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**Current concept in the diagnosis, treatment and rehabilitation of patients with congestive heart failure**

Sopek Merkaš I *et al*. Current concept in heart failure and rehabilitation

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**Abstract**

Heart failure (HF) is a major public health problem with a prevalence of 1%-2% in developed countries. The underlying pathophysiology of HF is complex and as a clinical syndrome is characterized by various symptoms and signs. HF is classified according to left ventricular ejection fraction (LVEF) and falls into three groups: LVEF ≥ 50% - HF with preserved ejection fraction (HFpEF), LVEF < 40% - HF with reduced ejection fraction (HFrEF), LVEF 40%-49% - HF with mid-range ejection fraction. Diagnosing HF is primarily a clinical approach and it is based on anamnesis, physical examination, echocardiogram, radiological findings of the heart and lungs and laboratory tests, including a specific markers of HF - brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide as well as other diagnostic tests in order to elucidate possible etiologies. Updated diagnostic algorithms for HFpEF have been recommended (H2FPEF, HFA-PEFF). New therapeutic options improve clinical outcomes as well as functional status in patients with HFrEF (*e.g.*, sodium-glucose cotransporter-2 - SGLT2 inhibitors) and such progress in treatment of HFrEF patients resulted in new working definition of the term “HF with recovered left ventricular ejection fraction”. In line with rapid development of HF treatment, cardiac rehabilitation becomes an increasingly important part of overall approach to patients with chronic HF for it has been proven that exercise training can relieve symptoms, improve exercise capacity and quality of life as well as reduce disability and hospitalization rates. We gave an overview of latest insights in HF diagnosis and treatment with special emphasize on the important role of cardiac rehabilitation in such patients.

**Key Words:** Heart failure; Classification of heart failure; Diagnosis of heart failure; Treatment of heart failure; Cardiac rehabilitation; Heart failure rehabilitation

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**Core Tip:** Diagnostic methods and treatment of heart failure (HF) are evolving rapidly. Making a firm diagnosis of HF with preserved ejection fraction is a challenge, and although diagnostic algorithms have been recommended further research is needed for better classification. Therapeutic options improve morbidity, mortality, as well as functional status of patients with HF with reduced ejection fraction and the new term - HF with recovered left ventricular ejection fraction is a result of successful therapy. Only a small part of patients with chronic HF participates in cardiac rehabilitation programs. Cardiac rehabilitation in patients with HF is an important part of care and should be implemented as a part of holistic approach because it improves exercise capacity and quality of life, reduces disability and hospitalization rates.

**INTRODUCTION**

Heart failure (HF) is one of the major public health problems with a prevalence of 1-2% in developed countries (varies by definition and region), and it increases with age (rising to over 10% in people over 70 years of age)[1]. Approximately 33% of men and 28% of women at the age of 55 have a lifetime risk of developing HF[1].

The pathophysiology of HF is complex and it is therefore a clinical syndrome characterized by various symptoms and signs, which is caused by structural and / or functional abnormalities of the heart. HF can be a terminal stage of many cardiovascular diseases, including myocardial infarction, heart valve disease, tachyarrhythmias, congenital heart defects, and cardiomyopathies[1]. Most commonly, HF develops as a consequence of a myocyte injury caused by coronary artery disease, uncontrolled arterial hypertension, valvular heart diseases and diabetes mellitus, and it is important to consider pulmonary disorders such as chronic obstructive pulmonary disease or pulmonary arterial hypertension as causes that can lead to HF[1-3].

The main pathophysiological mechanisms leading to HF are increased hemodynamic overload, ischemia, myocardial dysfunction and remodelling, excessive neuro-humoral stimulation - chronic sympathetic nervous system overactivity as one of the key pathophysiological mechanisms (in the acute phase, this upregulated sympathetic activity is an essential compensatory response initiated in order to compensate for reduced contractility, and cardiac output but in the long-term, it contributes to cardiac dysfunction as it leads to cardiac hypertrophy and cell dysfunction), activation of the renin-angiotensin-aldosterone system (RAAS), excessive or inadequate proliferation of the extracellular matrix, accelerated apoptosis, and genetic mutations[3-6] (Figure 1). HF is associated with a variety of complications, such as frequent hospitalizations, fatal arrhythmias, and death in the advanced stage of the disease.

**Classification**

As mentioned, HF is caused by a number of conditions, causing left and right ventricular dysfunction[6-8]. The most common classification of HF refers to the left ventricular ejection fraction (LVEF). Accordingly, HF is classified into three groups: with preserved left ventricular ejection fraction LVEF ≥ 50% - HFpEF, with reduced ejection fraction LVEF < 40% - HFrEF, and patients with a mid-range ejection fraction are between these two groups LVEF 40%-49% - HF with mid-range ejection fraction (HFmrEF)[1,2].

HF is often considered as a left-sided failure when caused primarily by left heart pathologies (*e.g.*, left ventricular, mitral valve, or aortic valve dysfunction). The ventricle fails in its ability to eject blood, or can do so only at the cost of high filling pressures[6,7]. Right-sided or right ventricular HF also has a complex pathophysiology and it is influenced by multiple factors (such as volume status, pulmonary vascular resistance, right ventricular, pulmonic valve, or tricuspid valve dysfunction, left ventricular function) and usually occurs as a result of left ventricular HF[8,9]. Left and right ventricular HF may overlap or occur separately and most patients with right HF have some elements of left HF.

Considering the clinical presentation, HF is divided into acute and chronic[1,2]. Patients with a low LVEF and no symptoms or signs of HF are characterized as asymptomatic patients with a reduced left ventricular systolic function. Those who have signs and symptoms of HF belong to the group of patients with chronic HF, and those who do not experience worsening of symptoms within at least a month are considered stable patients with chronic HF[6]. Acute HF includes the worsening of chronic HF, pulmonary oedema, and cardiogenic shock. There are a number of factors that can trigger acute HF, *e.g.,* myocardial disfunction, pericardial tamponade, and acute valve insufficiency, which are among the most frequent primary cardiac causes of acute HF[1,2]. Decompensation of chronic HF can occur without known precipitant factors, but infection, uncontrolled hypertension, rhythm disturbances, exacerbation of chronic obstructive pulmonary disease, or non-adherence to medicaments can be the cause of decompensation[1,2].

Chronic HF is a complex of multiorgan dysfunction, characterized by the impaired function of the heart, kidney, and skeletal muscles, with increased stimulation of the sympathetic nervous system and numerous humoral and neuroendocrine disorders. The severity of symptoms in chronic HF is classified according to the New York Heart Association (NYHA)[10] and American College of Cardiology/American Heart Association (ACC/AHA)[11] in four stages[2] (Table 1). The NYHA functional classification is an independent predictor of mortality and it is widely used in clinical practice[12].

**Clinical presentation**

Clinical signs and symptoms of HF include shortness of breath, dyspnoea (initially with severe physical exertion, and in the advanced stage at rest and worsening in the supine position), orthopnoea (dyspnoea in the supine position), paroxysmal nocturnal dyspnoea (sudden onset of shortness of breath at night), poor mobility, dizziness, lack of appetite, fatigue, and muscle weakness due to early fatigability. Due to compensatory mechanisms, in the early phase of HF patients do not have to present with all the specific symptoms and physical signs, such as those related to fluid retention. In the advanced stages, physical examination and auscultation can reveal abnormal pulmonary phenomena (wheezing, crepitation), the third heart murmur (S3 gallop) that can rarely be heard, presence of an oedema (generalized or localized), and cardiac cachexia (loss of muscle mass). The signs of predominantly right-sided HF are distended jugular veins, ascites, hepatojugular reflux (pressing the hands on the abdomen leads to a more pronounced filling of the jugular veins), and oedema of the legs[1-4].

**Diagnosis**

The cornerstone in the diagnosis of HF is primarily established by a clinician’s assessment and it is based upon a careful medical history (coronary heart disease, arterial hypertension, diabetes, valve disease, cardiotoxic drugs, irradiation, *etc.*), a physical examination, an electrocardiogram (ECG), an ultrasound of the heart (echocardiography), radiological findings of the heart and lungs, laboratory tests, including a specific markers of HF - brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), as well as other diagnostic tests, in order to elucidate possible aetiologies [*e.g.,* invasive coronary angiography, magnetic resonance (MR), or computed tomography (CT)][1,6-8].

Even though a decreased left ventricular ejection fraction identifies patients with HFrEF, the echocardiogram alone does not establish or exclude the diagnosis of HF, since approximately half of the patients with HF have a preserved left ventricular ejection fraction. The most common patients with HFpEF are elderly women with hypertension, ischemic heart disease, atrial fibrillation, obesity, diabetes mellitus, renal disease, or obstructive lung disease[13]. Echocardiography is important in revealing findings that go along with HF and in verifying possible causes of HF (*e.g.*, left ventricular diastolic dysfunction, left ventricular systolic dysfunction, valve dysfunction, regional wall motion abnormalities, left ventricular hypertrophy, left atrial enlargement).

Two algorithms, Heavy, 2 or more Hypertensive drugs, Atrial Fibrillation, Pulmonary hypertension, Elder age > 60, elevated Filling pressures (H2FPEF)[14] and HF Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology (HFA-PEFF)[15] may facilitate a HFpEF diagnosis[13]. The H2FPEF score, which relies on simple clinical characteristics and echocardiography, enables the discrimination of HFpEF from noncardiac causes of dyspnoea and assists in the determination of the need for further diagnostic testing[14]. Elevated natriuretic peptides support a diagnosis of HFpEF[16] but normal levels do not exclude it. Echocardiography has a relevant role in HFpEF and is used for the non-invasive hemodynamic assessment of high LV filling pressures (indirectly pulmonary capillary wedge pressure, PCWP). Early (E) transmitral filling velocities that are measured at the mitral leaflet tips by pulse wave Doppler, Tissue Doppler echocardiography which is performed to measure early (e′) diastolic tissue velocities at the septal and lateral mitral annulus, and the mean of the septal and lateral E/e′ ratio is used to estimate the PCWP[16,17]. Other important measures include the left atrial volume index, the LV mass index, the LV relative wall thickness, tricuspid regurgitation velocity, and the LV global longitudinal systolic strain[15]. According to the consensus recommendation from the HF Association (HFA) of the European Society of Cardiology (ESC) and the definition of HFA-PEFF score, the major (2 points) and minor (1 point) criteria were defined from these measures[15]. The score has functional, morphological, and biomarker domains (Figure 2). Within each domain, a major criterion scores 2 points or a minor criterion 1 point. If several major criteria within a single domain are positive, this domain still contributes 2 points. If no major but several minor criteria are positive the contribution still is 1 point. Major and minor criteria are not additive in a single domain and points are added only when they come from different domains[15].

Patients with mild or moderate HF may appear normal on physical examination, with normal vital signs. Euvolemic patients with chronic dyspnoea, symptoms of HF, and normal cardiac filling pressures at rest may have abnormal hemodynamic responses during exercise, suggesting that the chronic symptoms are related to HF[18-21]. These patients with normal cardiac output at rest have an inability to increase cardiac output during exercise without an excessive increase in filling pressures, resulting in fatigue and intolerance. Elevated resting E/e′ strongly supports the presence of high PCWP and thus HFpEF, but a normal resting E/e′ does not exclude HFpEF[15,18]. Exercise stress echocardiography on a bicycle or a treadmill with imaging during exercise is recommended, but there are no universally adopted protocols[15]. Exercise echocardiography should be considered abnormal if the average E/e’ ratio at peak stress increases to ≥15, with or without a peak tricuspid regurgitation (TR) velocity of >3.4 m/s[15]. An increase in only TR velocity should not be used to diagnose HFpEF because it might be a result of the normal hyperdynamic response to exercise (with increased pulmonary blood flow) without the LV diastolic dysfunction. For selected patients with suspected HF with uncertain diagnosis despite the evaluation, as described above, the clinical gold standard for the diagnosis of HF is the identification of an elevated PCWP on an invasive hemodynamic test (right heart catheterization with the PCWP assessed at rest or during exercise)[15,18]. The patient must have symptoms consistent with HF and PCWP ≥ 15 mmHg at rest or ≥ 25 mmHg during exercise for establishing a diagnosis of HF[18]. If these criteria are not fulfilled, further evaluation for other causes of dyspnoea is required. To summarize, echocardiography may help rule out HFpEF, although approaches to exclude HFpEF based solely on data at rest are of questionable accuracy, and furthermore, there is evidence that reinforces the value of exercise testing using invasive and non-invasive hemodynamic assessments to definitively confirm or rule out the diagnosis of HFpEF[18].

**Treatment**

The therapy for HFrEF aims to improve quality of life, reduce the rate of hospitalizations, as well as morbidity and mortality. Care for patients with HFrEF includes an overall approach - the treatment of possible causes and associated conditions (*e.g.*, hypertension, diabetes mellitus, and thyroid dysfunction, anemia) of HF, pharmacologic therapy, monitoring, education and cardiac rehabilitation, palliative care, device therapy and cardiac transplantation.

Antagonism of neurohormonal activation is the foundation of the modern HF therapy. The pharmacological treatment aims to alleviate the symptoms and to improve the quality of life, prevent complications and the need for hospitalization, and thereby reduce high mortality. Diuretics are used to facilitate the symptoms of congestion. Meta-analyses show that diuretics, compared with placebo, appear to reduce the risk of death and reduce symptoms, and compared with an active control, appear to improve the functional capacity of patients with HFrEF[22,23]. The progression of the disease of the heart muscle itself can be prevented by acting on the reflex mechanisms that are activated in the body when HF occurs.

The first line of treatment is angiotensin converting enzyme inhibitors (ACEi) and beta-adrenergic receptor blockers (beta-blockers), regardless of the aetiology of HF[1,2,24]. If the patient does not tolerate ACEi or they are contraindicated, then angiotensin receptor blockers (ARBs) are used. ACEi have been shown to reduce morbidity and mortality in patients with HFrEF[25-27], and data suggests that there are no differences among the available ACEi regarding their effects on symptoms or on survival[28]. The usage of beta-blockers showed an improvement of LVEF and a reduction of mortality and the number of hospitalizations[29]. Unlike ACEi, beta-blockers have no class effect and evidence of beneficial effects in the treatment of HF has been reported for bisoprolol, prolonged-release metoprolol, carvedilol, and nebivolol[30,31]. Therapy with ACEi and beta-blockers is complementary and can be started together. Beta-blockers are recommended as a start for clinically stable patients at a low dose, followed by titration to the maximum tolerated dose[1].

Mineralocorticoid receptor/aldosteron antagonists (MRA) - spironolactone and eplerenone are recommended in all symptomatic patients (who are on ACEi and beta-blocker therapy) with LVEF ≤ 35%[1,2]. Inhibition of aldosterone action results in decreased endothelial inflammation and decreased stimulation of the sympathetic system and RAAS systems with an antifibrotic effect. Studies show reduction of all-cause mortality (for spironolactone 30%[32]) and lower rate of hospitalization in patients treated with MRA[33-35]. Possible side effects are hyperkalemia, hyponatremia, reversible increase in blood urea and creatinine levels in patients with impaired renal function, hypotension in patients with low blood pressure (although recent study shows that MRA treatment had little effect on systolic blood pressure in patients with HFrEF and therefore low systolic blood pressure is not a reason to withhold MRA therapy in patients with HFrEF[36]). Spironolactone binds to both androgen and progesterone receptors, so men can experience breast enlargement - gynecomastia, while women can develop excessive farsightedness - hirsutism, and postmenopausal bleeding[8]. Due to its selective binding to the mineralocorticoid receptor, eplerenone has no endocrine side effects, has a lower risk of hyperkalemia, and it is a better choice in diabetics[8]. Caution should be exercised in the use of MRA in patients with impaired renal function and serum potassium level greater than 5.0 mmol/L[1].

If symptomatic HF persists (NYHA class II or III), replacement of ACEi (or ARB if used) by angiotensin receptor neprilysin inhibitor (sacubutril) - ARNI (angiotensin receptor neprilysin inhibitor) is recommended to further reduce morbidity and mortality[1,24,37]. Neprylisin inhibits natriuretic peptides (NP), bradykinin, adrenomedullin, and the β-amyloid (Aβ) peptide[37]. The combination of the renin–angiotensin system and neprilysin inhibition showed to be superior to a separate approach[38], but in clinical trials, the combination of ACEi and neprilysin was associated with serious angioedema[39,40]. Combined molecule LCZ696 consisting of sacubutril and valsartan minimizes the risk of serious angioedema, and the mechanism of action is inhibition of the neprilysin *via* the active metabolite of sacubitril and blocking of the angiotensin II receptor *via* valsartan[41,42]. There is an increase in the number of peptides that neprilysin degrades, such as A-type natriuretic peptide (ANP) and BNP, which bind to NP receptors. This results in vasodilation, the enhancement of natriuresis and diuresis, increased glomerular filtration, the inhibition of renin and aldosterone release, decreased sympathetic activity, as well as antihypertrophic and antifibrotic effects[43]. Considering described mechanism of action, BNP concentrations rise with neprilysin inhibition and the clinical validity of measuring BNP in patients treated with sacubitril/valsartan has been questioned. The use of NT-proBNP is preferred and recommended in assessing the effectiveness of therapy, although either biomarker predicts the risk of major adverse outcomes in patients treated with ARNI[44]. Monitoring of blood pressure and renal function is necessary in these patients and accordingly the dose increases to the maximum tolerated dose. The long-term use of ARNI has possible side effects such as amyloid deposition and cognitive disfunction, and these side effects may be associated with specific polymorphisms in individuals[45,46]. One small study on healthy individuals showed increase of β-amyloid protein in the soluble rather than the aggregable form, which may indicate cerebral safety[47]. Long-term safety, especially in patients at risk of Alzheimer disease, needs to be assessed[1,46].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are an insulin-independent class of oral antihyperglycemic medication that are used in the treatment of type 2 diabetes. They reduce blood glucose by the inhibition of glucose reabsorption at the proximal tubule of the kidney which results in glycosuria and natriuresis[48]. Effects in lowering body weight and decreasing systolic blood pressure, as well as side effects such as genital tract infections, lower leg amputations, electrolyte disturbances, bone fractures are noted[48]. According to the latest recommendations on HF, empagliflozin should be considered in patients with type 2 diabetes mellitus (T2DM) in order to prevent or delay the onset of HF or prolong life, and canagliflozin and dapagliflozin should also be considered for patients with T2DM and either established cardiovascular (CV) disease or at high CV risk[49]. Newest studies show that SGLT2 inhibitors reduce the risk of cardiovascular death or hospitalization in patients with HFrEF regardless of the presence or absence of diabetes[50,51]. Beneficial effects of SGLT2 inhibitors may complement and improve the effects of first line HF therapy (increase in natriuresis, decreasing LV wall stress, preload, afterload and interstitial oedema), alongside with clinically important benefit such as improving renal function in HF patients[50,51]. Therefore, compelling evidence suggest that SGLT2 inhibitors should be added to the current recommended treatments of HFrEF, even in the absence of diabetes (Figure 3).

In addition to the maximum tolerated dose of betablocker, ACEi (or ARB), and the MRA, ivabradine should also be considered in symptomatic patients with increased heart rate (more than 70 / min), in sinus rhythm and EFLV < 35%, to reduce the risk of HF hospitalization or cardiovascular death (or in patients who are unable to tolerate or have contraindications for a beta-blocker)[1,24].

In symptomatic patients (NYHA Class II-IV) with HFrEF who cannot tolerate ACEi nor ARB (or they are contra-indicated), hydralazine and isosorbide dinitrate may be considered to reduce the mortality[1,52]. Digoxin may be considered in symptomatic patients in sinus rhythm despite optimal medical therapy to reduce the risk of hospitalizations[1,53]. It is also used in patients with HF and atrial fibrillation (AF) to slow a rapid ventricular rate, but it is only recommended when adequate heart rate is not achieved with other therapeutic options[54,55]. Optimal ventricular rate for patients with HF and AF has not been well established but resting ventricular rate of 70-90/min is recommended based on current opinion (acceptable up to 110/min), rather than insisting on strict lower ventricular heart rate[56].

Non-dihydropyridine calcium-channel blockers (CCBs) are not recommended for the treatment of patients with HFrEF[1] (diltiazem and verapamil are considered to be unsafe in patients with HFrEF[57]). In case of compelling indications amlodipine and felodipine can be used in patients with HFrEF[1].

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) reduce the mortality and morbidity in patients with atherosclerotic disease, but there is no evidence of benefit or improvement of the prognosis in patients with HFrEF[58]. Patients who already receive statin because of coronary artery disease or hyperlipidemia should continue to use this therapy[1]. The n-3 polyunsaturated fatty acid (PUFAs) is not a routinely used supplement in patients with HFrEF since the randomized trial demonstrated minimal to no benefit[59].

***Novel therapeutic approaches***

The effect of a novel oral soluble guanylate cyclase stimulator – vericiguat was tested in patients with HFrEF and the result of the new randomized trial showed that the incidence of death from cardiovascular causes or hospitalization for HF was lower among subjects who received vericiguat in comparison to those who received placebo (HF hospitalizations were significantly reduced, while cardiovascular deaths were not significantly diminished)[60].

Omecamtiv mecarbil is a cardiac-specific myosin activator that improves cardiomyocyte contraction which is being studied for a potential role in the treatment of left ventricular systolic HF[61]. The latest trial showed a significant reduction of HF event or death from cardiovascular causes in subjects who received omecamtiv mecarbil twice daily in contrast to those who received the placebo[62].

The effect of the anticoagulant therapy in HF patients in sinus rhythm is being assessed since HF is associated with activation of thrombin-related pathways, which predicts a poor prognosis. Studies with rivaroxaban (factor Xa inhibitor) hypothesized that the treatment could reduce thrombin generation and improve outcomes for patients with worsening chronic HF and underlying coronary artery disease[63,64]. Rivaroxaban did not reduce HF hospitalization but did reduce the rate of stroke[63]. Thromboembolic events occurred frequently in patients with HF, coronary artery disease, and sinus rhythm. A post-hoc analysis revealed that rivaroxaban may reduce the risk of thromboembolic events in this population, but these events are not the major cause of morbidity and mortality in patients with recent worsening of HF where rivaroxaban had no effect[64]. Rivaroxaban at dose 2.5 mg twice daily in addition to aspirin may be considered for ambulatory patients with coronary artery disease (CAD) and chronic HF in NYHA class I/II with an LVEF > 30%, in order to reduce the risk of stroke and CV death[49,64]. For chronic HF patients in NYHA class III/IV and recent HF hospitalization, initiation of treatment with rivaroxaban is not recommended, as no benefit was shown[49].

The treatment of comorbidities that are present in chronic HF patients is an important part of holistic approach and improves outcomes of these patients. Iron deficiency is common in patients with and without anemia and has unfavorable clinical and prognostic consequences in patients with HFrEF. Important clinical trials have been conducted with ferric carboxymaltose (FCM)[65-67], and the treatment with FCM may result in the improvement of functional capacity, symptoms and quality of life (whether FCM is associated with an improved outcome in these high-risk patients needs further study). The trial including iron deficient patients hospitalized for acute HF showed that intravenous FCM compared to placebo was associated with reduction of total HF hospitalizations and CV death[68].

To conclude, there are important advances in the medicament treatment of HFrEF and therapeutic development is accelerated. These new therapeutic options improve clinical outcomes and functional status[69]. Accordingly, new working definition of HF with recovered left ventricular ejection fraction (HFrecEF) has been proposed[69,70]. HFrecEF is a complex clinical entity and definition includes: (1) documentation of a LVEF <40% at baseline, combined with (2) a ≥ 10% absolute improvement in LVEF; and (3) a second measurement of LVEF > 40%[69,70]. The proportion of patients with HFrecEF varies widely (10%-40%) and should be followed every 6 mo to 1 year, with imaging obtained every 3-5 years to monitor LV function[70]. HFpEF has a significant morbidity and mortality and so far, no treatment has clearly demonstrated an improvement of outcome in HFpEF, but rather it is limited to symptom relief, which effectively improves the quality of life[13,71,72]. The emphasis is on treatment of comorbidities - hypertension, atrial fibrillation, obesity, diabetes mellitus, renal disease, obstructive lung disease, or ischemic heart disease. Regular exercise program is an important part in the treatment of these patients[13].

***Device therapy***

Implantable cardioverter-defibrillator (ICD) is effective in correcting potentially lethal ventricular arrhythmias. Some antiarrhythmic drugs might reduce the rate of tachyarrhythmias and sudden death, however they do not reduce overall mortality and may even increase it[1]. An ICD is recommended in secondary prevention to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing hemodynamic instability, and who are expected to survive for more than one year with good functional status[1,73,74]. ICD therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in selected patients at least 40 days after myocardial infarction with LVEF of 35% or less, symptomatic while receiving optimal medical therapy, and who have reasonable expectation of survival for more than one year with good functional status[1,24,75,76]. There is no benefit in patients who had an ICD implanted within 40 d after a myocardial infarction[77]. Decision about ICD implantation should be made for each patient individually, taking into consideration patient’s opinion and their quality of life, the LVEF (survival benefit) and other diseases that can be cause of death within the following year[1,73,74]. ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy if they are not candidates for CRT, a ventricular assist device, or cardiac transplantation[1,78,79].

Cardiac resynchronization therapy (CRT) is recommended for symptomatic patients in sinus rhythm, with left bundle branch block (LBBB) QRS morphology, QRS ≥ 150 ms (and in patients with QRS duration of 130–149 ms) and EFLV ≤ 35% despite optimal medical therapy to improve symptoms and reduce morbidity and mortality[1,2,80-82]. For patients with ECG non-LBBB QRS morphology and QRS ≥ 150 msec CRT should be considered and CRT may be considered in patients with QRS 130–149 ms non-LBBB QRS morphology (in sinus rhythm)[1,2,80,83]. CRT rather than right ventricular pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing in order to reduce morbidity, although no clear effect on mortality was observed (this also includes individualized decision for patients with atrial fibrillation)[84-86].

Patients with severe symptoms despite optimal medical and device therapy are potentially eligible for mechanical circulatory support - mechanical ventricular assist VAD); left - sided (LVAD) or right - sided (RVAD), biventricular (BiVAD)[1,87]. Heart transplantation is the last line of treatment for patients with the end-stage chronic HF[1,88]. These patients need to be motivated, well informed, emotionally stable, capable of complying with the intensive treatment required postoperatively and in order for transplantation to be successful and increase survival, proper selection criteria need to be applied[88].

**role of cardiac rehabilitation in patients with chronic HF**

Although survival after diagnosis of HF has improved, the prognosis in such patients remains poor and quality of life severely reduced. The meta‐analysis (2019), including over 1.5 million all‐type HF patients, estimated the 1, 2, 5 and 10‐year survival to be 87%, 73%, 57% and 35%, respectively[89]. Analysis about long-term outcomes among patients hospitalized with HF (including all three groups – HFrEF, HFmrEF, HFpEF; 2017) shown very high 5‐year mortality rate of 75%, regardless of LVEF[90].

Chronic HF reduces the ability of physical activity in patients, which has detrimental effects on their daily life activities and reduces quality of life. Patients with HF have limited exercise capacity because of dyspnea and fatigue, so these symptoms make patients fearful of being active, moreover because exercise-induced dyspnea can be interpreted as worsening of their disease. In patients with stable HF, exercise training can relieve symptoms, improve the exercise capacity and quality of life, as well as reduce disability, hospitalization and mortality[91-93]. The Cochrane systematic review (2014) reported that exercise‐based cardiac rehabilitation (CR) compared to no exercise control shows improvement in health‐related quality of life (HRQoL) and hospital admission among people with HF, as well as possible reduction in mortality over long term[94]. A single large randomized controlled trial (RCT) with medically optimized and stable patients with systolic HF (LVEF ≤ 35%) showed a modest and non-significant reduction in the primary composite outcome of all-cause mortality or all-cause hospitalization, but improvement in self-reported health status compared with usual care without training that persisted over time[95,96]. Recent systematic review and meta-analysis (2019)[97], a meta-analysis of randomized trials (2018)[98] and the Cochrane meta-analysis (2019)[99] that included a total of 5783 patients, predominantly HFrEF (NYHA class II and III receiving center-based exercise-based CR programs) but also patients with HFpEF, showed that exercise rehabilitation reduced hospital admissions overall, as well as for HF, and clinically important improvement in HRQoL was shown. In patients with HFpEF clinically relevant improvements in exercise capacity can be achieved, without significant changes in LV function or structure[100,101], regardless of training modality[102].

In practice, it is reasonable to advise patients to avoid stimuli that cause worsening of the disease symptoms. There are many pathophysiological mechanisms of exercise intolerance in HF: cardiac (systolic and/or diastolic dysfunction, reduced stroke volume, elevated filling pressures, secondary pulmonary hypertension and right ventricle disfunction, mitral regurgitation, reduced chronotropic reserve), ventilatory system (exaggerated minute ventilation relative to CO2 production, ventilation/perfusion mismatch, alveolar edema), skeletal muscle (reduced muscle mass, reduced enzymes for oxidative metabolism and generation of ATP), endothelial function (reduced nitric oxide, increased reactive oxygen compounds, reduced vasodilatory response), neurohumoral system (increased sympathetic activity, low vagal activity, increased levels of pro-inflammatory cytokines)[103]. However, in chronic HF, poor exercise tolerance and quality of life can be successfully improved by dosed and tailored exercise training (ET)[96,104-107]. ET reduces sympathetic tone and increases the influence of the parasympathetic tone at rest, restores baroreflex sensitivity and decreases chemoreflex sensitivity in HF which is important in term of autonomic nervous system imbalance and chronic sympathetic nervous system overactivity as one of the key pathophysiological mechanisms in HF leading to vasoconstriction, altered renal blood flow and adverse remodeling – hypertrophy and cell disfunction. ET in HF also results in reduction of reactive oxygen species and a concomitant increase in nitric oxide signaling, a reduction in Angiotensin II type 1 receptor signaling and a restoration of the imbalance of Angiotensin converting enzyme (ACE) and ACE2 expression, as well as a decrease in circulating pro-inflammatory cytokines, all of which contribute to the improvement of autonomic imbalance[103,108].

The guidelines of the European Society of Cardiology[1], American College of Cardiology/American Heart Association[2] and Canadian Cardiovascular Society[109] have included evidence-based recommendations for the use of exercise training in the management of chronic HF. Exercise training (or regular physical activity) is safe and effective in the improvement of symptoms and functional capacity (Class I, level of evidence A)[1,2,109], the reduction of the risk of hospitalization from HF (Class I, level of evidence A)[1] and in the improvement of exercise duration, HRQoL and reduction of mortality (Class IIa, level of evidence B)[2].

A consensus document of the HF Association and the European Association for Cardiovascular Prevention and Rehabilitation[110] emphasizes that cardiac rehabilitation program for patients with HF should include multiple components such as medical evaluation and baseline patient assessment, appropriate evaluation of many risk factors associated with such patients (*e.g.*, concomitant diseases -anaemia, valvular heart disease, renal function, patients age), education concerning medication adherence, psychosocial support, as well as exercise training and physical activity counseling.In addition to adopting a change in lifestyle that includes daily life activities (*e.g.,* housework, gardening, walking, recreation, proper nutrition), conducting structured physical activity and ET is important for further maintenance of stable condition of these patients. Implementation of ET requires appropriate patient selection, training protocol identification, intensity level determination, and progression monitoring. ET is recommended for stable New York Heart Association (NYHA) class I–III HF patients[110]. Early mobilization of patients after an episode of acute HF is also recommended. At this stage, gradual mobilization, respiratory exercises, and small muscle groups exercises is needed to establish clinical stability and help patients to achieve a sufficient level of functional capacity and trust prior to conducting a symptom-limited cardiopulmonary exercise test (CPET) and initiating regular ET. Exercise modalities are known to be safe for HF patient when given at the right intensity and duration. The overall concept in ET is to be done gradually and individualized. When clinical stabilization is achieved, it is necessary to assess whether there are contraindications for conducting rehabilitation (Table 2). This includes reassessment of the patient's condition and functional evaluation (history, clinical examination, electrocardiogram, ultrasound of the heart and CPET, and if the patient is unable to perform, then six -minute walking test)[110].

The choice of exercise modality should take into account patients associated diseases, work habits, preferences and abilities, limitations as well as the availability of rehabilitation itself. Determining the appropriate level of ET intensity is key in achieving the desired effects, while simultaneously having control over the potential risks associated with these patients. There is no general agreement on modalities of exercise, instead an individual approach is recommended, with careful clinical assessment, taking into consideration patient's preferences[110,111]. Exercise protocols can be different depending on the variables: intensity (aerobic and anaerobic), type (endurance, resistance, strength), method (continuous and intermittent/interval), application (systemic, regional area, respiratory muscles), control (supervised and non‐supervised), setting (hospital and rehabilitation center or home-based). Three exercise modalities in different combinations have been proposed[110,111].

***Aerobic/endurance training***

Metabolic function can be assessed by maximum oxygen uptake which depends on the ability of the respiratory and cardiovascular systems to deliver oxygen from the atmosphere to the muscle and the ability of the working muscles to utilize oxygen. The volume of oxygen (VO2) measured in patients with chronic HF at the end of the exercise test is not the maximum VO2 value because such patients cannot reach it. Instead of the term VO2max we use the term VO2peak, by symptom-limited CPET. The CPET will give insight into the degree of cardiac impairment and will objectively measure VO2peak and help to determine training intensity and perform training adjustments[110]. The most used and evaluated exercise modality, the cornerstone of cardiac rehabilitation programs, is moderate continuous exercise (MCE)[112-114]. The intensity of training is thus usually prescribed relative to VO2peak, and the recommended intensity is 40%-50% at the beginning, with an increase during the exercise process to 70%-80% of VO2peak[110]. CPET is not always available in everyday clinical practice, so indirect methods have been proposed to assess the intensity of ET. In practice, heart rate (HR) reserve (HRR) - the difference between the basal and peak HR (the training in the range of 40%-70% HRR is recommended), and rating of perceived exertion (RPE) (training of 10/20–14/20 of the Borg RPE is recommended) are used. The intensity of physical training of 60% VO2peak corresponds to RPE from 12 to 13, and from 85% VO2peak corresponds to RPE 16[110]. High-intensity interval training (HIIT) programs have been considered as a valuable exercise modality for low-risk HF patients[111,115]. HIIT is not superior to moderate continuous training (MCT) in changing left ventricular remodeling or aerobic capacity[115] but the recent meta-analysis showed that improves VO2peak and should be considered as a component of care of HFrEF patients[116]. Aerobic training dominates among cardiac rehabilitation programs, as in patients with chronic HF because it has the highest level of evidence, and proven beneficial effects for this type of activity[110,111].

***Resistance/strength training***

Muscle contraction is performed against a specific opposite force and thus generating resistance (*e.g.*, lifting weights). It gradually overloads the musculoskeletal system, strengthens and tones the muscles and it is suggested as an anabolic intervention due to the risk of muscle mass loss[110]. A meta-analysis showed that resistance exercise as a single intervention can increase muscle strength, aerobic capacity, and quality of life in HFrEF patients, and may offer an alternative approach, especially for those unable to participate in aerobic training[117]. It can be used as an adjunct to aerobic training which is the mainstay in HF patients.

As HF patients suffer from easy fatiguability, the initiation of a resistance/strength training (RST) program must be individually adjusted to the patient under medical supervision and each patient must be individually introduced into the training regimen. The amount of cardiovascular stress expected during RST depends on the magnitude of the resistance [% of one repetition maximum (% 1-RM)], the size of the working muscle mass and the relation between the duration of the muscle contraction and rest period between repetitions[110]. The minimum recommendations for implementation of an RTS in three progressive steps are: 1. ‘’ Instruction phase” – pre-training to learn and practice slow conduction, without or at very low resistance (RPE < 12, < 30% 1-RM). 2. ‘’Resistance/endurance phase’’ – start of training with a high number of repetitions and a low intensity (RPE 12-13, 30%-40% 1-RM). 3. ‘’Strength phase’’ – higher intensity (RPE < 15, 40%-60% 1-RM), increasing muscle mass[110]. Surveillance over each step is necessary because of the possibility of abdominal straining and consequent blood pressure elevations so prescribing the appropriate level of training according to the patient’s clinical stability, motivation, and experience with RST is of great importance.

***Respiratory training***

The review of trials using inspiratory muscle training in patients with chronic HF suggested that such an intervention may improve the functional capacity and quality of life, especially in those with inspiratory muscle weakness[118]. Such additional exercises in combination with standard aerobic training might be useful.

 There are limited data about ET for a special group of patients with chronic HF and implanted ICD or CRT. Evidence show that physical activity and exercise can be safely applied with adequate supervision[119,120] and it was confirmed in the larger RCTanalysis of patients with ICD and HF[121]. It has been shown that physical activity can almost double the improvement in functional capacity and quality of life in CRT patients[122,123] and ET resulted in reduction of a number of ICD activations in the exercise group[120,121]. Moreover, non‐sustained ventricular tachycardia in the presence of an ICD is not a contraindication for aerobic training[121]. Patients with an ICD should begin training under medical supervision, and the HR must be monitored if it is possible to reach a HR close to the programmed intervention zone of the device. Patients who have symptomatic arrhythmias or ICD discharge should be directed to exercise modalities in which brief loss of consciousness due to ICD discharge may be less harmful (*e.g.*, avoiding swimming or climbing)[110]. Medical staff caring for such patients should be specially educated in understanding the possible challenges and problems associated with such patients.

Although progress has been made in rehabilitating patients with chronic HF, further RCT with large number of patients are needed to assess the effect and benefit from each training modality. Education of medical staff on the beneficial effects of physical exercise in patients with chronic HF and involvement of more patients in cardiac medical rehabilitation programs are crucial in order to provide complete care to chronic HF patients. A small part of patients with chronic HF participates in cardiac rehabilitation programs (the data vary, only 2.6% retrospectively[124], and in one observational study only 10% of eligible HF patients received cardiac rehabilitation referral at discharge after hospitalization for HF[125]), and this is partly due to the fact that chronic HF is not yet an indication for rehabilitation in many countries, at least not as a first diagnosis. Developing adequate and effective training methods and highlighting the beneficial effects of such an approach will result in improving the quality of life and providing better medical care to patients with chronic HF.

**CONCLUSION**

New diagnostic methods and treatment options of HF are evolving rapidly. Accordingly, the number of patients with recovered LVEF (HFrecEF) and improved functional status is increasing. Beside medicament options to maintain future stable state of the patients with HF, cardiac rehabilitation is an important part of care, ET is proved to be safe in HF patients and should be implemented as a part of overall approach. Nowadays it is important to emphasize the role of cardiac rehabilitation in patients with chronic HF, raise consciousness that HF is not yet an indication for rehabilitation in many countries, at least not as a first diagnosis, and nurture a holistic approach to patients with HF.

**REFERENCES**

1 **Ponikowski P**, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129-2200 [PMID: 27206819 DOI: 10.1093/eurheartj/ehw128]

2 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147-e239 [PMID: 23747642 DOI: 10.1016/j.jacc.2013.05.019]

3 **Borovac JA**, D'Amario D, Bozic J, Glavas D. Sympathetic nervous system activation and heart failure: Current state of evidence and the pathophysiology in the light of novel biomarkers. *World J Cardiol* 2020; **12**: 373-408 [PMID: 32879702 DOI: 10.4330/wjc.v12.i8.373]

4 **Inamdar AA**, Inamdar AC. Heart Failure: Diagnosis, Management and Utilization. *J Clin Med* 2016; **5** [PMID: 27367736 DOI: 10.3390/jcm5070062]

5 **Ziaeian B**, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016; **13**: 368-378 [PMID: 26935038 DOI: 10.1038/nrcardio.2016.25]

6 **Choi HM**, Park MS, Youn JC. Update on heart failure management and future directions. *Korean J Intern Med* 2019; **34**: 11-43 [PMID: 30612416 DOI: 10.3904/kjim.2018.428]

7 **Zile MR**, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM Jr, Abraham WT, Smart FW, Stevenson LW, Kueffer FJ, Bourge RC. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation* 2008; **118**: 1433-1441 [PMID: 18794390 DOI: 10.1161/CIRCULATIONAHA.108.783910]

8 **Pazos-López P**, Peteiro-Vázquez J, Carcía-Campos A, García-Bueno L, de Torres JP, Castro-Beiras A. The causes, consequences, and treatment of left or right heart failure. *Vasc Health Risk Manag* 2011; **7**: 237-254 [PMID: 21603593 DOI: 10.2147/VHRM.S10669]

9 **Le Jemtel TH**, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007; **49**: 171-180 [PMID: 17222727 DOI: 10.1016/j.jacc.2006.08.046]

10 **The Criteria Committee of the New York Heart Association.** Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th edition. Boston, Mass: Little & Brown; 1994: 253-256

11 **Hunt SA**, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; **119**: e391-e479 [PMID: 19324966 DOI: 10.1161/CIRCULATIONAHA.109.192065]

12 **Madsen BK**, Hansen JF, Stokholm KH, Brøns J, Husum D, Mortensen LS. Chronic congestive heart failure. Description and survival of 190 consecutive patients with a diagnosis of chronic congestive heart failure based on clinical signs and symptoms. *Eur Heart J* 1994; **15**: 303-310 [PMID: 8013501 DOI: 10.1093/oxfordjournals.eurheartj.a060495]

13 **Henning RJ**. Diagnosis and treatment of heart failure with preserved left ventricular ejection fraction. *World J Cardiol* 2020; **12**: 7-25 [PMID: 31984124 DOI: 10.4330/wjc.v12.i1.7]

14 **Reddy YNV**, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. *Circulation* 2018; **138**: 861-870 [PMID: 29792299 DOI: 10.1161/CIRCULATIONAHA.118.034646]

15 **Pieske B**, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019; **40**: 3297-3317 [PMID: 31504452 DOI: 10.1093/eurheartj/ehz641]

16 **Paulus WJ**, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; **28**: 2539-2550 [PMID: 17428822 DOI: 10.1093/eurheartj/ehm037]

17 **Nagueh SF**, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; **29**: 277-314 [PMID: 27037982 DOI: 10.1016/j.echo.2016.01.011]

18 **Obokata M**, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. *Circulation* 2017; **135**: 825-838 [PMID: 28039229 DOI: 10.1161/CIRCULATIONAHA.116.024822]

19 **Maron BA**, Cockrill BA, Waxman AB, Systrom DM. The invasive cardiopulmonary exercise test. *Circulation* 2013; **127**: 1157-1164 [PMID: 23479667 DOI: 10.1161/CIRCULATIONAHA.112.104463]

20 **Andersen MJ**, Olson TP, Melenovsky V, Kane GC, Borlaug BA. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ Heart Fail* 2015; **8**: 41-48 [PMID: 25342738 DOI: 10.1161/CIRCHEARTFAILURE.114.001731]

21 **Borlaug BA**, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010; **3**: 588-595 [PMID: 20543134 DOI: 10.1161/CIRCHEARTFAILURE.109.930701]

22 **Faris RF**, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane Database Syst Rev* 2012: CD003838 [PMID: 22336795 DOI: 10.1002/14651858.CD003838.pub3]

23 **Faris R**, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002; **82**: 149-158 [PMID: 11853901 DOI: 10.1016/s0167-5273(01)00600-3]

24 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017; **70**: 776-803 [PMID: 28461007 DOI: 10.1016/j.jacc.2017.04.025]

25 **Packer M**, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Rydén L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999; **100**: 2312-2318 [PMID: 10587334 DOI: 10.1161/01.cir.100.23.2312]

26 Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet* 1993; **342**: 821-828 [PMID: 8104270]

27 **Køber L**, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med* 1995; **333**: 1670-1676 [PMID: 7477219 DOI: 10.1056/NEJM199512213332503]

28 **Garg R**, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995; **273**: 1450-1456 [PMID: 7654275]

29 **Bristow MR**, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996; **94**: 2807-2816 [PMID: 8941106 DOI: 10.1161/01.cir.94.11.2807]

30 **Heidenreich PA**, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1997; **30**: 27-34 [PMID: 9207617 DOI: 10.1016/s0735-1097(97)00104-6]

31 **Choi KH**, Lee GY, Choi JO, Jeon ES, Lee HY, Lee SE, Kim JJ, Chae SC, Baek SH, Kang SM, Choi DJ, Yoo BS, Kim KH, Cho MC, Park HY, Oh BH. The mortality benefit of carvedilol *vs* bisoprolol in patients with heart failure with reduced ejection fraction. *Korean J Intern Med* 2019; **34**: 1030-1039 [PMID: 30317846 DOI: 10.3904/kjim.2018.009]

32 **Pitt B**, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341**: 709-717 [PMID: 10471456 DOI: 10.1056/NEJM199909023411001]

33 **Pitt B**, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**: 1309-1321 [PMID: 12668699 DOI: 10.1056/NEJMoa030207]

34 **Zannad F**, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; **364**: 11-21 [PMID: 21073363 DOI: 10.1056/NEJMoa1009492]

35 **Girerd N**, Collier T, Pocock S, Krum H, McMurray JJ, Swedberg K, Van Veldhuisen DJ, Vincent J, Pitt B, Zannad F. Clinical benefits of eplerenone in patients with systolic heart failure and mild symptoms when initiated shortly after hospital discharge: analysis from the EMPHASIS-HF trial. *Eur Heart J* 2015; **36**: 2310-2317 [PMID: 26093641 DOI: 10.1093/eurheartj/ehv273]

36 **Serenelli M**, Jackson A, Dewan P, Jhund PS, Petrie MC, Rossignol P, Campo G, Pitt B, Zannad F, Ferreira JP, McMurray JJV. Mineralocorticoid Receptor Antagonists, Blood Pressure, and Outcomes in Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail* 2020; **8**: 188-198 [PMID: 31926854 DOI: 10.1016/j.jchf.2019.09.011]

37 **McMurray JJ**, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition *vs* enalapril in heart failure. *N Engl J Med* 2014; **371**: 993-1004 [PMID: 25176015 DOI: 10.1056/NEJMoa1409077]

38 **Rademaker MT**, Charles CJ, Espiner EA, Nicholls MG, Richards AM, Kosoglou T. Combined neutral endopeptidase and angiotensin-converting enzyme inhibition in heart failure: role of natriuretic peptides and angiotensin II. *J Cardiovasc Pharmacol* 1998; **31**: 116-125 [PMID: 9456286 DOI: 10.1097/00005344-199801000-00017]

39 **Kostis JB**, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 2004; **17**: 103-111 [PMID: 14751650 DOI: 10.1016/j.amjhyper.2003.09.014]

40 **Packer M**, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, Swedberg K. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002; **106**: 920-926 [PMID: 12186794 DOI: 10.1161/01.cir.0000029801.86489.50]

41 **Gu J**, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, Maahs S, Ksander G, Rigel DF, Jeng AY, Lin TH, Zheng W, Dole WP. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol* 2010; **50**: 401-414 [PMID: 19934029 DOI: 10.1177/0091270009343932]

42 **Hegde LG**, Yu C, Renner T, Thibodeaux H, Armstrong SR, Park T, Cheruvu M, Olsufka R, Sandvik ER, Lane CE, Budman J, Hill CM, Klein U, Hegde SS. Concomitant angiotensin AT1 receptor antagonism and neprilysin inhibition produces omapatrilat-like antihypertensive effects without promoting tracheal plasma extravasation in the rat. *J Cardiovasc Pharmacol* 2011; **57**: 495-504 [PMID: 21297495 DOI: 10.1097/FJC.0b013e318210fc7e]

43 **Mangiafico S**, Costello-Boerrigter LC, Andersen IA, Cataliotti A, Burnett JC Jr. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. *Eur Heart J* 2013; **34**: 886-893c [PMID: 22942338 DOI: 10.1093/eurheartj/ehs262]

44 **Myhre PL**, Vaduganathan M, Claggett B, Packer M, Desai AS, Rouleau JL, Zile MR, Swedberg K, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. B-Type Natriuretic Peptide During Treatment With Sacubitril/Valsartan: The PARADIGM-HF Trial. *J Am Coll Cardiol* 2019; **73**: 1264-1272 [PMID: 30846338 DOI: 10.1016/j.jacc.2019.01.018]

45 **Krittanawong C**, Kitai T. Pharmacogenomics of angiotensin receptor/neprilysin inhibitor and its long-term side effects. *Cardiovasc Ther* 2017; **35** [PMID: 28489317 DOI: 10.1111/1755-5922.12272]

46 **Vodovar N**, Paquet C, Mebazaa A, Launay JM, Hugon J, Cohen-Solal A. Neprilysin, cardiovascular, and Alzheimer's diseases: the therapeutic split? *Eur Heart J* 2015; **36**: 902-905 [PMID: 25636748 DOI: 10.1093/eurheartj/ehv015]

47 **Langenickel TH**, Tsubouchi C, Ayalasomayajula S, Pal P, Valentin MA, Hinder M, Jhee S, Gevorkyan H, Rajman I. The effect of LCZ696 (sacubitril/valsartan) on amyloid-β concentrations in cerebrospinal fluid in healthy subjects. *Br J Clin Pharmacol* 2016; **81**: 878-890 [PMID: 26663387 DOI: 10.1111/bcp.12861]

48 **Simes BC**, MacGregor GG. Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors: A Clinician's Guide. *Diabetes Metab Syndr Obes* 2019; **12**: 2125-2136 [PMID: 31686884 DOI: 10.2147/DMSO.S212003]

49 **Seferovic PM**, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, de Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; **21**: 1169-1186 [PMID: 31129923 DOI: 10.1002/ejhf.1531]

50 **Packer M**, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; **383**: 1413-1424 [PMID: 32865377 DOI: 10.1056/NEJMoa2022190]

51 **Zannad F**, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020; **396**: 819-829 [PMID: 32877652 DOI: 10.1016/S0140-6736(20)31824-9]

52 **Cohn JN**, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986; **314**: 1547-1552 [PMID: 3520315 DOI: 10.1056/NEJM198606123142404]

53 **Digitalis Investigation Group.**. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; **336**: 525-533 [PMID: 9036306 DOI: 10.1056/NEJM199702203360801]

54 **Vamos M**, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. *Eur Heart J* 2015; **36**: 1831-1838 [PMID: 25939649 DOI: 10.1093/eurheartj/ehv143]

55 **Bavishi C**, Khan AR, Ather S. Digoxin in patients with atrial fibrillation and heart failure: A meta-analysis. *Int J Cardiol* 2015; **188**: 99-101 [PMID: 25900519 DOI: 10.1016/j.ijcard.2015.04.031]

56 **Mulder BA**, Van Veldhuisen DJ, Crijns HJ, Tijssen JG, Hillege HL, Alings M, Rienstra M, Groenveld HF, Van den Berg MP, Van Gelder IC; RACE II investigators. Lenient vs. strict rate control in patients with atrial fibrillation and heart failure: a post-hoc analysis of the RACE II study. *Eur J Heart Fail* 2013; **15**: 1311-1318 [PMID: 23759284 DOI: 10.1093/eurjhf/hft093]

57 **Goldstein RE**, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation* 1991; **83**: 52-60 [PMID: 1984898 DOI: 10.1161/01.cir.83.1.52]

58 **Kjekshus J**, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J; CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357**: 2248-2261 [PMID: 17984166 DOI: 10.1056/NEJMoa0706201]

59 **Tavazzi L**, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G; Gissi-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**: 1223-1230 [PMID: 18757090 DOI: 10.1016/S0140-6736(08)61239-8]

60 **Armstrong PW**, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM; VICTORIA Study Group. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2020; **382**: 1883-1893 [PMID: 32222134 DOI: 10.1056/NEJMoa1915928]

61 **Liu LC**, Dorhout B, van der Meer P, Teerlink JR, Voors AA. Omecamtiv mecarbil: a new cardiac myosin activator for the treatment of heart failure. *Expert Opin Investig Drugs* 2016; **25**: 117-127 [PMID: 26587768 DOI: 10.1517/13543784.2016.1123248]

62 **Teerlink JR**, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sørensen T, Böhm M, Bonderman D, Cleland JGF, Corbalan R, Crespo-Leiro MG, Dahlström U, Echeverria LE, Fang JC, Filippatos G, Fonseca C, Goncalvesova E, Goudev AR, Howlett JG, Lanfear DE, Li J, Lund M, Macdonald P, Mareev V, Momomura SI, O'Meara E, Parkhomenko A, Ponikowski P, Ramires FJA, Serpytis P, Sliwa K, Spinar J, Suter TM, Tomcsanyi J, Vandekerckhove H, Vinereanu D, Voors AA, Yilmaz MB, Zannad F, Sharpsten L, Legg JC, Varin C, Honarpour N, Abbasi SA, Malik FI, Kurtz CE; GALACTIC-HF Investigators. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. *N Engl J Med* 2021; **384**: 105-116 [PMID: 33185990 DOI: 10.1056/NEJMoa2025797]

63 **Zannad F**, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghiade M, Lam CSP, Mehra MR, Neaton JD, Nessel CC, Spiro TE, van Veldhuisen DJ, Greenberg B; COMMANDER HF Investigators. Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. *N Engl J Med* 2018; **379**: 1332-1342 [PMID: 30146935 DOI: 10.1056/NEJMoa1808848]

64 **Greenberg B**, Neaton JD, Anker SD, Byra WM, Cleland JGF, Deng H, Fu M, La Police DA, Lam CSP, Mehra MR, Nessel CC, Spiro TE, van Veldhuisen DJ, Vanden Boom CM, Zannad F. Association of Rivaroxaban With Thromboembolic Events in Patients With Heart Failure, Coronary Disease, and Sinus Rhythm: A Post Hoc Analysis of the COMMANDER HF Trial. *JAMA Cardiol* 2019; **4**: 515-523 [PMID: 31017637 DOI: 10.1001/jamacardio.2019.1049]

65 **Anker SD**, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**: 2436-2448 [PMID: 19920054 DOI: 10.1056/NEJMoa0908355]

66 **van Veldhuisen DJ**, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, Zakin L, Cohen-Solal A; EFFECT-HF Investigators. Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency. *Circulation* 2017; **136**: 1374-1383 [PMID: 28701470 DOI: 10.1161/CIRCULATIONAHA.117.027497]

67 **Ponikowski P**, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. *Eur Heart J* 2015; **36**: 657-668 [PMID: 25176939 DOI: 10.1093/eurheartj/ehu385]

68 **Ponikowski P**, Kirwan BA, Anker SD, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Haboubi T, Keren A, Khintibidze I, Kragten H, Martinez FA, McDonagh T, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Jankowska EA. Rationale and design of the AFFIRM-AHF trial: a randomised, double-blind, placebo-controlled trial comparing the effect of intravenous ferric carboxymaltose on hospitalisations and mortality in iron-deficient patients admitted for acute heart failure. *Eur J Heart Fail* 2019; **21**: 1651-1658 [PMID: 31883356 DOI: 10.1002/ejhf.1710]

69 **Bueno H**, Moura B, Lancellotti P, Bauersachs J. The year in cardiovascular medicine 2020: heart failure and cardiomyopathies. *Eur Heart J* 2021; **42**: 657-670 [PMID: 33388764 DOI: 10.1093/eurheartj/ehaa1061]

70 **Wilcox JE**, Fang JC, Margulies KB, Mann DL. Heart Failure With Recovered Left Ventricular Ejection Fraction: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2020; **76**: 719-734 [PMID: 32762907 DOI: 10.1016/j.jacc.2020.05.075]

71 **Ilieșiu AM**, Hodorogea AS. Treatment of Heart Failure with Preserved Ejection Fraction. *Adv Exp Med Biol* 2018; **1067**: 67-87 [PMID: 29498023 DOI: 10.1007/5584\_2018\_149]

72 **Wintrich J**, Kindermann I, Ukena C, Selejan S, Werner C, Maack C, Laufs U, Tschöpe C, Anker SD, Lam CSP, Voors AA, Böhm M. Therapeutic approaches in heart failure with preserved ejection fraction: past, present, and future. *Clin Res Cardiol* 2020; **109**: 1079-1098 [PMID: 32236720 DOI: 10.1007/s00392-020-01633-w]

73 **Connolly SJ**, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000; **101**: 1297-1302 [PMID: 10725290 DOI: 10.1161/01.cir.101.11.1297]

74 **Connolly SJ**, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann D, Gent M, Roberts RS. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics *vs* Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. *Eur Heart J* 2000; **21**: 2071-2078 [PMID: 11102258 DOI: 10.1053/euhj.2000.2476]

75 **Moss AJ**, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; **346**: 877-883 [PMID: 11907286 DOI: 10.1056/NEJMoa013474]

76 **Desai AS**, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA* 2004; **292**: 2874-2879 [PMID: 15598919 DOI: 10.1001/jama.292.23.2874]

77 **Steinbeck G**, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, Kornacewicz-Jach Z, Sredniawa B, Lupkovics G, Hofgärtner F, Lubinski A, Rosenqvist M, Habets A, Wegscheider K, Senges J; IRIS Investigators. Defibrillator implantation early after myocardial infarction. *N Engl J Med* 2009; **361**: 1427-1436 [PMID: 19812399 DOI: 10.1056/NEJMoa0901889]

78 **Steinberg BA**, Al-Khatib SM, Edwards R, Han J, Bardy GH, Bigger JT, Buxton AE, Moss AJ, Lee KL, Steinman R, Dorian P, Hallstrom A, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Inoue LY, Sanders GD. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities: results from a combined analysis of 4 randomized clinical trials. *JACC Heart Fail* 2014; **2**: 623-629 [PMID: 25306452 DOI: 10.1016/j.jchf.2014.06.007]

79 **Miller RJ**, Howlett JG, Exner DV, Campbell PM, Grant AD, Wilton SB. Baseline Functional Class and Therapeutic Efficacy of Common Heart Failure Interventions: A Systematic Review and Meta-analysis. *Can J Cardiol* 2015; **31**: 792-799 [PMID: 26022990 DOI: 10.1016/j.cjca.2014.12.031]

80 **Cleland JG**, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, Sherfesee L, Wells GA, Tang AS. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013; **34**: 3547-3556 [PMID: 23900696 DOI: 10.1093/eurheartj/eht290]

81 **Linde C**, Gold MR, Abraham WT, St John Sutton M, Ghio S, Cerkvenik J, Daubert C; REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction Study Group. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Eur Heart J* 2013; **34**: 2592-2599 [PMID: 23641006 DOI: 10.1093/eurheartj/eht160]

82 **Moss AJ**, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; **361**: 1329-1338 [PMID: 19723701 DOI: 10.1056/NEJMoa0906431]

83 **Woods B**, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, Klein H, Sculpher M, Plummer CJ, Cowie MR. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart* 2015; **101**: 1800-1806 [PMID: 26269413 DOI: 10.1136/heartjnl-2015-307634]

84 **Curtis AB**, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, Sutton MS; Biventricular *vs* Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013; **368**: 1585-1593 [PMID: 23614585 DOI: 10.1056/NEJMoa1210356]

85 **Brignole M**, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011; **32**: 2420-2429 [PMID: 21606084 DOI: 10.1093/eurheartj/ehr162]

86 **Tang AS**, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; **363**: 2385-2395 [PMID: 21073365 DOI: 10.1056/NEJMoa1009540]

87 **Stewart GC**, Givertz MM. Mechanical circulatory support for advanced heart failure: patients and technology in evolution. *Circulation* 2012; **125**: 1304-1315 [PMID: 22412091 DOI: 10.1161/CIRCULATIONAHA.111.060830]

88 **Banner NR**, Bonser RS, Clark AL, Clark S, Cowburn PJ, Gardner RS, Kalra PR, McDonagh T, Rogers CA, Swan L, Parameshwar J, Thomas HL, Williams SG. UK guidelines for referral and assessment of adults for heart transplantation. *Heart* 2011; **97**: 1520-1527 [PMID: 21856726 DOI: 10.1136/heartjnl-2011-300048]

89 **Jones NR**, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail* 2019; **21**: 1306-1325 [PMID: 31523902 DOI: 10.1002/ejhf.1594]

90 **Shah KS**, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, Devore AD, Yancy CW, Fonarow GC. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol* 2017; **70**: 2476-2486 [PMID: 29141781 DOI: 10.1016/j.jacc.2017.08.074]

91 **Piepoli MF**, Davos C, Francis DP, Coats AJ; ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004; **328**: 189 [PMID: 14729656 DOI: 10.1136/bmj.37938.645220.EE]

92 **van Tol BA**, Huijsmans RJ, Kroon DW, Schothorst M, Kwakkel G. Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis. *Eur J Heart Fail* 2006; **8**: 841-850 [PMID: 16713337 DOI: 10.1016/j.ejheart.2006.02.013]

93 **Piepoli MF**. Exercise training in chronic heart failure: mechanisms and therapies. *Neth Heart J* 2013; **21**: 85-90 [PMID: 23239451 DOI: 10.1007/s12471-012-0367-6]

94 **Taylor RS**, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014: CD003331 [PMID: 24771460 DOI: 10.1002/14651858.CD003331.pub4]

95 **O'Connor CM**, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301**: 1439-1450 [PMID: 19351941 DOI: 10.1001/jama.2009.454]

96 **Flynn KE**, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP; HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301**: 1451-1459 [PMID: 19351942 DOI: 10.1001/jama.2009.457]

97 **Taylor RS**, Long L, Mordi IR, Madsen MT, Davies EJ, Dalal H, Rees K, Singh SJ, Gluud C, Zwisler AD. Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis. *JACC Heart Fail* 2019; **7**: 691-705 [PMID: 31302050 DOI: 10.1016/j.jchf.2019.04.023]

98 **Taylor RS**, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, O'Connor C, Whellan D, Keteyian SJ, Coats A, Davos CH, Dalal HM, Dracup K, Evangelista L, Jolly K, Myers J, McKelvie RS, Nilsson BB, Passino C, Witham MD, Yeh GY, Zwisler AO; ExTraMATCH II Collaboration. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail* 2018; **20**: 1735-1743 [PMID: 30255969 DOI: 10.1002/ejhf.1311]

99 **Long L**, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ, Taylor RS. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev* 2019; **1**: CD003331 [PMID: 30695817 DOI: 10.1002/14651858.CD003331.pub5]

100 **Fukuta H**, Goto T, Wakami K, Kamiya T, Ohte N. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev* 2019; **24**: 535-547 [PMID: 31032533 DOI: 10.1007/s10741-019-09774-5]

101 **Leggio M**, Fusco A, Loreti C, Limongelli G, Bendini MG, Mazza A, Coraci D, Padua L. Effects of exercise training in heart failure with preserved ejection fraction: an updated systematic literature review. *Heart Fail Rev* 2020; **25**: 703-711 [PMID: 31399956 DOI: 10.1007/s10741-019-09841-x]

102 **Mueller S**, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, Pieske-Kraigher E, Beckers P, Bobenko A, Hommel J, Van de Heyning CM, Esefeld K, von Korn P, Christle JW, Haykowsky MJ, Linke A, Wisløff U, Adams V, Pieske B, van Craenenbroeck EM, Halle M; OptimEx-Clin Study Group. Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *JAMA* 2021; **325**: 542-551 [PMID: 33560320 DOI: 10.1001/jama.2020.26812]

103 **Downing J**, Balady GJ. The role of exercise training in heart failure. *J Am Coll Cardiol* 2011; **58**: 561-569 [PMID: 21798416 DOI: 10.1016/j.jacc.2011.04.020]

104 **Belardinelli R**, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; **99**: 1173-1182 [PMID: 10069785 DOI: 10.1161/01.cir.99.9.1173]

105 **Chicco AJ**, McCune SA, Emter CA, Sparagna GC, Rees ML, Bolden DA, Marshall KD, Murphy RC, Moore RL. Low-intensity exercise training delays heart failure and improves survival in female hypertensive heart failure rats. *Hypertension* 2008; **51**: 1096-1102 [PMID: 18259016 DOI: 10.1161/HYPERTENSIONAHA.107.107078]

106 **Piepoli MF**, Capucci A. Exercise training in heart failure: effect on morbidity and mortality. *Int J Cardiol* 2000; **73**: 3-6 [PMID: 10748303 DOI: 10.1016/s0167-5273(99)00220-x]

107 **Morris JH**, Chen L. Exercise Training and Heart Failure: A Review of the Literature. *Card Fail Rev* 2019; **5**: 57-61 [PMID: 30847247 DOI: 10.15420/cfr.2018.31.1]

108 **Haack KK**, Zucker IH. Central mechanisms for exercise training-induced reduction in sympatho-excitation in chronic heart failure. *Auton Neurosci* 2015; **188**: 44-50 [PMID: 25458427 DOI: 10.1016/j.autneu.2014.10.015]

109 **Ezekowitz JA**, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Rajda M, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, LeBlanc MH, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. *Can J Cardiol* 2017; **33**: 1342-1433 [PMID: 29111106 DOI: 10.1016/j.cjca.2017.08.022]

110 **Piepoli MF**, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T, McMurray J, Pieske B, Piotrowicz E, Schmid JP, Anker SD, Solal AC, Filippatos GS, Hoes AW, Gielen S, Giannuzzi P, Ponikowski PP. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail* 2011; **13**: 347-357 [PMID: 21436360 DOI: 10.1093/eurjhf/hfr017]

111 **Pelliccia A**, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesselink JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M; ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021; **42**: 17-96 [PMID: 32860412 DOI: 10.1093/eurheartj/ehaa605]

112 **Gayda M**, Ribeiro PA, Juneau M, Nigam A. Comparison of Different Forms of Exercise Training in Patients With Cardiac Disease: Where Does High-Intensity Interval Training Fit? *Can J Cardiol* 2016; **32**: 485-494 [PMID: 26927863 DOI: 10.1016/j.cjca.2016.01.017]

113 **Canadian Cardiovascular Society Heart Failure Management Primary Panel.**, Moe GW, Ezekowitz JA, O'Meara E, Howlett JG, Fremes SE, Al-Hesayen A, Heckman GA, Ducharme A, Estrella-Holder E, Grzeslo A, Harkness K, Lepage S, McDonald M, McKelvie RS, Nigam A, Rajda M, Rao V, Swiggum E, Virani S, Van Le V, Zieroth S; Canadian Cardiovascular Society Heart Failure Management Secondary Panel, Arnold JM, Ashton T, D'Astous M, Dorian P, Giannetti N, Haddad H, Isaac DL, Kouz S, Leblanc MH, Liu P, Ross HJ, Sussex B, White M. The 2013 Canadian Cardiovascular Society Heart Failure Management Guidelines Update: focus on rehabilitation and exercise and surgical coronary revascularization. *Can J Cardiol* 2014; **30**: 249-263 [PMID: 24480445 DOI: 10.1016/j.cjca.2013.10.010]

114 **European Association of Cardiovascular Prevention and Rehabilitation Committee for Science Guidelines**; EACPR, Corrà U, Piepoli MF, Carré F, Heuschmann P, Hoffmann U, Verschuren M, Halcox J; Document Reviewers, Giannuzzi P, Saner H, Wood D, Piepoli MF, Corrà U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, McGee H, Mendes M, Niebauer J, Zwisler AD, Schmid JP. Secondary prevention through cardiac rehabilitation: physical activity counselling and exercise training: key components of the position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur Heart J* 2010; **31**: 1967-1974 [PMID: 20643803 DOI: 10.1093/eurheartj/ehq236]

115 **Ellingsen Ø**, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, Larsen AI, Hole T, Mezzani A, Van Craenenbroeck EM, Videm V, Beckers P, Christle JW, Winzer E, Mangner N, Woitek F, Höllriegel R, Pressler A, Monk-Hansen T, Snoer M, Feiereisen P, Valborgland T, Kjekshus J, Hambrecht R, Gielen S, Karlsen T, Prescott E, Linke A; SMARTEX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure) Group. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. *Circulation* 2017; **135**: 839-849 [PMID: 28082387 DOI: 10.1161/CIRCULATIONAHA.116.022924]

116 **Gomes Neto M**, Durães AR, Conceição LSR, Saquetto MB, Ellingsen Ø, Carvalho VO. High intensity interval training *vs* moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. *Int J Cardiol* 2018; **261**: 134-141 [PMID: 29572084 DOI: 10.1016/j.ijcard.2018.02.076]

117 **Giuliano C**, Karahalios A, Neil C, Allen J, Levinger I. The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure - A meta-analysis. *Int J Cardiol* 2017; **227**: 413-423 [PMID: 27843045 DOI: 10.1016/j.ijcard.2016.11.023]

118 **Ribeiro JP**, Chiappa GR, Neder JA, Frankenstein L. Respiratory muscle function and exercise intolerance in heart failure. *Curr Heart Fail Rep* 2009; **6**: 95-101 [PMID: 19486593 DOI: 10.1007/s11897-009-0015-7]

119 **Fitchet A**, Doherty PJ, Bundy C, Bell W, Fitzpatrick AP, Garratt CJ. Comprehensive cardiac rehabilitation programme for implantable cardioverter-defibrillator patients: a randomised controlled trial. *Heart* 2003; **89**: 155-160 [PMID: 12527665 DOI: 10.1136/heart.89.2.155]

120 **Vanhees L**, Kornaat M, Defoor J, Aufdemkampe G, Schepers D, Stevens A, Van Exel H, Van Den Beld J, Heidbüchel H, Fagard R. Effect of exercise training in patients with an implantable cardioverter defibrillator. *Eur Heart J* 2004; **25**: 1120-1126 [PMID: 15231370 DOI: 10.1016/j.ehj.2004.04.034]

121 **Piccini JP**, Hellkamp AS, Whellan DJ, Ellis SJ, Keteyian SJ, Kraus WE, Hernandez AF, Daubert JP, Piña lL, O'Connor CM; HF-ACTION Investigators. Exercise training and implantable cardioverter-defibrillator shocks in patients with heart failure: results from HF-ACTION (Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing). *JACC Heart Fail* 2013; **1**: 142-148 [PMID: 23936756 DOI: 10.1016/j.jchf.2013.01.005]

122 **De Marco T**, Wolfel E, Feldman AM, Lowes B, Higginbotham MB, Ghali JK, Wagoner L, Kirlin PC, Kennett JD, Goel S, Saxon LA, Boehmer JP, Mann D, Galle E, Ecklund F, Yong P, Bristow MR. Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial sub-study. *J Card Fail* 2008; **14**: 9-18 [PMID: 18226768 DOI: 10.1016/j.cardfail.2007.08.003]

123 **Davids JS**, McPherson CA, Earley C, Batsford WP, Lampert R. Benefits of cardiac rehabilitation in patients with implantable cardioverter-defibrillators: a patient survey. *Arch Phys Med Rehabil* 2005; **86**: 1924-1928 [PMID: 16213232 DOI: 10.1016/j.apmr.2005.04.009]

124 **Park LG**, Schopfer DW, Zhang N, Shen H, Whooley MA. Participation in Cardiac Rehabilitation Among Patients With Heart Failure. *J Card Fail* 2017; **23**: 427-431 [PMID: 28232047 DOI: 10.1016/j.cardfail.2017.02.003]

125 **Golwala H**, Pandey A, Ju C, Butler J, Yancy C, Bhatt DL, Hernandez AF, Fonarow GC. Temporal Trends and Factors Associated With Cardiac Rehabilitation Referral Among Patients Hospitalized With Heart Failure: Findings From Get With The Guidelines-Heart Failure Registry. *J Am Coll Cardiol* 2015; **66**: 917-926 [PMID: 26293762 DOI: 10.1016/j.jacc.2015.06.1089]

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**Figure Legends**



**Figure 1 Pathophysiological mechanisms in chronic heart failure (data from[3]). RAAS: Renin-Angiotensin-Aldosterone System; SNS: Sympathetic nervous systems.**



**Figure 2 Heart failure – classification and criteria in diagnosis (data from[1,15]).** HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LAE: left atrial enlargement; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; LV: left ventricle; TR: tricuspid regurgitation; GLS: global longitudinal strain; LAVI: left atrial volume index; LVMI: left ventricular mass index; RWT: relative wall thickness; ECHO: echocardiography.



**Figure 3 Heart failure medication therapy (data from[1,51]).** HFrEF: heart failure with reduced ejection fraction; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; ARNI: angiotensin receptor neprilysin inhibitors; SGLT2: sodium-glucose co-transporter-2; LVEF: left ventricular ejection fraction.

**Table 1 Comparison of American College of Cardiology/American Heart Association Stages of HF and New York Heart Association Functional Classifications (data from[2])**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ACC/AHA Stages of HF |  | NYHA Functional Classification | Restriction of physical activity |
| A | At high risk for HF but without structural heartdisease or symptoms of HF (*e.g.,* diabetes, arterial hypertension) |  | / | / |
| B | Structural heart disease but without symptoms of HF. | I | Regular physical activity does not cause dyspnea and fatigue – asymptomatic. | No limitation of physical activity.  |
| C | Structural heart disease with prior or currentsymptoms of HF. | I | Regular physical activity does not cause dyspnea and fatigue – asymptomatic. | No limitation of physical activity. |
| II | Moderate physical activity results in milder dyspnea and fatigue. | Slight limitation of physical activity. |
| III | No difficulty at rest; minimal physical activity leads to exhaustion, dyspnea, and fatigue. | Marked limitation of physical activity. |
| IV | Symptomatic at rest. | Unable to carry on any physical activity without symptoms of HF. |
| D | Refractory HF requiring specialized interventions. | IV | Symptomatic at rest. | Unable to carry on any physical activity without symptoms of HF. |

ACC/AHA: American College of Cardiology/American Heart Association; HF: heart failure; NYHA: New York Heart Association.

**Table 2 Contraindications for exercise training and screening for increased risk for exercise training (data from[110])**

|  |  |
| --- | --- |
| **Contraindications to exercise training** | **Increased risk for exercise training** |
| Progressive worsening of exercise tolerance or dyspnea at rest over previous 3–5 d | > 1.8 kg increase in body mass over the previous 1-3 d |
| Significant ischemia during low‐intensity exercise (< 2 METs, < 50 W) | Concurrent, continuous, or intermittent dobutamine therapy |
| Uncontrolled diabetes | Decrease in systolic blood pressure with exercise |
| Recent embolism | NYHA functional class IV |
| Thrombophlebitis | Complex ventricular arrhythmia at rest or appearing with exertion |
| Supine resting heart rate > 100 b.p.m. |
| Pre‐existing co‐morbidities limiting exercise tolerance |

NYHA: New York Heart Association.