

Saudi Heart Association (SHA) guidelines for the management of heart failure



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Heart failure (HF) is the leading cause of morbidity and mortality worldwide and negatively impacts quality of life, healthcare costs, and longevity. Although data on HF in the Arab population are scarce, recently developed regional registries are a step forward to evaluating the quality of current patient care and providing an overview of the clinical picture. Despite the burden of HF in Saudi Arabia, there are currently no standardized protocols or guidelines for the management of patients with acute or chronic heart failure. Therefore, the Heart Failure Expert Committee, comprising 13 local specialists representing both public and private sectors, has developed guidelines to address the needs and challenges for the diagnosis and treatment of HF in Saudi Arabia. The ultimate aim of these guidelines is to assist healthcare professionals in delivering optimal care and standardized clinical practice across Saudi Arabia.

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1. Introduction

1.1. Epidemiology of heart failure in Saudi Arabia

Heat failure (HF) is a leading cause of morbidity and mortality worldwide [1,2] and negatively impacts quality of life (QoL), healthcare costs, and longevity [2]. The prevalence of HF ranges from 1% to 2% in adults from developed countries and is $\geq 10\%$ in those aged over 70 years, depending on the definition applied [3]. A myriad of diseases affecting the heart culminate in HF. Although data on HF in the Arab population are scarce, recently developed regional registries are a step forward to evaluating the quality of current patient care and to provide an overview of the clinical picture.

The heart function assessment registry trial in Saudi Arabia (HEARTS) was the first multicenter survey conducted in the Kingdom of Saudi Arabia (KSA) and the Arab population to study the clinical features, management, and short- and long-term outcomes of patients with acute heart failure (AHF) and high-risk chronic heart failure (HCHF; Table 1) [2].

The mean age of patients with AHF and CHF was 57–60 years in the KSA, which is almost 10 years younger than patients from developed countries [2]. Of the patients with AHF, 44.7% had a history of chronic heart failure (CHF), suggesting an early age of onset that may be related to the extremely high prevalence of coronary artery disease (CAD) risk factors [2]. In addition, the prevalence of diabetes mellitus was 60.7% in patients with AHF in the KSA, which is double the rate reported by global AHF registries; however, the rate of hypertension (70%) was similar to global registries despite the population being younger [2]. Similar findings were reported in patients with HCHF; however, the rates of diabetes mellitus (53%) were lower whereas hypertension (69%) was higher compared with patients with AHF. Almost three-quarters of the patients had moderate/severe left ventricle (LV)

Abbreviations

ACE-I	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AF	atrial fibrillation
AHF	acute heart failure
ARB	angiotensin II receptor blocker
ARDS	acute respiratory distress syndrome
ARNI	angiotensin receptor/neprilysin inhibitor
ARVC	arrhythmogenic right ventricular cardiomyopathy
AV	atrioventricular
b.i.d.	twice daily
BB	beta-blocker
BiPAP	bilevel positive airway pressure
BMI	body mass index
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft
CAD	coronary artery disease
CBC	complete blood count
CHF	chronic heart failure
CMR	cardiac magnetic resonance
CPE	cardiogenic pulmonary edema
CRF	chronic renal failure
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy defibrillator
DBP	diastolic blood pressure
ECG	electrocardiogram
EF	ejection fraction
EMF	endomyocardial fibrosis
FCM	ferric carboxymaltose
GH	growth hormone
Hb	hemoglobin
HCM	hypertrophic cardiomyopathy
HES	hypereosinophilic syndrome
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
ICD	implantable cardioverter defibrillator
IV	intravenous
LAD	left anterior descending
LBBB	left bundle branch block
LMWH	low-molecular-weight heparin
LSVD	left ventricular systolic dysfunction
LV	left ventricle
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVESV	left ventricle end-systolic volume index
MI	myocardial infarction
MR	mitral regurgitation
MRA	mineralocorticoid antagonist
NP	natriuretic peptide

NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
o.d.	once daily
OMT	optimal medical therapy
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PET	positron emission tomography
PMC	percutaneous mitral commissurotomy
RHD	rheumatic heart disease
RSVD	right ventricular systolic dysfunction
RV	right ventricle
SBP	systolic blood pressure
SPECT	single-photon emission computed tomography
TOE	transoesophageal echocardiograph
TR	tricuspid regurgitation
TS	tricuspid stenosis
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiography
VT/VF	ventricular tachycardia/ventricular fibrillation

dysfunction compared with one-half in other studies [2].

A more recent study (HEARTS-chronic) evaluating the clinical features and outcomes of 685 CHF patients enrolled in the registry between 2009 and 2011 reported that CHF patients presented young and commonly suffered from severe LV dysfunction [4]. For instance, the mean age at diagnosis of patients with CHF was 55 years, with CAD (38.8%), dilated cardiomyopathy (DCM; 36.5%), and hypertension (10.5%) being the most common etiologies of HF [4]. Severe LV dysfunction was reported in two-thirds of the patients with median N-terminal-pro B-type natriuretic peptide (NT-proBNP) of 29.34.37 pg/mL [4]. In addition, at 1 year, the all-cause mortality rate was 9% (cardiac related 93.7%), hospitalization rate was 39%, and emergency room visit was 50%, which could be attributed to the relatively high rate of CHF patients with severe LV dysfunction [4].

In general, beta-blockers, angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin II receptor blockers (ARBs), and diuretics were the most commonly used agents for the management of patients with AHF or CHF (Fig. 1) [2,4].

The HEARTS study also described independent predictors of death in patients with *de novo* AHF and acute CHF (ACHF). Patients with ACHF were older, compared with acute *de novo* patients (62.2 vs. 60.0 years, respectively); less likely to be men (64% vs. 69%) or smokers (31.6% vs. 36.7%); and more likely to have a history of diabetes mellitus (65.7% vs. 61.3%), hypertension (74% vs. 65%), and severe left ventricular dysfunction (52% vs.

40%). The ACHF group had a higher adjusted 3-year mortality rate [hazard ratio (HR) 1.6, 95% confidence interval (CI) 1.3–2.0; $p < 0.001$] than the acute *de novo* group. Overall, patients with ACHF had significantly higher long-term mortality rates than those with *de novo* AHF [5].

A study assessing the sex-specific differences in clinical features and outcomes of patients with AHF found that, compared with men, women were older (mean 63.6 vs. 60.2 years; $p < 0.001$) and more likely to have risk factors for atherosclerosis, a history of HF (67.8% vs. 62.3%; $p = 0.005$), and rheumatic heart disease (11.3% vs. 4.9%; $p < 0.001$). Ischemic heart disease was the primary cause of HF in men and women, but was less common in women than men (50.6% vs. 54.7%; $p = 0.046$). Women had higher rates of hypertensive heart disease and primary valve disease ($p < 0.001$ for both), whereas men were more likely to have severe LV systolic dysfunction. On discharge, men had a higher use of ACE-Is (62.8% vs. 53.4%; $p < 0.001$), beta-blockers (85.8% vs. 79.3%; $p < 0.001$), and aldosterone inhibitors (42.1% vs. 30.9%; $p < 0.001$) compared with women. Apart from higher atrial fibrillation (AF) in women (8.4% vs. 4.7% in men; $p < 0.001$) and higher ventricular arrhythmias in men (4.8% vs. 3% in women; $p = 0.029$), no differences were observed in hospital outcomes [6].

Dyslipidemia is a major risk factor for vascular diseases, including coronary heart disease, and is the most common cardiovascular risk factor in the KSA. Dyslipidemia affects both children and adults, and may overwhelm the public health sector in the long run if aggressive interventions are not implemented early. A low level of high-density lipoprotein cholesterol was the most common lipid disorder in patients with HF (82.9%), followed by hypertriglyceridemia (35.2%), atherogenic dyslipidemia (27.8%), and hypercholesterolemia (9.2%). Diabetes mellitus was the single most significant predictor of mortality ($p = 0.001$) in this population. Of the lipid disorders, only low levels of high-density lipoprotein cholesterol contributed to significant mortality risk [odds ratio (OR) 1.29, 95% CI 1.04–1.59; $p < 0.01$] adjusted for age, sex, and statin use [7].

HF is a chronic syndrome characterized by significant physical, psychological, and social burden, resulting in poor QoL. Data assessing the QoL of patients with HF revealed that QoL scores were low across all evaluated domains (measured using the Short Form-36 survey). LV ejection fraction (LVEF) was the strongest predictor of both

Table 1. An overview of demographics of patients included in the heart function assessment registry trial in Saudi Arabia (HEARTS) registry [2].

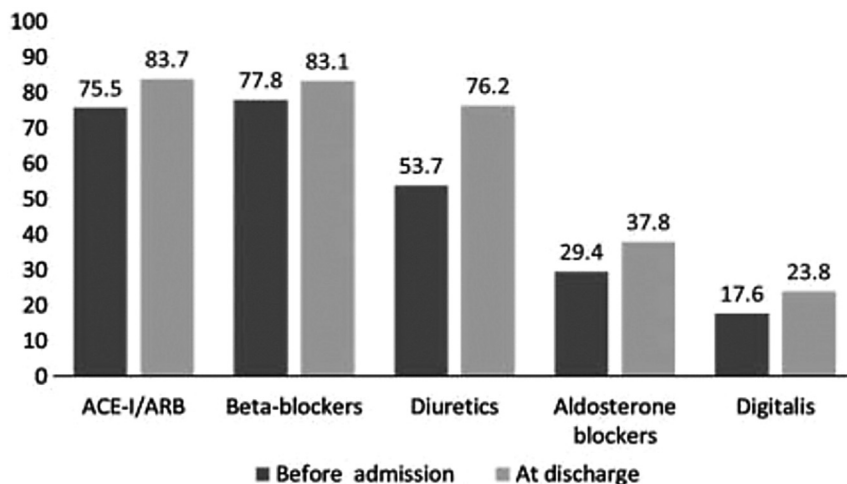
Variable	Acute heart failure	High-risk chronic heart failure
Age, mean yr (SD)	60.6 (15.3)	56.9 (15.5)
n (%)	772 (66.2)	368 (33.2)
Male, %	65.2	71.7
Body mass index (kg/m ²), mean ± SD	29.3 ± 6.8	29.2 ± 5.8
Central obesity, %	65.0	27.2
<i>Medical history, %</i>		
Coronary artery disease	50.0	41.8
Percutaneous coronary intervention	13.4	15.9
Coronary artery bypass graft	11.1	12.5
Rheumatic heart disease	7.2	3.3
Atrial fibrillation	15.4	13.5
Ventricular tachycardia/ventricular fibrillation	2.2	2.6
Implantable cardioverter defibrillator	10.0	28.8
Cardiac resynchronization therapy	5.3	8.0
Stroke	7.0	8.1
Peripheral artery disease	4.2	2.4
Chronic renal failure	30.7	28.1
On dialysis	6.8	1.9
Anemia	24.5	19.8
<i>Major risk factors, %</i>		
History of smoking	15.5	22.8
Current smoker	18.2	21.2
Hypertension	70.0	69.0
Hyperlipidemia	36.4	57.1
Diabetes mellitus	60.7	53.0
Taking insulin	41.6	20.9
<i>Vital signs at presentation</i>		
Systolic blood pressure, median (mmHg)	125	115
Diastolic blood pressure, median (mmHg)	72	69
Heart rate, median (mmHg)	88	77
<i>Major investigations</i>		
Positive serum troponin, %	30.0	—
Serum sodium (mmol/L)	135.2	137.0
Atrial fibrillation, %	18.0	11.8
QRS ≥120 ms, %	11.6	11.0
Serum NT-proBNP (N-terminal pro B-type natriuretic peptide; pg/mL)	4616	1596
Echocardiography, %	97.1	98.4
Preserved left ventricular function, %	27.5	24.7
Moderate/severe left ventricular systolic dysfunction, %	72.5	75.3
Right ventricular systolic dysfunction, %	27.2	6.6
Pulmonary hypertension, %	36.4	18.1
Coronary angiogram, %	31.6	—

physical and mental summaries [8,9]. Patients with HF had significant disruptive pain and limitations when performing everyday activities [9].

Given the availability of new data and various global guidelines, a group of local experts came together to develop customized guidelines that best reflect the needs and challenges for the diagnosis and treatment of HF in the KSA. These guidelines also offer an opportunity to address the differences between international guidelines that stem from variations in interpreting the HF literature. Despite the burden of HF in the KSA,

there are currently no standardized management protocols or guidelines for the management of patients presenting with AHF or CHF. This paper represents the consensus opinion of 13 experts and two reviewers practicing in the KSA. The aim of these guidelines is to assist healthcare professionals in delivering optimal and standardized clinical practice across the KSA. This paper provides a comprehensive overview of best practices keeping in mind the available local resources and practices. This paper enforces the importance of multidisciplinary care in HF management and

[A] AHF



[B] CHF

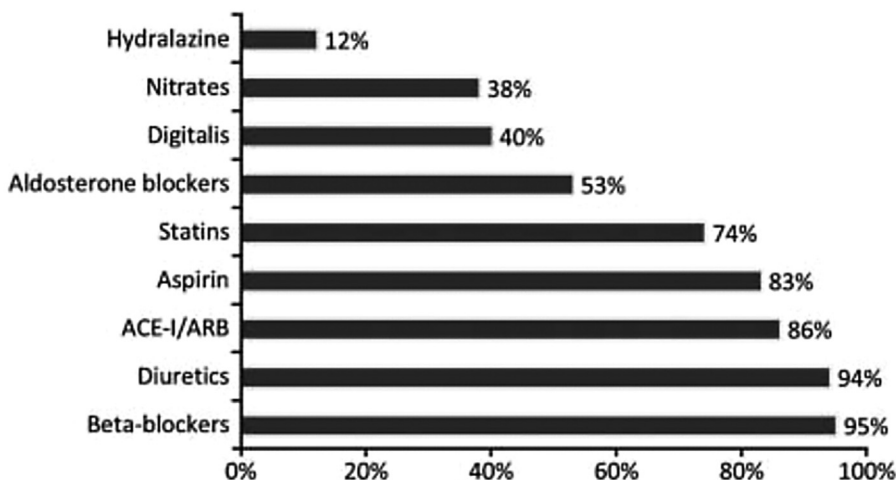


Fig. 1. Overview of medical therapy following diagnosis of patients with (A) acute heart failure (AHF) and (B) chronic heart failure (CHF) in the heart function assessment registry trial in Saudi Arabia (HEARTS) registry [2]. ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker. Note. Fig. 1A and B are taken from AlHabib KF, Elasar AA, AlBackr H, AlFaleh H, Hersi A, AlShaer F, et al. Design and preliminary results of the heart function assessment registry trial in Saudi Arabia (HEARTS) in patients with acute and chronic heart failure. *Eur J Heart Fail* 2011;13:1178–84. Reproduced with permission from Wiley.

discusses steps to measuring and improving quality of care.

2. Methods

2.1. Consensus approach

The Heart Failure Expert Committee, comprising 13 local specialists, representing both public and private sectors and practicing across the

KSA, met on October 7–8, 2016, to reach a consensus on the recommendations. This committee included experts practicing in different subspecialties in addition to their HF practice, such as interventional cardiology, cardiothoracic surgery, imaging, electrophysiology, and clinical pharmacology. Each of the expert committee members have a minimum of 10 years' clinical practice experience in cardiology. In addition, the two external reviewers are senior

Table 2. Definition and class of recommendations.

Color	Class	Definition
Green	Recommended/indicated	Evidence that a given treatment or procedure is useful and effective
Yellow	Should be considered	Conflicting evidence with favorable opinion about the usefulness or efficacy of a given treatment or procedure
Orange	May be considered	Conflicting evidence and opinion about efficacy that a given treatment or procedure is not well-established by evidence
Red	Not recommended	Evidence or general agreement that the given treatment or procedure is not useful/effective and, in some cases, may be harmful

cardiologists with over 20 years' clinical practice experience.

To reach consensus, a premeeting survey was conducted prior to drafting these recommendations, to gather opinions on diagnosis, treatment, and follow-up. Recommendations included in the premeeting survey were put together by referencing European and American clinical practice guidance documents. Each expert committee member voted on the key recommendations relating to their subspecialty through the survey, and provided critical feedback on whether they were relevant to practice in the KSA. Dr. Waleed AlHabeb reviewed all expert committee feedback and worked together with the medical writer on an initial draft for discussion at the expert committee meeting (October 7–8, 2016). During the meeting, all expert committee members discussed recommendations, and outlined clinical care pathways, keeping in mind the available local resources, current unmet needs, and published evidence. Special care was taken to review recent published landmark trials and meta-analysis before drafting treatment recommendations. Postmeeting the writer drafted a recommendation document based on feedback provided at the meeting, which was then critically reviewed by all authors as a validation of the consensus reached during the meeting. The final draft of the manuscript was critically appraised and validated by the two external reviewers.

2.2. Scope

This document is intended for use by local general physicians and cardiac specialists for the management of patients with AHF and CHF. However, physicians are required to manage patients based on the best available evidence and their clinical judgment, and should also take factors such as patient characteristics, drug profile, and available resources into consideration. Given that HF practices are standard globally,

there may be inevitable similarities between this paper and other published clinical practice guidance documents.

2.3. Literature review

A literature review was conducted premeeting and postmeeting, primarily using the National Library of Medicine PubMed database (limited to the English language). References were reviewed for relevance based on their title and abstract. References within selected papers were also checked for relevance. The strength of a recommendation for a particular management option was weighed and graded according to the predefined color scale outlined in Table 2.

3. Definition and classification of heart failure

HF can occur in a wide range of patients with different underlying etiologies, demographics, and comorbidities [3]; therefore, measurement of LVEF to define HF is a practical approach that can be used across all patient groups. Table 3 outlines the definition of HF, which includes three types of patients: reduced LVEF of $\leq 40\%$, borderline LVEF of 41–49%, and preserved LVEF of $\geq 50\%$.

Relevant terminologies related to the time course of HF includes (1) asymptomatic LV systolic dysfunction (a patient who has never exhibited the typical signs and/or symptoms of HF

Table 3. Definition of heart failure.

Classification	Ejection fraction (%)
Heart failure with reduced ejection fraction (HFrEF)	≤ 40
Heart failure with borderline ejection fraction (HFbEF)	41–49
Heart failure with preserved ejection fraction (HFpEF)	≥ 50

and with a reduced LVEF); (2) stable HF (a treated patient with signs and symptoms that have remained generally unchanged for at least 1 month); and (3) decompensated HF (if chronic stable HF deteriorates, the patient may be described as “decompensated”—this may happen suddenly or slowly) [3]. Staging the increasing severities of HF has been described by the American College of Cardiology Foundation/American Heart Association (AHA), who stratify patients based on the development and progression of disease [10].

4. Diagnosis

4.1. Etiologies

Given the lack of a well-defined classification of the etiologies of HF, the authors have endorsed

the 2016 European Society of Cardiology (ESC) guidelines’ scheme for classifying the causes of HF. The scheme divides the etiologies into two broad categories: HF secondary to diseased myocardium and HF secondary to abnormal loading conditions. The causes of HF are highlighted in Fig. 2.

4.2. Symptoms and signs

The symptoms of HF can be nonspecific, making it difficult for less experienced practitioners to make a definitive diagnosis (Fig. 3) [11]. Therefore, it is important to document a detailed medical history and to assess the signs and symptoms at each visit, especially for evidence of congestion. A patient’s response to treatment and stability over time is clearly reflected in their signs and symptoms. Persistence of symptoms while on treatment

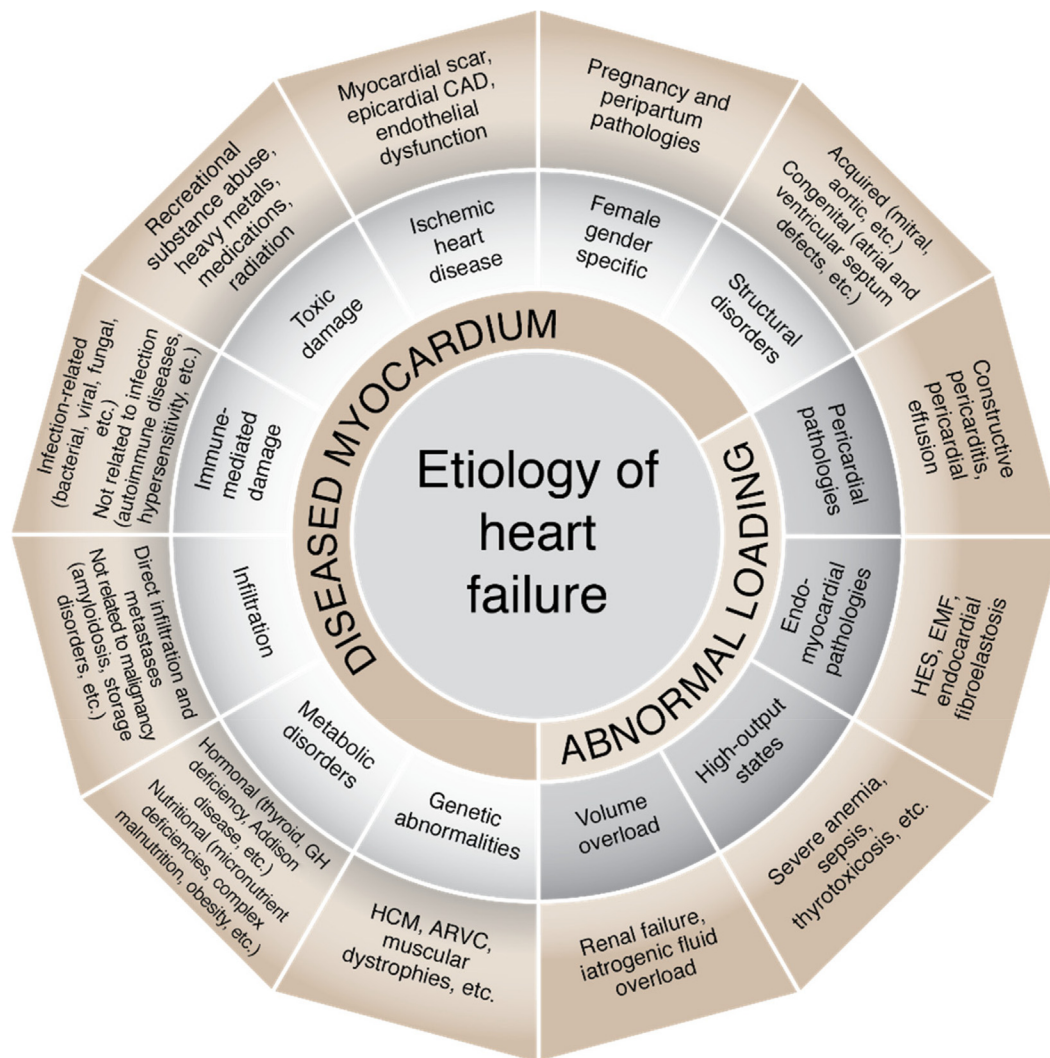


Fig. 2. Diagram summarizing the etiology of heart failure [3]. ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; EMF = endomyocardial fibrosis; GH = growth hormone; HCM = hypertrophic cardiomyopathy; HES = hyper eosinophilic syndrome. Note. Figure is based on content from [3].

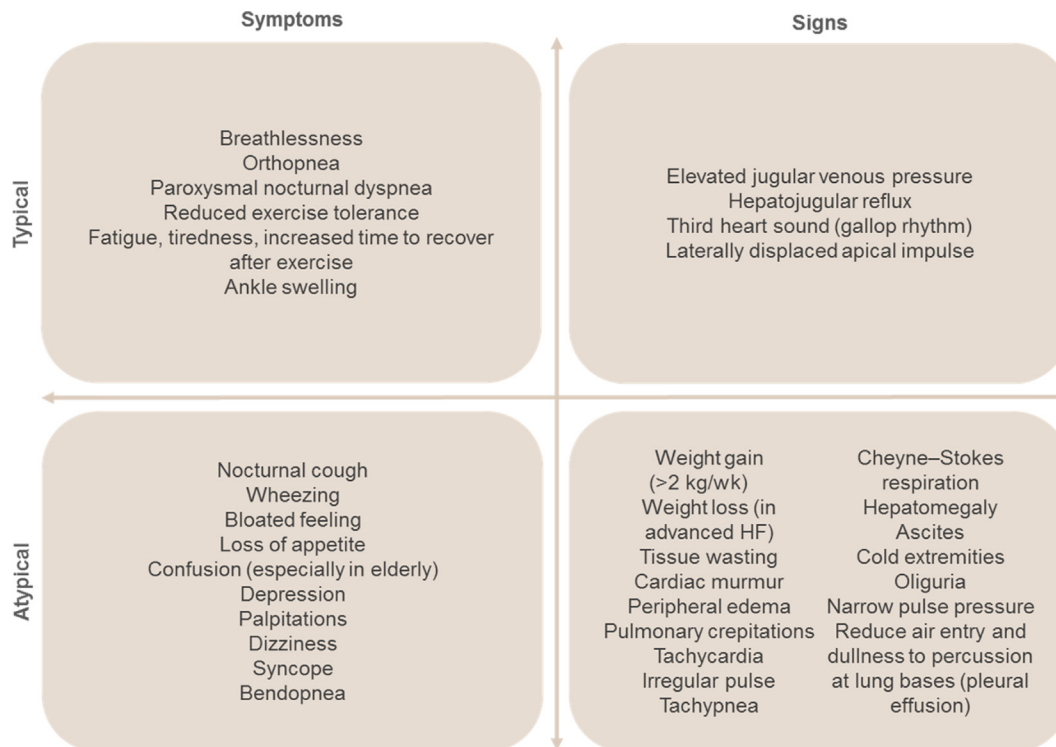


Fig. 3. Clinical signs and symptoms typical of heart failure (HF) [11].

warrants additional therapy. Prompt medical attention is only necessary when symptoms worsen. Although symptoms resolve over time with treatment, the underlying cardiac dysfunction may not necessarily resolve and the patient will continue to be at risk of decompensation. Assessment of patients' functional ability is also an important predictor of HF, because reduced exercise tolerance over time usually indicates worsening HF and physical deconditioning [11]. The New York Heart Association (NYHA) classification is a useful tool to measure a patient's physical limitations and for observing a patient's stability over time [11].

4.3. Diagnosing heart failure

For patients presenting for the first time with signs and symptoms suggestive of HF, it is important to consider the patient's prior clinical history, physical examination, and resting electrocardiogram. If all results are within the normal range, it is highly unlikely the patient has HF and other diagnoses should be considered.

BNP level is a biomarker for the diagnosis and prognosis of HF [12], and a normal NT-proBNP level has a high negative predictive value for HF [13]. A BNP level ≥ 100 pg/mL [14,15] and/or an NT-proBNP ≥ 300 pg/mL [16] (depending on age) would almost certainly confirm the presence of

HF. A BNP < 40 pg/mL and an NT-proBNP < 125 pg/mL excludes HF in a non-acute setting. The BNP cutoff values for "ruling in" and "ruling out" HF are referred to as "gray zone" values, and are seen in approximately 20% of patients with dyspnea in the emergency department [17]. It is important to remember that a gray zone value of NT-proBNP is not a benign finding, and these patients have a higher risk for adverse outcomes than patients with a negative result [17]. A few possible diagnoses to consider in patients with gray zone NT-proBNP levels include cardiac ischemia, AF, and infectious/inflammatory pulmonary disease [17].

A normal natriuretic peptide level would indicate that HF is unlikely, prompting consideration of other diagnoses. If another diagnosis cannot be determined, then the patient should undergo echocardiographic assessment. Echocardiography provides immediate information on chamber volumes, ventricular systolic and diastolic function, wall thickness, valve function, and pulmonary hypertension [3]. Confirmation of HF merits further investigation to determine the etiology and initiate the most appropriate treatment. Therefore, at this point, we recommend referring the patient to a specialist cardiologist to facilitate appropriate patient management. An algorithm for the diagnosis of HF is shown in Fig. 4.

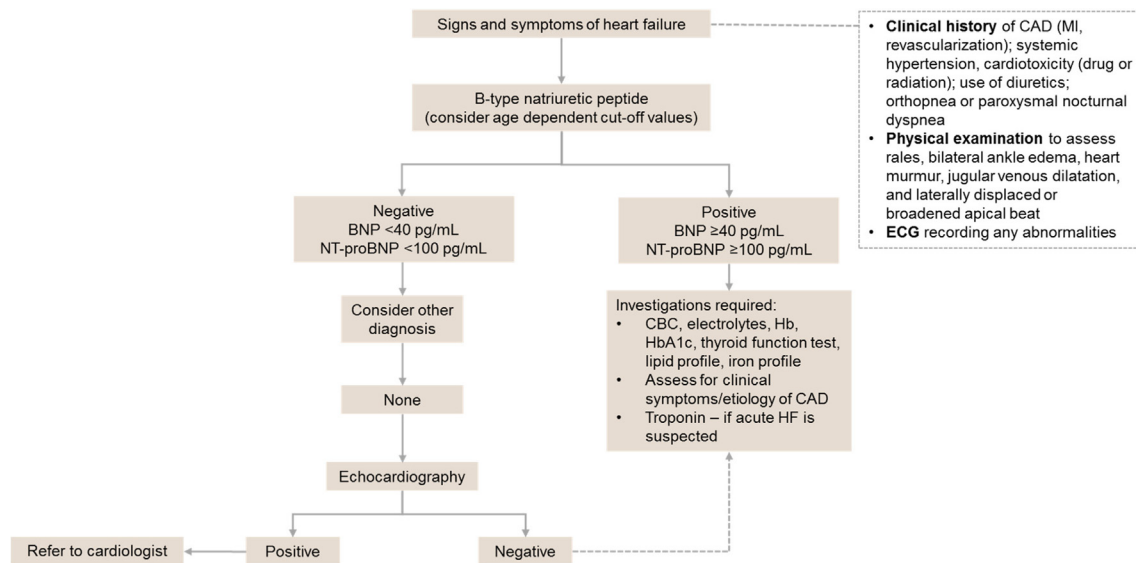


Fig. 4. Algorithm for the diagnosis of heart failure. BNP = B-type natriuretic peptide; CAD = coronary artery disease; CBC = complete blood count; ECG = electrocardiogram; Hb = hemoglobin; HF = heart failure; MI = myocardial infarction; NT-proBNP = N-terminal pro B-type natriuretic peptide.

4.4. Diagnosis of heart failure with preserved ejection fraction

HF with preserved EF (HFpEF) contributes to a substantial societal burden and is becoming a predominant phenotype of HF [18]. Various criteria have been suggested for the diagnosis of HFpEF; however, to make a definitive diagnosis, the presence of three key clinical, echocardiographic, and hemodynamic abnormalities are required (Fig. 5) [18].

The diagnosis of HFpEF is challenging because of the nonspecificity of the signs and symptoms, echocardiography, and relative paucity of markers for diastolic dysfunction [18]. Biomarkers are increasingly being used for screening, diagnosis, and risk stratification in HF. Data from the recent Swedish Heart Failure Registry found that decreases in NT-proBNP were associated with improved mortality and morbidity in patients with HF with borderline EF (HFbEF; EF 40–49%) and HFpEF (EF ≥50%) [19]. Although echocardiogra-

phy plays an important role in the diagnostic work-up of patients with HFpEF, evaluating LV diastolic dysfunction with conventional echocardiography produces variable profiles and has no impact on long-term survival. By contrast, right ventricle (RV) dysfunction, paradoxical septal motion, and higher RV systolic pressure were associated with poor survival [20]. Importantly, data from the RELAX trial showed that, in patients with HFpEF, impaired LV global longitudinal strain was indicative of covert systolic dysfunction despite normal LVEF. Impaired LV global longitudinal strain was associated with lower NT-proBNP and collagen synthesis and diastolic dysfunction, but was not associated with improved QoL or exercise capacity [21]. A recent study assessing biomarkers in 5000 individuals from the population-based Gutenberg Health Study reported that the index of CRP + GDF-15 + sST2/NT-proBNP may be used to discriminate HFpEF from HF with reduced EF (HFrEF) [22].

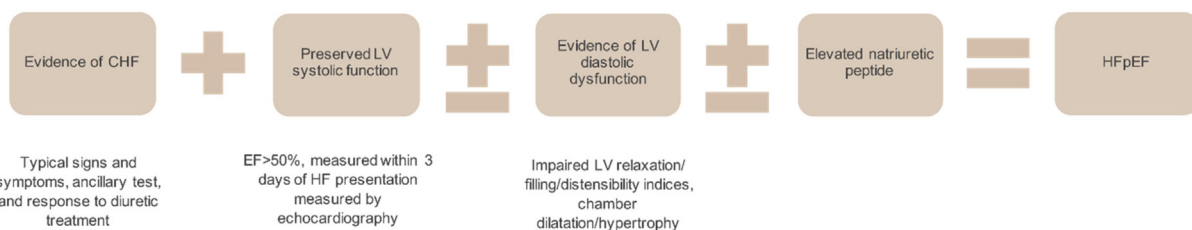


Fig. 5. Criteria for diagnosis of HFpEF [18]. CHF = chronic heart failure; EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LV = left ventricle.

Possible clinical parameters to aid diagnosis of HFpEF and minimize the need for invasive testing are listed in Table 4. HFpEF has a unique pathophysiology, characterized by severe dysfunction of the diastolic phase of the cardiac cycle that results in elevated ventricular pressures [18]. In addition, impairment of myocardial relaxation and stiffness lead to reduced LV filling, elevated diastolic pressures, and HF symptoms [18]. Hemodynamic measurements reveal prolonged isovolumic pressure decline and upward–leftward shift in the pressure–volume loop, with aberrant myocardial relaxation coupled with high indices of passive stiffness [18].

5. Cardiac imaging and diagnostic work-up

Identifying reduced LV function is critical to the diagnosis of HFrEF. It can be detected using multiple modalities (Tables 5–8), including transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), cardiac magnetic resonance (CMR) imaging, left ventriculography during cardiac catheterization, radionuclide ventriculography, and single-photon emission computed tomography (SPECT) [23].

5.1. Chest X-ray

Although the benefits of chest X-rays in the diagnostic work-up of patients with suspected HF are limited, it is the most useful tool in identifying an alternative pulmonary cause [3].

5.2. Transthoracic echocardiography

Echocardiography is an essential tool for establishing diagnosis and etiology, and understanding the pathophysiology of HF. It is recommended that all patients with signs and symptoms of HF, or incidental findings of a low EF on other imaging modalities, be evaluated with TTE as an initial depth analysis because of its well-established

accuracy, availability, safety, and low cost [24]. In addition, TTE is useful for assessing LV function. An initial and complete TTE study is pivotal and must include the following [25,26]:

1. LV chamber and wall assessment
2. LV function quantification
3. Transmitral Doppler patterns
4. Pulmonary venous flow patterns
5. Left atrial volume index
6. Valvular assessment
7. RV chamber size and function assessment

Where advanced echocardiography techniques are available, strain rates and global longitudinal strain imaging should be used, especially in patients who receive cardiotoxic cancer therapies.

5.3. Transesophageal echocardiography

TEE may be valuable for the diagnostic work-up of patients with valve disease, suspected aortic dissection, suspected endocarditis or its complications, or congenital heart disease, and for ruling out intracavitary thrombi in patients with AF requiring cardioversion [3]. It is also recommended that, when the severity of mitral or aortic valve disease is inconsistent with the patient's symptoms, TEE be used for confirmation [3].

5.4. Stress echocardiography

Stress echocardiography has multiple uses in patients with HF. It may be used to detect diastolic dysfunction related to exercise in patients with exertional dyspnea, preserved LVEF, and inconclusive diastolic parameters at rest. It is also useful for the assessment of inducible ischemia, myocardial viability, and in valve disease [3]. Resting echocardiography often underestimates the severity of HFpEF, therefore, exercise stress echocardiography and cardiopulmonary exercise testing are useful for dynamic assessment of HFpEF [27]. Practitioners are encouraged to use stress echocardiography especially in patients with shortness of breath and no clear resting abnormality. In HF patients with a normal EF, the deterioration of ventricular and peripheral performance is evident during exercise. Furthermore, patients with HF exhibit chronotropic noncompetence during exercise [28].

5.5. Cardiac magnetic resonance

CMR is the gold standard for measurements of volume, mass, and the EF of both the LVs and RVs [3]. CMR is preferred for assessment of myocardial fibrosis and complex congenital heart

Table 4. Clinical parameters for the diagnosis of heart failure with preserved ejection fraction [18].

Parameters
<ul style="list-style-type: none"> • Left atrial volume index • Left ventricular mass index • Left ventricular wall thickness • Transmitral Doppler and tissue Doppler indices • Longitudinal strain patterns • Tricuspid regurgitation velocity • Right ventricular systolic function • Tricuspid annular plane systolic excursion • Right ventricular systolic pressure

Table 5. Recommendations for cardiac imaging in patients with suspected or established heart failure.

No.	Recommendations
1	TTE is recommended for the assessment of myocardial structure and function in patients with suspected HF to establish a diagnosis of HFrEF, HFbEF, or HFpEF
2	TTE is recommended to assess LVEF to identify patients with HF suitable for evidence-based pharmacological treatment and device implantation (e.g., implantable cardioverter defibrillator, cardiac resynchronization therapy) recommended for HFrEF
3	TTE is recommended for the assessment of valve disease, right ventricular function, and pulmonary arterial pressure in patients with an already established diagnosis of HFrEF, HFbEF, or HFpEF to identify those suitable for correction of valve disease
4	TTE is recommended for the assessment of myocardial structure and function in patients to be exposed to cardiotoxic agents (e.g., chemotherapy)
5	Other techniques (including systolic tissue Doppler velocities, 3D assessment of LVEF, and global longitudinal strain) may be considered in a TTE protocol in those at risk of developing HF, to identify myocardial dysfunction at the preclinical stage as well as in patients exposed to cardiotoxic agents
6	CMR with late gadolinium enhancement is recommended for the assessment of all HF patients with cardiomyopathy
7	CMR should be conducted at an experienced center under the supervision of qualified and well-trained physicians who are familiar with standard methodology and protocols
8	CMR is recommended for the characterization of myocardial tissue in case of suspected myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease, noncompaction cardiomyopathy, hemochromatosis, hypertonic cardiomyopathy, stress-induced cardiomyopathy, and ARVC
9	Noninvasive stress imaging (perfusion CMR, stress echocardiography, SPECT or PET) may be considered for the assessment of myocardial viability in patients with HF and CAD (considered suitable for coronary revascularization) before the decision on revascularization. Noninvasive stress imaging should be conducted after coronary assessment
10	Invasive coronary angiography is recommended in patients with HF and angina pectoris recalcitrant to pharmacological therapy, symptomatic ventricular arrhythmias, or aborted cardiac arrest (who are considered suitable for potential coronary revascularization) to establish the diagnosis of CAD and its severity
11	Invasive coronary angiography should be considered in patients with HF (who are considered suitable for potential coronary revascularization) and intermediate-to-high pretest probability of CAD, and the presence of ischemia in noninvasive stress tests to establish the diagnosis of CAD and its severity
12	Noninvasive testing (preferably cardiac computed tomography, but also stress echocardiography, SPECT, PET, myocardial perfusion imaging) may be considered in patients with HF and low-to-intermediate pretest probability of CAD, to rule out coronary artery stenosis
12	Reassessment of myocardial structure and function using noninvasive imaging is recommended: <ul style="list-style-type: none"> – In patients presenting with worsening HF symptoms (including episodes of AHF) or experiencing any other important cardiovascular event – In patients with HF who have received evidence-based pharmacotherapy in maximal tolerated doses, before the decision on device implantation (ICD, CRT), to avoid misuse, overuse, or unjustified use – In patients exposed to therapies that may damage the myocardium (e.g., chemotherapy), serial assessments, or any medications that could lead to cardiotoxicity – In patients receiving CRT for the assessment of change in myocardial function, valvular regurgitation, and diastolic filling pressures

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AHF = acute heart failure; ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CRT = chronic heart failure; HF = heart failure; HFbEF = heart failure with borderline ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; PET = positron emission tomography; SPECT = single-photon emission computed tomography; TTE = transthoracic echocardiography.

disease, and may be useful for the assessment of myocardial ischemia and viability in patients with HF and CAD [3]. CMR facilitates the characterization of myocardial tissue of myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease, noncompaction cardiomyopathy, and hemochromatosis [3]. However, the usefulness of CMR in the Saudi local setting is limited by insufficient local expertise, availability, and cost, compared with echocardiography.

5.6. SPECT, radionuclide ventriculography, and positron emission tomography

SPECT may be useful in assessing myocardial viability or ischemia. Gated SPECT may be used to capture details on ventricular volumes and function; however, it exposes the patient to ionizing radiation [3]. Positron emission tomography (PET), with or without CT, may be used to assess ischemia and viability, but limited availability,

Table 6. Recommendations for conducting diagnostic tests in patients with heart failure.

No.	Recommendations
	The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF to evaluate the patient’s suitability for particular therapies, and to detect reversible/treatable causes of HF and comorbidities interfering with HF:
13	– Complete blood count – Sodium, potassium, urea, and creatinine (with estimated glomerular filtration rate) – Liver function tests (bilirubin, aspartate transaminase, alanine transaminase, gamma-glutamyl transpeptidase, and albumin) – Glucose and HbA1c – Lipid profile – Thyroid-stimulating hormone – Ferritin and transferrin saturation—total iron blood count
14	– Natriuretic peptides and troponin
15	Additional diagnostic tests aiming to identify other HF etiologies and comorbidities should be considered in individual patients with HF when there is a clinical suspicion of a particular pathology (see Fig. 2 on HF etiologies)
16	A 12-lead ECG is recommended in all patients with HF to determine heart rhythm, heart rate, QRS morphology, and QRS duration, and to detect other relevant abnormalities. This information is needed to plan and monitor treatment
17a	Exercise testing in patients with HF: – May be considered to assess response before and after treatment (functional capacity assessment with a 6-minute walk test)
17b	– Is recommended as a part of the evaluation for heart transplantation and/or mechanical circulatory support (cardiopulmonary exercise testing)
18	– Should be considered to optimize the prescription of exercise training (preferably cardiopulmonary exercise testing)
19	– Could be considered to identify the cause of unexplained dyspnea (cardiopulmonary exercise testing)
20	– May be considered to detect reversible myocardial ischemia
21	Chest radiography (X-ray) is recommended in patients with HF to detect/exclude alternative pulmonary or other diseases, which may contribute to dyspnea. It may also identify pulmonary congestion/edema and is more useful in patients with suspected HF in the acute setting
	Right heart catheterization with a pulmonary artery catheter:
22	– Is recommended in patients with severe HF being evaluated for heart transplantation or mechanical circulatory support
23	– Should be considered in patients with probable pulmonary hypertension assessed by echocardiography, to confirm pulmonary hypertension and its reversibility before the correction of valve/structural heart disease – Should be considered in patients with severe mitral regurgitation
24	– May be considered to adjust therapy in patients with HF who remain severely symptomatic or require hemodynamic support with parenteral vasoactive agents despite initial standard therapies and whose hemodynamic status is unclear
25	Endomyocardial biopsy should be considered in patients with rapidly progressive HF despite standard therapy
26	Ultrasound measurement of inferior vena cava diameter may be considered for the assessment of volume status in patients with HF

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

ECG = electrocardiogram; HF = heart failure.

Table 7. Recommendations for lung ultrasound in patients with heart failure.

No.	Recommendations
27	Lung ultrasound should be considered for the confirmation of pulmonary congestion and pleural effusion in patients with AHF
28	Lung ultrasound may be used to differentiate from respiratory causes of dyspnea, including pulmonary fibrosis and ARDS, and aids in monitoring of response to therapy in patients with CPE
29	Lung ultrasound is more accurate than portable X-ray in the detection of lung consolidation, and may be used in mechanically ventilated patients
30	Lung ultrasound should be performed by a trained physician

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AHF = acute heart failure; ARDS = acute respiratory distress syndrome; CPE = cardiogenic pulmonary edema.

Table 8. Recommendations for genetic testing.

No.	Recommendations
31	Genetic counseling is recommended in patients with hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, and ARVC
32	Restrictive cardiomyopathy and isolated noncompaction cardiomyopathies have a possible genetic origin and should also be considered for genetic testing
33	Screening of first-degree relatives for early detection is recommended from early adolescence onward, although earlier screening may be considered depending on the age of disease onset in other family members

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

ARVC = arrhythmogenic right ventricular cardiomyopathy.

radiation exposure, and cost are the main limitations [3].

5.7. Coronary angiography

Coronary angiography is recommended in patients with HF who suffer from angina pectoris recalcitrant to medical therapy, those with a history of symptomatic ventricular arrhythmia or aborted cardiac arrest, and may also be considered in patients with HF and intermediate-to-high pretest probability of CAD as well as the presence of ischemia (assessed by noninvasive stress tests) [3]. Invasive coronary angiography is the gold standard for the anatomical assessment of CAD in patients with HF [29].

5.8. Cardiac computed tomography

Computed tomography angiography (CTA) is an important noninvasive tool for the diagnosis of HF [23]. Compared with invasive coronary angiography, CT coronary angiography (CTCA) has several advantages, including reliability in proving or ruling out the presence of CAD in patients with low-or-intermediate pretest probability of CAD. Cardiac CT at high spatial and temporal resolution is fast, patient friendly, and is associated with declining doses of ionizing radiation [30].

CTA can be used to diagnose reduced LV function by determining EF, which correlates well with echocardiographic assessment [23]. Although CTA and CMR imaging have a strong correlation for EF calculation, CTA has limited temporal resolution compared with CMR imaging, resulting in slight overestimations of end-systolic volume and EF, especially in patients with HFrEF [23].

Although multiple echocardiographic indices (including mitral valve flow velocities and tissue Doppler velocities) are used to diagnose HF with preserved EF, CTA can measure diastolic properties and may have a future role in HFpEF [23].

5.9. Lung ultrasound

In patients with pleural effusion, lung ultrasound can assist in diagnosing the nature of effusion and visualization of internal echoes, either of mobile particles or septa, and is highly suggestive of exudate or hemothorax [31]. It is more accurate than a chest X-ray, particularly for the anterior-posterior view of a supine patient [31].

In patients with HF, lung ultrasound is an alternative tool for monitoring changes in pulmonary congestion during treatment, which are detected by variations in ultrasound patterns [31]. A study assessing the prognostic value of residual pulmonary congestion in HF inpatients reported that residual pulmonary congestion at discharge, assessed by a B-line count of ≥ 30 , was a strong predictor of all-cause death or HF rehospitalization [32]. Similarly, a prospective cohort study of patients with suspected AHF found that the 6-month event-free survival was lowest in patients with B-lines >15 ; and persistent congestion prior to discharge (B-lines >15) was a strong predictor of rehospitalization for HF at 6 months [33].

5.10. Genetic testing for heart failure

In the presence of adequate expertise, it is recommended that genetic counseling be offered to patients with hypertrophic cardiomyopathy (HCM), DCM, and arrhythmogenic right ventricular cardiomyopathy (ARVC). Combining the CMR findings with genetic testing can contribute greatly to the diagnosis and risk stratification of HCM, and to assessing the need for placement of implantable cardioverter defibrillators (ICDs) for primary prevention of complications [34].

DCM is characterized by genetic heterogeneity, with more than 40 genes implicated in the disease [35,36]. Idiopathic DCM is familial in 25% of cases and, although it may be difficult to identify asymptomatic relatives due to lack of a molecular marker, screening may result in early treatment,

which may improve prognosis in affected individuals [37]. Although genetic testing is challenging, it is a useful tool in the clinical management of DCM. Testing for pathogenic mutations facilitates appropriate treatment and may assist in predicting disease risk for family members before the onset of symptoms [38].

ARVC is an inherited disease of the heart muscle that may lead to life-threatening ventricular arrhythmias, sudden cardiac death, and/or biventricular HF [39]. ARVC is predominantly associated with mutations in desmosomal genes, and has a broad spectrum of phenotypic variation and age-related penetrance [40]. Although the diagnosis of ARVC is challenging due to lack of definitive testing methods, genetic testing and CMR imaging play an important role in the identification of disease [40]. ICD implantation is considered a life-saving therapy for patients with ARVC, and exercise restriction may delay disease progression [40].

In general, the approach to cardiac screening and genetic testing should be family specific and requires expertise in the genetics of cardiomyopathy [41].

6. Preventing heart failure (Table 9)

Antihypertensive drugs (diuretics, ACE-Is, ARBs, and beta-blockers) exert a strong protective effect against HF, particularly in older people [42–44]. The SPRINT study, involving 9361 high-risk, hypertensive, nondiabetic patients, showed that a target systolic blood pressure of <120 mmHg, compared with <140 mmHg, was

significantly effective in reducing the rates of myocardial infarction (MI), other acute coronary syndromes, stroke, HF, or death from cardiovascular causes (1.65% vs. 2.19% per year, HR with intensive treatment 0.75, 95% CI 0.64–0.89; $p < 0.001$) [45].

Smoking has been associated with a significant risk of HF [46]. In a separate study, the incidence of HF was measured at 11.4 per 1000 person-years in nonsmokers, 15.2 in past smokers (HR vs. nonsmokers 1.33, 95% CI 1.01–1.76; $p = 0.045$), and 21.9 in current smokers (HR vs. nonsmokers 1.93, 95% CI 1.30–2.84; $p = 0.001$) [47]. Smoking cessation has a significant and swift (within 2 years) effect on reducing morbidity and mortality in patients with LV dysfunction [48]. Abstinence from smoking for more than 15 years reduces the risk of HF and all-cause mortality to that of never-smokers [49].

There is a strong relationship between increased physical activity and a reduced risk of HF. In fact, a substantial risk reduction in HF was observed in individuals who engaged in physical activity two times (HR 0.81, 95% CI 0.77–0.86) and four times (HR 0.65, 95% CI 0.58–0.73) a week above the minimum guideline recommended levels (500 metabolic equivalent-minutes/week; 2008 US federal guidelines) [50].

Statins are considered to be promising candidates for HF treatment because of their role in improving endothelial function, enhancing nitric oxide synthesis, restoring impaired autonomic function, and inhibiting inflammatory cytokine release [51].

Table 9. Recommendations for the prevention of heart failure.

No.	Recommendations
1	Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life
2	Treatment with statins is recommended in patients with or at risk of CAD
3	Counseling and treatment for smoking (all types, including but not exclusive of cigarette, tobacco, <i>khat</i> , or <i>sheesha</i> smoking) and alcohol is recommended for people who smoke or who consume excess alcohol, to prevent or delay the onset of HF
4	Treating other risk factors of HF (e.g., obesity, dysglycemia) should be considered to prevent or delay the onset of HF
5	An ACE-I is recommended in patients with symptomatic or asymptomatic LV systolic dysfunction, to prevent or delay the onset of HF
6	An ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, to prevent or delay the onset of HF
7	A beta-blocker is recommended in patients with symptomatic or asymptomatic LV systolic dysfunction, to prevent or delay the onset of HF
8	An ICD is recommended in patients with asymptomatic LV systolic dysfunction (LVEF $\leq 30\%$) of ischemic origin, who are at least 40 days after acute myocardial infarction or 3 months after revascularization, to prevent sudden death and prolong life

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

ACE-I = angiotensin-converting enzyme inhibitor; CAD = coronary artery disease; HF = heart failure; ICD = implantable cardioverter defibrillator; LV = left ventricle; LVEF = left ventricle ejection fraction.

A meta-analysis involving 647,388 participants showed a risk ratio of 1.41 for the incidence of HF (95% CI 1.34–1.47), and 1.26 for HF mortality (95% CI 0.85–1.87) with every 5-unit increment in body mass index. Furthermore, every 0.1-unit increase in waist-to-hip ratio was associated with a risk ratio of 1.29 for HF incidence (95% CI 1.13–1.47) [52]. However, the benefit of weight loss in obese patients with HF remains unclear, which represents what is commonly known as the obesity paradox in HF [53].

Prophylactic implantation of a defibrillator improves survival in patients with prior MI and advanced LV dysfunction [54].

7. Pharmacological treatment of HFrEF (Tables 10, 11)

The algorithm for the pharmacological treatment of HFrEF is displayed in Fig. 6. Neurohormonal antagonists (ACE-Is and beta-blockers) have been shown to improve survival in patients with HFrEF and are recommended for the treatment of all patients with HFrEF, unless contraindicated or not tolerated. ARBs are recommended only as an alternative in patients who are intolerant of ACE-Is. A new compound (LCZ696), which combines the moieties of an ARB (valsartan) and a neprilysin inhibitor (sacubitril), has recently been

Table 10. Recommendations for pharmacological treatments for patients with HFrEF.

No.	Recommendations
1	An ACE-I, ^a in addition to a beta-blocker, is recommended for patients with HFrEF, to reduce the risk of hospitalization and death
2	A beta-blocker (extended-release metoprolol, bisoprolol, or carvedilol), in addition to an ACE-I, ^a is recommended for patients with HFrEF, to reduce the risk of hospitalization and death
3	An MRA is recommended for patients with HFrEF who remain symptomatic despite treatment with an ACE-I ^a and a beta-blocker, to reduce the risk of hospitalization and death. Renal function and potassium levels should be closely monitored in patients prescribed an MRA
<i>Diuretics</i>	
4	Diuretics are recommended to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion
5	Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion
<i>Angiotensin receptor neprilysin inhibitor</i>	
6	Sacubitril/valsartan is recommended as a replacement for an ACE-I (or ARB) to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I/ARB and a beta-blocker
<i>Angiotensin II receptor blockers</i>	
7	An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I
<i>Hydralazine and isosorbide dinitrate</i>	
8	Hydralazine and isosorbide dinitrate should be considered in symptomatic patients with HFrEF who cannot tolerate an ACE-I or an ARB (or for whom they are contraindicated), to reduce the risk of death
9	Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF despite treatment with an ACE-I, ARB, a beta-blocker, and an MRA, to reduce the risk of HF hospitalization and death
<i>I_f-channel inhibitor</i>	
10	Ivabradine should be considered to reduce the risk of HF hospitalization in symptomatic patients with an LVEF ≤35%, sinus rhythm, and who have a resting heart rate ≥70 bpm, despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), in addition to an ACE-I (or ARB) and an MRA
11	Ivabradine should be considered to reduce the risk of HF hospitalization in symptomatic patients with an LVEF ≤35%, sinus rhythm, and who have a resting heart rate ≥70 bpm and are unable to tolerate or have contraindications for beta-blockers. Patients should also receive an ACE-I (or ARB) and an MRA
<i>Other treatments with less-certain benefits</i>	
12	Digoxin may be considered in patients who are symptomatic despite treatment with an ACE-I (or ARB), a beta-blocker, and an MRA to reduce the risk of hospitalization (both all-cause and HF hospitalizations). For therapeutic benefit, maintain low digoxin serum concentrations (0.5–0.9 ng/mL)

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

^aOr an ARB if the ACE-I is not tolerated or contraindicated.

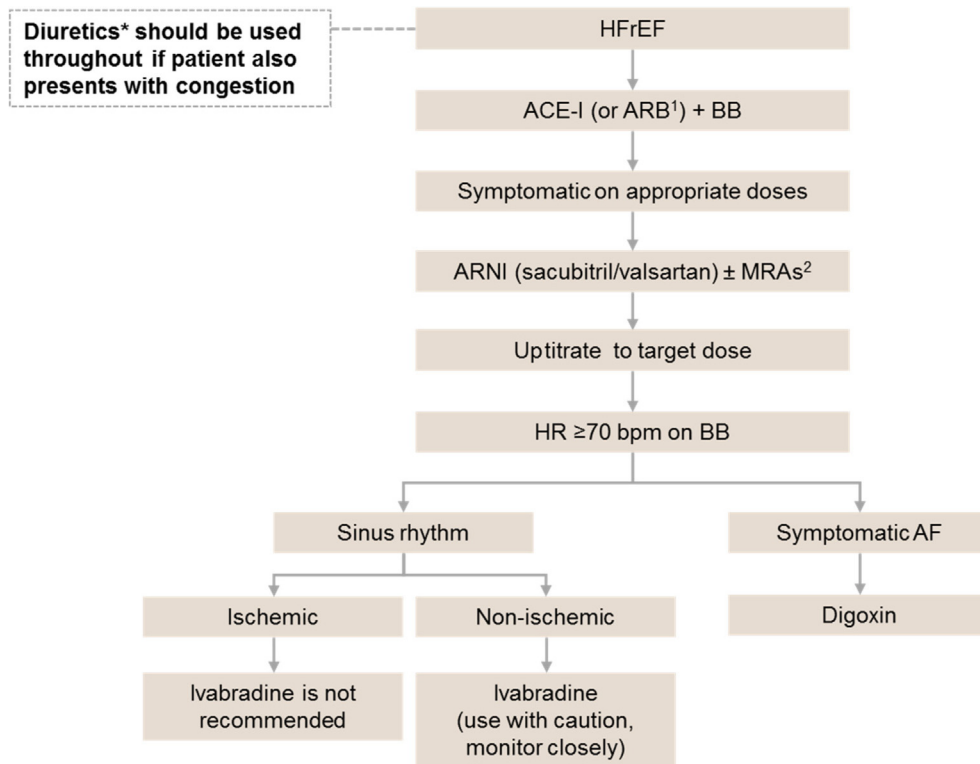
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist.

Table 11. Recommendations for treatment combinations that may cause harm in patients with HFrEF.

No.	Recommendations
13	Thiazolidinediones (glitazones) are not recommended in patients with HF because they increase the risk of HF worsening and HF hospitalization
14	NSAIDs or COX-2 inhibitors are not recommended in patients with HF because they increase the risk of HF worsening and HF hospitalization
15	Diltiazem or verapamil are not recommended in patients with HFrEF because they increase the risk of HF worsening and HF hospitalization
16	The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF because of the increased risk of renal dysfunction and hyperkalemia
17	Ivabradine should not be used in patients who had a myocardial infarction within the past 2 months

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; COX = cyclooxygenase; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid antagonist; NSAID = non-steroidal anti-inflammatory drug.



* Use the lowest dose of diuretic for the shortest period

¹ As an alternative to ACE-I, if intolerant

² Consider MRAs if EF ≤ 35% and K⁺ < 5.0 mmol/L

Fig. 6. Algorithm for pharmacological treatment of HFrEF. ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; BB = beta-blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; MRA = mineralocorticoid antagonist.

shown to be superior to an ACE-I (enalapril) in reducing the risk of death and of hospitalization for HF in a single trial with strict inclusion/exclusion criteria [55]. Therefore, sacubitril/valsartan is recommended to replace ACE-Is in ambulatory HFrEF patients who remain symptomatic despite

optimal therapy and who fit these trial criteria. Digoxin may be considered in patients with AF with symptomatic HFrEF to reduce the risk of hospitalization (both all-cause and HF hospitalizations). A recent meta-analysis concluded, based on non-randomized controlled trials (RCTs), that

digoxin has no deleterious effect on mortality in patients with AF and concomitant HF, most of whom had HFrEF [56].

7.1. Treatments recommended in all symptomatic patients with HFrEF

7.1.1. Renin–angiotensin–aldosterone system inhibitors and beta-blockers

A recent meta-analysis conducted by Thomsen et al. [57] evaluated RCTs of drugs recommended by the ESC and AHA guidelines for the treatment of patients with HFrEF. The analysis included 47 RCTs that included patients with an average age of 63 years, 22% of whom were women, and looked at outcomes of all-cause mortality and hospitalization due to HF [57].

The relative risk (RR) for mortality was similar for drugs targeting the renin–angiotensin–aldoster

one system (RAAS), beta-blockers, cardiac resynchronization therapy (CRT), and ICDs (Fig. 7A). Although drugs targeting the RAAS, beta-blockers, digoxin, and CRT substantially reduced the risk of HF hospitalization, ICDs were associated with a significantly increased risk of HF hospitalization (34%) [57]. Overall, ivabradine showed no significant effect on reducing the risk of mortality or HF hospitalization [57]. Although drugs recommended for HFrEF offer significant benefit, studies included in the analysis were from the 1990s or earlier and included a population of men with a different age distribution than the current average for HF [57]. Therefore, the authors advise that extrapolating results to the current population should be done with caution.

In a recent network meta-analysis by Burnett et al. [58] including 57 RCTs, the random-effects model suggested that the combination of an

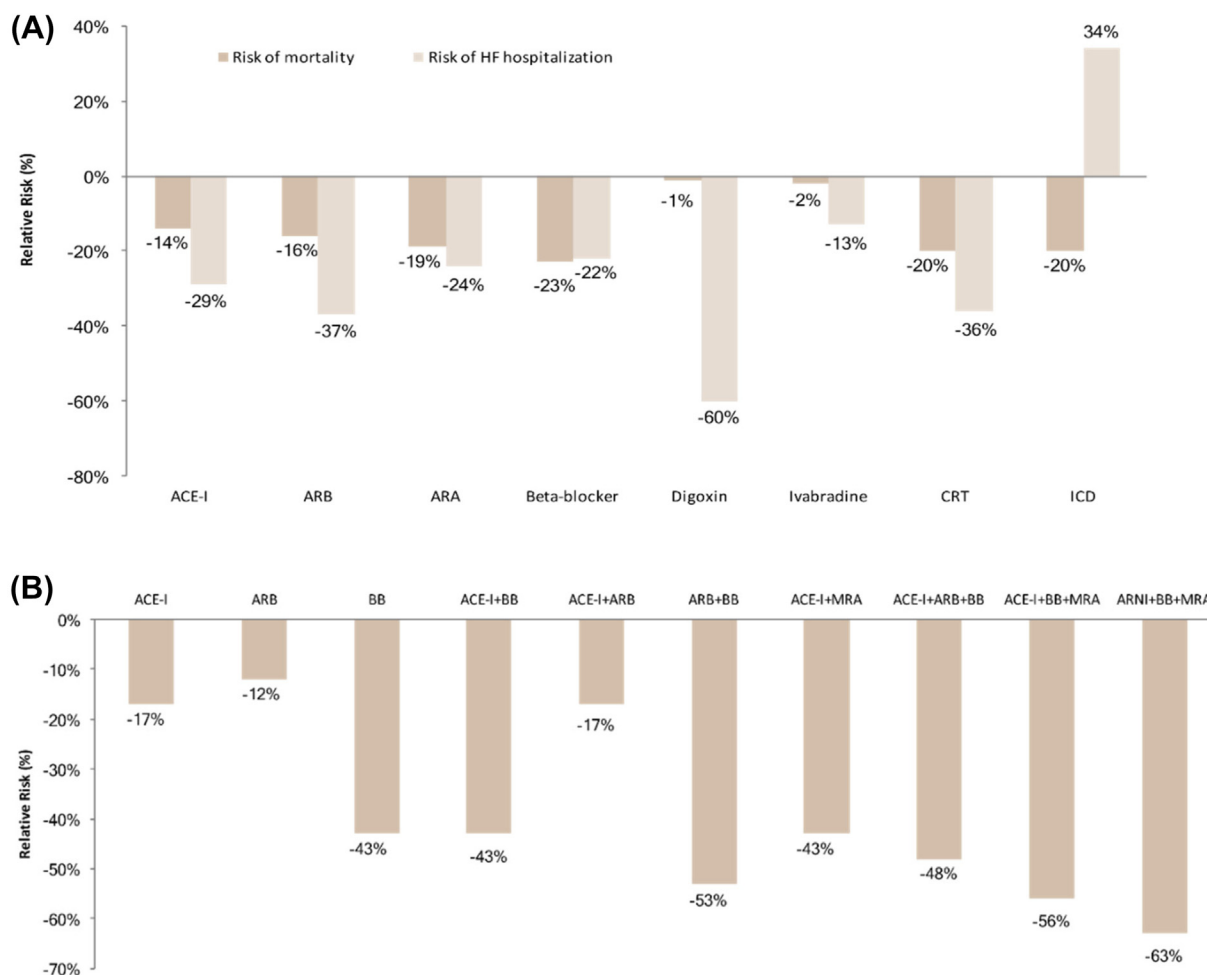


Fig. 7. (A) Relative risk for mortality and HF hospitalization categorized by treatment group [57]. (B) Relative risk for all-cause mortality categorized by treatment group [58]. ACE-I = angiotensin-converting enzyme inhibitor; ARA = aldosterone receptor antagonist; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; BB = beta-blocker; HF = heart failure; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; MRA = mineralocorticoid receptor antagonist.

ACE-I plus a beta-blocker plus a mineralocorticoid antagonist (MRA) was associated with a 56% reduction in mortality versus placebo [HR 0.44, 95% credible interval (CrI) 0.26–0.66], and an angiotensin receptor/neprilysin inhibitor (ARNI) plus a beta-blocker plus an MRA was associated with a 63% reduction in all-cause mortality versus placebo (HR 0.37, 95% CrI 0.19–0.65; Fig. 7B) [58].

A recent sensitivity analysis of nine RCTs with a high background use of an ACE-I and/or an ARB (>80%) indicated that adding an aldosterone receptor antagonist (ARA) to current standard therapy substantially reduced mortality by 27% (OR 0.73, 95% CrI 0.51–0.95) and hospitalization risk by 33% (OR 0.67, 95% CrI 0.47–0.87), and did not significantly increase the discontinuation risk (OR 1.29, 95% CrI 0.83–2.31) [59].

Beta-blockers have been the backbone of HF treatment because of their ability to reverse the neurohumoral effects of the sympathetic nervous system, with prognostic and symptomatic benefits. A meta-analysis of 21 clinical trials including 23,122 patients treated with beta-blockers (focusing on atenolol, bisoprolol, bucindolol, carvedilol, metoprolol, and nebivolol) reported that beta-blockers reduced the risk of mortality compared with placebo or standard treatment after a median of 12 months of treatment (OR 0.69, 95% CrI 0.56–0.80) [60]. When comparing the different beta-blockers for risk of death, sudden cardiac death, death due to pump failure, or drug discontinuation, no differences were found [60]. Improvements in LVEF were also similar irrespective of the individual study drug, indicative of a class effect [60]. A more recent meta-analysis of 11 trials including 13,833 patients (aged 40–85 years, of whom 24% were women) found that beta-blockers were effective in reducing mortality across all ages: the absolute reduction in mortality was 4.3% over a median follow-up of 1.3 years (number needed to treat 23) [61]. The rate of drug discontinuation was found to be similar irrespective of treatment allocation, age, or sex, with 14.4% discontinuations in patients on beta-blockers and 15.6% in those receiving placebo [61].

7.1.2. Angiotensin receptor/neprilysin inhibitors

In the landmark PARADIGM-HF trials, sacubitril/valsartan, a first-in-class ARNI, was reported to be superior to enalapril in reducing the risk of death from cardiovascular causes or first hospitalization for HF (HR 0.80, 95% CI 0.73–0.87; $p < 0.001$), risk of death from cardiovascular

causes (HR 0.80, 95% CI 0.71–0.89; $p < 0.001$), and risk of hospitalization for HF (HR 0.79, 95% CI 0.71–0.89; $p < 0.001$) [55]. Furthermore, sacubitril/valsartan was more beneficial than enalapril across all age categories (<55, 55–64, 65–74, and ≥ 75 years) in terms of benefit–risk profile. Treatment withdrawal due to intolerance was uncommon, even in elderly individuals [62]. Sacubitril/valsartan also led to significant treatment for outpatient worsening (HR 0.84, 95% CI 0.74–0.94; $p = 0.003$), emergency department visits for HF (HR 0.66, 95% CI 0.52–0.85; $p < 0.001$), cardiovascular hospitalization (HR 0.88, 95% CI 0.81–0.95; $p < 0.001$), all-cause hospitalization (HR 0.88, 95% CI 0.82–0.94; $p < 0.001$), and intensive care unit (ICU) admission (HR 0.87, 95% CI 0.78–0.98; $p = 0.019$) [63]. In addition, it is important to note that not all patients in the PARADIGM trial were on MRA.

RAAS blockers are effective therapies for patients with HF and reduced EF or LV dysfunction [59]. A recent meta-analysis of 21 double-blind RCTs including 69,229 patients reported that, compared with placebo, an ARNI had the highest probability of reducing all-cause mortality (OR 0.67, 95% CrI 0.48–0.86), followed by an ARA (OR 0.74, 95% CrI 0.62–0.88) and an ACE-I (OR 0.80, 95% CrI 0.71–0.89) [59]. An ARNI was found to be the most efficacious therapy for preventing HF hospitalization (OR 0.55, 95% CrI 0.40–0.71), followed by an ARB plus an ACE-I (OR 0.61, 95% CrI 0.49–0.75) and an ACE-I alone (OR 0.69, 95% CrI 0.61–0.77) [59]. Therefore, it was concluded that ARNI has the highest probability of being the most efficacious therapy for HF with reduced EF in reducing death and hospitalization for HF.

7.1.3. I_f channel inhibitor

A high resting heart rate (≥ 70 –75 bpm) is a sign of sympathetic hyperactivity and/or reduced parasympathetic tone, and has several detrimental consequences including the acceleration of coronary atherosclerosis, plaque rupture, subclinical inflammation, reactive oxygen species generation, myocardial ischemia, induction of left ventricular dysfunction, and life-threatening arrhythmias [64].

The BEAUTIFUL study, which assessed the effect of ivabradine in patients with stable CAD and left ventricular systolic dysfunction in 10,917 patients (5479 ivabradine, 5438 placebo), reported that although ivabradine reduced heart rate by 6 bpm at 12 months, it did not improve cardiac outcomes (HR 1.00, 95% CI 0.91–1.1; $p = 0.94$) [65]. In a subgroup analysis of patients on placebo

(2693 had ≥ 70 bpm, 2745 had < 70 bpm), it was found that for every increase of 5 bpm, there were significant increases in cardiovascular death (8%; $p = 0.0005$), hospital admissions for HF (16%; $p < 0.0001$), admission to hospital for MI (7%; $p = 0.052$), and coronary revascularization (8%; $p = 0.034$) [66].

Contrary to the findings of the BEAUTIFUL study, the SHIFT trial, which randomized 3268 patients to ivabradine and 3290 patients to placebo, reported a significant risk reduction of 18% (HR 0.82, 95% CI 0.75–0.90; $p < 0.0001$) in the composite primary endpoint (cardiovascular death or hospital admission for worsening HF) in those on ivabradine versus placebo [67]. These effects were mainly due to reduced hospital admissions for worsening HF (21% vs. 16%, HR 0.74, 95% CI 0.66–0.83; $p < 0.0001$) and reduced deaths due to HF (5% vs. 3%, HR 0.74, 95% CI 0.58–0.94; $p = 0.014$) [67]. Analysis of cardiovascular outcomes revealed that the risk of primary composite endpoint events increased by 3% with every beat increase from baseline heart rate, and 16% for every 5 bpm increase [68]. In the ivabradine group, the heart rate achieved at 28 days on treatment was directly associated with cardiac outcome [68]. Patients with heart rates lower than 60 bpm after 28 days on treatment had fewer primary composite endpoint events during the study ($n = 1192$, event rate 17.4%, 95% CI 15.3–19.6) than patients with higher heart rates [68].

Similar to the SHIFT trial, the INTENSIFY study reported that after 4 months of treatment with ivabradine, heart rate was reduced to 67 ± 8.9 bpm from 85 ± 11.8 bpm at baseline [69]. In addition, the proportion of patients with signs of decompensation reduced from 22.7% to 5.4%, and the proportion of BNP levels > 400 pg/mL reduced from 53.9% to 26.7% [69]. These benefits were also accompanied by improved QoL and good general tolerability [69].

7.1.4. Mineralocorticoid antagonists

MRAs have been shown to reduce mortality and morbidity in patients with mild-to-severe HF with reduced LVEF, however, their use is limited as they cause hyperkalemia [70]. An analysis of the EMPHASIS-HF study showed that in patients with chronic HFrEF, in NYHA functional Class II and meeting specific inclusion and exclusion criteria (including an estimated glomerular filtration rate > 30 mL/min/1.73 m² and potassium < 5.0 mmol/L), eplerenone was both efficacious and safe when carefully monitored, even in

subgroups with a high risk of developing hyperkalemia or worsening renal function [71].

By contrast, it was still unclear whether elevations in potassium reduced the clinical benefit of MRAs in patients with severe HF. Therefore, the RALES study assessed the incidence and predictors of hyperkalemia (potassium ≥ 5.5 mmol/L) and hypokalemia (potassium < 3.5 mmol/L), and hypothesized that hyperkalemia would not modify the efficacy of spironolactone (25 mg) in 1663 patients with severe HF [70].

The RALES study revealed that 1 month after initiating treatment, mean potassium levels increased in the spironolactone group but not in the placebo group (4.54 ± 0.49 vs. 4.28 ± 0.50 mmol/L; $p < 0.001$), and remained elevated during the trial. Participants randomized to spironolactone had a higher risk of hyperkalemia and a lower risk of hypokalemia compared with those randomized to placebo [70]. Furthermore, those attaining a spironolactone dose of 25 mg had a 13.5% risk of hyperkalemia and those reaching a dose of 50 mg had a 41.4% risk of hyperkalemia, with no difference noted in mortality rates [70]. Compared with placebo, mortality rates were highest in patients with the lowest (< 3.5 mmol/L) and highest (> 6.0 mmol/L) 4-week potassium values [70]. In general, mortality rates were higher in participants randomized to placebo compared with those taking spironolactone, at all potassium levels ($p < 0.0001$) [70]. The treatment benefit of spironolactone was maintained when potassium levels exceeded 5.5 mmol/L, although this benefit lost statistical significance as potassium value neared 6.0 mmol/L [70].

7.1.5. Diuretics

Diuretics are regarded as the first-line treatment for patients with CHF because they provide symptomatic relief. A Cochrane review of 14 trials (7 placebo controlled, 7 active controlled) including 525 patients reported that mortality was lower for patients receiving diuretics compared with placebo (OR 0.24, 95% CI 0.07–0.83; $p = 0.02$), and admission for worsening HF was reported to be lower in two trials (OR 0.07, 95% CI 0.01–0.52; $p = 0.01$) [72]. Diuretics were found to improve exercise capacity compared with active comparators [weighted mean difference (MD) 0.72, 95% CI 0.40–1.04; $p < 0.0001$] in four of the trials [72].

Diuretics are particularly effective in ameliorating clinical signs and symptoms of HF, especially systemic and pulmonary congestion [73]. Although diuretics are the most commonly

prescribed drugs for HF management, there is little quality evidence to guide their use [73]. In addition, observation data suggest that diuretics may be harmful and contribute to neurohormonal activation, renal dysfunction, and ultimately, mortality [73]. Despite these concerns, diuretics are the mainstay of HF management: the main classes include loop diuretics, potassium-sparing diuretics, and thiazides [73]. It is important that electrolytes and renal function are carefully monitored during diuretic therapy [73]. Furthermore, fluid overload refractory to loop diuretics can complicate HF patient management, and the CLOROTIC trial, which is the first large-scale trial to evaluate the safety and efficacy of the addition of a thiazide diuretic to a loop diuretic for improving congestive symptoms resulting from HF, may provide important information on treatment strategy in such patients [74].

7.1.6. Combination of hydralazine and isosorbide dinitrate

The V-Heft I trial evaluated the combination of hydralazine and isosorbide dinitrate in 642 men over a 5-year period versus placebo with prazosin [75]. It was found that peak oxygen consumption (VO_2) significantly increased at 2 months ($p < 0.16$) and was sustained up to 1 year ($p < 0.04$) with hydralazine and isosorbide dinitrate compared with placebo [75]. In the V-Heft II trial, hydralazine and isosorbide dinitrate significantly increased peak VO_2 compared with enalapril ($p < 0.01$ at 3 months; $p < 0.02$ at 6 months and 2 years) [75]. The authors concluded that long-term data were confounded by mortality and other events, which may have led to the benefits of hydralazine and isosorbide dinitrate over placebo, and enalapril on exercise performance, being underestimated. Overall, the authors concluded that short-term improvement in exercise performance is a suitable therapeutic endpoint. In addition, an RCT conducted in self-identified patients of African descent found that the addition of hydralazine and isosorbide dinitrate reduced mortality and HF hospitalization in patients with HFrEF (NYHA Class III–IV), compared with conventional therapy (ACE-Is, beta-blockers, and MRAs) [76]. It is difficult to translate data from this study to patients of other racial and ethnic origins, so the combination of hydralazine and isosorbide dinitrate should be considered in symptomatic patients with HFrEF who can tolerate neither ACE-Is nor ARBs to reduce mortality [3].

7.1.7. Digoxin

Observational studies report conflicting results on the association of digoxin with mortality in patients with HF. In the ENGAGE AF TIMI 48 trial, in patients with AF and HF ($n = 12,124$), digoxin use was associated with a 37% increased risk of all-cause death, cardiovascular death, sudden cardiac death, and death caused by HF/cardiogenic shock ($p < 0.01$ for each) [77]. Given that there is strong evidence suggesting an association

Table 12. Recommended target doses of disease-modifying agents and diuretics for HF.

Disease-modifying agents	Target doses (mg)
<i>ACE-Is</i>	
Captopril	50 t.i.d.
Enalapril	20 b.i.d.
Lisinopril	20–40 o.d.
Ramipril	10 o.d.
Trandolapril	4 o.d.
<i>Beta-blockers</i>	
Bisoprolol	10 o.d.
Carvedilol	25 b.i.d.
Metoprolol succinate	200 o.d.
Nebivolol	10 o.d.
<i>ARBs</i>	
Candesartan	32 o.d.
Valsartan	160 b.i.d.
Losartan	150 o.d.
<i>Mineralocorticoid antagonist</i>	
Eplerenone	50 o.d.
Spirolactone	50 o.d.
<i>Angiotensin receptor/neprilysin inhibitor</i>	
Sacubitril/valsartan	97/103 b.i.d.
<i>I_f channel blocker</i>	
Ivabradine	7.5 b.i.d.
Diuretic	Usual daily doses (mg)
<i>Loop diuretics</i>	
Furosemide	40–240
Bumetanide	1–5
Torsemide	10–20
<i>Thiazides</i>	
Hydrochlorothiazide	12.5–100
Metolazone	2.5–10
Indapamide	2.5–5
<i>Potassium-sparing diuretics +ACE-I/ARB</i>	
Spirolactone/eplerenone	50
Amiloride	5–10
Triamterene	100
<i>–ACE-I/ARB</i>	
Spirolactone/eplerenone	100–200
Amiloride	10–20
Triamterene	200

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HF = heart failure; b.i.d. = twice daily; mg = milligrams; o.d. = once daily; t.i.d. = thrice daily.

of serum concentration of digoxin with its safety and efficacy, it is necessary to achieve low serum digoxin concentrations (0.5–0.9 ng/mL) to optimize therapeutic benefit and avoid harm [78].

Recommended target doses of key agents used for managing patients with HF are outlined in Table 12.

8. Nonsurgical device treatment of HFrEF (Tables 13, 14)

8.1. Implantable cardioverter defibrillator

Patients who survive an out-of-hospital cardiac arrest or symptomatic sustained ventricular tachycardia are at considerable risk of recurrence of these arrhythmias and of death [79], and ICDs play a major role in the prevention of sudden cardiac death [80]. An ICD leads to a 28% reduction in RR of death, which is primarily due to a 50% reduction in arrhythmic death [79]. Patients with an LVEF $\leq 35\%$ were reported to derive significantly more benefit from ICD therapy than those with a better preserved LV function, as per a meta-analysis of three RCTs (AVID, CASH, and CIDS). Based on a subanalysis of secondary prevention trials of ICDs, patients treated with an ICD in the AVID study had a maximal survival benefit when the EF was 20–34%, compared with amiodarone [81]. Greater survival benefit (50%

reduction in risk of mortality) was observed in the higher-risk group, described as those older than 70 years, EF $< 35\%$, and NYHA Class III–IV, in the CIDS study [81]. Of note, in the AVID study, the recurrence of arrhythmia was 64% after 3 years in patients with the ICD [81]. Similar results were reported by the Sudden Cardiac Death in Heart Failure Trial, where patients with NYHA Class II or III CHF and an LVEF $\leq 35\%$ did not experience a favorable effect on survival with amiodarone, but shock-only ICD therapy was found to reduce overall mortality by 23% [82].

A combined analysis of four RCTs found that the unadjusted HR of death for patients with an ICD versus those without was significantly lower, especially in patients with two or more comorbidities (HR 0.71, 95% CI 0.61–0.84) compared with patients with less than two comorbidities (HR 0.59, 95% CI 0.40–0.87) [80]. In addition, after adjustment, increasing comorbidity was associated with decreasing treatment benefit from an ICD ($p = 0.004$) [80]. A recent pooled analysis of five major ICD trials reported that the survival benefit of an ICD is attenuated with increasing age: HR 0.48 (95% posterior CrI 0.33–0.69) in patients aged < 55 years, HR 0.69 (95% posterior CrI 0.53–0.90) in patients aged 55–64 years, HR 0.67 (95% posterior CrI 0.53–0.85) in patients aged 65–74 years, and HR 0.54 (95% posterior CrI 0.37–0.78) in patients aged ≥ 75 years [83]. This may be

Table 13. Recommendations for implantable cardioverter defibrillators in patients with HF.

No.	Recommendations
1	Secondary prevention – An ICD implantation is recommended in patients who have recovered from VT/VF arrest, in the absence of a reversible cause – An ICD implantation should be considered for secondary prevention in patients with a structurally abnormal heart and documented sustained VT (not within 48 hours after MI) in the absence of a reversible cause
2	Primary prevention – An ICD implantation is recommended to reduce the risk of sudden cardiac death in patients with symptomatic ischemic cardiomyopathy and an LVEF $\leq 35\%$ despite ≥ 3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status
3	Primary prevention ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis
4	ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation
5	An ICD implantation may be considered to reduce the risk of sudden cardiac death in selected patients with symptomatic non-ischemic cardiomyopathy and an LVEF $\leq 35\%$ despite ≥ 3 months of OMT
6	Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed
7	A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to a final device decision

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with preserved ejection fraction; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; OMT = optimal medical therapy; VT/VF = ventricular tachycardia/ventricular fibrillation.

Table 14. Recommendations for cardiac resynchronization therapy implantation in patients with HF.

No.	Recommendations
8	CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥ 130 ms and LBBB QRS morphology and with an LVEF $\leq 35\%$ despite OMT, to improve symptoms and reduce morbidity and mortality
9	CRT rather than RV pacing is recommended for patients with an EF $< 50\%$, regardless of NYHA class, who have an indication for ventricular pacing and high-degree atrioventricular (AV) block, to reduce morbidity. This includes patients with AF
10	CRT should be considered for patients with LBBB QRS morphology and an LVEF $\leq 35\%$ in NYHA Class III–IV despite OMT, to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥ 130 ms, provided a strategy to ensure biventricular capture is in place or the patient is expected to return to sinus rhythm
11	AV nodal ablation may be considered if patients do not have adequate biventricular pacing and continues to be in AF, to optimize response
	Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT, and who have a high proportion of RV pacing, may be considered for upgrade to CRT. This does not apply to patients with stable HF

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AF = atrial fibrillation; CRT = cardiac resynchronization therapy; EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; RV = right ventricle.

due to a higher burden of comorbid illness, competing causes of death, or the limited sample size of patients [83]. Furthermore, no evidence was found that age influenced the likelihood of rehospitalization after ICD placement [83]. In addition, a meta-analysis reported that ICD-only therapy provided survival benefit (arrhythmic mortality RR 0.40, 95% CI 0.27–0.67; and all-cause mortality RR 0.73, 95% CI 0.64–0.82) in patients with ischemic or non-ischemic heart disease, with an LVEF $\leq 35\%$, 40 days from MI, and ≤ 3 months from CRT [84].

Although ICDs are considered effective in primary and secondary prevention of sudden cardiac death, they are expensive. A systematic review of cost-effectiveness that analyzed data from 34 studies showed that ICDs may be a cost-effective option in patients at high risk of sudden cardiac death in comparison with conventional treatments [85]. Several factors influence the cost-effectiveness of ICDs, including device implantation cost, frequency and cost of battery replacement, and patient demographics and risk profile. These warrant the need for continuous research to ensure the cost-effective use of ICD therapy [85].

8.2. Cardiac resynchronization therapy

An individual patient meta-analysis of five RCTs comparing CRT with no active device or with a defibrillator showed that QRS duration (QRSD) was a powerful predictor of the effects of CRT on morbidity and mortality in patients with symptomatic HF and LV systolic dysfunction who are in sinus rhythm [86]. A QRSD that exceeds 140 ms was determined to lead to substantial survival

benefit from CRT. QRS morphology did not provide additional information about clinical response [86].

The REVERSE trial found that, after 24 months of CRT, LV end-systolic volume index (LVESVI) decreased by a mean of 27.5 ± 31.8 mL/m² versus 2.7 ± 25.8 mL/m² in patients not on CRT ($p < 0.0001$) [86]. Time to hospital stay or death was also delayed significantly by CRT (HR 0.38; $p = 0.003$), suggesting that CRT prevents the progression of disease in patients with asymptomatic or mildly symptomatic LV dysfunction [87]. In a subgroup analysis, patients with an LVEF $> 30\%$ on CRT showed significant reductions in LVESVI (-6.7 ± 21.1 vs. 2.1 ± 17.6 mL/m²; $p = 0.01$) and LV mass (-20.6 ± 50.5 vs. 5.0 ± 42.4 g; $p = 0.04$) after 12 months, in comparison with patients not on CRT, and a trend of improvement in clinical composite response with CRT ($p = 0.06$) [88]. It was also demonstrated that left bundle branch block (LBBB) and QRS prolongation were markers of reverse remodeling and clinical benefit with CRT in mild HF [89]. In addition, long-term follow-up revealed that CRT was associated with a 68% reduction in mortality in patients with $\geq 15\%$ decrease in LVESVI [90]. Multivariate analysis showed that a change in LVESVI was a strong independent predictor of mortality ($p = 0.0002$), with a 14% reduction in mortality for every 10% decrease in LVESVI [90]. Longer QRSD, smaller LVESVI, CRT defibrillator (CRT-D) recipients, and women were associated with better survival [90]. Overall, it can be concluded that CRT in addition to optimal medical therapy produces long-standing clinical benefits in mild HF [91].

In patients at increased risk of arrhythmia-related sudden death and HF, placement of an ICD has been shown to improve survival and reduce risk of sudden death in appropriately selected patients [92]. However, an ICD is associated with an increased risk of first and recurrent HF events. CRT with biventricular pacing may be an effective adjunctive therapy to pharmacologic management in reducing the rates of hospitalizations in patients with NYHA Class III–IV symptoms, an EF $\leq 35\%$, and intraventricular conduction delay of ≥ 120 ms [92].

In the MADIT-CRT trial, during an average follow-up of 2.4 years, the primary endpoint of death from any cause or a nonfatal HF event occurred in 17.2% in the CRT-ICD group and 25.3% in the ICD-only group (HR 0.66, 95% CI 0.52–0.84; $p = 0.001$ for the CRT-ICD group) [92]. However, no difference in the overall risk of death was observed between treatment groups. In a subgroup of patients with a QRSD of ≥ 150 ms, CRT use was associated with a 41% reduction in the risk of HF events [92]. A multivariate analysis showed that CRT-D was associated with significant reduction in the risk of the first HF event (HR 0.54, 95% CI 0.44–0.67; $p < 0.001$) and subsequent events (HR 0.62, 95% CI 0.45–0.85; $p = 0.003$) [93]. Prevention of HF events was found to be pronounced among patients with LBBB for first (HR 0.38, 95% CI 0.29–0.49; $p < 0.001$) and subsequent (HR 0.50, 95% CI 0.33–0.76; $p < 0.001$) events [93]. Overall, sevenfold and 19-fold increases in risk of mortality were reported to be associated with first and second HF events, respectively [93]. Long-term follow-up (7 years) indicated that in patients with mild HF symptoms, LV dysfunction, and LBBB, early intervention with a CRT-D was associated with a significant long-term survival benefit [94]. Of note, the clinical benefit of a CRT-D was not attenuated in patients with LBBB with a history of intermittent atrial tachyarrhythmias or by development of in-trial atrial tachyarrhythmias [95].

Although the MADIT-CRT trial did not show a difference in survival benefit between patients with ischemic or non-ischemic cardiomyopathy [92], a recent meta-analysis of 19 studies including 12,378 patients reported that survival benefit appears to be more pronounced in patients with ischemic cardiomyopathy (HR 0.70, 95% CI 0.59–0.83; $p < 0.001$, $I^2 = 0\%$) compared with non-ischemic cardiomyopathy (HR 0.79, 95% CI 0.61–1.02; $p = 0.07$, $I^2 = 36\%$) [96]. Although the majority of patients treated with CRT had LBBB morphology (QRS < 150 ms), its role in non-LBBB

morphology (QRSD ≥ 150 ms) is unclear, with evidence often indicating that CRT should be discouraged in the non-LBBB setting due to lack of benefit [97]. This is clearly shown by a recent study of 973 patients with HF treated with CRT in which LBBB morphology was significantly associated with better survival (HR 0.737, 95% CI 0.584–0.93; $p = 0.010$), whereas there was no statistically significant association between non-LBBB morphology and survival (HR 0.889, 95% CI 0.726–1.088; $p = 0.252$) [98]. Therefore, the authors concluded that QRS morphology was independently associated with long-term survival in patients with HF treated with CRT.

In addition, an economic analysis revealed that in patients with an LVEF $\leq 30\%$, QRSD of ≥ 120 ms, and NYHA Class II symptoms, CRT-D is a more cost-effective alternative to ICD alone in terms of survival benefit [99].

A recent study examining outcomes in 24,960 patients reported a greater survival benefit with CRT-D versus standard ICD in patients with LBBB and QRSD ≥ 180 ms (HR 0.65, 95% CI 0.59–0.72) than in those with QRSD of 120–149 ms (HR 0.85, 95% CI 0.80–0.92) and QRSD of 150–179 ms (HR 0.87, 95% CI 0.81–0.93) [100]. Compared with standard ICD, CRT-D was found to reduce the risk of death by 22% in patients with an LBBB and QRSD ≥ 180 ms (HR 0.78, 95% CI 0.68–0.91), but not in those with an LBBB and QRSD of 150–179 ms (adjusted HR 1.06, 95% CI 0.95–1.19) [100].

9. Treatment of HFpEF (Table 15)

HF with preserved EF is a complex clinical syndrome that comprises approximately half of all patients with HF [101]. The leading cause of death in patients with HFpEF is non-cardiovascular [102]. Guidelines for the treatment and diagnosis of HFpEF are lacking and complicated by the heterogeneous population: multiple comorbidities, race, age, and etiology. Longitudinal studies on this patient population are required for the design of adequate interventional therapies [103]. Health-related quality of life (HRQoL) in symptomatic patients with HF is equally impaired in preserved and low LVEF populations and therefore remains an important treatment target in patients with HFpEF [104]. A meta-analysis of five RCTs involving 245 patients with HFpEF showed that exercise training improved peak exercise oxygen uptake (VO_2 ; weighted MD 2.283, 95% CI 1.318–3.248, mL/min/kg), 6-minute walk distance (30.275 m, 95% CI 4.315–56.234), and Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score

Table 15. Recommendations for treatment of HFpEF.

No.	Recommendations
1	It is recommended to screen patients with HFpEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated, provided safe and effective interventions exist to improve symptoms, well-being, and/or prognosis
2	Diuretics are recommended in congested patients with HFpEF to alleviate symptoms and signs

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

HFpEF = heart failure with preserved ejection fraction.

(8.974 points, 95% CI 3.321–14.627) compared with usual care [105].

Although several large-scale trials in HFpEF have not met their primary outcome (often mortality), several drugs do improve QoL and exercise capacity, and reduce HF hospitalizations, which are more meaningful outcomes for elderly and debilitated patients with HFpEF compared with reduced mortality [101]. HFpEF, being a heterogeneous syndrome, requires a nuanced, phenotype-specific patient management approach, rather than a one-size-fits-all approach [101].

Evidence supporting the role of diuretics in HF was presented in a meta-analysis of RCTs which showed that treatment with diuretics improved mortality rates, hospitalization rates, and exercise capacity in patients with congestive HF [106]. ACE inhibitors (perindopril 4 mg/day) have been shown to reduce HF hospitalizations and improve symptoms and exercise capacity [101]. Because ACE-Is are indicated for several comorbidities (diabetes, hypertension and chronic kidney disease), they are widely used in patients with HFpEF [101]. The effect of ARBs have been evaluated in two large RCTs, CHARM-Preserved and I-PRESERVE, which have shown that both candesartan and irbesartan reduce overall HF hospitalization and may be useful in less-severe HFpEF and in patients with lower levels of natriuretic peptides [101]. MRAs were shown to consistently improve cardiac structure and function in patients with HFpEF, but not exercise capacity in the ALDO-DHF trial [101]. Although the TOPCAT trial showed similar results, it also found that patients in the lowest tertile of natriuretic peptides were the ones who benefited most from spironolactone [101]. Beta-blockers are commonly used in HFpEF and are the only class of drugs shown to have a potential mortality benefit in patients with HFpEF [107,108]. A meta-analysis by Bavishi et al. [108] of 15 observational studies and two RCTs including 27,099 patients found that in the observational studies, beta-blocker therapy reduced all-cause mortality by 19% (RR 0.81, 95% CI 0.72–0.90;

$p < 0.001$), but not HF hospitalization (RR 0.79, 95% CI 0.57–1.10; $p < 0.001$). Based on data from the two RCTs, beta-blockers were not associated with reductions in all-cause mortality or HF hospitalization. It is important to note that beta-blocker survival benefit is limited to studies with a mean age <75 years [108]. A more recent meta-analysis reported that overall, beta-blockers reduced the risk of mortality by 21% (RR 0.79, 95% CI 0.71–0.88). This reduced risk of mortality was reflected through pooled analysis of six observational cohort studies (15,275 patients), and not in a pooled analysis of three RCTs (1046 patients) [107]. However, there is a need for well-designed and powered studies to confirm the survival benefit reported in observational studies.

10. Arrhythmias and conduction disturbances (Tables 16–20)

10.1. Rate control

Electrical cardioversion can help reduce the risk of stroke, improve cardiovascular hemodynamics, and preclude the need for long-term anticoagulation, by restoring sinus rhythm. A Cochrane-based systematic review evaluated the use of electrical cardioversion versus rate control in 927 participants across four trials (Hot Cafe, RACE, STAF, and J-RHYTHM), and showed that electrical cardioversion helped to significantly improve physical functioning, physical role function, and vitality compared with rate control [109]. An intravenous bolus of amiodarone can immediately control heart rate in patients with AF and a high ventricular rate [110,111]. RCTs investigating the rates of mortality and morbidity of digoxin in patients with AF are not available. Retrospective analyses of various trials, including AFFIRM, RACE II, and ROCKET-AF, have provided conflicting results regarding the impact of digoxin on mortality in patients with AF [112] and therefore should be interpreted with caution.

Table 16. Recommendations for the initial management of a rapid ventricular rate in patients with HF and AF in the acute or chronic setting.

No.	Recommendations
1	Urgent electrical cardioversion is recommended if AF is thought to be contributing to the patient’s hemodynamic compromise to improve the patient’s clinical condition
2	For patients with rapid AF in NYHA Class IV, in addition to treatment for AHF, an intravenous bolus of amiodarone or, in digoxin-naïve patients, an intravenous bolus of digoxin should be considered to reduce the ventricular rate
3	For patients in NYHA Class I–III, a beta-blocker, usually given orally, is safe and therefore is recommended as first-line treatment to control ventricular rate, provided the patient is euvolemic
4	For patients in NYHA Class I–III, digoxin should be considered when ventricular rate remains high despite beta-blockers or when beta-blockers are not tolerated or contraindicated
5	AV node catheter ablation may be considered to control heart rate and relieve symptoms in patients who are unresponsive or intolerant to intensive pharmacological rate and rhythm control therapy, accepting that these patients will become pacemaker dependent
6	Treatment with dronedarone to improve ventricular rate control is not recommended due to safety concerns

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AF = atrial fibrillation; AHF = acute heart failure; AV = atrioventricular; HF = heart failure; NYHA = New York Heart Association.

Table 17. Recommendations for rhythm control management strategy in patients with atrial fibrillation, symptomatic heart failure (NYHA Class II–IV), left ventricular systolic dysfunction, and no evidence of acute decompensation.

No.	Recommendations
7	Electrical cardioversion or pharmacological cardioversion with amiodarone may be considered in patients with persisting symptoms and/or signs of HF, despite OMT and adequate control of ventricular rate, to improve clinical/symptomatic status
8	AF ablation may be considered to restore sinus rhythm in patients with persisting symptoms and/or signs of HF, despite OMT and adequate control of ventricular rate, to improve clinical/symptomatic status
9	Amiodarone may be considered prior to, and following, successful electrical cardioversion to maintain sinus rhythm
10	Dronedarone is not recommended because of an increased risk of hospital admissions for cardiovascular causes and an increased risk of premature death in NYHA Class III–IV patients
11	Class I antiarrhythmic agents are not recommended because of an increased risk of sudden death

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AF = atrial fibrillation; HF = heart failure; NYHA = New York Heart Association; OMT = optimal medical therapy.

Table 18. Recommendations for the prevention of thromboembolism in patients with symptomatic heart failure (NYHA Class II–IV) and paroxysmal or persistent/permanent atrial fibrillation.

No.	Recommendations
12	The CHA ₂ DS ₂ -VASc and HAS-BLED scores are recommended tools in patients with HF for the estimation of the risk of thromboembolism and the risk of bleeding associated with oral anticoagulation, respectively
13	An oral anticoagulant is recommended to prevent thromboembolism for all patients with paroxysmal or persistent/permanent AF and a CHA ₂ DS ₂ -VASc score ≥ 2 , without contraindications, and irrespective of whether a rate or rhythm management strategy is used (including after successful cardioversion)
14	An oral anticoagulant may be considered to prevent thromboembolism for all patients with paroxysmal or persistent/permanent AF and a CHA ₂ DS ₂ -VASc score ≥ 1 , without contraindications, and irrespective of whether a rate or rhythm management strategy is used (including after successful cardioversion)
15	NOAC treatment is contraindicated in patients with mechanical valves or at least moderate or severe mitral stenosis.
16	In patients with AF of ≥ 48 h duration, or when the duration of AF is unknown, an oral anticoagulant is recommended at a therapeutic dose for ≥ 3 weeks prior to electrical or pharmacological cardioversion
17	Intravenous heparin or LMWH and TOE-guided strategy is recommended for patients who have not been treated with an anticoagulant dose for ≥ 3 weeks and require urgent electrical or pharmacological cardioversion for a life-threatening arrhythmia
18	For patients with HF and non-valvular AF eligible for an anticoagulant, based on a CHA ₂ DS ₂ -VASc score, NOACs rather than warfarin should be considered as NOACs are associated with a lower risk of stroke, intracranial hemorrhage, and mortality, which outweigh the increased risk of gastrointestinal hemorrhage

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AF = atrial fibrillation; HF = heart failure; LMWH = low-molecular-weight heparin; NOAC = non-vitamin oral anticoagulant; NYHA = New York Heart Association; TOE = transesophageal echocardiograph.

Table 19. Recommendations for the management of VT in HF.

No.	Recommendations
19	Potential aggravating/precipitating factors (e.g., low serum potassium/magnesium, ongoing ischemia) should be sought and corrected in patients with ventricular arrhythmias
20	Treatment with a beta-blocker, MRA, and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias
21	Implantation of an ICD or CRT-D device is recommended for selected patients with HFrEF
22	Several strategies should be considered to reduce recurrent symptomatic arrhythmias in patients with an ICD (or in those who are not eligible for an ICD), including attention to risk factors and optimal pharmacological treatment of HF, amiodarone, catheter ablation, and CRT
23	Routine use of antiarrhythmic agents (except beta-blockers) is not recommended in patients with HF and asymptomatic non-ventricular arrhythmias because of safety concerns (worsening HF, proarrhythmia, and death)

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy defibrillator; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator; MRA = mineralocorticoid antagonist; VT = ventricular tachycardia.

Table 20. Recommendations for the management of bradyarrhythmias in heart failure.

No.	Recommendations
24	When pauses >3 seconds are identified on the ECG, or if the bradycardia is symptomatic and the resting ventricular rate is <50 bpm in sinus rhythm or <60 bpm in AF, it should be considered whether there is need for any rate-limiting medications prescribed; for patients in sinus rhythm, beta-blockers should be reduced in dose or withdrawn only as a last resort
25	For patients with symptomatic, prolonged or frequent pauses despite adjustment of rate-limiting medication, either beta-blocker withdrawal or pacing may be considered as the next step
26	Pacing solely to permit initiation or titration of beta-blocker therapy in the absence of a conventional pacing indication is not recommended
27	In patients with HFrEF who require pacing and who have high-degree AV block, CRT rather than RV pacing is recommended
28	In patients with HFrEF who require pacing and who do not have high-degree AV block, pacing modes that avoid inducing or exacerbating ventricular dyssynchrony should be considered

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AF = atrial fibrillation; AV = atrioventricular; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; HFrEF = heart failure with reduced ejection fraction; RV = right ventricle.

If the patient remains symptomatic despite pharmacological treatment, or suffers drug-related adverse effects, then atrioventricular (AV) node catheter ablation may be considered, however, this procedure renders the patient pacemaker dependent [113]. Because of safety concerns, dronedarone is not recommended in patients with HF or AF. A study enrolling 3236 patients with permanent AF and at risk for major vascular events showed that patients receiving dronedarone had increased incidences of mortality (HR 2.11, 95% CI 1.00–4.49; $p = 0.046$), stroke (HR 2.32, 95% CI 1.11–4.88; $p = 0.02$), and hospitalization for HF (HR 1.81, 95% CI 1.10–2.99; $p = 0.02$) compared with the placebo group [114]. A separate study similarly showed increased early mortality related to worsening HF in dronedarone-treated patients with severe HF and left ventricular systolic dysfunction [115].

10.2. Rhythm control

The CHF-STAT study involving 103 congestive patients with HF showed that amiodarone has a significant potential to spontaneously convert patients in AF to sinus rhythm, prevent new-onset AF, and significantly reduce the VR in patients with persistent AF [116]. A meta-analysis of 11 studies with 1481 patients showed superiority of catheter ablation over antiarrhythmic drug therapy in the maintenance of sinus rhythm in drug naïve, resistant, and intolerant patients with AF [117]. A separate meta-analysis comprising 21,305 patients across 59 studies showed that although several Class IA, IC, and III antiarrhythmic drugs were moderately effective in maintaining sinus rhythm after conversion of AF, they were associated with an increase in adverse events and, in a select few, mortality [118].

10.3. Prevention of thromboembolism

According to the nationwide prospective cohort study using Danish registries that included 42,987 patients (21.9% with concomitant AF) not receiving anticoagulation and diagnosed with HF, a high CHA2DS2-VASc score was associated with increased risk of ischemic stroke, thromboembolism, and death. Risks were greater with increasing CHA2DS2-VASc scores as follows: for scores of 1 through 6, respectively: ischemic stroke: 4.5%, 3.7%, 3.2%, 4.3%, 5.6%, and 8.4%; all-cause death: 19.8%, 19.5%, 26.1%, 35.1%, 37.7%, and 45.5%. At high CHA2DS2-VASc scores (≥ 4), the absolute risk of thromboembolism was high regardless of presence of AF (for a score of 4, 9.7% vs. 8.2% for patients without and with concomitant AF, respectively; overall $p < 0.001$ for interaction). However, the clinical value of the CHA2DS2-VASc score remains to be determined in patients with HF [119]. A meta-analysis involving 11 studies showed that HAS-BLED had superior performance compared with HEMORR2 HAGES and ATRIA for bleeding scores and with CHADS2 and CHA2DS2-VASc scores for bleeding prediction [120].

A meta-analysis of four RCTs [RELY (dabigatran), ROCKET-AF (rivaroxaban), ARISTOTLE (apixaban), and ENGAGE-TM (edoxaban)] of a total of 19,122 AF patients with HF showed that single-/high-dose non-vitamin oral anticoagulants (NOACs) were significantly better at reducing the risk of stroke/systemic embolic events (OR 0.86, 95% CI 0.76–0.98) and major bleeding (OR 0.76, 95% CI 0.67–0.86) [121]. Dabigatran is the only NOAC investigated in clinical trials in patients with mechanical heart valves [122], but this trial was terminated early due to increased rates of thromboembolic and bleeding complications [123].

10.4. Management of ventricular tachycardia in heart failure

Electrolyte imbalance is a potentially dangerous complication in patients with HF, warranting early recognition and correction [124]. Regarding pharmacological intervention, the COPERNICUS and CAPRICORN trials showed the benefit of carvedilol in reducing ventricular tachycardia and ventricular fibrillation in patients with HF. The MERIT-HF and CIBIS-II trials demonstrated the benefits of metoprolol succinate and bisoprolol, respectively, in preventing arrhythmic deaths in CHF [125]. A prospective study involving 1663 patients assessed the effect of spironolactone in patients with severe HF and reported fewer events

of ventricular arrhythmias in the treated group compared with the placebo group [126]. Although still unproven, it has been postulated that sacubitril/valsartan could confer protection against ventricular arrhythmias through reduction in myocardial fibrosis [127].

The AVID, CIDS, and CASH trials studied the treatment of ICD compared with antiarrhythmic drug therapy in patients who had suffered a cardiac arrest or life-threatening VA [128]. A meta-analysis of these three trials showed that ICD therapy was associated with a 50% reduction in arrhythmic mortality (95% CI 0.37–0.67; $p = 0.0001$) and a 28% reduction in total mortality (95% CI 0.60–0.87; $p = 0.006$) [79]. A subanalysis of these trials identified that, based on results from the AVID trial, individuals with an EF between 20% and 34% conferred the highest benefit with ICD therapy [81].

10.5. Management of bradyarrhythmias in heart failure

In patients with HFrEF who require pacing and who have high-degree AV block, CRT rather than RV pacing is recommended. A prospective multicenter study involving 186 patients with severely symptomatic permanent AF in whom AV junction ablation and CRT device implantation had been successfully performed showed death from HF, hospitalization due to HF, or worsening HF in 11% of patients in the CRT group compared with 26% of patients in the RV group (CRT vs. RV group: subhazard ratio 0.37, 95% CI 0.18–0.73; $p = 0.005$) [129].

11. Comorbidities (Tables 21–25)

11.1. Treatment of stable angina pectoris in patients with symptomatic HFrEF

Beta-blockers are effective in prolonging and improving symptoms of HF and LVEF in patients with HFrEF [60], and are therefore the preferred first-line treatment for the relief of angina. The vasodilatory effects of nitrates have implicated their use as an effective treatment in angina pectoris and acute coronary syndromes [130–133]. A recent systematic review, involving 17 RCTs with 9975 participants, assessing the role of ranolazine in patients with stable angina pectoris concluded that there was uncertainty about the effect of ranolazine on all-cause mortality, QoL, and the incidence of nonfatal acute MI [134]. Diltiazem treatment in postinfarction patients with a reduced EF increases

Table 21. Recommendations for the treatment of stable angina pectoris in patients with symptomatic HFrEF.

No.	Recommendations
<i>Step 1</i>	
1	A beta-blocker (in an evidence-based dose or maximum tolerated) is recommended as the preferred first-line treatment to relieve angina because of the associated benefits of this treatment (reducing the risk of HF hospitalization and the risk of premature death)
<i>Step 2: For additional angina symptom relief—except from any combination not recommended</i>	
2	A short-acting oral or transcutaneous nitrate should be considered (effective antianginal treatment, safe in HF)
3	A long-acting oral or transcutaneous nitrate should be considered (effective antianginal treatment, not extensively studied in HF)
4	Ranolazine may be considered in patients unable to tolerate a beta-blocker to relieve angina (effective antianginal treatment, but safety in HF is uncertain)
<i>Step 3: Myocardial revascularization</i>	
5	Myocardial revascularization is recommended when angina persists
6	The following are NOT recommended: (1) Ivabradine for stable CAD and patients who had ACS for the last 2 months (2) Combination of any of ivabradine, ranolazine, and nicorandil because of unknown safety (3) Combination of nicorandil and a nitrate (because of lack of additional efficacy)
7	Diltiazem and verapamil are not recommended because of their negative inotropic action and risk of worsening HF

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

ACS = acute coronary syndrome; CAD = coronary artery disease; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.

Table 22. Recommendations for the treatment of hypertension in patients with symptomatic HFrEF.

No.	Recommendations
<i>Step 1</i>	
8	ACE-I (or ARB), a beta-blocker, or an MRA is recommended to reduce blood pressure
<i>Step 2</i>	
9	A thiazide diuretic (or if the patient is being treated with a thiazide diuretic, switching to a loop diuretic) is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together with an ACE-I), a beta-blocker, and an MRA
<i>Step 3</i>	
10	Amlodipine or hydralazine is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively an ARB, but not with ACE-I and ARB combined), a beta-blocker, an MRA, and a diuretic
11	Alpha-adrenoceptor antagonists are not recommended to reduce blood pressure because of safety concerns in patients with HFrEF (neurohormonal activation, fluid retention, worsening HF)
12	Diltiazem and verapamil are not recommended to reduce blood pressure in patients with HFrEF because of their negative inotropic action and risk of worsening HF

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid antagonist.

the risk for subsequent congestive HF and is therefore not recommended in patients with left ventricular dysfunction [3].

Ivabradine is of symptomatic value in patients with CAD, but has no prognostic value in this population [64], as evidenced by the SIGNIFY trial [135]. This trial, involving 19,102 patients with both stable CAD without clinical HF and a heart rate of ≥ 70 bpm, showed that although ivabradine treatment, compared with placebo, was able to reduce heart rate (60.7 ± 9.0 vs. 70.6 ± 10.1 bpm, respec-

tively), there was no significant difference in the incidence of a composite of death from cardiovascular causes or nonfatal MI (6.8% and 6.4%, HR, 1.08; 95% CI 0.96–1.20; $p = 0.20$). Furthermore, ivabradine was associated with an increase in the incidence of a composite of death from cardiovascular causes or nonfatal MI among patients with activity-limiting angina, but not among those without activity-limiting angina ($p = 0.02$ for interaction) and a higher incidence of bradycardia (18.0% vs. 2.3%; $p < 0.001$).

Table 23. Recommendations for the treatment of other comorbidities in patients with HF.

No.	Recommendations
<i>Iron deficiency</i>	
13	Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L or ferritin between 100 µg/L and 299 µg/L and transferrin saturation <20%, regardless of hemoglobin levels) to alleviate HF symptoms, and improve exercise capacity and quality of life
14	FCM should be administered via drip infusion (up to a maximum single dose of 1000 mg of iron, but not exceeding 15 mg/kg or the calculated cumulative dose) or bolus injection (at a maximum single dose of up to 200 mg of iron up to three times per week)
<i>Diabetes</i>	
15	Metformin should be considered as a first-line treatment of glycemic control in patients with diabetes and HF, unless contraindicated
<i>Depression</i>	
16	Selective serotonin reuptake inhibitors may be considered as treatment for depression, unless contraindicated
<i>Vaccination</i>	
17	Immunization against influenza and pneumococcal disease should be considered
<i>Cancer</i>	
18	Cancer patients treated with potentially cardiotoxic therapy are at high risk of developing HF and should receive medical care aimed at obtaining strict control of cardiovascular risk factors
19	LVEF should be determined before, and periodically during, treatment for early detection of cardiac dysfunction in patients receiving potentially cardiotoxic chemotherapy, with a method that provides sufficient image quality and, preferably, using the same method during follow-up
20	The lower limit of normal of LVEF in echocardiography as 50% should be considered, in line with the definition of cardiotoxicity commonly used in registries and trials in patients with cancer
21	A patient with a significant decrease in LVEF (e.g., a decrease >10%) to a value that does not drop below the lower limit of normal should undergo repeated assessment of LVEF shortly after and during the duration of cancer treatment
22	If LVEF decreases >10% to a value below the lower limit of normal (considered as an LVEF <50%), ACE-Is (or ARBs) in combination with beta-blockers are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated, as these patients are at high risk of developing HF
23	ACE-Is (or ARBs) and beta-blockers are recommended in patients with symptomatic HF or asymptomatic cardiac dysfunction unless contraindicated

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; FCM = ferric carboxymaltose; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction.

Table 24. Treatments not recommended of other comorbidities in patients with HF.

No.	Recommendations
<i>Sleep apnea</i>	
24a	Adaptive servoventilation is not recommended in patients with HFrEF and predominant central sleep apnea because of an increased all-cause and cardiovascular mortality
24b	Treatment of sleep apnea and obesity hypoventilation syndrome is recommended with noninvasive ventilation as per the guidance of the sleep experts
24c	Continuous positive airway pressure may be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea
<i>Diabetes</i>	
25	Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization
<i>Arthritis</i>	
26	NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

COX = cyclooxygenase; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NSAID = non-steroidal anti-inflammatory drug.

Table 25. Recommendations for the treatment of valvular diseases in patients with HF.

No.	Recommendations
27	In symptomatic patients with reduced LVEF and “low-flow, low-gradient” aortic stenosis (valve area <1 cm ² , LVEF <40%, mean pressure gradient <40 mmHg), low-dose dobutamine stress echocardiography should be considered to identify those with severe aortic stenosis suitable for valve replacement
28	In patients with severe aortic regurgitation (in presence of HFrEF), aortic valve repair or replacement is recommended in all symptomatic patients and in asymptomatic patients with resting LVEF ≤50%, who are otherwise fit for surgery
29	Evidence-based medical and device therapy in patients with HFrEF is recommended to reduce functional mitral regurgitation
30	Combined surgery of secondary mitral regurgitation and coronary artery bypass grafting should be considered in symptomatic patients with LV systolic dysfunction, requiring coronary revascularization. Percutaneous mitral clip may be considered if patients are already medically exhausted
31	Isolated surgery of the non-ischemic regurgitant mitral valve in patients with severe functional mitral regurgitation and severe LV systolic dysfunction (LVEF <30%) may be considered in selected cases to avoid or postpone transplantation

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

11.2. Treatment of hypertension in patients with symptomatic HFrEF

If an ACE-Is (or an ARB), a beta-blocker, an MRA, and a diuretic fail to control blood pressure, then amlodipine or hydralazine can be safely used. The safety and efficacy of amlodipine for the treatment of hypertension in patients with left ventricular dysfunction have been established, with CHF patients reporting fewer cases of hypertension with amlodipine treatment compared with placebo [3].

The ALLHAT study showed that the risk of congestive HF was doubled in patients with hypertension receiving doxazosin compared with the diuretic chlorthalidone (4-year rates, 8.13% vs. 4.45%, RR 2.04, 95% CI 1.79–2.32; $p < 0.001$) [136]. The induction of neurohormonal activation, fluid retention, and worsening HF associated with alpha-adrenoceptor antagonists make it unsafe in patients with HFrEF. The negative inotropic effects of diltiazem and verapamil make them similarly unsafe in this patient population [3].

11.2.1. Iron deficiency

The FAIR-HF trial, involving 459 patients, showed that administering intravenous iron to patients with CHF and iron deficiency with or without anemia, improved symptoms, functional capacity, and QoL [137]. These outcomes were sustained over a 1-year period in the CONFIRM-HF trial, which also demonstrated that intravenous iron reduced the risk of hospitalization for worsening HF [138]. Results from a recent meta-analysis of RCTs, involving 551 patients with systolic HF and iron deficiency, are consistent with these findings. Intravenous iron therapy reduced the risk of the combined endpoint of

all-cause death or cardiovascular hospitalization (OR 0.44, 95% CI 0.30–0.64; $p < 0.0001$), and reduced the NYHA class (OR –0.54, 95% CI –0.87 to –0.21; $p = 0.001$) compared with the control group [139].

11.2.2. Diabetes

A systematic review of observational studies involving 34,000 patients confirmed that the use of metformin in patients with diabetes and HF reduced mortality compared with controls (23% vs. 37%, pooled adjusted risk estimates: 0.80; 0.74–0.87; $I^2 = 15%$; $p < 0.001$) and was as safe as other glucose-lowering treatments [140]. Metformin is contraindicated in patients with severe renal or hepatic impairment because of the risk of lactic acidosis [3].

Empagliflozin has been shown to reduce HF hospitalizations and cardiovascular-induced death in HF patients with diabetes. Further studies are required to assess the effects of empagliflozin on LV structure and function, NYHA class, and hemodynamics in addition to its long-term safety [141]. Linagliptin is similarly effective for glycemic control in patients with diabetes [142], with data showing no association with cardiovascular risk versus pooled active comparators or placebo [143,144]. Data are still required to assess the efficacy of linagliptin in patients with diabetes and HF. Thiazolidinediones (glitazones) have been significantly associated with the increased risk of HF-induced mortality and hospitalization, and are therefore not recommended in patients with HF [145,146].

11.2.3. Depression

Depression often accompanies HF and is associated with increased financial burden, somatic

symptoms, hospitalization, poor QoL, poor prognosis, increased mortality, and is a predictor of future cardiac events [147–149]. Selective serotonin reuptake inhibitors may improve the symptoms of depression and prognosis in patients with HF [150], but only after the consideration of comorbidities and the potential for drug interactions [151]. In another study (MOOD-HF), the use of escitalopram did not significantly reduce mortality and hospitalization or the symptoms of depression; therefore, the study authors did not recommend the routine use of antidepressants in patients with heart failure and depression [152]. Tricyclic antidepressants may cause hypotension, arrhythmias, and worsening HF, and should therefore be avoided [3].

11.2.4. Vaccinations

Vaccinations against influenza are associated with a reduced risk of hospitalization due to heart disease, pneumonia, and influenza [153]. Vaccination against pneumococcal disease and influenza should therefore be considered in patients with HF [154].

11.2.5. Sleep apnea

A study on treated patients with CHF showed that 61% of patients presented with either central or obstructive sleep apnea [155]. The SERVE-HF trial, which studied HFrEF patients with predominant central sleep apnea, showed that use of adaptive servoventilation had no significant effect on the primary endpoints (all-cause death, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening HF), and was associated with increased all-cause death (HR 1.28, 95% CI 1.06–1.55; $p = 0.01$) and cardiovascular mortality (HR 1.34, 95% CI 1.09–1.65; $p = 0.006$) [156].

In patients with central sleep apnea and HF, continuous positive airway pressure significantly improved nocturnal oxygenation ($1.6 \pm 2.8\%$ vs. $0.4 \pm 2.5\%$; $p < 0.001$), lowered norepinephrine levels (-1.03 ± 1.84 vs. 0.02 ± 0.99 nmol/L; $p = 0.009$), increased EFs ($2.2 \pm 5.4\%$ vs. $0.4 \pm 5.3\%$; $p = 0.02$), and increased the distance walked in 6 minutes (20.0 ± 55 vs. -0.8 ± 64.8 m; $p = 0.016$), but failed to affect survival compared with the control group [157].

11.3. Treatment of valvular disease in patients with heart failure

The accurate assessment of the grade of aortic stenosis is vital to selecting the appropriate treatment [158]. Dobutamine stress echocardiography may help to assess the aortic valve area in a differ-

ent flow status and differentiate between fix severe aortic stenosis and pseudo-severe aortic stenosis [158]. An observational analysis, involving 114,125 patients aged ≥ 65 years who underwent aortic valve replacement, showed that concomitant HF negatively impacted both operative mortality and long-term survival [159]. Furthermore, longer duration of HF symptoms before aortic valve replacement was associated with worse outcomes. Overall, these data show that careful clinical judgment is required when managing patients with both severe aortic stenosis and HF [159].

11.4. Treatment of heart failure patients with cancer

Myocardial dysfunction and HF are the most concerning cardiovascular complications of cancer treatment. It is important for specialists to work together to prevent and manage cardiotoxicity without compromising cancer care and optimizing patient outcome [160].

Some cancer treatments, such as anthracyclines, may induce progressive cardiac remodeling as a late consequence of earlier myocyte damage, resulting in late cardiomyopathy, whereas others may cause transient cardiac dysfunction without long-term consequences. Data show that anthracycline-associated cardiac dysfunction detected early and treated with HF medications frequently leads to good functional cardiac recovery [160].

Other conventional chemotherapies such as cyclophosphamide, cisplatin, ifosfamide, and taxanes are also known to induce myocardial dysfunction. More recently introduced immunotherapies and targeted therapies, such as HER2 antagonists and tyrosine kinase inhibitors, appear to have similar cardiotoxicity profiles to trastuzumab. Vascular endothelial growth factor inhibitors are known to induce cardiac dysfunction in 3–15% of patients and symptomatic HF in 1–10% of patients. Similarly, other agents such as BCR-ABL kinase inhibitors and proteasome inhibitors, also lead to cardiotoxicity, with carfilzomib (a proteasome inhibitor) being associated with a high risk of HF (up to 25%) [160].

Radiotherapy is associated with an absolute excess risk for mortality ranging from 9.3 to 28 per 10,000 person-years of follow-up, and a 4.9-fold increased risk of HF in survivors. Although the actual incidence of radiation-induced cardiotoxicity is difficult to evaluate, some studies have reported the RR of fatal cardiovascular events to range between 2.2 and 12.7 in survivors

of Hodgkin lymphoma and between 1 and 2.2 in patients with breast cancer [160].

Therefore, it is imperative to first identify patients at risk of cardiotoxicity by taking into account the patient's clinical history, examination, and baseline measurements of cardiac function. Screening and detection of cardiotoxicity may include cardiac imaging (echocardiography, nuclear imaging, CMR) and biomarkers (troponin, natriuretic peptides) based on local expertise and availability. It is important to remember that risk stratification assessment is a guide to ensure that patients at higher risk have an earlier review to avoid missing early signs of toxicity [160].

11.5. Treatment of heart failure patients with infection

Certain antibiotics such as macrolides can cause, or aggravate, LV systolic dysfunction in HF. Macrolides include the antibiotics erythromycin, azithromycin (Zithromax), clarithromycin (Biaxin), and quinolone. A meta-analysis of 33 studies involving 20,779,963 participants revealed that patients taking macrolides experienced an increased risk of developing sudden cardiac death or ventricular tachyarrhythmias (RR 2.42; 95% CI 1.61–3.63), sudden cardiac death (RR 2.52; 95% CI 1.91–3.31), and cardiovascular death (RR 1.31; 95% CI 1.06–1.62), compared with those who did not take macrolides [160]. However, no association was found between macrolide use and all-cause death or any cardiovascular events [161].

12. Acute heart failure

12.1. Definition and classification

AHF is characterized by the sudden worsening of signs and/or symptoms of HF. AHF can be clinically classified into four different hemodynamic

profiles, stratified by adequacy of perfusion (warm or cold) and degree of congestion (dry and wet). Perfusion is characterized by cold sweaty extremities, oliguria, mental confusion, dizziness, and narrow pulse pressure [3]. Congestion is characterized by pulmonary congestion, orthopnea/paroxysmal nocturnal dyspnea, peripheral edema, jugular venous dilatation, congested hepatomegaly, gut congestion, ascites, and hepatojugular reflux [3]. Such classification can help guide therapy and predict prognosis [162]. For instance, to achieve a “warm and dry” profile, diuresis may be indicated, or for a “wet and cold” profile vasoactive therapy with diuresis may be indicated [162].

12.2. Management of acute heart failure (Tables 26–32)

An algorithm for the management of AHF is shown in Fig. 8. Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms and a less-than-optimal response following the use of diuretics necessitates further treatment. Intravenous vasodilators should be considered for symptomatic relief in AHF with SBP >90 mmHg and without symptomatic hypotension. Short-term, intravenous infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg); dobutamine if SBP is 70–90 mmHg and dopamine if SBP is <70 mmHg.

12.3. Diagnostic measurements in acute heart failure

The lower recommended threshold for the diagnosis of AHF for BNP and NT-proBNP is <100 pg/mL and <300 pg/mL, respectively. Use of these thresholds in clinical practice provides an excel-

Table 26. Recommendations for applied diagnostic measurements in AHF.

No.	Recommendations
1	Upon presentation, a measurement of plasma natriuretic peptide level is recommended in all patients with acute dyspnea and suspected AHF to help in the differentiation of AHF from noncardiac causes of acute dyspnea
2	At admission, in all patients presenting with suspected AHF, the following diagnostic tests are recommended: <ol style="list-style-type: none"> 12-lead ECG Chest X-ray to assess signs of pulmonary congestion and detect other cardiac or non-cardiac diseases that may cause or contribute to the patient's symptoms Laboratory assessments in the blood, including cardiac troponins, blood urea nitrogen (or urea), creatinine, electrolytes (sodium and potassium), glucose, complete blood count, liver function tests, and TSH
3	Echocardiography is recommended immediately in hemodynamically unstable AHF patients and within 48 hours when cardiac structure and function are either not known or may have changed since previous studies

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AHF = acute heart failure; ECG = electrocardiogram; TSH = thyroid-stimulating hormone.

Table 27. Recommendations for the management of patients with AHF—oxygen therapy and ventilatory support.

No.	Recommendations
4	Monitoring of transcutaneous arterial oxygen saturation (SpO ₂) is recommended
5	Measurement of blood pH and carbon dioxide tension (possibly including lactate) should be considered, especially in patients with acute pulmonary edema or previous history of COPD using venous blood. In patients with cardiogenic shock arterial blood is preferable
6	Oxygen therapy is recommended in patients with AHF and SpO ₂ <90% or partial pressure of arterial oxygen (PaO ₂) <60 mmHg (8.0 kPa) to correct hypoxemia
7	Noninvasive positive pressure ventilation (CPAP, BiPAP) should be considered in patients with respiratory distress (respiratory rate >25 breaths/min, SpO ₂ <90%) and started as soon as possible to decrease respiratory distress and reduce the rate of mechanical endotracheal intubation Noninvasive positive pressure ventilation can reduce blood pressure and should be used with caution in hypotensive patients. Blood pressure should be monitored regularly when this treatment is used
8	Intubation is recommended during respiratory failure, leading to hypoxemia [PaO ₂ <60 mmHg (8.0 kPa)], hypercapnia [PaCO ₂ >50 mmHg (6.65 kPa)], and acidosis (pH <7.35), if cannot be managed noninvasively

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AHF = acute heart failure; BiPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; PaCO₂ = partial pressure of carbon dioxide.

lent ability for the rapid and accurate exclusion of AHF. A meta-analysis evaluating 15,263 test results showed that using these thresholds for BNP (<100 pg/mL) and NT-proBNP (<300 pg/mL) was associated with a sensitivity of 0.95 (95% CI 0.93–0.96) and 0.99 (95% CI 0.97–1.00) and negative predictive values of 0.94 (95% CI 0.90–0.96) and 0.98 (95% CI 0.89–1.0), respectively, for the diagnosis of AHF. At the lower recommended threshold of 120 pmol/L, MR-pro-atrial natriuretic peptide (MR-proANP) has a sensitivity ranging from 0.95 (0.90–0.98) to 0.97 (0.95–0.98) and a negative predictive value ranging from 0.90 (0.80–0.96) to 0.97 (0.96–0.98) [162]. However, specificity may vary, and thus imaging is required to confirm diagnosis [162]. NT-proBNP and MR-proANP are as useful as BNP in the diagnosis of AHF [163,164]. Mandating the use of NT-proBNP in the management of patients suspected of AHF significantly enhanced the accuracy of diagnosis and reduced the duration of emergency department visits, hospitalizations, and subsequent outpatient services [165].

12.4. Pharmacotherapy

Diuretics are recommended to relieve the signs and symptoms of fluid overload [166]. Recent data have shown that timely administration of intravenous diuretics in the emergency department is strongly associated with improved outcomes and reduction in the readmission rate. Based on the recent data available, we strongly recommend that intravenous diuretics are administered ideally within 60 minutes of first medical contact, and no later than 120 minutes [167–169]. The least effective intravenous diuretic dose may be administered to reach euvolemia in the shortest time

possible. Studies have shown no difference in the patient's global assessment of symptoms when administering diuretic therapy as a bolus infusion compared with continuous infusion [170]. Combining diuretic therapy with thiazide-type diuretics can help induce diuresis in patients resistant to high doses of loop diuresis, but increased the risks of hypokalemia, hypotension, hyponatremia, and worsening renal function [171].

Use of intravenous vasodilators is effective in improving hemodynamics and organ perfusion in patients with AHF [172]. Although useful in improving forward flow and organ perfusion, inotropic agents have been associated with increased mortality and therefore require careful patient assessment before use [173].

In a meta-analysis involving 19,958 at-risk hospitalized medical patients, thromboembolism prophylaxis was effective in reducing incidences of deep vein thrombosis (RR 0.47, 95% CI 0.22–1.00) and pulmonary embolism (RR 0.43, 95% CI 0.26–0.71) [174].

12.5. Oxygen therapy and ventilatory support

Noninvasive positive pressure ventilation (NPPV) is widely used to alleviate the signs and symptoms of respiratory distress due to cardiogenic pulmonary edema. Both continuous positive airway press and bilevel positive airway pressure provide a more rapid improvement in respiratory distress and metabolic disturbance compared with standard therapy [175–179]. Further large-scale trials are needed to evaluate the potential benefit of NPPV in reducing mortality.

Table 28. Recommendations for the management of patients with AHF—pharmacotherapy.

No.	Recommendations
<i>Diuretics</i>	
9a	Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function, and electrolytes during use of intravenous diuretics
9b	It is recommended to administer IV loop diuretics within 1 hour of first medical contact to reduce the readmission rate
10	In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20–40-mg intravenous furosemide (or equivalent); for those on chronic diuretic therapy, initial intravenous dose should be at least equivalent to the oral dose or the least effective dose required to reach euvolemia in the shortest time
11	It is recommended to give diuretics either as intermittent boluses or as a continuous infusion, and the dose and duration should be adjusted according to patients' symptoms and clinical status
12	The combination of a loop diuretic, with either a thiazide-type diuretic or spironolactone, may be considered in patients with resistant edema or insufficient symptomatic response
<i>Vasodilators</i>	
13	Intravenous vasodilators should be considered for symptomatic relief in AHF with SBP >90 mmHg and without symptomatic hypotension. Symptoms and blood pressure should be monitored frequently during the administration of intravenous vasodilators
14	In patients with hypertensive AHF, intravenous vasodilators should be considered as the initial therapy to improve symptoms and reduce congestion
<i>Inotropic agents—dobutamine, dopamine, milrinone</i>	
15a	Inotropic agents should not be considered in the absence of cardiogenic shock
15b	Short-term, intravenous infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function
<i>Vasopressors</i>	
16	A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and vital organ perfusion
17	ECG and blood pressure (preferably intra-arterial blood pressure) monitoring should be undertaken when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischemia, and even hypotension
<i>Thromboembolism prophylaxis</i>	
18	Thromboembolism prophylaxis (e.g., with LMWH) is recommended in patients not already on anticoagulants and with no contraindication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism
<i>Other drugs</i>	
For acute control of the ventricular rate in patients with AF (decompensated patients):	
19	a. Digoxin and/or beta-blockers should be considered as the first-line therapy
20	b. Amiodarone may be considered
21	Opiates may be considered for cautious use to relieve dyspnea and anxiety in patients with severe dyspnea but nausea and hypopnea may occur

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

AF = atrial fibrillation; AHF = acute heart failure; ECG = electrocardiogram; HF = heart failure; IV = intravenous; LMWH = low-molecular-weight heparin; SBP = systolic blood pressure.

Table 29. Recommendations for renal replacement therapy in patients with acute heart failure.

No.	Recommendations
22	Ultrafiltration may be considered for patients with refractory congestion who failed to respond to diuretic-based strategies
23	Renal replacement therapy should be considered in patients with refractory volume overload and acute kidney injury

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

Opiates should be cautiously used to relieve dyspnea, as data from 147,362 patients with acute decompensated HF (ADHF) in the ADHERE study showed that patients on morphine had more ICU

admissions (38.7% vs. 14.4%), a longer median hospitalization (5.6 vs. 4.2 days), and greater mortality (13.0% vs. 2.4%), and were more likely to require mechanical ventilation (15.4% vs. 2.8%;

Table 30. Recommendations for oral evidence-based disease-modifying therapies in patients with acute heart failure.

No.	Recommendations
24	In case of worsening of chronic failure with reduced ejection fraction, every attempt should be made to continue evidence-based, disease-modifying therapies, in the absence of hemodynamic instability or contraindications

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

Table 31. Recommendations for the management of patients with cardiogenic shock.

No.	Recommendations
25	In all patients with suspected cardiogenic shock, immediate ECG and echocardiography are recommended
26	All patients with cardiogenic shock should be considered for transfer to a tertiary care center
27	In patients with cardiogenic shock complicating ACS, an urgent coronary angiography is recommended with an intent to perform coronary revascularization
28	Continuous ECG and blood pressure monitoring are recommended
29	Invasive monitoring with an arterial line is recommended
30	Fluid challenge should be considered if there is no sign of overt fluid overload or if unsure of the patient's volume status or cause of shock
31	Intravenous inotropic agents (dobutamine) may be considered to increase cardiac output
32	Vasopressors (norepinephrine preferable over dopamine) may be considered if there is a need to maintain SBP in the presence of persistent hypoperfusion
33	Intra-aortic balloon pump is not routinely recommended in cardiogenic shock
34	Short-term mechanical circulatory support may be considered in refractory cardiogenic shock depending on the patient's age, comorbidities, and neurological function

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

ACS = acute coronary syndrome; ECG = electrocardiogram; SBP = systolic blood pressure.

Table 32. Recommendations for monitoring clinical status of patients hospitalized due to acute heart failure.

No.	Recommendations
35	Standard noninvasive monitoring of heart rate, rhythm, respiratory rate, oxygen saturation and blood pressure is recommended
36	It is recommended that patients should be weighed daily and have an accurate fluid balance chart completed
37	It is recommended to evaluate signs and symptoms relevant to heart failure (e.g., dyspnea, pulmonary rales, peripheral edema, and weight) daily to assess the correction of fluid overload
38	Frequent, often daily, measurement of renal function (blood urea, creatinine) and electrolytes (potassium, sodium) during intravenous therapy and when renin-angiotensin-aldosterone system antagonists are initiated is recommended
39	An intra-arterial line should be considered in patients with hypotension and persistent symptoms despite treatment
40	A pulmonary artery catheter may be considered in patients who, despite pharmacological treatment, present refractory symptoms (particularly with hypotension and hypoperfusion)

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

all $p < 0.001$) compared with patients who did not receive morphine [180].

12.6. Monitoring clinical status of patients hospitalized due to acute heart failure

Pulmonary edema and low tissue perfusion can lead to changes in the blood acid-base balance and may be related to worse outcomes in patients with AHF. The Korean Heart Failure Registry, which involved 1982 patients, showed that 19% and 44% of AHF patients had acidosis and alkalo-

sis, respectively. In addition, acidosis was associated with higher mortality (acidosis 19.5%, neutral pH 13.7%, alkalosis 14.9%; $p = 0.007$). Therefore, assessment of pH provides an additional prognostic value in AHF patients and may be used to optimize risk stratification [181].

12.7. Renal replacement therapy

A meta-analysis of 12 RCTs involving 659 patients with ADHF showed that ultrafiltration treatment was effective in reducing fluid retention

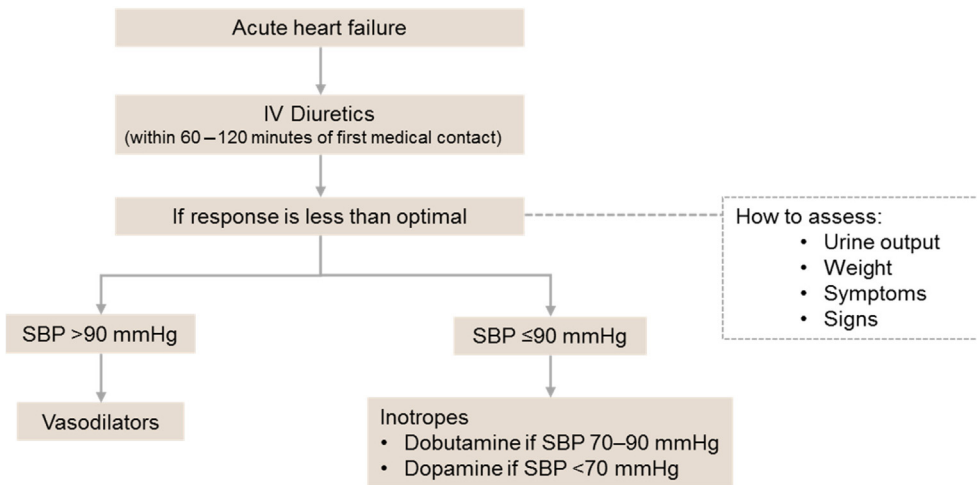


Fig. 8. Algorithm for the management of acute heart failure. IV = intravenous; SBP = systolic blood pressure.

(MD 1.28, 95% CI 0.43–2.12; $p = 0.003$) and inducing weight loss (MD 1.23, 95% CI 0.03–2.44; $p = 0.04$), but had no significant effect on all-cause mortality (OR 1.08, 95% CI 0.63–1.86; $p = 0.77$) or all-cause hospitalization (OR 0.89, 95% CI 0.39–2.00; $p = 0.77$) [182]. A separate meta-analysis of 477 patients with AHF showed no significant difference in adverse events between the ultrafiltration and intravenous diuretic treatment groups [183]. Caution is still advised with ultrafiltration treatment, particularly in the setting of worsening renal function [184–186].

12.8. Cardiogenic shock

The use of norepinephrine for the treatment of cardiogenic shock is associated with fewer numbers of arrhythmic events compared with dopamine (12.4% vs. 24.1%; $p < 0.001$) [187], and thus is the preferred vasopressor. Supplementing dobutamine with epinephrine in patients with cardiogenic shock has been shown to improve cardiac output (103 ± 8 mL/kg to 125 ± 9 mL/kg) and central venous oxygen saturation ($49\% \pm 3\%$ to $59\% \pm 4\%$) compared with dobutamine treatment alone because of an increased heart rate and con-

tractility with minimal change in systemic vascular resistance [188].

Intra-aortic balloon pump is not recommended for routine use in patients with cardiogenic shock because evidence from the IABP-SHOCK II trial (600 patients) failed to show any significant improvement in rates of mortality (RR 1.01, 95% CI 0.86–1.18; $p = 0.91$), reinfarction (RR 2.60, 95% CI 0.95–7.10; $p = 0.05$), recurrent revascularization (RR 0.91, 95% CI 0.58–1.41; $p = 0.77$), or stroke (RR 1.50, 95% CI 0.25–8.84; $p = 1.00$) [189].

13. Mechanical circulatory support and heart transplantation (Tables 33–35)

13.1. Heart transplantation

In Saudi Arabia, a total of 30 whole heart transplantations were carried out and 17 hearts were recovered as a source of valves in 2015 [190]; however, there is a need for epidemiological studies on the management of patients undergoing heart transplantation. In general, heart transplantation may be considered in patients with end-stage HF with severe symptoms, a poor prognosis, and no

Table 33. Recommendations for the implantation of mechanical circulatory support in patients with refractory heart failure.

No.	Recommendations
1	An LVAD should be considered in patients who have end-stage HFrEF, despite optimal medical and device therapy, and who are eligible for heart transplantation to improve symptoms, reduce the risk of HF hospitalization and the risk of premature death (bridge to decision)
2	An LVAD should be considered in patients who have end-stage HFrEF despite optimal medical and device therapy and who are not eligible for heart transplantation, to reduce the risk of premature death

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACC/AHA) [10].

HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVAD = left ventricular assist device.

Table 34. Recommendations on revascularizations in patients with chronic heart failure and systolic LV dysfunction (ejection fraction $\leq 35\%$).

No.	Recommendations
3	CABG is recommended for patients with significant LAD artery stenosis and multivessel disease to reduce death and hospitalization for cardiovascular causes
4	LV aneurysmectomy during CABG should be considered in patients with a large LV aneurysm if there is a risk of rupture, large thrombus formation, or the aneurysm is the origin of arrhythmias
5	Myocardial revascularization should be considered in the presence of viable myocardium
6	CABG with surgical ventricular restoration may be considered in patients with scarred LAD territory (only at specialized centers), especially if a postoperative LVESV index $< 70 \text{ mL/m}^2$ can be predictably achieved
7	PCI may be considered if the anatomy is suitable, in the presence of viable myocardium, and surgery is not indicated

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

CABG = coronary artery bypass graft; LAD = left anterior descending; LV = left ventricle; LVESV = left ventricle end-systolic volume index; PCI = percutaneous coronary intervention.

Table 35. Recommendations for the management of patients with valvular heart disease.

No.	Recommendation
<i>Indications for surgery in severe primary MR</i>	
8	Surgery is indicated in symptomatic patients with an LVEF $> 30\%$ and an LVESD $< 55 \text{ mm}$
<i>Indications for mitral valve surgery in chronic secondary mitral regurgitation</i>	
9	Surgery is indicated in patients with severe MR undergoing CABG, and an LVEF $> 30\%$
<i>Indications for tricuspid valve surgery</i>	
10	Surgery is indicated in patients with severe TS undergoing left-sided valve intervention (percutaneous balloon valvuloplasty can be attempted if PMC can be performed on the mitral valve)
11	Surgery is indicated in patients with severe primary or secondary TR undergoing left-sided valve surgery
12	Surgery should be considered in patients with mild or moderate secondary TR with a dilated annulus ($\geq 40 \text{ mm}$ or $> 21 \text{ mm/m}^2$), undergoing left-sided valve surgery
13	Surgery should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary TR and progressive right ventricular dilatation or deterioration of their right ventricular function

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; PMC = percutaneous mitral commissurotomy; TR = tricuspid regurgitation; TS = tricuspid stenosis.

remaining alternative treatment options [3]. Patients that are capable of complying with intensive postoperative treatment may also be considered for heart transplantation [3]. Patients with an active infection, severe peripheral arterial or cerebrovascular disease, pharmacologically irreversible pulmonary hypertension, cancer, irreversible renal dysfunction (e.g. creatinine clearance $< 30 \text{ mL/min}$), multiorgan systemic disease, body mass index over 35 kg/m^2 , current alcohol or drug abuse, and/or other serious comorbidities with poor prognosis are not eligible for heart transplantation [3]. In addition, heart transplantation is contraindicated in any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting [3]. Relatively, patients above 65 years, and/or patients with the inability to relocate to a city which has a secondary care facility with a trained cardiologist to follow-up the care and refer to an

advanced HF center, should ideally not be considered for heart transplantation [3].

13.2. Implantation of mechanical circulatory support in patients with refractory heart failure

A left ventricular assist device (LVAD) is an established treatment for patients with advanced HF, with most patients hospitalized and dependent on intravenous inotropic support [190]. The seventh INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry report of $> 15,000$ LVAD-supported patients over a 9-year period found that the actuarial survival rates at Year 1 and Year 2 were 80% and 70%, respectively, for all patients with continuous-flow LVAD [191]. A more recent cohort of the HeartMate II destination therapy postapproval found that survival rates were 82% at Year 1 and 69% for Year 2 for INTERMACS

Profiles 4–7, compared with 72% at Year 1 and 60% at Year 2 for INTERMACS Profiles 1–3 [192]. Furthermore, for INTERMACS Level I patients who are known to have a higher risk of mortality after VAD implantation, preoperative optimization using initial venoarterial extracorporeal life support with deferred VAD implantation substantially improves renal, hepatic, and pulmonary function over a period of 8 days [193]. The 30-day and in-hospital mortality rates after VAD implantation were 4.5% and 9.1%, respectively, and overall 1-year survival was 86.4% [193]. During extracorporeal life support, catecholamine dosage may also be reduced [193].

In addition, a prognostic evaluation of ambulatory patients with advanced HF found that patients with systolic HF, a heavy symptom burden, and at least one recent HF hospitalization were at high risk for death or LVAD rescue [194]. Of note, a retrospective, longitudinal, comparative study evaluating the performance of the HeartMate Risk Score reported that patients within each INTERMACS profile group had a wide spectrum of mortality risk and therefore, low INTERMACS profiles should not be considered a contraindication to mechanical support [195].

Despite technological improvements, bleeding, thromboembolism (both of which can cause a stroke), pump thrombosis, driveline infections, and device failure remain significant problems and affect the long-term outcome of patients on mechanical circulatory support [3]. Therefore, newly established advanced centers performing LVAD implantation and/or heart transplant should consult local experts to assess the degree of readiness and to assure that this advanced and highly specialized service is being provided in a way that assures patient safety and produces high-quality outcomes.

13.3. Myocardial revascularization

The role of coronary artery bypass grafting (CABG) in the treatment of patients with CAD and left ventricular dysfunction ($EF \leq 35\%$) was assessed in the Surgical Treatment for Ischemic Heart Failure (STICH) trial [196]. Of the 1212 patients recruited, the primary outcome of death from any cause occurred in 41% of patients on medical therapy and 36% of patients undergoing CABG ($p = 0.12$) [196]. Although CABG did not significantly reduce the risk of death from any cause compared with medical therapy, the rate from death from any cause or hospitalization for cardiovascular causes was lower within the CABG

group (58%) than those on medical therapy (68%; $p < 0.001$) [196]. Importantly, according to the propensity-matched, risk-adjusted observational cohort of patients with CAD, an LVEF $< 35\%$, and no left main disease $\geq 50\%$, CABG is associated with a survival advantage over medical therapy, over a 10-year follow-up period [197].

The presence of viable myocardium has been shown to be associated with a greater likelihood of survival in patients with CAD and left ventricular dysfunction [198]. Although the STICH trial did not show improvement in survival with revascularization of viable myocardium, the results were limited by the viability of the imaging techniques used and the lack of inducible ischemia information [199]. During a mean follow-up of 2.8 years, 27.5% of the 648 patients died, and hibernating myocardium ($p = 0.0015$), ischemic myocardium ($p = 0.0038$), and scarred myocardium ($p = 0.001$) were associated with all-cause death [199]. Hibernating myocardium, especially when the extent of the viability exceeded 10% of the myocardium, was associated with improved survival [199].

Left ventricular reconstruction was also shown to provide durable improvements in left ventricular function in patients with a large scarred ventricular wall and who were systematically excluded from the STICH trial [200]. In this study, of the 101 patients with CHF, magnetic resonance imaging revealed that EF improved from 26% preoperatively to 40% at 1 month and 44% at 1 year postoperatively [200]. Simultaneously, the end-diastolic volume index reduced from $130 \pm 43 \text{ mL/m}^2$ to $81 \pm 27 \text{ mL/m}^2$ and $82 \pm 25 \text{ mL/m}^2$, respectively, and end-systolic volume index reduced from $96 \pm 45 \text{ mL/m}^2$ to $50 \pm 21 \text{ mL/m}^2$ and $47 \pm 20 \text{ mL/m}^2$, respectively [200]. Therefore, care should be taken when extrapolating study results and/or restricting treatment to a select group of patients. Furthermore, an analysis of left ventricular volumes at baseline and 4 months after surgery showed that surgical ventricular reconstruction (SVR) resulted in improved survival compared with CABG alone, when the postoperative end-systolic volume index was $\leq 70 \text{ mL/m}^2$ [201]. Subgroup analysis of the STICH trial also suggested that patients with less dilated LV (LVESVI $< 60 \text{ mL/m}^2$) and better LVEF ($\geq 33\%$) may benefit from SVR compared with patients with larger LV ($> 90 \text{ mL/m}^2$) and poorer LVEF ($\leq 25\%$) [202].

Meta-analysis data from clinical studies show that percutaneous coronary intervention (PCI) among patients with left ventricular dysfunction

yields similar outcomes to CABG, with acceptable in-hospital and long-term mortality. However, both interventions need to be used in tandem with pharmacological therapy for improved outcomes [203]. Of note, according to the APPROACH study in patients with CAD and left ventricular dysfunction, CABG was associated with lower rates of repeat revascularization and improved survival over PCI at 1, 5, 10, and 15 years [204].

13.4. Valvular heart disease

Approximately 30–50% of patients with MI will develop ischemic mitral regurgitation [205]. For patients with moderate regurgitation, the Cardiothoracic Surgical Trials Network found that at 1 year, the addition of mitral valve repair to CABG did not result in a higher degree of LV reverse remodeling [206]. At the 2-year follow-up, mitral valve repair was associated with a significantly higher incidence of moderate or greater recurrent MR, with no difference in the indices of left ventricular reverse remodeling, compared with valve replacement [205].

Although the management of tricuspid regurgitation in patients with mitral regurgitation is controversial, tricuspid repair is indicated in patients undergoing left-sided valve surgery with mild or moderate coexistent tricuspid regurgitation if the annulus is >40 mm or >21 mm/m² [207].

14. Multidisciplinary team management (Table 36)

It is important that each HF case be managed collaboratively, with a process used to assess,

plan, implement, coordinate, monitor, and evaluate the services required to meet a patient’s health and service needs [208]. Several patients suffer from multimorbidity, which has been identified to play a critical role in driving both early and late readmissions in HF, with about 60% of patients requiring readmission within 30 days for a condition other than HF [208].

It is important to remember that patients with HF are often prescribed a complex therapeutic regimen that consists of medication, diet, fluid restriction, and recommendations on activity and rest [209]. Integrating these changes into the patient’s existing regimen related to other comorbidities increases the chances of noncompliance, which is likely to lead to worsening symptoms and/or rehospitalization [209]. Therefore, education and counseling by a multidisciplinary team, each focusing on specific areas, are important to improving compliance and subsequent health-related outcomes [209].

The interdisciplinary approach also plays an important role in HF patient management, such as in primary care or with nursing home residents [208]. Data from three studies show that multidisciplinary care reduces hospital admissions and ER visits, and improves overall QoL in both CHF and AHF settings [210–214]. Data show that physiotherapy-based treatments not only assist in the prevention of falls, but also reduce functional deficits in those with cardiovascular disease [208]. Aerobic or resistance training has been shown to improve physical performance and HRQoL, and may increase the probability of older patients remaining independent, with home-based exercise programs found to be as effective

Table 36. Recommendations for exercise, multidisciplinary management, and monitoring of patients with heart failure.

No.	Recommendations
1	It is recommended that regular aerobic exercise be encouraged in patients with HF to improve functional capacity and symptoms
2	It is recommended that regular aerobic exercise is encouraged in stable patients with HF _{rEF} to reduce the risk of HF hospitalization
3	It is recommended that patients with HF are enrolled in a multidisciplinary care management program to reduce the risk of HF hospitalization and mortality
4	Referral to primary care for long-term follow-up may be considered for stable patients with HF who are on optimal therapy to monitor the effectiveness of the treatment, disease progression, and patient adherence
5	Monitoring of pulmonary artery pressures using a wireless implantable hemodynamic monitoring system (CardioMEMS) may be considered in symptomatic patients with HF with previous HF hospitalization to reduce the risk of recurrent HF hospitalization
6	Multiparameter monitoring based on an ICD (IN-TIME approach) may be considered in symptomatic patients with HF _{rEF} (LVEF ≤35%) to improve clinical outcomes

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

HF = heart failure; HF_{rEF} = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction.

as supervised exercise programs [208]. A recent meta-analysis of 46 RCTs found that exercise-based cardiac rehabilitation in patients with HF significantly reduces the risk of hospital admission by 35% (RR 0.65, 95% CI 0.50–0.84; $p = 0.001$) [215]. Besides, another meta-analysis of 55 trials found that increasing exercise intensity was associated with a greater level of postrehabilitation exercise capacity in patients with HF [216]. A Cochrane review of 33 trials including 4740 patients, predominantly with reduced EF (<40%), found that exercise-based cardiac rehabilitation leads to improvements in HRQoL and reductions in hospitalization, regardless of the cardiac rehabilitation program, and may reduce mortality in the long term [217].

Research shows that multimorbid or high-risk patients are most likely to benefit from home-based patient-centered management programs [208]. This was further highlighted by data from the CHAMPION trial reporting that a wireless implantable hemodynamic monitoring system has a long-term benefit in lowering hospital admission rates for HF [218,219]. Furthermore, automatic, daily, implant-based, multiparameter telemonitoring was shown to significantly improve clinical outcomes in patients with HF [220].

14.1. Establishing a multidisciplinary team

Management of HF is complex, requiring the cooperation of various specialists [221]. A good HF service would typically include an experienced HF cardiology lead supported by primary care physicians, nurse specialists, hospital pharmacists, and community pharmacists with the ability to provide remote care [221].

For patients presenting with AHF, initial stabilization requires cooperation from emergency care providers, interventional cardiologists, heart surgeons, intensive care specialists, nurses, clinical pharmacists, and discharge managers [221]. To facilitate the transition from an inpatient to an outpatient setting, a general practitioner may be

key and will likely help improve readmission rates [221].

However, the key to a successful multidisciplinary HF program is coordination of care delivered by various services within the healthcare system and across the spectrum of HF severity [221]. As patients transition from the inpatient to outpatient setting, pharmacists are key to assuring consistency in management [222] and predicting and improving medication adherence in patients with HF [222–224], making them an invaluable member of the multidisciplinary HF team. In addition, pharmacists are integral for optimizing care for elderly patients with HF [225] to significantly reduce the risk of discrepancies and prescription errors in HF medication postdischarge [222,225–227], contribute to lower HF readmission rates and emergency department visits [222,228], improve overall wellness and perception of self, through education and active involvement [222,227], and reduce clinically relevant drug–drug interactions [229,230].

15. Quality metrics (Tables 37, 38)

To achieve optimal outcomes in patients with HF, in addition to establishing a robust multidisciplinary HF team, there is a need for continuous monitoring of healthcare services at a program, provider, and patient level for consistency and quality. Some potentially useful performance indicators are outlined in Table 38 and a patient management pathway to promote organized and efficient patient care is outlined in Fig. 9.

16. Current limitations

Despite the advances in clinical practice and HF treatment modalities, there is a need for the creation of robust patient care pathways and quality improvement measures to improve overall health and reduce associated costs at both a community and national level. There was general consensus among the Heart Failure Expert Committee on

Table 37. Recommendations for performance measures in HF.

No.	Recommendations
1	Performance measures based on professionally developed clinical practice guidelines should be used with the goal of improving quality of care for HF
2	Participation in quality improvement programs and patient registries based on nationally endorsed, clinical practice guideline-based quality and performance measures can be beneficial in improving the quality of HF care

Based on guidance published by the European Society of Cardiology (ESC) [3] and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [10].

HF = heart failure.

Table 38. Performance indicators for HF.

Process related	<ul style="list-style-type: none"> • Proportion of patients with HFrEF discharged on beta-blocker therapy • Proportion of patients with HFrEF discharged on an ACE-I, ARB, or ARNi • Proportion of patients with HFrEF discharged on MRA • Proportion of patients with HFrEF implanted with an ICD • Proportion of patients with LBBB and HFrEF who were implanted with a CRT-D • Time from discharge to first outpatient clinic appointment • Proportion of patients aged >18 years with a diagnosis of HF for whom the ECHO results document heart failure within 12 months (LVEF assessment; outpatient setting) • Proportion of patients age >18 years with a discharge diagnosis of HF with documentation in the hospital records of an LVEF assessment performed during hospitalization • Proportion of patients counseled on medication, fluid intake, diet, and activity on discharge • Proportion of patients adherent to medication • Proportion of patients satisfied with treatment and overall care • Proportion of HF patient managed by a multidisciplinary team
Outcome related	<ul style="list-style-type: none"> • Proportion of patients readmitted to hospital within 30 days of discharge • Proportion of patients visiting the emergency department within 30 days of discharge • Proportion of patients readmitted to hospital within 12 months of discharge • In-hospital mortality rate of patients with HF • Mortality rate within 30 days, 60 days, and 1 year of discharge

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNi = angiotensin receptor/neprilysin inhibitor; CRT-D = cardiac resynchronization therapy-defibrillator; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist.

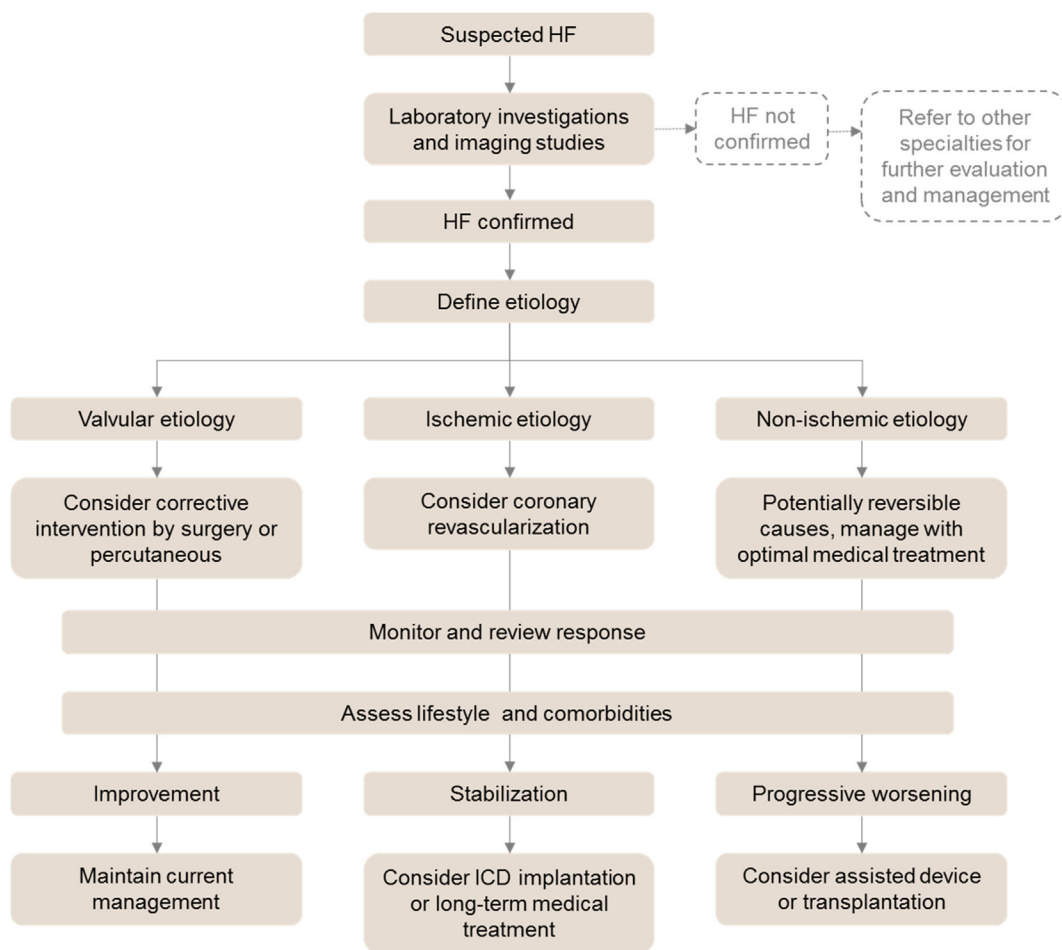


Fig. 9. Patient management pathway for HF. HF = heart failure; ICD = implantable cardioverter defibrillator.

the need for more epidemiological research in patients with HF. Studies looking at average salt intake, effectiveness of multidisciplinary care pro-

grams, prognostic markers, preferred imaging techniques, and rate of misdiagnosis in Saudi Arabia are necessary to improve patient management.

In terms of current practice, the Committee pointed out the lack of clarity on the percentage of patients presenting with HF symptoms who did not receive a definitive diagnosis, whether all patients with cardiomyopathy received a complete work-up, the percentage of patients with cardiomyopathy leaving with a presumed diagnosis of HF, and whether all centers assessing HF conduct imaging tests for all patients.

Owing to the lack of a national registry in Saudi Arabia, monitoring HF programs at a national level is difficult. However, the Saudi Health Council is currently working toward building sustainable healthcare registries with a focus on cardiovascular disease, which have the potential to shed light on several aspects of patient management in the country.

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Authors' contribution

This manuscript has been written by the Saudi Heart Failure Working Group, of the Saudi Heart Association. Dr. Waleed AlHabeb, President of the Saudi Heart Failure Working Group, of the SHA, and lead author of the manuscript was actively involved in the conception and execution of this project. All authors are board members of the Saudi Heart Failure Working Group, of the Saudi Heart Association, and have actively participated in recommendation generation. The final manuscript was approved by the board of the Saudi Heart Association.

Waleed AlHabeb, Fakhr Al-Ayoubi, Kamal AlGhalayini, Fahad Al Ghofaili, Yahya Al Hebaishi, Abdulrazaq Al-Jazairi, Mouaz H. Al-Mallah, Ali AlMasood, Maryam Al Qaseer, Shukri Al-Saif, Ammar Chaudhary, Abdelfatah Elasar, and Adel Tash participated in the premeeting survey and conducted literature review in support of the recommendations; participated in the consensus meeting for generating recommendations for management of HF in Saudi Arabia; and contributed to the development, review, and finalization of the manuscript. Mohamed Arafa and

Walid Hassan were responsible for overall critical review of the recommendations and manuscript content. All authors approved the submitted version of the manuscript.

Conflicts of interest

All arrangements for consensus generation such as meeting arrangements, travel, and follow-up were conducted by the SHA. Although the consensus meeting (held on October 7–8, 2016, in Riyadh, Saudi Arabia), and the medical writing was funded by Novartis through a research grant [SA1610535252], Novartis played no direct role in the collection, analysis, and interpretation of data or in the preparation of this manuscript. Dr. Waleed AlHabeb has received speaker honoraria from Novartis, Pfizer, Merck, MSD, Bayer, and Servier. Yahya Al Hebaishi has received speaker honoraria from Pfizer and Bayer. Mouaz H. Al-Mallah has received speaker honoraria from GE Healthcare. Ali AlMasood has received speaker honoraria from Novartis. Maryam Al Qaseer has received speaker honoraria from Novartis and Bayer. Shukri Al-Saif has received speaker honoraria from Merck and AstraZeneca, and is a clinical investigator for Novartis-sponsored research. Ammar Chaudhary has received speaker honoraria from Novartis. Fakhr Al-Ayoubi, Kamal AlGhalayini, Fahad Al Ghofaili, Abdulrazaq Al-Jazairi, Abdelfatah Elasar, Adel Tash, Mohamed Arafa, and Walid Hassan have no conflicts of interest to declare.

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