Review Article

A Comprehensive Review of Epidemiology, Pathophysiology and Treatment of Acute Decompensated Heart Failure

Abstract

Acute decompensated heart failure is a heterogeneous clinical syndrome most often leading to the need for hospitalization due to the confluence of interrelated abnormalities of renal dysfunction, decreased cardiac performance, and alterations in vascular compliance. Admission with a diagnosis of acute decompensated heart failure is associated with excessive morbidity and mortality rates, with nearly half of these patients readmitted for management within 6 months, and a high short-term (5% in-hospital) and long-term cardiovascular mortality (20% at 1 year). Importantly, long-term aggregate outcomes remain poor, with a combined incidence of cardiovascular deaths, heart failure hospitalizations, myocardial infarction, strokes, or sudden death reaching 50% at 12 months after hospitalization. The treatment of these patients has remained very difficult and principally revolves around volume control and decrease of vascular impedance while maintaining attention to end-organ perfusion (coronary and renal).

Keywords : Heart Failure, Acute Decompensated Heart Failure, Hospitalization, Loop Diuretics, Congestion, Pulmonary Congestion.

Introduction

Acute decompensated heart failure is a syndrome characterized by dyspnea, worsening fatigue, and edema that results from deteriorating heart function and usually leads to hospital admission or unscheduled medical intervention [1]. The primary principle of management of these patients is to discover and tackle known precipitants of decompensation [2]. Identification and management of medication nonadherence and use of prescribed medicines such as nonsteroidal anti-inflammatory drugs, cold and flu preparations with cardiac stimulants, and herbal preparations, including herbal forms of ephedrine, licorice, and ginseng, are required. Overt or covert pulmonary thromboembolism and active infection should be sought, identified, and treated when clinical clues suggest such direction [3]. Possibly, arrhythmias should be corrected by controlling the heart rate or restoring sinus rhythm in patients with poorly tolerated rapid atrial fibrillation and by correcting current ischemia with coronary revascularization or correcting offenders such as current bleeding in demand-related ischemia [4]. A parallel step in treatment involves the stabilization of hemodynamics in those with instability. The regular use of a pulmonary artery catheter is not approved and should be restricted to those who respond poorly to diuresis or experience hypotension or signs and symptoms suggestive of a low cardiac output where therapeutic targets are uncertain [5]. Analysis of in-hospital registries has discovered many parameters associated with terrible outcomes: systolic blood pressure less than 115 mmHg, a blood urea nitrogen level greater than 43 mg/dL (to convert to mmol/L, multiply by 0.357), a serum

creatinine level more than 2.75 mg/dL (to convert to µmol/L, multiply by 88.4), and an elevated troponin I level [6].

Definition

Acute decompensated heart failure is the new onset or recurrence of clinical features of heart failure which require immediate treatment and most times results in hospitalization. A certain number of other terms have been used in the literature including: acute decompensation of chronic heart failure (ADCHF), acute heart failure syndromes (AHFS), and acute heart failure (AHF). Terms used in the literature indicates that acute decompensation heart failure is not a single diagnosis, rather it is a group of similar syndromes caused by different primary underlying diseases of the cardiovascular system that may be made worse by a variety of cardiac and non-cardiac conditions [1,2]. In patients suffering from ADHF, there is a crucial heterogeneity in the underlying pathophysiology, precipitants, time course, clinical presentation and underlying cause of heart disease. However, pulmonary congestion due to increased left atrial pressure in association with dyspnea, with or without clinical evidence of low cardiac output is a consistent finding in patients with this syndrome [7]. About 80% of patients hospitalized with acute decompensated heart failure have a previous diagnosis of heart failure, 15% have new onset heart failure, while the remaining 5% have advanced or refractory heart failure. Underlying cardiac diseases including cardiomyopathy, coronary artery disease, hypertension, and valvular heart disease are often present. Non-cardiovascular conditions including anemia, kidney dysfunction, pulmonary disease, diabetes, thyroid disease, substance abuse, obesity, sleep apnea, and infections are often present and may contribute to heart failure decompensation [8].

Epidemiology

The number of hospitalized patients with heart failure as a fundamental diagnosis tripled from 1979 to 2004, rising from 1,274,000 in 1974 to 3,860,000 in 2004. heart failure was the primary diagnosis in 30-35 % of these admissions. Age-adjusted hospitalization rates also increased during this period. More than 80% of these hospitalizations were in patients age 65 years or older and were paid by medicare or medicaid [9]. There is still a recent decline noted in hospitalization rates for acute decompensated heart failure. In accordance with the analysis of the hospitalized patients national claims history files from the centers for medicare & medicaid services (CMS) which identified all fee-for-service medicare beneficiaries who were hospitalized for heart failure from 1998 to 2008, the heart failure hospitalization rates adjustted for the age, gender and race declined from 2845 per 100,000 individual-years in 1998 to 2007 per 100,000 individual-years in 2008 (a decrease of 29.5%; $p < 0.001$). Black men had the smallest rate of age-adjusted decline for all race-gender categories. Importantly, risk-adjusted 1-year mortality after hospitalization reduced from 31.7 % in 1999 to 29.6 % in 2008 (a decline of 6.6 %; $p < 0.001$) [10]. Various multicenter observational registries in the united states and europe have significantly improved our understanding of the management patterns, demographics, clinical characteristics, comorbidities, and results of patients admitted with acute decompensated heart failure. Prior to these registries, our understanding of acute decompensated heart failure came mainly from studies of younger patients with

moderate to severe systolic dysfunction that were enrolled in single-center or multicenter randomized controlled clinical trials conducted mainly at academic heart failure centers. The observational registries were organized to enroll a more representative sample of patients with acute decompensated heart failure that involved all patients admitted with heart failure at geographically diverse academic and non-academic medical centers. Ascertainment methods were used by the organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF) to identify 48,612 patients hospitalized at 259 centers in the united states for new or worsening heart failure as the primary cause of admission or who developed significant heart failure symptoms during hospitalization for a different diagnosis. Using a web-based registry, detailed data were collected including medical history, demographics, signs and symptoms, medications, laboratories, diagnostic testing procedures, discharge status, outcomes and adherence to performance indicators. A pre-specified subgroup that was ≥ 10 % of the total number of patients was followed for 60-90 days after discharge for the collection of outcomes data [11]. The acute decompensated heart failure national data registry (ADHERE) database was a prospective observational registry that was created to provide a large national database to describe clinical characteristics, management and outcomes of inpatients with heart failure at 286 hospitals in the united states. Thirty-one percent of the participating organizations were academic hospitals. From 2002 to 2004, data were collected from 159,168 hospitalizations starting with the point of initial care and ending with the patient's discharge or in-hospital death [12-14]. The euroheart failure survey I (EHFS I) was a retrospective registry in which demises or discharges from 117 hospitals (50% university hospitals) from 25 european countries were examined to discover patients with known or suspected heart failure. Clinical characteristics, evaluation, demographics, treatment and outcomes were assessed [15-17]. The euroheart failure survey II (EHFS II) was a prospective observational registry that recruited 3580 patients hospitalized for heart failure at 133 centers (47% university hospitals) in 30 european countries. Using the web based registry, a comprehensive data was collected including demographics, clinical characteristics, etiology, treatment and outcome [18]. The findings from the U.S. and european trials are largely concordant. Acute decompensated heart failure disproportionately affects the elderly patients; the mean age in the registries was 73 years. About a quarter of the patients in OPTIMIZE-HF were beyond 83 years old [19]. Men and women were uniformly represented in the U.S. registries while men represented two-thirds of the inpatients in EHFS II [18]. Women with acute decompensated heart failure tend to be older, are unlikely to have coronary artery disease and are likely to have preserved systolic function and hypertension [19]. More than 70% of patients suffering from acute decompensated heart failure in the U.S. registries had a history of hypertension. A history of hypertension was recorded in about 63% of patients in EHFS II [18]. Increased systolic blood pressure is common at the time of presentation to the emergency department. Mean primary systolic blood pressure on presentation to the emergency department was 143 mmHg in OPTIMIZE-HF and 144 mmHg in ADHERE. Half of the patients in ADHERE and OPTIMIZE-HF had an initial systolic pressure of more than 140 mmHg [12, 20]. Renal dysfunction is common. The mean serum creatinine was 1.8 mg/dL in both ADHERE and OPTIMIZE; 20% of patients in ADHERE had a serum creatinine of greater than 2.0 mg/dL [12, 20]. About half of patients in ADHERE and OPTIMIZE had normal or near normal systolic function defined as a left ventricular ejection fraction (LVEF) ≥ 40 % [21, 22]. Patients with heart failure with preserved ejection fraction (HFpEF) were more likely to be older, female, caucasian, and have a greater systolic blood pressure on admission and unlikely to have had a prior myocardial infarction when compared with

patients with heart failure with reduced ejection fraction (HFrEF). In-hospital mortality was lower in patients with HFpEF compared to patients with HFrEF in both ADHERE (2.8 % vs. 3.9 %) and OPTIMIZE-HF (2.9 % vs. 3.9 %). In ADHERE, patients with HFpEF had a related length of stay and duration of intensive care unit stay when compared with patients suffering from HFrEF [21]. In OPTIMIZE-HF, patients with HFpEF and HFrEF had similar 60-90 day post-discharge mortality (9.5 % vs. 9.8 %, respectively) and rehospitalization rates (29.2 % vs. 29.9 %, respectively). Findings were similar when patients with an LVEF between 40-50 % were compared with patients with an LVEF ≥ 50 % [22]. In an analysis of the data from EHFS I, mortality in the 12th week post discharge follow-up period was elevated in patients with HFrEF compared to patients with HFpEF (12% vs 10%). There were no discrepancies in readmission rates during the 12th week follow up period [23]. About 18% of patients in OPTIMIZE-HF and 20% of patients in ADHERE were african american. African-american patients in OPTIMIZE-HF were more younger (mean age 63.6 years compared with 75.2 years for non-african american patients), were very likely to have systolic dysfunction and a hypertensive aetiology of heart failure and significantly less likely to have ischemic heart disease than non-african american patients. African american patients were very likely to receive evidence-based medications but unlikely to receive discharge instructions and smoking cessation counseling. African-american race was an autonomous predictor of lower in-hospital mortality but not of hospital length of stay or multivariable adjusted post-discharge results [24]. In ADHERE, 75% of patients had a prior history of heart failure and 33% had a heart failure admission within the prior 6 months. About 88% of patients in OPTIMIZE-HF had a prior history of heart failure. 37% of patients in EHFS II had new onset HF; 42% of these patients presented with an acute coronary syndrome [12,18,19]. Comorbid conditions are common in patients admitted with acute decompensated heart failure. A history of hypertension was significantly present in over 70% of patients in the U.S. registries and about 53% and 62.5% in EHFS I and II, respectively. More than 40% of patients had diabetes mellitus in the U.S. registries (27% and 32.8% in EHFS I and II, respectively). Renal insufficiency was also present in 30% of patients and chronic lung disease was present in 30% of patients in the U.S. registries.

Pathophysiology

Acute decompensated heart failure is a syndrome caused by a broad range of cardiovascular diseases [25]. The underlying pathophysiology is heterogeneous and it lies on the nature, time course and severity of the underlying cardiovascular disease and the presence and severity of non-cardiovascular precipitating factors. The heterogeneity of patients with acute decompensated heart failure makes it difficult to develop a single pathophysiologic model [26]. Despite this heterogeneity, there are some important themes in patients with acute decompensated heart failure that guide the approach to patient management. In heart failure, there is a reduction in cardiac output which results in activation of baroreceptors in the central circulation in response to vascular under-filling. This causes activation of the sympathetic nervous system leading to an increase in sympathetic outflow to the kidney and systemic vasoconstriction [26]. Reduced renal blood flow and sympathetic stimulation of the kidney cause release of renin from the juxtaglomerular apparatus which, in turn, leads to conversion of angiotensinogen to angiotensin I which is changed to angiotensin II by angiotensin converting enzyme (ACE) and other tissue proteases [25, 26]. Angiotensin II is a vasoconstrictor that causes systemic

vasoconstriction, renal arterial efferent >afferent vasoconstriction, activation of the sympathetic nervous system, release of aldosterone, stimulation of sodium retention in the proximal tubule of the kidney, release of arginine vasopressin, and stimulation of thirst centers in the brain. Sodium and water reabsorption is increased by aldosterone in the distal tubule and collecting duct contributing to extracellular fluid expansion and systemic congestion. Aldosterone also elevates sodium and water absorption in the colon. Hepatic congestion in the setting of elevated right atrial pressure reduces aldosterone metabolism causing increased aldosterone levels [27]. Patients do not have aldosterone escapein heart failure so that, unlike patients with isolated hyperaldosteronism, the distal tubule goes on to reabsorb sodium in response to increased aldosterone levels. Stimulation of increased angiotensin II levels and central baroreceptors stimulate the non-osmotic production of arginine vasopressin from the posterior pituitary gland. This causes an increased free water reabsorption in the collecting ducts which makes volume overload worse and it leads to the development of hyponatremia [25]. There is retention of sodium and water in heart failure, which is mediated by activation of the sympathetic nervous system, decreased systemic and renal perfusion, and activation of the renin angiotensin aldosterone system (RAAS). In some patients, salt and water retention cannot be reversed by pharmacologic blockade of the RAAS and sympathetic nervous system suggesting that neurohormonal activation is not the only mechanism accountable for salt and water retention [25-27]. An Increase in sodium and water consumption are mediated by a rise in thirst caused by stimulation of central thirst centers mediated by activation of baroreceptors in the central circulation and excessive production of angiotensin II. Systemic congestion is a result of an increase in total body salt and water mediated by a reduction in sodium and water excretion and an increase in intake. Activation of the sympathetic nervous system and RAAS lead to systemic vasoconstriction and a rise in systemic vascular resistance (SVR). Increases in SVR cause a reduction in stroke volume and cardiac output in patients with systolic dysfunction and an increase in functional mitral regurgitation in patients with ventricular dilation [12]. A lot of patients with acute decompensated heart failure present with the primary symptom of dyspnea either at rest or with activity. This is certain for people with new-onset or chronic heart failure and also for patients with and without systolic dysfunction. Many patients have signs on physical exams of pulmonary and systemic venous congestion [12,14]. Breathlessness in patients with acute decompensated heart failure is caused by an increase in left atrial and pulmonary capillary pressure. The fluid movement from the pulmonary capillary space to the pulmonary interstitium is ascertained by a balance between hydrostatic and oncotic pressures in the pulmonary capillary and the pulmonary interstitial space. The main factor that results in fluid to move out of the capillary is a difference between the increased hydrostatic pressure within the pulmonary capillary and the lower hydrostatic pressure in the surrounding interstitium [14]. This action of fluid is opposed by the difference between the colloid osmotic pressure (which is primarily provided by the concentration of albumin) in the capillary space and the interstitium, which decreases the transudation of fluid out of the tiny blood vessel. In normal physiology, lymphatic washout of albumin that goes into the interstitium causes an increase in the osmotic gradient between the interstitium and pulmonary capillary which reduces transudation of fluid [12]. In normal physiology, fluid continues to move from the capillary space into the interstitium and is then eliminated by the lymphatic system. When hydrostatic pressure in the pulmonary capillary significantly goes up, transudation of fluid into the interstitium increases with potential for spilloverinto the alveolar space [28]. There are various defensive mechanisms that prevent

the development of pulmonary edema. First, the alveolar capillary unit is made up of a thin and thick side. The thin side comprised of a capillary closely opposed to the alveolar air space. The epithelium of alveolar and capillary endothelium are attenuated, the basal laminae of the alveolar epithelium and capillary endothelium are combined and the permeability to salt and water is low [28]. The thick part of the alveolar capillary unit contains an interstitial matrix with a gel-like protein component that separates the alveolar epithelium from the capillary endothelium. With a rise in capillary hydrostatic pressure, edema is first formed in the interstitial compartment away from areas of gas exchange. Second, as fluid goes into the interstitial compartment, hydrostatic pressure increases and oncotic pressure decreases, which serves to oppose further movement into the interstitial space [29]. Third, the fluid that forms in the interstitium goes along a negative pressure gradient to the interlobular septae, the bronchovascular space and the hila. The edema also collects in the pleural space. Lymphatic vessels in the peribronchovascular sheath, interlobular septae, and pleura facilitate clearance of lung water [30]. Pulmonary lymphatics are greatly recruitable and, over time, are able to increase clearance of lung water by more than tenfold. Fourth, active sodium ion transport across the alveolar-capillary barrier by type II alveolar epithelial cells lining the alveoli is responsible for clearance of alveolar edema. Sodium ion enters the alveolar epithelial cells through apical amiloride sensitive sodium ion channels and other sodium ion channels and, by a process that consumes energy, is pumped out of the cell by the sodium ion, K+-ATPase located in the basolateral membrane [28-30]. In patients with HFrEF and HFpEF, the left ventricular filling pressure required to support a given amount of left ventricular work is elevated. As left ventricular end-diastolic pressure (LVEDP) increases, so do left atrial and pulmonary capillary pressures. As pulmonary capillary pressure goes up, there is an increase in the transmural filtration of fluid into the pulmonary interstitium. There is a stage at which the capacity of the lymphatic system to eliminate fluid from the interstitium is surpassed and fluid starts to accumulate in the alveoli [30]. The cumulation of extravascular fluid in the pulmonary interstitium and alveoli is associated with clinical symptoms of paroxysmal dyspnea, impaired gas exchange, orthopnea, and dyspnea [21]. The functions of lungs and symptoms are influenced by water content of the lungs. The underlying pathophysiology of dyspnea in acute decompensated heart failure is multifactorial and complex with contributions from: decreased lung volume; airflow obstruction from reflex bronchoconstriction; geometric reduction in airway size from reduced lung volumes, intraluminal edema and mucosal swelling; reduced lung compliance; reduced alveolar-capillary membrane conductance with acute and chronic decreases in DLCO; impaired gas exchange due to alveolar swelling; arterial hypoxemia; raised work of breathing; respiratory muscle weakness in the critically ill patient; activation of chest wall sensors, an increase in the elastic work of breathing caused by cardiac enlargement and vascular engorgement with chest wall expansion past the usual or physiologic position; and stimulation of nerve endings in response to vascular distention and interstitial swelling [28]. A traditional understanding of why patients suffering from chronic heart failure develop acute decompensated heart failure indicates that patients with chronic heart failure commonly have a gradual rise in total body salt and water reflected by gradual weight gain and the gradual development of clinical features of pulmonary and systemic venous congestion [23]. While this paradigm happens in some of the patients with chronic heart failure, it may not be applicable to a huge number of patients with acute decompensated heart failure. A nested case-control study of patients referred to a home monitoring system by managed care organizations matched 134 case patients with heart failure hospitalization with 134 control patients without heart failure hospitalization [29]. Case

patients experienced gradual weight gain starting about 30 days before admission to hospital. Within 7 days of hospitalization, weight patterns between case and control patients started to diverge more substantially with greater weight gain strongly associated with a greater odds ratio for hospital admission for (>2-5 lbs HR 2.77; >5-10 lbs HR 4.46; >10 lbs HR 5.65). However, only 46 % of case patients hospitalized for acute decompensated heart failure gained more than two pounds suggesting that in approximately half of patients, weight gain was not the precipitating cause of admission to the hospital.

Classification of ADHF

Heart failure is the last common pathway for a broad range of cardiovascular diseases. Patients suffering from ADHF have diverse underlying causes of cardiovascular dysfunction, time course of symptom development, co-morbid conditions and precipitants, and underlying pathophysiology. A certain number of attempts have been made to classify acute decompensated heart failure based on onset, underlying heart disease, underlying hemodynamic abnormalities and clinical profiles.

An emphasis was made on the time course to develop heart failure by the International Working Group on acute heart failure syndrome [8]. However, the American College of Cardiology/American Heart Association (ACC/AHA) stage in their classification of ADHF:

1. Worsening chronic heart failure: with decreased or preserved LVEF. ACC/AHA Stage C heart failure. 70% of all admissions.

2. De novo heart failure: this is mostly due to acute coronary syndrome; also, sudden increase in blood pressure in a patient with a non-compliant left ventricle, or acute myocarditis. People with either ACC/AHA Stage A (risk factors but no structural heart disorder) or Stage B (pre-existing structural heart disease but without clinical features of heart failure). 25% of all admissions.

3. In advanced heart failure: severe left ventricular systolic dysfunction, in association with continuously worsening low output state, refractory to conventional heart failure therapy and requiring specialized therapies (LVAD, heart transplant, hospice). ACC/AHA Stage D 5% of all admissions.

The 2009 ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults [12] have reported 3 clinical profiles of patients with acute decompensated heart failure which focus on clinical presentations of systemic perfusion and congestion:

1. The patient with hypervolemia, presented with pulmonary and systemic congestion, frequently caused by an acute increase in chronic hypertension

2. The patient with profound low cardiac output presented with renal insufficiency, hypotension, and shock syndrome

3. The patient with clinical features of both fluid overload and shock.

The European Society of Cardiology has stated six clinical scenarios for patients presenting with acute decompensated heart failure in their 2008 Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [17]. EHFS II used a modification of the ESC outlines to classify patients included in the registry [18]:

1. Deteriorating or decompensated chronic heart failure: history of progressive worsening of known chronic heart failure. Clinical signs and symptoms of worsening heart failure with evidence of systemic and pulmonary venous congestion [16]. Patients may have either decreased or preserved ejection fraction. (65% of patients in EHFS II).

2. Pulmonary edema: Patients who have fast breathing with diffuse pulmonary rales, severe respiratory distress, hypoxia with oxygen saturation less than 90% (without supplemental oxygen) with alveolar edema on chest X-ray. (16% of patients in EHFS II) [18].

3. In hypertensive heart failure: Patients have clinical features of heart failure with high blood pressure. There is evidence of high sympathetic tone with fast heartbeat and signs of vasoconstriction. Patients are likely to have preserved systolic function. Most often, these patients have evidence of pulmonary congestion with no signs of systemic congestion [16]. The response to heart failure therapy is generally rapid and the in-hospital mortality is low (1.5% in EHFS II). (11% of patients in EHFS II).

4. In cardiogenic shock: The patients with evidence of end-organ hypoperfusion secondary to heart failure with adequate or increased left ventricular end-diastolic pressure [18]. Typically, these patients have low urine output, a decreased systolic blood pressure, and low cardiac index (<2.2 L/min/m2). A lot of the patients will also have severe pulmonary congestion and the mortality rate in this population is high. (4% of patients in EHFS II)

5. In isolated right heart failure: There is clear evidence of raised jugular venous pressure, systemic venous congestion, and low cardiac output with no evidence of pulmonary congestion [17].

6. In acute coronary syndrome complicated by heart failure: (This was not added as a different classification in EHFS II) heart failure with a clinical feature and laboratory evidence of an acute coronary syndrome. About 13.6% of patients with acute coronary syndrome have associated clinical evidence of heart failure [17,18]. In EHFS II, acute coronary syndrome was the precipitating factor in 42% of patients who presented with new onset or de novo heart failure and 23% of patients who had pre-existing heart failure.

Causes of acute decompensated HF

Decompensation of preexisting chronic HF from a precipitating factor (e.g., natural progression of underlying disease, dietary indiscretion [excessive fluid or salt intake], medication nonadherence, infection, new myocardial ischemia, metabolic stress [e.g., anemia, hyperthyroidism], medication use [e.g., nonsteroidal antiinflammatory medications that lead to sodium retention]) [30]. Hypertensive crisis (e.g., hypertensive emergency). Myocardial infarction or ischemia, especially if a papillary muscle is involved, leading to severe mitral regurgitation; a massive anterior myocardial infarction occurs; or a

right ventricular infarct results in a low cardiac output state [28]. Acute tachyarrhythmia. Acute endocarditis leading to severe regurgitation. Acute dilated cardiomyopathy (e.g., myocarditis, cocaine, toxins). Cardiac tamponade [29]. High-output HF (e.g., paget disease, thyrotoxicosis, beriberi, sepsis).

Clinical manifestations

The cardinal features of heart failure are dyspnea and fatigue. Generally, fatigue has been attributed to the low cardiac output in heart failure, it is likely that the skeletal-muscle abnormalities and other noncardiac comorbidities (e.g., anemia) also contribute to this symptom [21]. In the early stages of heart failure, shortness of breath is observed only during exertion; however, as the disease advances, shortness of breath occurs with less strenuous activity, and it eventually may occur even at rest. The origin of shortness of breath in heart failure is likely multifactorial [8, 21]. The prime mechanism is pulmonary congestion with accumulation of interstitial or intra-alveolar fluid, which activates juxtacapillary J receptors, which in turn stimulate the rapid, shallow breathing characteristic of cardiac dyspnea. Additional factors that contribute to shortness of breath on exertion include increased airway resistance, reductions in pulmonary compliance, respiratory muscle and/or diaphragm fatigue, and anemia [1]. Shortness of breath may become less frequent with the onset of tricuspid regurgitation and right ventricular failure. Orthopnea: this is breathlessness occurring in the recumbent position. It is traditionally a later manifestation of heart failure than is exertional dyspnea [3]. It occurs when fluid from the splanchnic circulation and lower extremities is redistributed into the central circulation during recumbency, with a resultant elevation in lungs capillary pressure. Nocturnal cough is a regular manifestation of this process and a frequently neglected symptom of heart failure. Orthopnea normally is relieved by sleeping with additional pillows or sitting upright. Although orthopnea is a very specific symptom of heart failure, it may happen in patients with ascites or abdominal obesity, and patients suffering from pulmonary disease whose lung mechanics favor an upright posture [1-3]. Cheyne-stokes respiration: refers to the periodic respiration or cyclic respiration, cheyne-stokes respiration occurs in about 40% of patients with advanced heart failure and normally is in association with low cardiac output [27]. It is caused by an increase in the sensitivity of the respiratory center to arterial PCO2 and a lengthy circulatory time. There is an apneic stage, during which arterial PO2 reduces and arterial PCO2 increases [14]. These changes in the arterial blood gas (ABG) content stimulate the respiratory center, leading to hypocapnia and hyperventilation, followed by recurrence of apnea [27]. Acute pulmonary edema: additional symptoms patients with heart failure may present with are gastrointestinal symptoms [14]. Anorexia, nausea, and early satiety in association with abdominal pain and bloating are usual complaints and may be linked to edema of the bowel wall and/or a congested liver. Hepatic congestion and stretching of its capsule may cause right upper-quadrant pain [27]. Cerebral manifestations such as disorientation, confusion, and sleep and mood disturbances may be seen in patients with severe heart failure, especially elderly patients with cerebral arteriosclerosis and low cerebral perfusion. Nocturia is common in heart failure and may contribute to insomnia [24].

Physical examination

A thorough physical examination is often warranted in the assessment of patients with heart failure, in order to ascertain the cause of heart failure, also to evaluate the severity of the syndrome [30]. The

general appearance and vital signs in mild and moderately severe heart failure, the patient appears in no distress at rest except for feeling uncomfortable when in a prone position for more than a few minutes. In more severe heart failure, the patient must sit upright, may have labored respiration, and may be unable to complete a sentence because of dyspnea [25]. Systolic blood pressure may be normal or high in early heart failure, but it commonly is decreased in advanced heart failure because of severe left ventricular dysfunction. The pulse pressure may be decreased, indicating a deduction in stroke volume. Sinus tachycardia is a nonspecific sign caused by high adrenergic activity [23]. Peripheral vasoconstriction leading to cool peripheral extremities and cyanosis of the lips and nail beds is also due to excessive adrenergic activity. Jugular veins: assessment of the jugular veins provides an estimation of right atrial pressure. The JVP (jugular venous pressure) is best appreciated with the patient lying recumbent, with the head tilted at 45°. The JVP is quantified in centimeters of water by estimating the height of the venous column of blood above the sternal angle in centimeters and then adding 5cm. In the early phases of heart failure, the venous pressure may be normal at rest but may become abnormally increased with sustained pressure on the abdomen (positive abdominojugular reflux). Giant v waves signifies the presence of tricuspid regurgitation [28]. Pulmonary examination: crepitations or rales originate from the transudation of intravascular fluid into the alveoli [27]. In people with pulmonary edema, rales may be heard widely over both lung fields and may be followed by expiratory wheezing (cardiac asthma). When present in people without concomitant lung disorder, rales are specific for heart failure. Importantly, rales are occasionally not seen in patients with chronic heart failure, even when left ventricular filling pressures are increased, because of elevated lymphatic drainage of alveolar fluid. Pleural effusions result from the increase of pleural capillary pressure and the resulting transudation of fluid into the pleural cavities [27-29]. Cardiac examination: examination of the heart, although important, generally does not provide helpful information about the severity of heart failure [30]. If cardiomegaly is present, the point of maximal impulse is displaced below the 5th intercostal space and lateral to the midclavicular line, and the impulse is felt over two interspaces. Severe left ventricular hypertrophy leads to a sustained PMI. In some patients, a 3rd heart sound is audible and felt at the apex [20]. Patients with enlarged right ventricles may have a sustained and prolonged left parasternal impulse extending throughout systole. An S3 is commonly heard in patients with volume overload who have tachypnea and tachycardia, and it frequently indicates severe hemodynamic compromise. A fourth heart sound is not a specific indicator of heart failure but is usually present in patients with diastolic dysfunction. The murmurs of mitral and tricuspid regurgitation are often present in patients with advanced heart failure [23]. Abdomen and extremities: hepatomegaly is an essential sign in patients with heart failure. When it occurs, the enlarged liver is often tender and may pulsate during systole if tricuspid regurgitation is present [28]. Ascites, a late sign, occurs as a result of increased pressure in the hepatic veins and the veins draining the peritoneum. Jaundice, is also a late finding in heart failure, results from impairment of hepatic function secondary to hepatic congestion and hepatocellular hypoxemia and is associated with elevations of both direct and indirect bilirubin [23]. Peripheral edema is a prime manifestation of heart failure, but it is nonspecific and usually is absent in patients who have been treated satisfactorily with diuretics [21]. Peripheral edema is generally symmetric and dependent in heart failure and occurs mainly in the ankles and the pretibial region in ambulatory patients. In bedridden people, edema may be found in the scrotum and sacral area. Prolonged edema may be associated with indurated and pigmented skin [23]. Cardiac cachexia: with

severe chronic heart failure, there may be significant weight loss and cachexia. Although the mechanism of cachexia is not completely understood, it is probably multifactorial. When present, cachexia augurs a poor overall prognosis [22, 23].

Diagnosis

The diagnosis of heart failure is relatively straightforward when the patient presents with classic signs and symptoms of heart failure; however, the clinical features of heart failure are neither specific nor sensitive. The key to arriving at the diagnosis is to have a high index of suspicion, especially for patients with high risk [1,2,8]. When these patients present with signs or symptoms of heart failure, additional laboratory investigations should be performed. Routine laboratory testing: patients with new-onset heart failure and those with acute decompensated heart failure and chronic heart failure should have a complete blood count (CBC), a hepatic panel, a panel of electrolytes, serum creatinine, blood urea nitrogen, and a urinalysis [25]. Selected patients should have evaluation for diabetes mellitus, dyslipidemia, and thyroid abnormalities. Electrocardiogram (ECG): a routine twelve-lead ECG is recommended [25]. The major importance of the electrocardiogram is to evaluate cardiac rhythm and determine the presence of left ventricular hypertrophy or a prior MI as well as to determine QRS width to ascertain if the patient may benefit from resynchronization therapy. A normal electrocardiogram virtually does not include left ventricular systolic dysfunction [24]. Chest x-ray: a chest x-ray provides useful evidence about heart size and shape, also the state of the pulmonary vasculature, and may recognize non-cardiac causes of the patients symptoms [22]. Although patients with acute heart failure have evidence of pulmonary hypertension, and interstitial edema, the majority of patients with chronic heart failure do not. The absence of these findings in patients with chronic heart failure reflects the increased capacity of the lymphatics to eliminate interstitial fluid [15]. Assessment of left ventricular function: noninvasive cardiac imaging is crucial for the assessment, diagnosis, and management of heart failure. Two-dimensional (2-D) echocardiogram/doppler is the most useful test, it provides a semiquantitative assessment of left ventricular size and function as well as the presence or absence of valvular and/or regional wall motion abnormalities [21]. The presence of left atrial dilation and left ventricular hypertrophy, together with abnormalities of left ventricular diastolic filling provided by pulse-wave and tissue doppler, is helpful for the evaluation of heart failure with a preserved ejection fraction. The 2-D echocardiogram/doppler is also useful in assessing right ventricular size and pulmonary pressures, which are critical in the assessment and management of cor pulmonale [15]. Magnetic resonance imaging also provides a complete analysis of cardiac anatomy and function and is now the gold standard for assessing left ventricular mass and volumes. MRI also is emerging as an invaluable and accurate imaging modality for assessing patients with heart failure, both in terms of evaluating left ventricular structure and for determining the cause of heart failure [22]. Biomarkers: circulating levels of natriuretic peptides are helpful and prime adjunctive tools in the diagnosis of patients with heart failure [6]. Both B-type natriuretic peptide and N-terminal pro-BNP, which are released from the failing heart, are relatively sensitive markers for the presence of heart failure with depressed ejection fraction; they are also increased in heart failure patients with a preserved ejection fraction, albeit to a lesser degree [21]. In ambulatory patients with shortness of breath, the measurement of BNP or NT-proBNP is helpful to support clinical decision-making concerning the diagnosis of heart failure, particularly in the setting of

clinical uncertainty. Additionally, the measurement of BNP or NT-proBNP is helpful for establishing prognosis or disease severity in chronic heart failure and can be helpful to achieve optimal dosing of medical therapy in select clinically euvolemic patients [20]. Nevertheless, it is important to identify that natriuretic peptide levels increase with age and renal impairment, are more increased in women, and can be increased in right heart failure from any cause. BNP levels may rise in patients taking angiotensin receptor-neprilysin inhibitors [5, 30]. Levels can be falsely decreased in obese patients. Other biomarkers, like soluble ST-2 and galectin-3, are newer biomarkers that can be used for determining the prognosis of heart failure patients. Exercise testing: treadmill or bicycle exercise testing is routinely unrecommended for patients with heart failure, but either is useful for assessing the need for cardiac transplantation in patients with advanced heart failure [30]. A peak oxygen uptake (vo2) less than 14 mL/kg per min is associated with a relatively poor prognosis. Patients with a vo2 less than14 mL/kg per min have been shown, in general, to have better survival when transplanted than when treated medically [22].

Medical management

The main objectives of treatment for heart failure (HF) are to improve prognosis, reduce the burden of symptoms, and ultimately decrease morbidity and mortality. Additionally, it also includes: reducing the length of hospital stay and frequency of readmission, prevent end-organ damage, and to adequately manage co-morbid conditions that may worsen the outcome [30]. The 2010 HFSA (heart failure society of america) guidelines, the updated 2013 ACA/AHA (american college of cardiology/american heart association) guidelines, and the 2008 ESC (european society of cardiology) guidelines, all provide different levels of evidence for the management of HF patients. This reports management of HF cases will be under two categories; In-hospital and out-patient care [19, 29, 30]. In-hospital management: it is so recommended to admit the patient to the telemetry bed or the intensive care unit (ICU) and provide care based on the - oxygen levels (PaO2 less than 60% or SaO2 less than 90%), and noninvasive positive pressure ventilation (NIPPV) given in cases with respiratory distress to support ventilation. Several pharmacological agents can be administered depending on presenting signs/symptoms and on the contributing factors: Diuretics: loop diuretics, thiazides, and potassium-sparing diuretics for years have been the mainstay for managing HF cases. Loop diuretics inhibit NA-K-2CL cotransporter on the luminal membrane of the ascending limb of the loop of henle to reduce renal reabsorption of sodium chloride. Examples are furosemide, torsemide, bumetanide, and ethacrynic acid as an option in cases of sulfa allergy [22, 27]. Diuretics reduce volume overload in HF patients. Angiotensin-converting enzyme inhibitors (ACEIs)/or angiotensin receptor blockers (ARBs)/angiotensin-neprilysin receptor. Blockers: this category works by suppressing the renin-angiotensin-aldosterone system (RAAS) and is considered the gold standard to modulate RAAS in HF patients for more than two decades [24]. ACEIs block the conversion of angiotensin one to angiotensin two. However, it potentiates bradykinin accumulation which promotes both positive and negative effects. ARBs are the alternatives to ACEIs in patients that cannot tolerate ACEIs. ARBs specifically block the angiotensin ii receptors and do not decrease the breakdown of bradykinin online ACEIs [25]. A newer therapy class, the angiotensin receptor neprilysin inhibitor (ARNI), was brought about by adding a neprilysin inhibitor to angiotensin receptor inhibition [26]. Being an endopeptidase, neprilysin breaks down various endogenous vasoactive peptides [27].

These effects lead to appreciable hypotensive outcomes and are massively beneficial in comparison with ACEIs or ARBs. The ARNI is fast replacing ACEI/ARB as the gold standard RAAS blocker due to its clinical advantages for HF cases [27, 5]. Beta blockers (BBs): by inhibiting the actions of the sympathetic nervous system, BBs have shown improved outcomes for HF management. Subsequently, BBs decrease ischemia of the myocardium and possesses antiarrhythmic effects which help to maintain energy levels required for myocyte function by enabling glucose instead of fatty acid metabolism. As well, beta blockers inhibit renin secretion [28]. Mineralocorticoid receptor anatagonists (MRAs): this class of drugs prevent the binding of aldosterone to the mineralocorticoid receptors, mostly found in the vascular smooth muscle cells and in the myocardium. Furthermore, they demonstrate antifibrotic effects by suppressing the production of matrix metalloproteinases and other factors that contribute to myocardial remodelling [22, 24, 26, 28]. Sodium-glucose cotransporter - 2 (SGLT-2) inhibitors: recently proven to be efficacious in treating Hf, especially HF with reduced ejection fraction (HFrEF). It increases renal glucose excretion by blocking SGLT-2, promoting osmotic diuresis and natriuresis [23]. Although it was originally manufactured as an anti-diabetic agent, it has clinical benefits for HFrEF in both diabetic and non-diabetic patients [24]. Ivabradine: patients benefit from the use of this drug as a result of its inhibition of the inward rectifying potassium channel (funny currents inhibitor), which slows depolarization during diastole eventually reducing the heart rate [25]. Thromboembolism risk is reduced by anticoagulants if needed. Vasodilators: such as hydralazine and nitrates combined are substantially considered to improve patient symptoms. Hydralazine is a direct arteriolar vasodilating agent whereas nitrates primarily mediate venodilation, lowering ventricular preload [26]. Oral soluble guanylate cyclase stimulators: example - vericiguat. Lately, found to enhance positive end results among HF patients at high risk. Its main mechanism of action involves boosting endogenous nitric oxide by directly binding to and stimulating the soluble guanylate cyclase [27]. Positive oral inotropes: restores perfusion and decreases congestion in HFrEF patients so as to increase cardiac output. It includes digoxin and omecamtiv mecarbil. The latter is a new drug, acting as an activator of cardiac myosin beneficially improving the left ventricular function [28, 29]. In summary, the proper medical management should follow the steps below: reduce preload (preferably with loop diuretics). Administer oxygen if hypoxemia is present. Reduce afterload with ACEI if systolic blood pressure measures more than 100mmHg. Intravenous agents are recommended if hypertensive crisis is present (i.e., sodium nitroprusside). Increase inotropy if there are evidences of hypoperfusion (i.e., milrinone, dobutamine), but beware of increase in ventricular arrhythmias with inotropic agents. Digoxin reduces hospitalizations and improves clinical symptoms, but does not lower mortality rate. Consider adding digoxin when patients have symptoms despite adequate therapy with ACEI, β-blockers, and AA. NB: β-blockers are successfully used later when heart failure is compensated and stroke volume improves. They can worsen decompensated heart failure by their inotropic effects. Mineralocorticoid antagonist e.g,. spironolactone, which helps reduce morbidity and mortality. Funny current inhibitor e.g,. ivabradine which significantly increases survival rate by 120% and prolongs average survival time by 20%. Angiotensin receptor-neprilysin inhibitor, e.g,. sacubitril/valsartan. Certain agents from the above listed have been demonstrated to significantly lower morbidity and mortality, hospitalizations, and prevent cardiac remodelling. They are; beta blockers, ACEIs/ARBs, MRA, and ARNI(sacubitril/valsartan) [22-26]. SGLT-2 inhibitors also highly improve quality of life when incorporated into current standard drugs [24, 26, 28]. Out-patient management: [29, 30] counsel should be tailored to meet the patients specific needs, patient education,

promote self-care, strategies to enhance patient medication adherence, observing signs and symptoms of fluid overload, regular follow-up, access to healthcare services and assistance as required.

Implantable devices and surgical procedures to treat heart failure:

Cardiac resynchronization therapy (CRT) is done to help the heart beat with the right rhythm. It uses a pacemaker to restore the original timing pattern of the heartbeat [23]. Left ventricular assist device: this device is used for patients who have reached the last stage of heart failure. It is a battery-operated, mechanical pump, which is surgically fixed in the chest. It helps the main pumping chamber of the heart (left ventricle) to pump blood to the rest of the body [23, 25]. HeartMate 3: this is a centrifugal, continuous flow pump that is placed in the thorax and is engineered to be a more hemocompatible LVAS. The device is created with a fully magnetically levitated motor, offers wider blood flow paths, and even exhibits a fixed intrinsic pulse (by the motor ramping its speed up and down at 2 s intervals) [25]. Total artificial heart: it is not every patient that is a candidate for a LVAS, especially those with severe right-sided heart failure or conditions that do not permit placement of an LVAS (massive anterior myocardial infarction, restrictive cardiomyopathy, complex congenital heart disease). In similar patients, either a biventricular assist device approach or a total artificial heart pump can be considered [30]. The syncardia total artificial heart is a pulsatile, implantable pump that comprises two polyurethane ventricles with pneumatically driven diaphragms, and four tilting disc valves. This requires excision of the native ventricles and hence cannot be employed as a myocardial recovery strategy. There are a lot of specific clinical issues that are peculiar to the total artificial heart management [24]. This machine operates on a steep physiological curve and has little adaptability to tolerate either systemic blood pressure changes or large shifts in blood volume. Heart valve surgery: diseased heart valves can be treated with both traditional heart valve surgery and balloon valvuloplasty [30]. Coronary artery bypass grafting surgery: this is considered in heart failure caused by coronary artery disease [27]. Heart transplantation: some patients have severe, progressive heart failure that cant be helped by drugs or dietary and lifestyle changes. In similar cases, a heart transplant may be the only beneficial treatment option. The damaged heart is changed with a healthy heart from a donor who has been declared brain dead [23]. However, it takes some time to find a donor whose heart matches the tissues of the recipient.

Conclusions

Acute decompensated heart failure is a regular cause of hospitalization and has a tall risk of rehospitalization and mortality. From the diagnosis and risk stratification of the acute decompensated heart failure, determination of the clinical hemodynamic profile is essential to guide therapy including pharmacological and non-pharmacological measures, and, in refractory cases, VAD and cardiac transplantation.

References

1. Braunwald E. Heart failure: JACC Heart Fail. 2013, 1:1-20. 10.1016/j.jchf.2012.10.002
2. Braunwald E: The war against heart failure: the. Lancet lecture. Lancet. 2015, 28:812-24. 10.1016/S0140-6736(14)61889-4

3. Cowie MR, Woehrle H, Wegscheider K, et al.: Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med. 2015, 17:1095-105. 10.1056/NEJMoa1506459
4. Kusumoto FM, Calkins H, Boehmer J, et al.: HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. Circulation. 20141, 130:94-125. 10.1161/CIR.0000000000000056
5. McMurray JJ, Packer M, Desai AS, et al.: Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014, 11:993-1004. 10.1056/NEJMoa1409077
6. Sundström J, Ingelsson E, Berglund L, et al.: Cardiac troponin-I and risk of heart failure: a community-based cohort study. Eur Heart J. 2009, 30:773-81. 10.1093/eurheartj/ehp047
7. Redfield MM, Anstrom KJ, Levine JA, et al.: NHLBI Heart Failure Clinical Research Network. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2015, 10:2314-24. 10.1056/NEJMoa1510774
8. Gheorghiade M, Zannad F, Sopko G, et al.: International Working Group on Acute Heart Failure Syndromes. Acute heart failure syndromes: current state and framework for future research. Circulation. 200520, 112:3958-68. 10.1161/CIRCULATIONAHA.105.590091
9. Fang J, Mensah GA, Croft JB, et al.: Heart failure-related hospitalization in the U.S., 1979 to 2004. J Am Coll Cardiol. 2008, 52:428-34. 10.1016/j.jacc.2008.03.061
10. Chen J, Normand SL, Wang Y, et al.: National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. JAMA. 2011, 306:1669-78. 10.1001/jama.2011.1474
11. Fonarow GC, Abraham WT, Albert NM, et al.: Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. Am Heart J. 2004, 148:43-51. 10.1016/j.ahj.2004.03.004
12. Adams KF Jr, Fonarow GC, Emerman CL, et al.: Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005, 149:209-16. 10.1016/j.ahj.2004.08.005
13. Fonarow GC, Heywood JT, Heidenreich PA, et al.: Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2007, 153:1021-8. 10.1016/j.ahj.2007.03.012
14. Fonarow GC, Corday E; ADHERE Scientific Advisory Committee: Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. Heart Fail Rev. 2004, 9:179-85. 10.1007/s10741-005-6127-6
15. Cleland JG, Swedberg K, Cohen-Solal A, et al.: The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail. 2000, 2:123-32. 10.1016/s1388-9842(00)00081-7
16. Cleland JG, Swedberg K, Follath F, et al.: Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme-- a survey on the

quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003, 24:442-63. 10.1016/s0195-668x(02)00823-0
17. Komajda M, Follath F, Swedberg K, et al.: Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure Survey programme - a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J. 2003, 24:464-74. 10.1016/S0195-668X(02)00700-5
18. Nieminen MS, Brutsaert D, Dickstein K, et al.: Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006, 27:2725-36. 10.1093/eurheartj/ehl193
19. Fonarow GC, Abraham WT, Albert NM, et al.: Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). Am J Cardiol. 2009, 104:107-15. 10.1016/j.amjcard.2009.02.057
20. Gheorghiade M, Abraham WT, Albert NM, et al.: Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006, 8:2217-26. 10.1001/jama.296.18.2217
21. Yancy CW, Lopatin M, Stevenson LW, et al.: Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol. 2006 Jan 3. 47:76-84. 10.1016/j.jacc.2005.09.022
22. Tamargo J, López-Sendón J: Novel therapeutic targets for the treatment of heart failure. Nat Rev Drug Discov. 2011, 24:536-55. 10.1038/nrd3431
23. Felker GM, Ellison DH, Mullens W, et al.: Diuretic Therapy for Patients With Heart Failure. JACC State-of-the-Art Review. J Am Coll Cardiol. 2020, 17:1178-1195. 10.1016/j.jacc.2019.12.059
24. Zannad F, Gattis Stough W, Rossignol P, et al.: Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. Eur Heart J. 2012, 33:2782-95. 10.1093/eurheartj/ehs257
25. Hua Y, Wang I, Liu B, et al.: Angiotensin receptor neprilysin inhibitor LCZ696: pharmacology, pharmacokinetics and clinical development. Future Cardiol. 2017, 13:103-115. 10.2217/fca-2016-0057
26. Cullington D, Goode KM, Clark AL, et al.: Heart rate achieved or beta-blocker dose in patients with chronic heart failure: which is the better target?. Eur J Heart Fail. 2012, 14:737-47. 10.1093/eurjhf/hfs060
27. Bao J, Kan R, Chen J, et al.: Combination pharmacotherapies for cardiac reverse remodeling in heart failure patients with reduced ejection fraction: A systematic review and network meta-analysis of randomized clinical trials. Pharmacol Res. 2021, 169:105573. 10.1016/j.phrs.2021.105573
28. Campbell TJ, MacDonald PS: Digoxin in heart failure and cardiac arrhythmias. Med J Aust. 2003, 21:98-102. 10.5694/j.1326-5377.2003.tb05445.x
29. Komajda M, Böhm M, Borer JS, et al.: Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. Eur J Heart Fail. 2018, 20:1315-1322. 10.1002/ejhf.1234

30. Bauersachs J: Heart failure drug treatment: the fantastic four. Eur Heart J. 2021, 11:681-683. 10.1093/eurheartj/ehaa1012