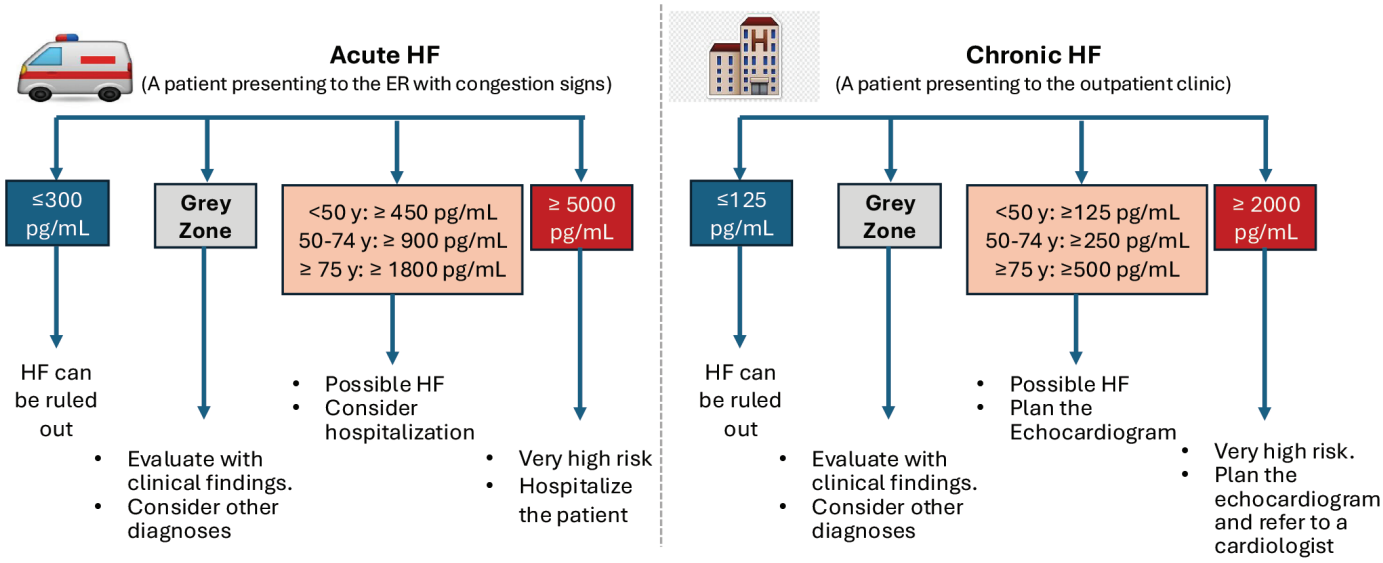

FIG. 4. NT-proBNP levels in the diagnosis of heart failure for patients presenting to the emergency department and outpatient clinics.
NT-proBNP, N-terminus pro-B-type natriuretic peptide; HF, heart failure.

TABLE 2. Conditions Influencing Natriuretic Peptide Levels.

Conditions with expected NP level increase	Conditions with inadequate NP level increase
Cardiac causes	**Cardiac causes**
Acute and chronic coronary syndromes	Sudden (flash) pulmonary edema
Arrhythmias and atrial fibrillation	Constrictive pericarditis
Heart valve diseases	Mitral stenosis
Cardiac amyloidosis	Acute mitral insufficiency
Hypertrophic cardiomyopathy	Advanced-stage cardiomyopathy
Myocarditis	
Pulmonary hypertension	
Right ventricular dysfunction	
Congenital heart disease	
Cardiac damage and infiltration	
Malignancy	
Cardioversion, ICD shock	
Non-cardiac causes	**Non-cardiac causes**
Advanced age	Obesity
Female gender	Genetic variation
Severe anemia	Biotin use
Kidney failure	
Pulmonary embolism	
Metabolic and endocrinological diseases	
Ischemic or hemorrhagic stroke	
Chronic obstructive pulmonary disease, pneumonia	
Sepsis, cytokine syndrome	
Liver disease	

NP, natriuretic peptide; ICD, implantable cardioverter-defibrillator.

chronic HF patients, this effect may be even more pronounced in obese patients. Thus, the cut-off values recommended by the ESC Heart Failure Guidelines (BNP ≥ 35 pg/ml or NT-proBNP ≥ 125 pg/ml) should only be used for diagnosing HF in obese patients, with greater caution when ruling out HF.

In patients with AF, irrespective of whether HF is present, NP levels are elevated, which can be attributed to the increased atrial pressure and volume resulting from the loss of atrial contraction, followed by increased ventricular filling and wall stress, which increases the NP production. The increased ventricular stress can induce myocardial ischemia, leading to more volume and pressure overload, which may create a vicious cycle. In AF patients, NP values three times higher than those in patients with sinus rhythm are recommended for diagnosing HF.

- Treatment

The main goals of treatment in HF patients are to reduce mortality, prevent hospitalizations, and improve the quality of life. The first line of treatment options can be classified into lifestyle changes, medication therapy, and the management of comorbidities.

- Lifestyle changes

The first step in managing HF is to ensure that the patient adopts lifestyle changes. These changes include restricting excessive salt intake and engaging in regular physical activity. Patient education is crucial to explain the reasons for these changes and their impact on health.

- Medication therapy

Although effective medication approaches for HFrEF are well established, there is no proven treatment option to reduce mortality in HFpEF patients. Essential treatments for HFrEF patients include renin-angiotensin receptor blockers (such as angiotensin receptor-neprilysin inhibitors (ARNi), ACEi, angiotensin receptor blockers), beta-blockers, mineralocorticoid receptor antagonists (such as spironolactone, eplerenone), and SGLT-2i (such as empagliflozin and dapagliflozin) (Table 3). Patients with HFpEF and preserved EF should primarily receive SGLT-2i. They may also use renin-angiotensin receptor blockers (such as angiotensin ARNi, ACEi, angiotensin receptor blockers), beta-blockers, and mineralocorticoid receptor antagonists, albeit these are not mandatory medications for them. Diuretic therapy should be used in all HF patients when there are signs of congestion. The effectiveness and side effects of medication therapy should be regularly monitored, and dose adjustments should be made when necessary.

- Management of comorbidities

HF often coexists with other health conditions such as hypertension, diabetes, chronic kidney disease, and iron deficiency or anemia. The treatment of comorbidities can improve HF symptoms and enhance the quality of life of patients.[15]

- Patient monitoring

In primary care, the monitoring of HF patients is a critical part of treatment, as it aims to regularly assess the clinical symptoms, ensure medication adherence, prevent hospitalizations, and improve the quality of life.

- Clinical assessment

Symptoms such as shortness of breath, fatigue, and edema should be regularly queried in HF patients. Congestion signs like peripheral edema, jugular venous distension, and lung auscultation should also be assessed. The severity of the disease should be monitored with reference to the NYHA classification, and patients showing a deterioration in their functional capacity should be referred to a cardiologist.

- Assessment of medication adherence

Adherence to medications that have been proven to reduce morbidity and mortality is vital for effective HF management. Patients should be encouraged to take their medications regularly, the treatment response should be monitored, and dose adjustments should be made when necessary.[3]

- Clinical and laboratory monitoring

Kidney function, electrolytes, and NP levels should be monitored at regular intervals.

TABLE 3. Key Medication Treatment Options and Indication Levels in Patients with Heart Failure.

	SGLT-2i	RAAS-B	BB	MRA	Diuretics
HFrEF	Class I	Class I	Class I	Class I	Class I
HFmrEF	Class I	Class II	Class II	Class II	Class I
HFpEF	Class I	Class II	Class II	Class II	Class I

HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; RAAS-B, renin-angiotensin aldosterone system blockers; BB, beta blockers; MRA, mineralocorticoid receptor antagonists.

- Education and support

Education and support for HF patients are crucial for treatment success. Patients should be informed about their general condition, treatment duration, and emergencies, as well as when they should seek healthcare.[4] Family members and caregivers should be involved in educational programs so as to create a supportive environment.[5]

a. Sodium intake

Daily sodium intake is restricted to < 5 g as per the European Cardiology Guidelines. However, there is no proven benefit of salt restriction in HF patients, and, in fact, excessive restriction can be harmful. It is therefore recommended to maintain a daily sodium intake of 3.75-10 g (1.5-4 g/day sodium) and to avoid processed foods rather than only excessively restricting salt.[25]

b. Fluid intake

HF patients, especially those with congestion symptoms, should avoid excessive fluid intake. In patients with difficulty in maintaining fluid balance, the fluid intake may be restricted to 1-1.5 l/day until euvolemia is achieved. However, most HF patients do not require fluid restriction and should drink according to their thirst. Typically, the normal fluid intake is 1.5-2.5 l/day; this amount is not expected to cause any problems in HF patients.

c. Weight monitoring

Daily weight gain in HF patients is typically a sign of fluid accumulation and may indicate worsening of HF symptoms. Patients should therefore be advised to weigh themselves each morning before breakfast, after urination, and in light clothing. If they gain more than 2 kg in 3 days or 5 kg in a week, they should contact their healthcare provider.

d. Exercise

HF patients should engage in regular exercise, ensuring that the exercise plan is tailored to their general condition and functional capacity. Walking and light aerobic exercises are generally recommended, whereas heavy exercise should be avoided.[26]

e. Smoking and alcohol use

Smoking and alcohol consumption worsen HF symptoms and prognosis. Smoking increases the heart's oxygen demand, which further worsens HF. Alcohol can directly damage the heart muscles, resulting in alcoholic cardiomyopathy. Therefore, patients should be strongly advised to quit smoking and stop alcohol consumption. Referral to smoking cessation programs may be considered in such cases.

f. Immunization

Infections can worsen HF symptoms and increase the hospitalization risk. Therefore, HF patients should be recommended to receive pneumonia, shingles, and annual flu vaccinations, and any signs of infection should be carefully monitored and addressed in a timely manner.[27,28]

6.3. Use of natriuretic peptides for monitoring

The main goal of HF monitoring is to reduce mortality and hospital admissions. Therefore, there is a need for prognostic markers that can detect the risk of mortality and hospitalization early. NPs are valuable not only for diagnosis but also for treatment monitoring and prognostic assessment. Especially with the introduction of angiotensin ARNi and SGLT-2i in recent years, the significance of NPs in HF clinical monitoring and management has increased. Decreases in the BNP or NT-proBNP levels in both acute and chronic HF follow-up have been associated with better patient outcomes.[29] As such, particularly high and, more importantly, rising NP values indicate a worsening disease course in HF.

NP measurement can be performed during HF monitoring as it provides information on treatment response, congestion status, and cardiac remodeling in addition to the prognosis. In acute decompensated HF, the NP levels measured a few days after starting the treatment prove valuable in assessing the clinical progress. In hospitalized patients, a ≥ 30% reduction in NT-proBNP measured before discharge may predict reduced mortality and rehospitalization risk in the first 6 months post-discharge.[30]

In outpatient HF patients, measuring NPs at each clinical assessment, especially in those with worsening HF symptoms, can provide information about whether treatment intensification is warranted (e.g., increasing the diuretic doses). Persistently high and unresponsive NP levels during clinical monitoring should raise concerns and require referral to a higher center. Importantly, it should be considered that worsening kidney function and the presence of AF can affect BNP or NT-proBNP measurements, and any elevation in NPs in the presence of these conditions should be interpreted carefully. In addition, in patients receiving ARNi therapy, BNP elevations are a natural result of ARNi's effect and do not indicate a worsening condition. Measuring NT-proBNP instead of BNP in ARNi-treated patients facilitates HF monitoring.

The STRONG-HF study demonstrated that the early initiation of quadruple baseline therapy before discharge in patients hospitalized with decompensated HF, followed by rapid upward titration within the first 6 weeks, resulted in a significant reduction in mortality and rehospitalization in the following 6 months.[31] In this study, NT-proBNP was measured at weeks 1, 2, 3, and 6. In patients with ≥ 30% reduction in NT-proBNP, the upward titration of ACEi/ARNi/

MRA and beta-blockers was performed, and the diuretic doses were reduced in clinically stable patients not showing any signs of congestion. In patients with ≥ 10% increase in NT-proBNP levels, the upward titration of beta-blockers was stopped, and the diuretic doses were increased. Following this study, the ESC 2023 Heart Failure Guidelines recommended the initiation of guideline-based medical treatment in patients hospitalized with decompensated HF before discharge, with a rapid upward titration within 6 weeks' post-discharge at a class 1 recommendation level. The STRONG-HF protocol is now being implemented in many hospitals in clinical practice. While applying this protocol, NT-proBNP levels should be monitored along with examination for clinical congestion, heart rate, and the level of blood pressure, creatinine, and potassium.

In conclusion, BNP or NT-proBNP is not only the cornerstone for the diagnosis and prognosis of HF but also for HF monitoring and management. When applied in clinical practice, these markers can facilitate clinicians in monitoring risk, intensifying or reducing treatment, and deciding about a referral to a higher center in a disease as complex as HF.

6.4. Referral to secondary and tertiary care centers

Patients with HF who exhibit any of the following conditions should be referred to secondary or tertiary care centers or a cardiology clinic during follow-up (**Table 4**).

6.5. Consistency and differences with the international guidelines

This guideline aligns with major international HF management guidelines, such as those from the ESC and the American Heart Association, in emphasizing the importance of natNPs for the diagnosis and management of HF. For example, the thresholds of NT-proBNP (≥ 125 pg/ml for chronic HF and ≥ 300 pg/ml for acute HF) and BNP (≥ 35 pg/ml for chronic HF and ≥ 100 pg/ml for acute HF) are consistent with those recommended by the ESC and AHA guidelines.[2,15] Moreover, all guidelines underscore the utility of NP testing for risk stratification and monitoring the treatment response.

However, this consensus report places a stronger emphasis on the integration of NP testing in primary care settings, especially in resource-limited environments, so as to facilitate early detection and timely intervention. When compared with the ESC and AHA guidelines, which are often tailored to tertiary care frameworks, this guideline provides practical recommendations for family physicians to address the challenges unique to primary care. This focus ensures that the benefits of biomarker testing are accessible to a broader patient population, particularly those at risk of delayed diagnoses due to systemic barriers.

In summary, while broadly aligned with international standards, this guideline provides additional practical tools and context for primary care implementation, addressing regional healthcare system dynamics and emphasizing cost-effective strategies for early HF management.

7. CONCLUSION

The approach to HF in primary care aims to optimize patient health through early diagnosis via screening high-risk individuals and managing symptoms in symptomatic HF, with a focus on symptom management, treatment planning, and regular follow-up monitoring. This approach can improve the quality of life and prevent disease progression. The ability of primary care physicians to manage this condition can have a significant impact on patient health outcomes.

HF patients visiting family medicine centers can be categorized into two groups: those with chronic HF and those with acute HF who are hospitalized and present in the early post-discharge period (first 3 months). Regardless of the reason for the visit (i.e.,

TABLE 4. Indications for the Referral of Heart Failure Patients to Secondary or Tertiary Care.

Conditions requiring referral	Explanation
1. Inadequate drug therapy	Patients with deficiencies in essential drug therapies (regardless of the reason).
2. Deterioration in the NYHA functional capacity	Patients showing deterioration in NYHA functional capacity when compared with previous evaluations (even in the absence of systemic congestion signs).
3. Systemic congestion	Patients exhibiting systemic congestion (even in the absence of a decline in the NYHA functional capacity).
4. Impaired kidney function	Patients with a serum creatinine increase ≥ 0.3 mg/dl or an estimated GFR decrease >25%.[32]
5. Electrolyte abnormalities	Patients with hyponatremia (< 135 mEq/l), hypokalemia (< 3.5 mEq/l), or hyperkalemia (> 5.5 mEq/l).
6. Increased natriuretic peptide levels	Patients with a > 30% increase in the natriuretic peptide levels compared with previous levels (even in the absence of a decline in the NYHA capacity and/or systemic congestion).[33,34]
7. Electrocardiographic findings	Patients with frequent ventricular ectopy or newly developed atrial fibrillation.

NYHA, New York Heart Association; GFR, glomerular filtration rate.

prescription, complaint, or routine check), family physicians play a crucial role as a contact point in managing HF patients. The use of clinical symptoms, findings, and serum NP measurements can offer significant benefits in their management.

In this study, the treatment strategies differed among the HFrEF, HFmrEF, and HFpEF groups, but the follow-up approaches for these patients were quite similar. Therefore, our recommendations for managing HF patients in primary care are independent of the left ventricular EF, except for certain differences.

Approaches for HF patients hospitalized due to chronic or acute HF and seen within the first 3 months post-discharge should be as follows: based on the patient's phenotype, drug therapies such as renin-angiotensin-aldosterone system inhibitors, beta-blockers, MRAs, and SGLT-2i should be initiated. In addition, BNP or NT-proBNP measurements should be taken regularly to assess the treatment response.

Early diagnosis of HF is crucial for improving an individual's quality of life and preventing severe complications as well as the economic burden that these complications may cause in the long term. HF is a progressive disease, and delayed diagnosis increases the treatment costs and complicates disease management. This situation causes a significant decline in the quality of life for the patient along with irreversible financial burdens on the healthcare system.

Although the recommended tests may initially represent a cost factor, the screening will contribute significantly to the health budget in the long term by providing substantial cost-effectiveness. Early diagnosis allows for appropriate treatment and lifestyle changes before disease progression, thereby reducing hospitalizations, emergency visits, and intervention frequencies related to complications, alleviating the burden on secondary and tertiary healthcare services.

Therefore, particularly in individuals over 45 years of age, careful screening for risk factors is necessary. Their risk factors include DM, exposure to cardiotoxic agents, history of acute coronary syndrome, genetic predisposition to cardiomyopathy or family history, target organ damage with or without stage 2-3 hypertension, and metabolic syndrome. Considering that HF imposes a direct cost exceeding 1 billion dollars on our healthcare system,[12] regular screening of individuals in this high-risk group is expected to provide an opportunity for effective intervention before disease progression, which can positively affect patient health while allowing more efficient use of healthcare resources. The consensus algorithm outlining the appropriate utilization of NPs in primary care settings has been comprehensively summarized and visually represented in **Figure 5** for better understanding and clarity. This algorithm simplifies decision-making in primary care by summarizing the steps necessary for diagnosing and managing HF based on NP levels. It emphasizes the integration of BNP and NT-proBNP measurements in routine care and outlines the referral pathways for high-risk patients, thereby streamlining the primary care workflow.

- Future perspectives

The role of NPs in HF management continues to evolve, with potential developments aimed at improving diagnostic and therapeutic strategies. Emerging biomarkers such as midregional-proadrenomedullin and soluble suppression of tumorigenicity-2 show promise in complementing NPs by providing additional prognostic information. These biomarkers can help refine risk stratification and guide treatment more precisely in HF patients.[34,35]

Advancements in technology are also shaping the future of HF screening and management. Portable devices and home-based monitoring tools for NP measurements are being developed, allowing for more frequent and convenient monitoring of at-risk individuals. These innovations have the potential to improve patient adherence to care plans and enable earlier interventions.[36]

Currently, artificial intelligence (AI) and machine-learning algorithms are being explored to integrate NP levels with other clinical data so as to predict disease progression and personalize treatment plans. These tools are expected to assist clinicians in making more informed decisions and optimizing the outcomes for HF patients.[37,38]

In conclusion, the continued integration of novel biomarkers, advanced screening tools, and AI-driven analytics holds significant promise for enhancing the utility of NPs in HF care. These developments could lead to the development of more precise, efficient, and patient-centered approaches for managing this complex condition.

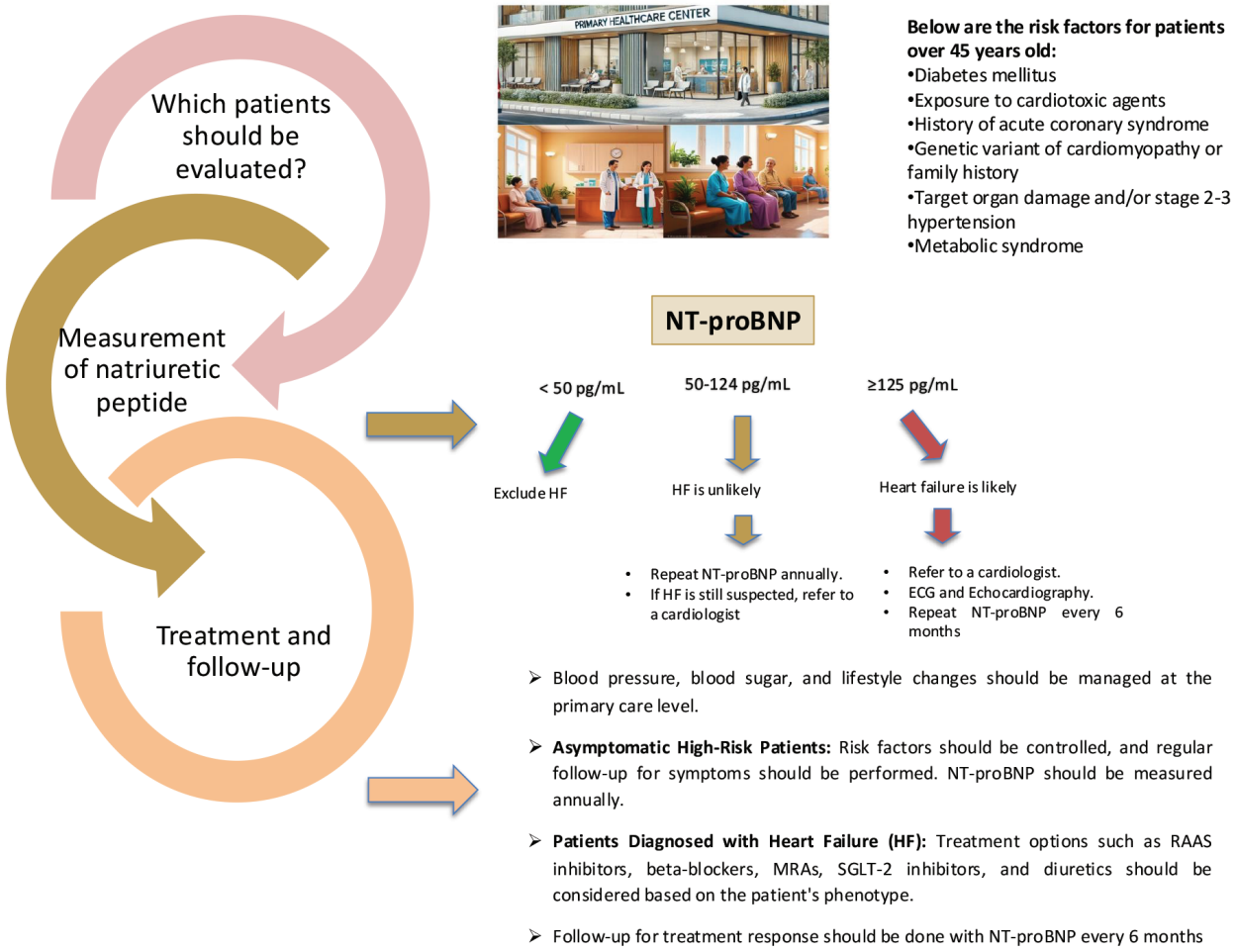

FIG. 5. Consensus algorithm for the use of natriuretic peptides in primary care.
NT-proBNP, N-terminus pro-B-type natriuretic peptide; HF, heart failure; ECG, electrocardiogram; RAAS-B, renin-angiotensin aldosterone system blockers; MRA, mineralocorticoid receptor antagonists; SGLT-2, sodium-glucose cotransporter-2 inhibitors.

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REFERENCES

1. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. 2021;23:352-380. [CrossRef]
2. Heidenreich PA, Bozkurt B, Aguilar D, et al.; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895-e1032. [CrossRef]
3. Çavuşoğlu Y, Çelik A, Altay H, et al. Heart failure with non-reduced ejection fraction: epidemiology, pathophysiology, phenotypes, diagnosis and treatment approaches. *Turk Kardiyol Dern Ars*. 2022;50(Suppl 1):S1-S34. [CrossRef]
4. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2023;118:3272-3287. [CrossRef]
5. Seferović PM, Vardas P, Jankowska EA, et al.; National Heart Failure Societies of the ESC member countries (see Appendix). The Heart Failure Association Atlas: Heart Failure Epidemiology and Management Statistics 2019. *Eur J Heart Fail*. 2021;23:906-914. [CrossRef]
6. Çelik A, Ural D, Şahin A, et al. Trends in heart failure between 2016 and 2022 in Türkiye (TRends-HF): a nationwide retrospective cohort study of 85 million individuals across entire population of all ages. *Lancet Reg Health Eur*. 2023;33:100723. [CrossRef]
7. Şahin A, Çöllüoğlu T, Çelik A, et al. Exploring Regional disparities in heart failure epidemiology and outcomes: a comprehensive study across geographical regions in Türkiye. Balkan Med J 2024;41:47-53. [CrossRef]
8. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2022 Update: a report from the American Heart Association. *Circulation*. 2022;145:e153-e639. [CrossRef]

9. Yılmaz MB, Çelik A, Çavuşoğlu Y, et al. Snapshot evaluation of heart failure in Turkey: baseline characteristics of SELFIE-TR. *Turk Kardiyol Dern Ars.* 2019;47:198-206. [CrossRef]
10. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. *Eur J Heart Fail.* 2014;16:772-777. [CrossRef]
11. Maggioni AP, Dahlström U, Filippatos G, et al.; Heart Failure Association of the European Society of Cardiology (HFA). EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail.* 2013;15:808-817. [CrossRef]
12. Çavuşoğlu Y, Altay H, Aras D, et al. Cost-of-disease of heart failure in Turkey: a Delphi panel-based analysis of direct and indirect costs. *Balkan Med J*. 2022;39:282-289. [CrossRef]
13. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. *Eur J Heart Fail.* 2004;6:261-268. [CrossRef]
14. Nakagawa Y, Nishikimi T, Kuwahara K. Atrial and brain natriuretic peptides: hormones secreted from the heart. *Peptides*. 2019;111:18-25. [CrossRef]
15. McDonagh TA, Metra M, Adamo M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42:3599-3726. [CrossRef]
16. McEvoy JW, McCarthy CP, Bruno RM, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J.* 2024;45:3912-4018. [CrossRef]
17. Lyon AR, López-Fernández T, Couch LS, et al.; ESC 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J.* 2022;43:4229-4361. [CrossRef]
18. Bayes-Genis A, Docherty KF, Petrie MC, et al. Practical algorithms for early diagnosis of heart failure and heart stress using NT-proBNP: a clinical consensus statement from the Heart Failure Association of the ESC. *Eur J Heart Fail*. 2023;23:1891-1898. [CrossRef]
19. Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2017;19:1574-1585. [CrossRef]
20. Taylor CJ, Ordóñez-Mena JM, Lay-Flurrie SL, et al. Natriuretic peptide testing and heart failure diagnosis in primary care: diagnostic accuracy study. *Br J Gen Pract*. 2022;73:e1-e8. [CrossRef]
21. Taylor CJ, Moore J, O'Flynn N. Diagnosis and management of chronic heart failure: NICE guideline update 2018. *Br J Gen Pract*. 2019;69:265-266. [CrossRef]
22. Lee DJW, Aw TC. Natriuretic peptides in clinical practice: a current review. *J Immunological Sci.* 2023;7:28-34. [CrossRef]
23. McCullough PA, Duc P, Omland T, et al. Breathing not properly multinational study investigators. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the breathing not properly multinational study. *Am J Kidney Dis*. 2003;41:571-579. [CrossRef]
24. Reinmann M, Meyer P. B-type natriuretic peptide and obesity in heart failure: a mysterious but important association in clinical practice. *Cardiovasc Med*. 2020;23:w02095. [CrossRef]
25. Mullens W, Damman K, Dhont S, et al. Dietary sodium and fluid intake in heart failure. A clinical consensus statement of the Heart Failure Association of the ESC. *Eur J Heart Fail*. 2024;26:730-741. [CrossRef]
26. Jaarsma T, Hill L, Bayes-Genis A, et al. Self-care of heart failure patients: practical management recommendations from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2021;23:157-174. [CrossRef]
27. Çelik A, Altay H, Azap A, et al. Vaccination of adults with heart failure and chronic heart conditions: expert opinion. *Turk Kardiyol Dern Ars*. 2018;46:723-734. [CrossRef]
28. Türkiye EKMUD. Adult Immunization Guide. 2023. [CrossRef]
29. Daubert MA, Adams K, Yow E, et al. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFrEF. *JACC Heart Fail*. 2019;7:158-168. [CrossRef]
30. Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation*. 2004;110: 2168-2174. [CrossRef]
31. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022;400:1938-1952. [CrossRef]
32. Damman K, Tang WH, Testani JM, McMurray JJ. Terminology and definition of changes renal function in heart failure. *Eur Heart J.* 2014;35:3413-3416. [CrossRef]
33. Greene SJ, Bauersachs J, Brugts JJ, et al. Worsening heart failure: nomenclature, epidemiology, and future directions: JACC review topic of the week. *J Am Coll Cardiol.* 2023;81:413-424. [CrossRef]
34. Januzzi JL Jr, Ahmad T, Mulder H, et al. Natriuretic peptide response and outcomes in chronic heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;74:1205-1217. [CrossRef]
35. Januzzi JL, Mebazaa A, Di Somma S. ST2 and prognosis in acutely decompensated heart failure: the International ST2 Consensus Panel. *Am J Cardiol.* 2015;115(Suppl7):26B-31B. [CrossRef]
36. Cowie MR, Lam CSP. Remote monitoring and digital health tools in CVD management. *Nat Rev Cardiol.* 2021;18:457-458. [CrossRef]
37. Krittanawong C, Zhang H, Wang Z, Aydar M, Kitai T. Artificial intelligence in precision cardiovascular medicine. *J Am Coll Cardiol*. 2017;69:2657-2664. [CrossRef]
38. Ouyang D, He B, Ghorbani A, et al. Video-based AI for beat-to-beat assessment of cardiac function. *Nature.* 2020;580:252-256. [CrossRef]