

Heart failure with reduced ejection fraction: A review of clinical status and meta-analyses of diagnosis by 3D echocardiography and natriuretic peptides-guided heart failure therapy

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Abstract

Heart failure (HF) with reduced ejection fraction (HFrEF) is a clinical syndrome in which pathological myocardial stress or injury leads to cardiac inability to perfuse the body's vital organs at rest or during exertion, usually documented by left ventricular ejection fraction $\leq 40\%$ on echocardiography. HFrEF constitutes about a half of all HF hospitalizations and remains the most common discharge diagnosis in older adults. Despite major advancements in the treatment of HFrEF and concomitant improvement in both outcomes and survival, nonspecific symptoms continue to make diagnosis difficult as well as HFrEF has the most ominous prognosis relative to HF with mid-range and preserved ejection fraction. Even upon diagnosis, predicting which patients are at a greater risk of death or major cardiovascular events remains a clinical challenge. In a critical appraisal of published evidence on HFrEF, this review purposes to provide a comprehensive understanding of the clinical status and management of HFrEF.

Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) is a complex and progressive clinical syndrome characterized by unacceptably high rates of post-discharge mortality, hospital length of stay, re-hospitalization, compromised functional capacity, reduced quality of life and substantial caregiver burden [1-3]. HFrEF accounts for about half of all the reported cases of HF and its prevalence continues to increase principally attributed to major therapeutic advances (improved survival rates) and an increasingly ageing population [4]. In older adults, HFrEF often represents the final pathway of many cardiovascular diseases [5]. In the effort to improve the management of HFrEF, the majority of recent studies have shifted focus from pathophysiology, prognosis and diagnosis to researching novel clinical and non-clinical care-based management strategies [6-11]. However, many non-specific symptoms (of limited diagnostic value) continue to make diagnosis difficult, post-diagnosis identification of patients at an elevated risk of death or cardiovascular events challenging and prognosis ominous [12]. Further, despite post hoc analysis of hospitalized heart failure registries revealing significant progress in the diagnosis and treatment of HFrEF, high mortality rates of 15% to 20% during the first year of diagnosis and rising to 40% to 50% within five years of diagnosis have remained relatively consistent over recent decades [5]. Such reports suggest HFrEF continues to represent a significant clinical problem even for the best performing healthcare systems. Thus, in a critical appraisal of published literature and meta-analyses of 3D echocardiography assessment of LV systolic function, and natriuretic (NP)-guided HF therapy, this review seeks to aggregate current scholarly and practitioner evidence on epidemiology, etiopathophysiology, diagnosis and clinical management to advance both the understanding and management of HFrEF.

Definition, epidemiology and prognosis

Definition

Previously, HFrEF was defined as a condition in which the heart fails to discharge its contents adequately [13] or a pathophysiological state in which an abnormality of cardiac function caused the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues [14]. Although these definitions accurately described the principal pathologic mechanism of HFrEF, they were difficult to apply in a clinical setting [15]. Today, most clinical trials and practice rely on or cite the definitions of the European Society of Cardiology (ESC) HF guidelines [16] or the American College of Cardiology Foundation/American Heart Association (ACC/AHA) Task Force on the management of HF [17].

The 2016 ESC guidelines define HF as a clinical syndrome in which patients exhibit typical symptoms (peripheral edema, fatigue, and dyspnea) and signs (elevated jugular venous pressure, pulmonary crepitation and displaced apex beat) caused by structural and/or functional cardiac abnormality resulting into reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress [16]. The 2013 ACC/AHA guidelines define HF as a complex clinical

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syndrome resulting from any structural or functional impairment of ventricular filling or ejection of blood with clinical manifestations of dyspnea, fatigue, limited exertional tolerance and fluid retention leading to splanchnic congestion and/or peripheral edema [17]. In both definitions, the diagnostic hallmark of HFrEF is left-ventricular ejection fraction (LVEF) equal to or less than 40% [16,17].

Taken the two definitions together, HFrEF is a clinical syndrome characterized by the cardinal triad of edema, fatigue and dyspnea resulting from an impairment of ventricular ejection of blood usually documented by LVEF of 40% or less. Although HFrEF is sometimes referred to as systolic dysfunction, it is not entirely accurate since some HFrEF patients may develop subtle diastolic dysfunction [16]. About one in every four females and one in every six males with HFrEF may show echocardiographic signs of an impaired diastolic function [4].

Classification: HFrEF is a progressive syndrome that worsens overtime resulting in a general decline in health and/or function. Several classification systems have been developed to assist in the objective determination of HFrEF stage based on symptomatic severity and/or the presence or absence of structural heart disease. The two most frequently cited classification systems are the ACCF/AHA stages of HF [18] and the New York Heart Association (NYHA) functional classification [19]. The ACCF/AHA stages of HF focused on disease development and progression, and could even be useful in describing both individuals and populations (Table1).

The ACCF/AHA classifies HF into four progressive and inviolate stages of HF (A-D) – once a patient has progressed to a higher stage, regression to an earlier stage is not observed. In the initial Stage A, patients are at a high risk of developing HFrEF but lack any demonstrable structural heart disease or symptoms. This stage includes patients with hypertension, CAD and DM. In Stage B, patients have demonstrable structural heart disease in the absence of signs or symptoms. This stage includes patients with LV hypertrophy and asymptomatic LV systolic dysfunction. In Stage C, patients have demonstrable structural disease and previous or current HF symptoms. This stage includes patients with HF-related dyspnea and fatigue. In the final Stage D, patients have structural heart disease and refractory to HF therapy. This stage includes patients with end stage HF [18]. The basis of the ACCF/AHA classification are abnormalities of cardiac structure and symptoms, quantified from a lower to a higher stage using a 5-year reduction in survival and an increase in the levels of plasma natriuretic peptides [20]. The four stages also provide guidance in therapeutic interventions: modifying risk factors (Stage A), treating structural heart disease (Stage B), and reducing morbidity and mortality (Stages C and D) [18]. The

NYHA functional classification on the other hand focuses on exercise (exertional) capacity and symptomatic status of HFrEF (Table 2).

The NYHA functional classification estimates symptomatic severity in those with structural heart disease (relating to Stages C and D in ACCF/AHA HF Stages). It is a subjective assessment, in which functional class can change frequently over short periods. Its main determinant is functional ability. In NYHA I, patients show no limitation in physical activities or symptoms. In NYHA II, patients exhibit HF symptoms during ordinary physical activities but not at rest. In NYHA III, patients have marked limitation of physical activities and ordinary activities may induce HF symptoms. In NYHA IV, patients are unable to carry any activities without inducing HF symptoms, which may also occur at rest [19]. It has reproducibility and validity challenges but remains an independent predictor of mortality in HFrEF patients [21,22] and widely adopted in clinical practice as a tool for determining eligibility of patients to receive certain health services [21].

Epidemiology: The precise estimate of HFrEF incidence and trends in the global population are scarce and at most unreliable. Most of the literature on HFrEF epidemiology is derived from high-income developed nations where the incidence may be plateauing or even decreasing [23]. On the other hand, while epidemiological data from North America and Europe estimates the prevalence of HF at 1% to 2% [24], the exact prevalence of HFrEF remains poorly understood. Most epidemiological studies and clinical registries that have included the HFrEF phenotype report high variability of its prevalence. The variation may be attributed to dissimilar definitions of HFrEF (different cut-off thresholds for LVEF), clinical setting (primary care, ambulatory care or hospital) and population characteristics (age, gender and history of myocardial infarction) used in individual studies [13,14]. In addition, epidemiological data on HFrEF prevalence from developing nations are conspicuously lacking [16]. Despite the variation, population-based studies conducted between 1997 and 2010 involving older patients (≥ 60 years) report prevalence rates of between 2.4% to 4.8%, with higher rates for males (range = 3.3% to 7.2%) than females (range = 1.5% to 4.1%) (Table 3).

The combined HFrEF prevalence in the four studies is 3.3%, range: 2.4% to 5.8% [28]. Besides gender, the prevalence of HFrEF has a positive correlation with age. Individuals aged 50 years or below are unlikely to have HFrEF but in those aged above > 50years, the prevalence and incidence increases progressively. One in six older adults > 65 years presenting to a primary care with exertional dyspnea will have unrecognized HF [16]. Increasing incidence of HF with age might explain the high prevalence rates in Raymond et al. [24] and Tiller et al. [4] studies, which recruited much older patients.

Table 1. The ACCF/AHA stages of heart failure

HF Stage	Description	Example
A	High risk, no structural heart disease and/or symptoms	Hypertension, coronary artery disease (CAD), diabetes mellitus (DM)
B	Structural heart disease no signs and/or symptoms	LV hypertrophy, asymptomatic left ventricular systolic dysfunction
C	Structural heart disease, prior or current symptoms	Dyspnea or fatigue due to HF
D	Structural heart disease, refractory HF	Patients with end stage heart failure

Adapted from Hunt, *et al.* 2009 Focused update of the ACC/AHA 2005 HF Guidelines [18]

Table 2. The NYHA functional classification

NYHA Class	Description (based on physical activity and symptoms)
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

Adapted from the Criteria Committee of the New York Heart Association [19]

Risk factors and prognosis: Risk factors are individual characteristics, attributes or co-occurring diseases that may precipitate or aggravate the natural cause of HFrEF. The most frequent independent risk factors are cardiac conditions such as coronary artery disease, myocardial infarction and hypertension; extra cardiac conditions such as diabetes mellitus, chronic kidney disease and anemia; and patient characteristics such as the male gender and older age (Table 4).

Coronary artery disease and hypertension have been identified as the major risk factors for the incidence and accelerated progression of HFrEF [4,28,29]. These two risk factors frequently co-exist in HFrEF patients each conferring an additive effect on the onset or progression of LV remodeling and HFrEF [29]. Coronary artery disease with antecedent myocardial infarction is also a major risk factor for the development of HFrEF [31]. Extra cardiac conditions such as diabetes mellitus, impaired kidney function and anemia may also increase the risk of HFrEF but not as intense as in HF patients with preserved ejection fraction [17,33-37]. While CAD, hypertension and myocardial infarction increase the risk of HFrEF, the effect vary based on age, gender and race [28]. Older age and male gender impose an independent risk on the likelihood of developing HFrEF associated with increased prevalence and burden of CAD in older adults [4,17].

HFrEF shares many risk factors (although at varying degrees) with HF with mid-range ejection fraction (HFmEF) and HF with preserved ejection fraction (HFpEF) but has the most ominous prognosis irrespective of age, gender and etiology [38,39]. Knowledge of HFrEF prognosis for morbidity, disability and mortality is important to guide the most appropriate type and timing of therapy [16]. The ESC HF guidelines list many prognostic factors of mortality and hospitalization in HFrEF patients (Table 5).

Despite the poor prognosis, advances in pharmacotherapy (beta-blockers, angiotensin-converting enzyme-inhibitors/angiotensin

receptor blockers [ACE-I/ARB]) and device therapies (implantable cardioverter-defibrillator [ICD] and cardiac resynchronization therapy [CRT]) have significantly improved prognosis of mortality and hospitalization rates relative to HFpEF [41]. If HFrEF therapies are included in prognostic studies comparing HFrEF, HFmEF and HFpEF, prognosis of HFrEF may be lower because of greater number evidence-based therapies with proven clinical efficacy in the reduction of mortality and hospitalization relative to HFmEF and HFpEF phenotypes [41,42].

Etiology and pathophysiology

Etiology: Overall, etiology of HF is diverse both within and among world regions. There is a lack of a single classification system for the causes of HF, with much overlap between HFrEF, HFmEF and HFpEF phenotypes. Several different pathologies (cardiac and extra-cardiac) could conspire to cause HF, and the identification of such pathologies should form part of the diagnostic work-up of HF phenotypes [16]. The ESC HF guidelines list pathological myocardial injury (coronary artery disease, cardiomyopathies, viral infection and toxins), abnormal loading conditions (arterial hypertension and valvular diseases) and arrhythmias (tachyarrhythmias and bradyarrhythmias) as the principal etiology of HFrEF (Table 6).

Pathophysiology: The functional hallmark of HF is the inability of cardiac performance to meet the metabolic demands of body tissues. Three key factors conspire to impair cardiac performance: (a) increased preload (or volume overload); (b) the loss of intrinsic contractility; and (c) increased afterload (or pressure overload), which cause a reduction in stroke volume [43]. Preload (also known as LV end-diastolic pressure) refers to the degree of ventricular stretch at the end of diastole. It is reflected by blood volume filling the ventricle prior to contraction and thus changes in blood volume causes alterations in both preload and stroke volume. [43,44] Afterload refers to the pressure

Table 3. Reported prevalence of HFrEF in patients ≥ 60 Year

Ist Author [Ref #]	Period	LVEF Cut-off	All Patients	Male	Female
Raymond et al. [25]	1997-2000	40%	4.0	5.5	2.9
Abhayaratna et al. [26]	2002-2003	50%	2.5	NR	NR
Tiller et al. [4]	2002-2004	50%	5.8	7.2	4.1
Mureddu et al. [27]	2007-2010	50%	2.4	3.3	1.4

Table 4. Independent risk factors for heart failure with reduced ejection fraction

Categories	Specific Conditions/Characteristics
Cardiac conditions	Coronary artery disease [4,28-32], arterial hypertension [4,17,29], myocardial infarction [4,28,30-32]
Extra-cardiac conditions	Diabetes mellitus [17,33], impaired kidney function [34, 35,36], anemia [33,34]
Patient Characteristics	Older age [4,16,17,28,33,37], male gender [4,16,17,28,33,37], and race [17,28,29].

Table 5. Prognostic predictors of death and hospitalization in left heart failure

Predictors of an Ominous Prognosis	Description of Specific Predictors of an Ominous Prognosis (Death and/or Hospitalization)
Patient demographics	Older age, male sex, low socio-economic status.
Clinical markers	NYHA III-IV, limited exercise tolerance, reduced functional state or poor quality of life, pulmonary congestion, splanchnic congestion, peripheral edema, jugular venous dilation and hepatomegaly, high resting heart rate and frailty
Severity of ventricular dysfunction	Depressed LVEF, LV dilatation, severe diastolic LV dysfunction, elevated LV filling pressure, mitral regurgitation, aortic stenosis, LV hypertrophy, left atrial dilatation, RV dysfunction, pulmonary hypertension, and ventricular dyssynchrony,
Biomarkers (for cardiac damage/dysfunction, neurohormonal activation and/or inflammation)	Low sodium, high natriuretic peptides, high plasma renin activity, high aldosterone and catecholamine, high endothelin-1, high adrenomedullin, and high vasopressin
Cardiovascular co-morbidities	Atrial fibrillation (AF), ventricular arrhythmia, non-revascularizable coronary artery disease, previous stroke/ transient ischemic attack, peripheral artery disease.
Extra-cardiac co-morbidities	Diabetes, anemia, iron deficiency, chronic obstructive pulmonary disease, renal failure, liver dysfunction, sleep apnea, cognitive impairment, and depression.
Clinical events	Non-adherence with treatment, HF-related hospitalization, aborted cardiac arrest and implantable cardioverter defibrillator shocks.

HF: Heart Failure; **LV:** Left Ventricular; **LVEF:** Left Ventricular Ejection Fraction; **NYHA:** New York Heart Association. Adapted from the 2012 ESC Guidelines for diagnosis and treatment of acute/chronic heart failure [40]

Table 6. Principal etiologies of heart failure with reduced ejection fraction

Etiology	Conditions	Description	Effect on Cardiac Function/Structure
Myocardial injury	Coronary artery disease	Blockages in your coronary arteries that limit blood flow to your heart muscle	It weakens or damages the myocardium and impairs its ability to eject blood.
	Cardiomyopathy	A progressive myocardial disorder	Weakens the myocardium impairing contractility and decreasing stroke volume.
	Viral myocarditis	Viral infection of the myocardium	Causes inflammation in the myocardium affecting its ability to contract and eject blood.
	Toxins	Alcohol, chemotherapy agents and radiation	Continued exposure may affect the myocardium and impairs its ability to eject blood.
Abnormal loading conditions	Arterial hypertension	Elevates arterial pressure	Increases cardiac workload to eject blood against increased pressure, which weakens the myocardium
	Aortic stenosis	Narrows the opening of aortic valve and impairs blood flow	Increases cardiac workload to eject blood through the narrowed valve, weakening the myocardium.
	Mitral regurgitation	Improper closure of the mitral valve, leading to leakage on left side of the heart	Increases blood volume leading to dilatation and weakened myocardium.
Arrhythmias	Tachyarrhythmias, bradyarrhythmias	Causes irregular heart rhythm	Irregular rhythm decreases cardiac pumping effectiveness

the ventricles have to work against when ejecting blood generated by pulmonary and systemic circulations. A rise in peripheral vascular resistance increases ventricular stroke work [45]. Contractility refers to ventricular force used to eject blood usually affected by myocardial injury (cardiomyocyte necrosis) [43]. While all the three factors may occur in HFrEF, the loss of contractility is the cardinal pathologic process resulting from ventricular remodeling and neurohormonal changes through the activation of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) [46].

Activation of renin-angiotensin-aldosterone system: Cardiac inability to function effectively as a pump activates the renin-angiotensin-aldosterone system (RAAS). Reduced blood flow due to decreased cardiac output stimulates the kidney to secrete renin, which participates in the conversion of angiotensin I into active hormone angiotensin II angiotensin-converting enzyme (ACE) found in the lungs [43]. Angiotensin II, a potent vasoconstrictive peptide, exert a deleterious effect to cardiac tissues by causing blood vessels to narrow, resulting into elevated blood pressure and cardiomyocyte hypertrophy. Angiotensin II also stimulates the release of aldosterone hormone, which causes sodium and water retention in turn increasing blood volume and cardiac output [43]. Increased blood volume by aldosterone and vasoconstriction by angiotensin II leads to additional cardiomyocyte damage and fibrosis to occur [44]. Another hormone causing water retention and vasoconstriction is arginine vasopressin (an anti-diuretic hormone [ADH]), which is released because of atrial stretching and decreased cardiac output. Atrial overstretching due to increased volume overload increases preload and decreases cardiac output [43]. Vasoconstriction and water retention causes an increase in afterload (pressure overload) leading to increased cardiac workload and consequently an increase in metabolic demands. When compensatory mechanisms of cardiomyocytes cannot keep up with metabolic demands, LV remodeling and hypertrophy occurs, perpetuating the cycle of HF [44].

Activation of sympathetic nervous system: Decreased blood pressure and cardiac output also activates the sympathetic nervous system (SNS). Activation of the SNS stimulates the release of noradrenaline norepinephrine, which in turn triggers beta-receptors to increase the heart rate, strength and rapidity of contractions [45]. Increased heart rate, the LV begins to hypertrophy and collagen depositions occur causing pathologic LV remodeling [43]. Left ventricular remodeling conveys a substantial negative effect on cardiac contractility. Mechanical stimulation of the myocardium is the key process leading to ventricular hypertrophy. Myocardial fibrosis on the other hand, may be the result of the activation of neurohormonal compensatory mechanisms such as

cytokines and hormones [46]. Overtime, compensatory mechanisms can turn toxic to the cardiomyocytes and render them unable to respond to the body's attempt to compensate [43]. The activation of the RAAS and the SNS neurohormonal systems are linked to the development of HF symptoms and poor prognosis over time leading to diminished quality of life, decreased functional capacity, re-hospitalization, and premature death secondary to pump failure or ventricular arrhythmias. As such, the interruption of RAAS and SNS neurohormonal response is the basis of much of the current treatment of HFrEF [43,46].

Left ventricular remodeling: Whereas neuro-hormonal activation contributes to depressed LV function (LVEF), the key pathophysiologic mechanism of depressed LVEF is ventricular remodeling, referring to a process in which mechanical, neurohormonal and genetic factors regulate the size, shape and function of the ventricles. Ventricular remodeling is a normal physiological and adaptive process but may also be pathological, occurring in the setting of cardiac conditions such as acute myocardial infarction, hypertension, cardiomyopathy and valvular heart disease [46]. During ischemia or post-infarction, three major cell death modalities – apoptosis, necrosis and autophagy – occur in cardiomyocytes [47]. Upon increased cardiomyocyte death, inflammatory reaction occurs, which is a prerequisite for healing and scar formation. However, chronic inflammation can become pathologic. In the later stages of HF, increased loading conditions and chronic inflammation may induce compensatory changes such as LV hypertrophy and dilatation as adaptive processes to LV remodeling to offset increasing load, attenuate progressive LV dilatation and stabilize LV contractility [46,48].

Damaged myocardium produces reactive oxygen species (ROS) causing stress, inflammation and cardiomyocyte necrosis and leading to the release of pro-inflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor - alpha (TNF-α) [49]. These molecules exacerbate LV failure by increasing leukocyte attraction, inflammatory response and endothelial destruction. In turn endothelial destruction leads to the reduction of vasodilator nitric oxide causing vasoconstriction [48]. Vasoconstriction continues to stimulate neurohormonal and inflammatory response proliferating the cycle of myocardial injury [44]. If left untreated, LV remodeling progressively worsens over time characterized with increasing LV dilatation and declining LVEF [13,41]. In addition to ventricular remodeling, limited cardiac reserve in HFrEF patients depends on several other mechanisms including atrial contraction, synchronized LV/RV contraction and ventricular interdependence. Events that effect any of these mechanisms such as atrial fibrillation, conduction abnormalities or additional hemodynamic load could lead to acute decompensation [46].

Clinical presentation and diagnosis

Clinical presentation: Patients with HF usually present with the classic triad of symptoms – edema, fatigue, and dyspnea. Other typical symptoms may include orthopnea, paroxysmal nocturnal dyspnea, reduced exercise tolerance, and increased time to recover from exercise. Less typical signs include nocturnal cough, wheezing, bloated feeling, loss of appetite, confusion (especially the elderly), depression, palpitations, dizziness, syncope and bendopnea [12,16]. However, symptoms are non-specific and non-sensitive, and therefore are less useful in discriminating HFrEF from HFmEF or HFpEF. In addition, atypical presentation should be considered when evaluating obese patients and older adults because of potentially different etiology, clinical presentation and outcome compared to the general population [50-53]. Typical signs of HFrEF include elevated-jugular venous pressure, gallop rhythm, hepatojugular reflux, and laterally displaced apical impulse. Less typical symptoms include weight gain, cachexia (tissue wasting), cardiac murmur, peripheral edema (ankle, sacral, scrotal), pulmonary rales, tachycardia, irregular pulse, tachypnea, hepatomegaly, ascites, cold extremities, oliguria and narrow pulse pressure [16]. The assessment of signs and symptoms is clinically significant to suggest the likelihood of HFrEF as well as to monitor response to therapy and stability overtime. Persistent symptoms despite treatment often suggest the need for additional therapy and worsening of symptoms often suggest serious development and the need for prompt medical attention [16].

Diagnosis

Diagnosis work-up: Diagnosis of HFrEF is made when symptoms and physical signs of congestion and decreased tissue perfusion are documented in the setting of systolic and/or diastolic dysfunction. The 2016 ESC, the 2013 AHA and the 2012 Canadian HF guidelines recommend diagnostic work-up for the assessment of HFrEF should follow the general heart failure algorithm but distinguished using echocardiography-defined LVEF < 40%. The diagnostic work-up include assessment of clinical history and physical examination, laboratory examination, and echocardiography assessment of LV structure and function. If echocardiography is inconclusive, additional tests imaging tests such as radionuclide, cardiac catheterization, magnetic resonance imaging, computed tomography (CT), scan and endomyocardial biopsy, and cardiopulmonary exercise testing may be considered to confirm diagnosis (Figure 1).

History/physical examination: The 2013 ACCF/AHA HF guidelines recommends the initial step in the diagnosis of HFrEF is the assessment of the history and physical examination to determine typical HF signs and symptoms, and diseases that can cause HF or contribute to its progression. [17]. Table 7 summarizes medical history and physical examination and their suggestive diagnostic clues. Clinical history should include assessment of symptoms, functional limitation, prior cardiac diseases, presence of risk factors, exacerbating factors, comorbidities, and previous or current drugs. Physical examination should include assessment of vital signs, weight, volume status, heart, lung, abdomen and vascular [12].

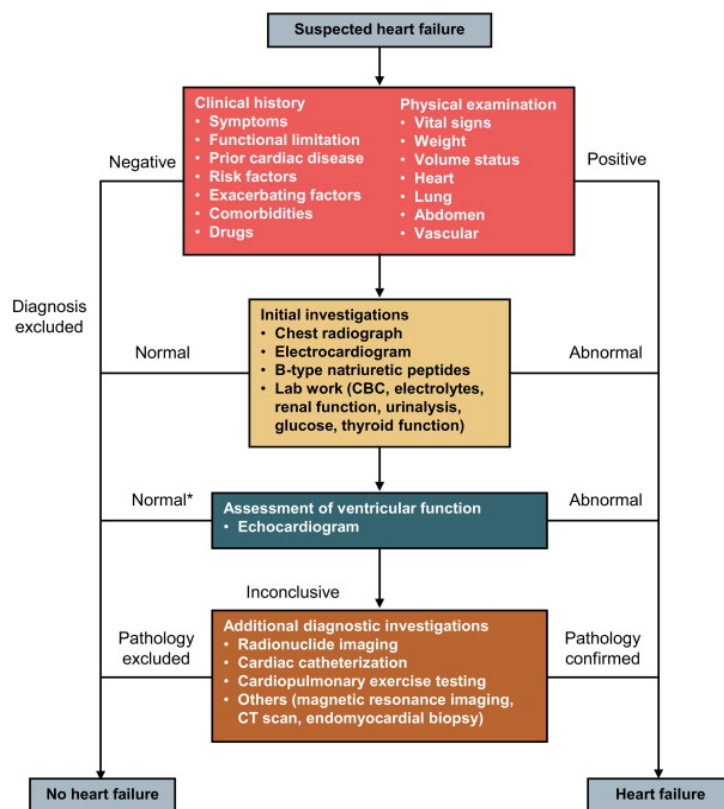


Figure 1. Algorithm for diagnosis of heart failure

Diagnosis of HFrEF begins with the assessment of clinical history and physical examination to determine risk factors, and signs and symptoms. If all the findings are normal HFrEF is excluded otherwise clinical investigations (chest radiography, ECG and/or natriuretic peptide assessment) should be considered. If one of the findings is abnormal, echocardiography should be done to confirm diagnosis. If the findings remain unclear or inconclusive, additional diagnostic tests should be considered such as radionuclide imaging, cardiac catheterization, cardiopulmonary exercise, magnetic resonance imaging, CT scan or endomyocardial biopsy) to confirm diagnosis

Laboratory tests: If patient history and physical examination suggests abnormal signs and symptoms related to HF, 12-lead electrocardiogram (ECG) should be performed. Although ECG increases the diagnostic likelihood for HFrEF, it has very low specificity [37,50,54,55]. Usually, ECG is used to determine abnormalities in heart rhythm, heart rate, QRS duration and morphology [12]. Abnormal ECG increases the likelihood of HFrEF diagnosis or provide information on possible etiologies such as myocardial infarction as well as indication for therapy such as anticoagulation for atrial fibrillation and pacing for bradycardia. Completely normal ECG has a high sensitivity and useful to rule out HFrEF [16].

The assessment of the levels of serum natriuretic peptides (NPs) is recommended in non-acute settings especially when echocardiography is not immediately available. Normal serum NPs levels indicates a very low likelihood of HFrEF (Table 8).

Threshold values (upper limit for normal serum NPs) are lower in non-acute setting relative to acute setting. The threshold values have low positive predictive values in non-acute and acute settings (44% to 67%) but with high negative predictive values (94% to 98%) [56-59]. Thus, the use of serum NPs is recommended for the exclusion of HFrEF rather than to establish diagnosis [12,16]. Other potential cardiac and extras cardiac causes of elevated NPs such as atrial fibrillation, obesity, age and renal failure should be considered during interpretation. In obese patients, NPs maybe disproportionately low [60].

Echocardiography: Echocardiography should be considered in all suspected HFrEF patients with abnormal signs and symptoms, and/or abnormal ECG and elevated levels of serum NPs [16,17]. Echocardiograph is useful for the assessment of cardiac structure and function to quantify LV function for establishing diagnosis, prognostic stratification and planning for treatment [12]. It provides immediate information on cardiac chamber volumes, ventricular systolic function, LV wall thickness, valve function and pulmonary hypertension [61-67]. The LVEF cut off values of 40% or less confirms the diagnosis of HFrEF. Other abnormalities include LV hypertrophy and dilatation [16].

Other Tests: If echocardiography evaluation is inconclusive or uncertain such as suboptimal images or an unusual cause of HFrEF is suspected, additional tests should be considered to confirm diagnosis. The 2016 ESC recommends cardiac magnetic resonance (CMR) imaging for assessing myocardial structure and function in patients with poor acoustic window and complex congenital heart diseases and in cases of suspected myocarditis, amyloidosis, myocarditis, and sarcoidosis. In addition, CMR with late gadolinium enhancement may be considered in patients with dilated cardiomyopathy to distinguish ischemic and non-ischemic myocardial injury. Invasive coronary angiography is recommended in patients with a history of symptomatic ventricular arrhythmia or aborted cardiac arrest. It may also be considered in patients with HF and intermediate-to-high probability of CAD, or angina pectoris deemed candidates for coronary revascularization. Cardiac CT may be considered in HF patients with intermediate to high probability of CAD or with equivocal non-invasive stress tests to exclude coronary stenosis. Chest radiography (X-ray) is recommended in HF patients to determine or exclude alternative pulmonary or other diseases contributing to dyspnea or identify pulmonary congestion/edema more helpful in suspected HF patients in the acute setting. Non-invasive imaging re-assessment of myocardial structure and function should be considered in patients with worsening symptoms, patients receiving maximal dose of pharmacotherapy as a bridge before the decision on device implantation and to patients exposed to therapies with the potential to injure the myocardium [16].

Meta-Analysis of diagnosis methods: The mainstay of the diagnosis of HFrEF is the assessment of LV systolic dysfunction defined using LVEF < 40% [12,16,17]. The conventional two-dimensional echocardiography (2DE) is the most widely used imaging technique for assessing LV size and dysfunction in clinical practice because of its wide availability, portability, inexpensive, radiation free and timely [17]. However, concerns have been raised on its reliability, reproducibility and accuracy in the measurement of LVEF and volumes due to errors of foreshortening, narrow echocardiograph windows, poor endocardial definition and assumptions on LV shape [68]. On the other hand, because of the ability of the CMR imaging modality to visualize the

Table 7. Medical history and physical examination and their suggestive diagnostic clues

Assessment	Signs/Symptoms	Suggestive Diagnostic Clues	
Detailed history	Clues suggesting HF etiology	Genetic etiology as familial cardiomyopathy.	
	Duration of illness or symptoms	Recent onset of HF	
	Anorexia, early satiety	Gastrointestinal abnormalities	
	Rapid weight gain	Volume overload	
	Palpitations, syncope	Paroxysmal AF or ventricular tachycardia.	
	Transient ischemic attack	Thromboembolism	
	Peripheral edema/ascites	Volume overload	
	Disordered nocturnal breathing or sleep problems	Pulmonary hypertension due to sleep apnea	
	Physical Examination	Body mass index/weight loss	Obesity a contributory factor cachexia suggests poor prognosis
		Blood pressure in supine/upright	Hypertension or hypotension
Jugular pressure at rest		Congestion	
Third heart sound and murmurs		Valvular disease and adverse prognosis	
Hepatomegaly/ascites		Markers of volume overload	
Peripheral edema		Peripheral rather than cardiac causes	
	Cold extremities	Inadequate cardiac output	

Adapted from 2012 ACCF/AHA Heart Failure Guidelines

Table 8. Threshold for natriuretic peptides for exclusion of HFrEF diagnosis

Serum Natriuretic Peptides	Non-Acute Setting	Acute Setting
B-type natriuretic peptide (BNP)	< 35 pg/mL	< 100 pg/mL
N-terminal pro-BNP	< 125 pg/mL,	< 300 pg/mL
Mid-regional pro A-type natriuretic peptide (MR-proANP)	--	< 120 pmol/L

entire heart in multiple planes and has excellent endocardial definition, it is considered the gold standard for assessing LV volumes and ejection fraction, but due to limited availability and great expense, it is impractical for widespread use [69,70]. Some echocardiography laboratories have begun using three-dimensional echocardiography (3DE) to assess LV volumes and ejection fraction. However, it is not clear whether 3DE provides superior diagnostic accuracy compared to 2DE in the assessment of LV volumes and ejection fraction. The present meta-analysis seeks to combine current real-time (or live) 3DE published literature to evaluate its diagnostic performance relative to CNR and its utility relative to the conventional 2DE in the assessment of LVEF and end diastolic volumes in HFrEF patients.

Search strategy and inclusion criteria: Published studies evaluating 2DE, real-time 3DE (RT3DE) and CMR on the assessment of LV structure and function were searched in PubMed, EMBASE, Clinical Trials, the Cochrane Central Register of Controlled, National Institutes of Health ClinicalTrials.gov, and UpToDate Online. Supplementary checks were conducted on citations of all studies that met the inclusion criteria and relevant review articles. Grey literature, databases and conference proceedings were also searched to obtain a comprehensive list of included studies. Variations and combinations of the following key search terms were used: two-dimensional echocardiography, real-time/live three-dimensional echocardiography, cardiac magnetic resonance imaging and ventricular systolic function, ejection fraction, end diastolic volume. The inclusion criteria were, the studies (a) included patients with reduced ejection fraction; (b) compared RT3DE, 2DE and/or CMR for the assessment of LV function; (b) provided correlation between RT3DE and 2DE with CMR on estimates of LVEF and LV end-diastolic volumes, and Bland-Altman values. The exclusion criteria were studies including animal models, did not use CMR as a reference standard, and studies with only abstracts. There was no restriction on publication year or language. Two reviewers independently assessed qualifying studies against the inclusion criteria and any disagreements resolved through consensus. Both reviewers independently abstracted data relevant to the study topic and did quality assessment using the Quality Assessment of Diagnostic Accuracy of Studies (QUADAS) criteria. The abstracted data included first author, patient sample and mean age and clinical outcomes (Bland-Altman values, and correlation of RT3DE and 2DE with CMR on LV end-diastolic volume (LVEDV) and ejection fraction (EF) (Tables 9 and 10).

Study characteristics and outcomes: The online search and screening of bibliographies yielded 102 potential studies. After exclusion based on title and keywords, and screening against the inclusion/exclusion criteria, 94 studies were excluded because they contained abstracts only, did not provide Bland-Altman values, evaluated 2DE/RT3DE strain, did not include CMR, reported LV mass only, included children or reported right ventricular function and/or mass. Ultimately, eight (8) studies [71-78] were included comprising of 416 patients with reduced LV ejection fraction (mean age = 59 years; range – 32 to 66) with a majority being male (71%). Reasons for referral to cardiac imaging included various cardiac condition including a history of myocardial infarction, coronary artery disease (CAD), dilated cardiomyopathy (DCM), ischemic/non-ischemic cardiomyopathy, congenital heart diseases and valvular disease, which suggest LV systolic dysfunction. Analysis of RT3DE required < 2 minutes per patient. Considering cardiac magnetic resonance (CMR) imaging as the reference standard for the assessment of LV systolic function (LVEDV and LVEF), RT3DE showed an excellent correlation with CMR for LVEDV (0.95) and LVEF (0.89) with slight underestimation of volumes (-11) and ejection fraction (-0.29%). On the other hand, 2DE had a relatively lower correlation with CMR for LVEDV (0.79) and LVEF (0.71) and with higher underestimation of volumes (-38.38) and ejection fraction (-2.53). The findings reveal that RT3DE is suitable for clinical use because it demonstrates superior performance (accuracy and precision) in the assessment of LVEDV and LVEF compared to 2DE.

Discussion of outcomes: Accurate quantification of LV volumes and ejection fraction is of critical importance to the practice of cardiology. Measures of LVEDV and LVEF are useful to inform prognosis in most patients with cardiac diseases, determine treatment decisions for a variety of therapies and provides eligibility criteria in clinical trials [79,79-81]. Current clinical guidelines, the Canadian Cardiovascular Society [12], ESC [16], and the ACCF/AHA [17] recommend the basis of a variety of therapeutic decision should be volumetric and LVEF measures in various patient cohorts including HF, valvular disease and cardiomyopathies. Although the most ubiquitous imaging technique in clinical practice to assess LVEDV and LVEF is the 2DE, its accuracy and reproducibility have significant limitations due to foreshortening errors and reliance on geometric models that may less accurate in diseased hearts [82-85]. Whereas CMR is the gold standard for assessing

Table 9. Summary of patient characteristics in included studies

	Jenkins et al. [71]	Gutiérrez-Chico et al [72]	Jacobs et al. [73]	Jenkins et al. [74]	Jenkins et al. [75]19	Bicudo et al. [76]	Chukwu et al. [77]	Marsan et al. [78]
Year	2004	2005	2005	2006	2007	2008	2008	2011
Sample	50	35	50	30	110	20	69	52
Age	64(8)	61(17)	58(19)	66(7)	63(11)	32(15)	66(5)	62(10)

Table 10. Summary of correlation and band altman in included studies

1st Author [Ref #]	RT3D Echocardiography				2D Echocardiography			
	r LVEDV	r LVEF	BA LVEDV	BA LVEF	r LVEDV	r LVEF	BA LVEDV	BA LVEF
Jenkins et al. [71]	0.98	0.92	-4(29)	0(7)	0.92	0.66	-54(33)	-1(13)
Gutiérrez-Chico et al [72]	0.99	0.98	-13(34)	NR	0.78	0.92	-25(13)	-21(11)
Jacobs et al. [73]	0.96	0.93	-14(34)	-1(13)	0.89	0.86	-23(58)	0.8(19)
Jenkins et al. [74]	0.86	0.81	-15(28)	-1(8)	0.68	0.70	-70(39)	-3(11)
Jenkins et al. [75]	0.89	0.92	-15(31)	-1(7)	0.72	0.65	-57(40)	-5(12)
Bicudo et al. [76]	0.94	0.83	-4(16)	-2(11)	0.91	0.73	1(23)	-1(14)
Chukwu et al. [77]	0.99	0.79	-1(10)	2(8)	0.50	0.23	-38(51)	9(16)
Marsan et al. [78]	0.97	0.97	-22(40)	1(5)	0.94	0.96	-41(49)	1(5)

2D: Two-dimensional; **BA:** Bland-Altman; **LVEDV:** Left Ventricular End-Diastolic Volume; **LVEF:** Left Ventricular Ejection Fraction; **r:** Correlation; **RT3DE:** Real-time three-dimensional echocardiography.

LVEDV and LVEF, high cost and limited availability problematizes its use in routine clinical practice [69,60]. Efforts to improve diagnosis and prognosis in HF patients has motivated research interest into the validity and benefits of newer cardiac imaging modalities, including 3DE, whose utility in assessing LV structure and function has already been embraced by some echocardiography clinics. The present meta-analysis sought to compare the accuracy of RT3DE compared to CMR in assessing LV volumes and ejection fraction.

The present analysis finds RT3DE has a stronger correlation to CMR in assessing both LV volumes and ejection fraction compared to 2DE. While correlation analysis indicate a strong relationship, Bland-Altman analysis reveals RT3DE has a lower underestimation of volumes and better agreement with CMR compared to 2DE. Two studies [71,73] also compared the reproducibility of 3DE with 2DE based on intra-observer and inter-observer agreement or variability. For all parameters (LVEDV and EF), Jenkins et al. [71] reported higher inter-observer agreement with 3DE (LEVDV: $r = 0.95$; LEVF: $r = 0.88$) compared to 2DE (LEVDV: $r = 0.76$; LEVF: $r = 0.61$) and intra-observer agreement with RT3DE (LEVDV: $r = 0.98$; LEVF: $r = 0.97$) compared to 2DE (LEVDV: $r = 0.90$; LEVF: $r = 0.61$). Jacobs et al. [73] reported lower intra-observer variability with RT3DE vs. 2DE (LVEDV: 7.9% vs. 23%) and lower inter-observer variability (11% vs. 26%), with 3DE having an excellent correlation with CMR values ($r = 0.94$ and 0.98) [73]. The findings indicate RT3DE has superior reproducibility (lower re-test variability) compared to 2DE in the assessment of LV volumes and ejection fraction. Higher observer agreement is particularly important in clinical practice with a variety of reader and sonographers interpreting imaging results for patients undergoing serial examination to determine disease or therapeutic progress.

The superiority of 3DE to 2DE in the assessment and reproducibility of LV volumes and ejection fraction has been reported in previous clinical trials and review articles [86-89]. The superiority is associated with the RT3DE modality using recently developed matrix array echocardiographic probes to visualize the entire heart in ≤ 8 beats per minute providing volumes with minimal post-processing [90]. In the U.S., some echocardiography clinical have already embraced the RT3DE modality for routine clinical practice [91]. However, if RT3DE is not fully automated, it will remain time-consuming and resource-intensive with sub-optimal intra-observer and inter-observer agreement, which may undermine its implementation in routine clinical practice. There is need for additional developments in both hardware and software including fully automated knowledge-based algorithm for assessing and quantifying ventricular volumes and ejection fraction [88]. In the present medical era, where new imaging technology may escalate medical costs, RT3DE require thorough evaluation prior to any recommendations to widespread use.

Clinical management

Pharmacotherapy: Pharmacologic therapy remains the cornerstone of clinical management of HFrEF [16,17,92,93]. Diagnostic algorithm for pharmacologic support includes the main validated HF medication – angiotensin-converting enzyme-inhibitors (ACE-I)/Angiotensin Receptor Blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRA), digoxin, ivabradine, arterial vasodilator (Figure 2).

Angiotensin-converting enzyme inhibitors: The efficacy of ACE-I in reducing mortality in HFrEF patients and in patients with myocardial infarction complicated by reduced ejection fraction [94-98]. ACE-I are the initial indications for HFrEF unless contraindicated or not tolerated in asymptomatic patient. For optimal outcomes,

ACE-I should be titrated up to the maximum tolerated doses to achieve adequate inhibition of the RAAS system. Sub-optimal doses reported in a majority of patients in clinical practice may not achieve the maximal medication benefit [99]. ACE-I are also indicated in patients with asymptomatic LV systolic dysfunction to reduce the risk of developing HF or HF-related hospitalization or mortality [16]. In patients contraindicated to ACE-I, ARBs should be considered. ARBs have been demonstrated to be non-inferior to ACE-I in patients with HFrEF or with MI patients complicated by reduced ejection fraction [99-101].

Beta-blockers: Beta-blockers such as bisoprolol, metoprolol and carvedilol have been demonstrated to reduce mortality and morbidity in symptomatic HFrEF patients despite treatment with ACE-I and/or diuretic [102-105]. Beta-blockers are also recommended in patients with a history of MI and asymptomatic LV systolic dysfunction. There is increasing consensus that beta-blockers may complement ACE-I, and thus, a dual therapy of beta-blocker is frequently used as the initial pharmacotherapy in HFrEF patients [12,16]. Initiation of beta-blockers in stable patients should begin at a low dose and gradually up-titrated to the maximum tolerated doses. In patients admitted with acute HF, beta-blockers should be cautiously initiated in hospital setting after stabilizing the patient [12].

Mineralocorticoid receptor antagonists: Mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone are recommended in all symptomatic HFrEF patients despite the use of ACE-I and beta-blockers to reduce mortality and HF hospitalization [106,107]. However, caution should be observed when MRAs are given to patients with renal dysfunction and those with elevated serum potassium levels (> 5.0 mmol/L) with regular assessment of serum potassium concentration and renal function [16].

Diuretics: Diuretics are indicated in HFrEF patients to reduce signs and symptoms for congestion. Although their effect on mortality and morbidity have not been conclusively investigated, a meta-analysis reports loop and thiazide diuretics in chronic HF patients reduces the risk of death and worsening [108] and improves exercise function [108,109]. Loop diuretics produce a more intense and shorter diuresis effect than thiazides. Loop diuretics and thiazides act synergistically and their combination may be considered in the treatment of edema but with caution of frequent adverse effects. Diuretics dosage should be adjusted according to individual needs over time. The use of diuretics may be temporarily discontinued in euvolemic or hypovolemic patients [17].

If channel antagonist: Ivabradine, an If channel antagonist slows heart rate and indicated for HFrEF patients in sinus rhythm and a resting heart rate of ≥ 70 beats per minute who have a contra-indication or intolerant to beta-blocker. Ivabradine should be used together with ACE-I/ARBs or MRA/ARB. Ivabradine has been shown to reduce composite clinical endpoint of mortality and re-hospitalization in symptomatic HFrEF patients with a heart rate of ≥ 70 beats per minute [16].

Digoxin: Digoxin may be considered in symptomatic HFrEF patients in sinus rhythm despite treatment with ACE-I/ARBs, beta-blocker and MRAs. The aim of using digoxin is to reduce the risk of hospitalization [110].

Non-pharmacological therapy: In HFrEF patients intolerant or non-responsive to pharmacotherapy, device therapy using ICD or CRT should be considered to prevent sudden cardiac death [12,16].

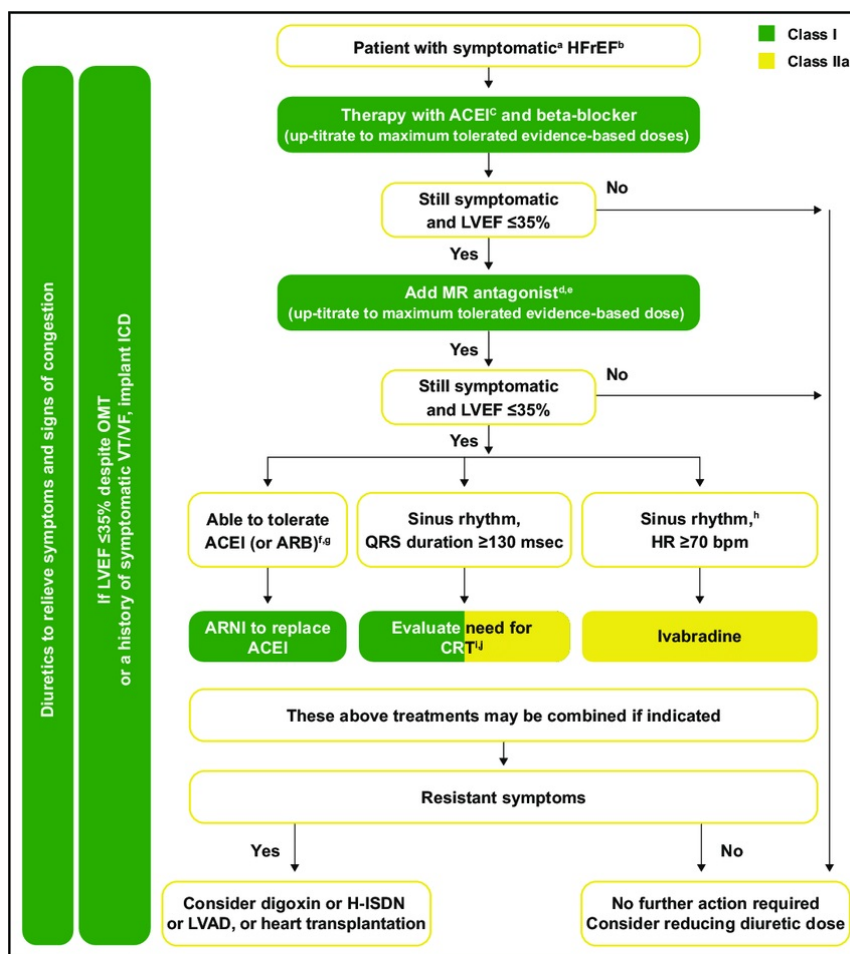


Figure 2. 2016 ESC recommended pharmacologic management for symptomatic HFrEF

Frontline medical therapy for HFrEF are ACE-I and beta-blocker, and diuretics for symptom relief. If still symptomatic and LVEF ≤35%, ARNI should replace ACE-I, Ivabradine or cardiac resynchronization therapy should be considered. If still asymptomatic, digoxin, LV assist device or heart transplantation should be considered [16]

Implantable cardioverter-defibrillator: Device therapy using implantable cardioverter-defibrillator (ICD) is recommended for secondary prevention of sudden cardiac death and all-cause mortality. It is indicated in HFrEF patients who have recovered from ventricular arrhythmias causing hemodynamic instability and expected to survive for more than one year. ICD is also recommended for the primary prevention of sudden death and all-cause mortality in symptomatic HFrEF patients, NYHA functional class II-III despite over three months of optimal medical therapy and expected to survive more than one year and have ischemic heart disease or dilated cardiomyopathy. However, ICD is not recommended for HFrEF patients in NYHA functional class IV with severe symptoms refractory to optimal medical therapy [16].

Cardiac resynchronization therapy: Cardiac resynchronization therapy (CRT) is another validated device therapy for HFrEF. It is recommended for symptomatic HFrEF patients in sinus rhythm with QRS duration ≥ 150 msec and with or without LBBB QRS morphology despite optimal medical therapy to improve symptoms and reduce mortality and morbidity. CRT is also indicated with HFrEF patients who have received conventional pacemaker or ICD and develop worsening symptoms despite optimal medical therapy, and have a high proportion of RV pacing considered for upgrade to CRT. However, CRT is contraindicated in patients with QRS < 130 msec [16].

Lifestyle modification: Effective clinical management of HFrEF should consider all available patient and clinical factors [16,17,92]. It should include both clinical management strategies (pharmacotherapy and non-pharmacotherapy) and non-clinical strategies (self-management and lifestyle modification). Non-clinical strategies require patient and family education on the disease to improve self-management. Lifestyle changes is an important part of self-management, which should include smoking cessation, decreased alcohol intake, and increase exercise [92]. Diet modification including low sodium and fluid intake, and daily monitoring of weight [45].

Meta-analysis of clinical management: Measurement of serum natriuretic peptides (BNP and NTpro-BNP) have an established role in the diagnosis of HFrEF. Although they are non-specific for the diagnosis of HFrEF, they have high sensitivity (excellent negative predictive values) for the exclusion of HFrEF diagnosis as well as in the appropriate selection of patients for echocardiography assessment of LV function [56-59]. They also provide valuable prognostic information for HFrEF progression and therapeutic response, HFrEF patients with reducing NPs levels may suggest better prognosis and vice-versa [57,58]. Despite the diagnostic and prognostic value of serum NPs, several published clinical trials investigating changes in serum concentration of NPs in guiding treatment in HFrEF patients have not established conclusively its clinical benefits. The present systematic review and meta-analysis

sought to aggregate current research evidence to determine the overall effect of BNP-guided therapy in HFrEF patients on mortality and hospitalization.

Search strategy and inclusion criteria: The search for relevant published studies was conducted in PubMed, EMBASE, the Cochrane Controlled Clinical Trials Register Database, and the ClinicalTrials.gov. Variations and combination of the key terms used in the search were B-type natriuretic peptide, N-terminal pro-BNP, heart failure, and therapy. Complementary manual search of citations of the retrieved studies were screened to obtain a comprehensive list of included studies. Studies were included if they satisfied the following criteria: (a) enrolled patients with HFrEF; (b) randomized patients based on a strategy of titrating medication based on the concertation of serum NPs compared to a control group; and (c) reported all-cause mortality. There was no restriction on the publication language and year. Two reviewed independently reviewed qualifying studies against the inclusion criteria using a hierarchical strategy: title, abstract and full-text screening. Both reviewers also abstracted data relevant data from the included studies and resolved any discrepancy by consensus. The included studies were assessed for patient characteristics, usual care and BNP-guide groups, clinical outcomes (all-cause mortality and survival free of hospitalization (Table 11).

Study characteristics and outcomes: Seven (7) studies meeting the inclusion criteria were included in this meta-analysis [9,111-116]. The studies compared NP-guided therapy with usual care or symptom guided therapy. The seven studies recruited a combined population of 2,261 patient undergoing HF therapy (medical and/or device therapy) constituting 1,120 in the NP-guided therapy group with (mean age = 70 years; male 57%) and 1,141 in the control group (mean age = 71 years; male 50%). Two natriuretic peptides (NP) used to guide therapy were BNP [11,112,115] and NTpro-BNP [9,113,114,116]. Therapy guided by NPs were medication (beta-blocker, ACE-I/ARB, neprilysin inhibitor, mineralocorticoid antagonist) and device therapies (implantable cardioverter-defibrillator [ICD] and cardiac resynchronization therapy [CRT]). Patients were followed for a mean of 14.5 months. NP-guided therapy has better clinical outcomes in reducing hospitalization (27.7%) and HF related mortality (12.6%) when compared to usual care, hospitalization (37%) and HF-related mortality (19.6%). The findings reveal NP-guided therapy has superior effect in protecting against HF-mortality and hospitalization compared to usual care.

Discussion of outcomes: Despite therapeutic advances, approximately 30% of HFrEF patients get re-admitted within two to three months after HF hospitalization and about 10% die within this period [117]. Attributable to such poor discharge outcomes may be sub-optimal care linked to poor treatment compliance and inadequate markers for follow-up [118]. Biomarkers play a significant role in medical practice and in cardiovascular care in particular. Natriuretic

peptides have been demonstrated as powerful diagnostic and prognostic tools. However, the extent to which NPS could be used to guide titration of medical therapy for HFrEF patients remains uncertain. The primary finding in the present meta-analysis reveals utility of serial assessment of NPs to aid of titration of medical therapy conveys a superior effect compared to the usual HF care or symptom-guided care in the reduction of HF-related hospitalization and mortality in HF patients with reduced ejection fraction (<40%).

Besides the reduction of HF mortality and hospitalization, individual studies provide additional important findings. Beck-da-Silva et al. [111] report that BNP-guided therapy significantly improves LVEF by 8.1±10.7% and a trend towards improvement of quality of life scores and NYHA functional class. The study also reported the effect on age on BNP-guided therapy, where patients aged 60-74 years benefited with hospitalization-free survival whereas patients aged ≥ 70 years did not. Jourdain et al. [112] report BNP-guided therapy might confer better clinical outcomes because of frequent changes of all types of medication used, and higher dosage of beta-blockers compared to usual care.

The beneficial outcomes of NP-guided therapy in protecting against HF-hospitalization and mortality in HFrEF patients have been demonstrated elsewhere. In an earlier meta-analysis, Felker et al. [120] finds NP-guided heart failure therapy, incorporating serial measurements of BNP and/or NT-proBNP significantly reduces all-cause mortality compared to usual care patients. In another earlier meta-analysis, Porapakkhram et al. [121] supports the findings that NP-guided therapy reduces all-cause and cardiovascular-related mortality with more noticeable effect in HF patients aged < 75 years. However, the effect of NP-guided therapy on the reduction of all-cause hospitalization and hospitalization-free survival was not significant [121]. The inconsistent findings suggests the need for large-scale clinical trials with long-term follow-up to establish the value of NP-guided therapy in reducing HF-related hospitalization and mortality in HFrEF patients.

Conclusion

Heart failure (HF) with reduced ejection fraction (HFrEF) is the originally described HF phenotype defined by left ventricular ejection fraction (LVEF) < 40% on echocardiography. It accounts for approximately half of all reported hospitalized HF cases. Its main etiology is cardiac and extra cardiac conditions that lead to myocardial injury, abnormal loading conditions and pathologic ventricular arrhythmias. The key pathophysiologic perturbations of HFrEF include activation of neurohormonal systems (sympathetic nervous system and renin-angiotensin-aldosterone system), which may precipitate or aggravate cardiomyocyte necrosis leading to myocardial injury and remodeling, and ultimately impairing left ventricular systolic function. Typical clinical symptoms and signs include edema, fatigue, dyspnea, reduced

Table 11. Summary of studies on natriuretic peptide-guided therapy

Author	Study Year	Patient Size		NP-Guided		Control		NP	Follow-up	All-cause Mortality		Hospitalization	
		NP	C	Age (yrs.)	Male (%)	Age (yrs.)	Male (%)			NP	C	NP	C
Felker et al. [9]	2017	446	448	62	69	64	67	NT-proBNP	15	12	13	33	32
Beck-da-Silva et al. [111]	2005	21	20	64.5	33	65.5	35	BNP	3	9.5	30	4.7	10
Jourdain et al. [112]	2007	110	110	65	59	66	56	BNP	15	2.7	8.2	20	44
Pfisterer et al. [113]	2009	251	248	76	68	77	63	NT-proBNP	18	8	9	59	60
Eurlings et al. [114]	2010	174	171	72	55	73	31	NT-proBNP	24	25	33	NR	NR
Berger et al. [115]	2010	92	20	70	40	71	30	BNP	12	28	40	22	39
Persson et al. [116]	2010	126	124	78	76	77	66	NT-proBNP	NR	3	4	NR	NR

BNP: B-Type Natriuretic Peptide; **NT-proBNP:** N-terminal pro-BNP

exercise tolerance and orthopnea elevated-jugular venous pressure, gallop rhythm, hepatojugal reflux, and a laterally displaced apical impulse. Symptoms are non-specific and non-sensitive, and obese and elderly patients may present with atypical symptoms. Diagnosis work-up begins with the assessment of clinical history and physical examination followed by laboratory tests (electrocardiography assessment and evaluation of the concentration of serum natriuretic peptides). Patients with at least one abnormal finding in physical examination or laboratory assessment should be considered for echocardiography to assess LV systolic function. In case of inconclusive echocardiography findings, further imaging tests such as cardiac magnetic resonance or endomyocardial biopsy should be considered to confirm diagnosis. The mainstay method of clinical management is pharmacotherapy; however, if intolerant or non-responsive, device therapy (implantable cardioverter-defibrillator or cardiac resynchronization therapy) should be considered. Lifestyle modification therapy – increased exercise, smoking cessation, minimal alcohol intake, and low dietary intake of sodium and fluids – is a recommended complementary therapy to slow down the progression of HFrEF.

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