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A REVIEW ARTICLE ON ACUTE HEART FAILURE

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ABSTRACT

Acute heart failure (AHF) is a syndrome defined as the new onset (de novo heart failure (HF)) or worsening (acutely decompensated heart failure (ADHF)) of symptoms and signs of HF, mostly related to systemic congestion. In the presence of an underlying structural or functional cardiac dysfunction (whether chronic in ADHF or undiagnosed in de novo HF), one or more precipitating factors can induce AHF, although sometimes de novo HF can result directly from the onset of a new cardiac dysfunction, most frequently an acute coronary syndrome. Despite leading to similar clinical presentations, the underlying cardiac disease and precipitating factors mayvary greatly and, therefore, the pathophysiology of AHF is highly heterogeneous. Left ventricular diastolic or systolic dysfunction results in increased preload and afterload, which in turn lead to pulmonary congestion. Fluid retention and redistribution result in systemic congestion, eventually causing organ dysfunction due to hypoperfusion. Current treatment of AHF is mostly symptomatic, centred on decongestive drugs, at best tailored according to the initial haemodynamic status with little regard to the underlying pathophysiological particularities. As a consequence, AHF is still associated with high mortality and hospital readmission rates. There is an unmet need for increased individualization of in-hospital management, including treatments targeting the causative factors, and continuation of treatment after hospital discharge to improve long-term

outcomes.

KEYWORDS: ICD- International Classification of Disease, GBD- Global Burden of Disease AHF- Acute heart failure, LV- Left ventricle ECG-Electrocardiogram, TSH- thyroid stimulating hormone, QOL- quality of life, CRS- cardiorenal syndrome, GFR- glomerular filtration rate, MACE- major adverse cardiovascular event.

1. INTRODUCTION

Heart failure (HF) is a chronic and progressive clinical syndrome induced by structural or functional cardiac abnormalities displaying either reduced (in HF with reduced ejection fraction (HFrEF)) or preserved (in HF with preserved ejection fraction (HFpEF)) left ventricular ejection fraction (LVEF).[1][7] Acute HF (AHF) is defined as new or worsening of symptoms and signs of HF and is the most frequent cause of unplanned hospital admission in patients of >65 years of age.[2] The clinical presentation of AHF is characterized mostly by symptoms and signs related to systemic congestion (that is, extracellular fluid accumulation, initiated by increased biventricular cardiac filling pressures).[4][5] Cardiac dysfunction leads to elevated cardiac filling pressures at rest and during stress.[1] Accordingly, the initial treatment in most patients with AHF consists of non-invasive ventilation and intravenous diuretics, which are administered alone or, especially in Europe and Asia, in combination with short-acting vasodilators.[6] This figure may underestimate the true scale of disease as the estimated prevalence of those with asymptomatic left ventricular (LV) systolic dysfunction in those aged over 65 years is 5.5%.[3] These patients present with a rapid onset of disease, often in the context of preexisting cardiomyopathy, and their admission to hospital heralds a poor prognosis with a high risk of readmission and death post-discharge. Data from the UK National Heart Failure Audit demonstrate mortality rates during the index admission of around 10% with a post-discharge 30-day and 1-year mortality of 6.5% and 30%, respectively.[5] Only a minority of patients with AHF present with cardiogenic shock, a critical condition characterized by the presence of clinical signs of peripheral tissue hypoperfusion; cardiogenic shock has a tenfold higher in-hospital mortality than AHF without shock and requires specific treatments.[7][8] In contrast to the substantial improvements in the treatment of chronic HFrEF, AHF is still associated with poor outcomes, with 90-day readmission rates and 1-year mortality reaching 10–30%.[9,10]

1.1 Epidemiology of Acute Heart Failure

There are several reasons why global data on AHF are very limited. Differential coding of the

syndrome, coupled with nuanced differences in case definitions, defies simple regional comparison. The International Classification of Disease (ICD) system classifies AHF and chronic HF as intermediate conditions and not underlying causes of death. The ICD also does not distinguish between de novo HF and ADHF as reasons for hospital admission. No global data on the proportion of HFrEF and HFpEF as underlying causes of AHF are available. The Global Burden of Disease (GBD) collaborators reported on global, regional and national age-specific and sex-specific mortality of 282 causes of death in 195 countries for the period 1980–2017, including cardiovascular diseases such as rheumatic heart disease, ischaemic heart disease and cardiomyopathy, but they did not list AHF.[8] Data on annual hospitalizations for HF are only available for the USA and Europe and exceed 1 million in both regions.[2] Among these hospitalizations, >90% were due to symptoms and signs of fluid accumulation (indicating AHF). In addition, up to one in four patients (24%) are readmitted within 30 days, readmission rates in the first 3 months after hospitalization for AHF may reach 30% in the USA and in other countries and one in two patients (50%) are readmitted within 6 months.[2] However, a substantial proportion of these patients are readmitted for a non-HF-related cause.[10] Medical comorbidities precipitate rehospitalization and, when poorly managed, contribute to worsening HF over time.[10] Psychosocial factors such as anxiety, depression, cognitive impairment and social isolation also confer increased risk of unplanned recurrent readmission or death of patients following hospitalization for AHF.[11] In high-income regions with associated high scores in the human development index (a statistical tool that takes into account life expectancy, education and income), patients with AHF typically have a median age of >75 years at presentation, whereas in other areas, such as Latin America and sub-Saharan Africa, the median age of patients with AHF is up to two decades lower.[13] This difference could be due to poorly treated hypertension, ischaemic heart disease and late diagnosed rheumatic heart disease leading to HF presentation in younger age groups. In addition, there are differences between regions in the sex distribution; for example, rheumatic heart disease commonly affects women more than men.[14] and peripartum cardiomyopathy is particularly common in Africa.[15] As the obesity epidemic also affects women disproportionately, hypertensive heart disease leading to HF is commonly more prevalent in women than men.[15]

2. Risk Factors and Precipitating Causes

In high-income regions with associated high scores in the human development index (a statistical tool that takes into account life expectancy, education and income), patients with AHF typically have a median age of >75 years at presentation, whereas in other areas, such as

Latin America and sub-Saharan Africa, the median age of patients with AHF is up to two decades lower.[11] This difference could be due to poorly treated hypertension, ischaemic heart disease and late diagnosed rheumatic heart disease leading to HF presentation in younger age groups. In addition, there are differences between regions in the sex distribution; for example, rheumatic heart disease commonly affects women more than men.[31,32] and peripartum cardiomyopathy is particularly common in Africa.[14] As the obesity epidemic also affects women disproportionately, hypertensive heart disease leading to HF is commonly more prevalent in women than men.[11]

Table 2. Classification Based on Clinical Profiles.

Class	Description
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

3. Mechanisms/ pathophysiology

Pathophysiological mechanisms of AHF an underlying structural or functional cardiac condition is a prerequisite for AHF and includes a multitude of different acute (for example, myocardial infarction) or chronic (for example, dilated cardiomyopathy and ischaemic heart disease) cardiac pathologies. The underlying cardiac disease leads to the activation of several pathophysiological pathways (at first adaptive responses, which with time become maladaptive) that counter the negative effects of HF on oxygen delivery to the peripheral tissues, but such pathways can also eventually cause systemic congestion, ventricular remodelling and organ dysfunction.[15] Conditions in which end-diastolic LV stiffness may be increased (and, therefore, also conditions with an increased risk of AHF precipitated by ischaemia) include chronic LV systolic dysfunction with raised LV end-diastolic volume and structural fibrosis and/or hypertrophy, both of which could result from diabetes mellitus, chronic hypertension, chronic kidney disease, chronic aortic stenosis and ageing.[16] LV filling may also be impaired by the sudden development of atrial fibrillation with the accompanying loss of atrial contraction, which may substantially increase filling pressures when there is already pre-existing diastolic dysfunction. For example, severe mitral stenosis

(which is a common manifestation of rheumatic heart disease) is a type of diastolic dysfunction due to the valve abnormality rather than LV structural disease, and it can also induce atrial fibrillation.[15]

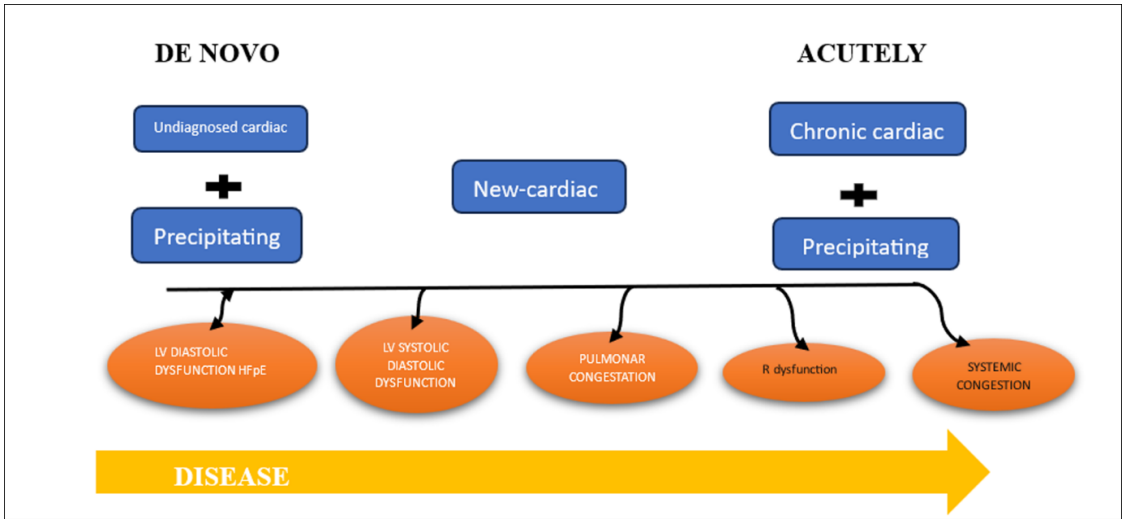

Figure 1: Neuroendocrine stimulation and inflammation.

3.1 Congestion and organ dysfunction

In the heart, elevated ventricular filling pressures lead to increased ventricular wall tension, myocardial stretch and remodelling, contributing to a progressive worsening in cardiac contractility, valvular regurgitation and systemic congestion.[17] In response to the increased wall tension, circulating natriuretic peptides (which stimulate diuresis and vasodilation) are physiologically released by atrial and ventricular cardiomyocytes as a compensatory mechanism, and often high-sensitivity cardiac troponins are detectable in a large proportion of patients with AHF, revealing nonischaemic myocyte injury or necrosis.[18] Increases in left atrial pressure and mitral valve regurgitation will increase the hydrostatic pressure in the pulmonary capillaries, thereby increasing fluid filtration rate from the capillaries to the pulmonary interstitium, causing lung stiffness and dyspnea.[19] Heart failure can also arise from pump dysfunction following an acute myocardial infarction. Mechanistically, the loss of a significant portion of myocardial tissue leads to immediate symptoms. In cases where symptomatic hypotension occurs with insufficient perfusion, cardiogenic shock is present (refer to chapter 50 "Cardiogenic Shock").[33] The onset of acute pulmonary edema can be sudden and marks the clinical manifestation of a deteriorating condition characterized by a rapid decline in cardiac output and an increase in systemic vascular resistance, superimposed on preexisting cardiac dysfunction.[34] The emergence of acute pulmonary edema can occur suddenly and signifies the clinical presentation of a worsening condition characterized by a

swift decrease in cardiac output and a rise in systemic vascular resistance, occurring atop preexisting cardiac dysfunction.[33] Acute heart failure refers to the onset of new symptoms or exacerbation of existing ones, often necessitating prompt intensification of treatment and hospitalization.[19] Of greater significance, the degree of congestion and the quantity of organs affected by congestion hold prognostic significance in patients with heart failure. An underlying structural or functional cardiac issue is a prerequisite for acute heart failure (AHF), encompassing various acute (such as myocardial infarction) or chronic (such as dilated cardiomyopathy and ischemic heart disease) cardiac conditions. The underlying cardiac ailment triggers the activation of numerous pathophysiological pathways.[35,33]

3.2 Contracting Heart

We observed that administering Blebbistatin significantly alters the dynamics of action potential vortex waves during ventriculaOn average, contracting hearts fibrillate faster than once while contracting (top) and once while arrested with Blebbistatin (bottom). Refer to the Supplementary for more details.r fibrillation (VF).[36] To ensure comparability, the optical maps in both cases display the heart surface after numerical motion tracking and stabilization. The signals are equally normalized in each pixel over time (normalized units [n. u.] ∈ [0, 1], with black representing depolarized tissue and white representing repolarized tissue).[37] It is immediately noticeable that the fibrillatory waves on the contracting heart surface (top) are smaller and more fragmented compared to the waves on the uncoupled, non-contracting heart surface (bottom), which are larger and have longer wavelengths. We confirmed that contracting hearts typically fibrillate much faster than those treated with Blebbistatin in a sample of N = 10 hearts (see Figures 9D–G).[36] We observed frequencies of approximately 13.1 ± 4.9 Hz in the contracting hearts and 7.9 ± 2.1 Hz in the contraction-inhibited hearts. The frequency decreased from around 14.7 ± 3.8 Hz to 8.6 ± 1.9 Hz with Blebbistatin (hearts 1, 2, 4, 5, 9, 10). In three cases, the frequencies were already below 10 Hz (hearts 3, 7, 8). Of these, two cases (hearts 7, 8 showed a slight during contraction further decrease, while one (heart 3) remained the same.[38]

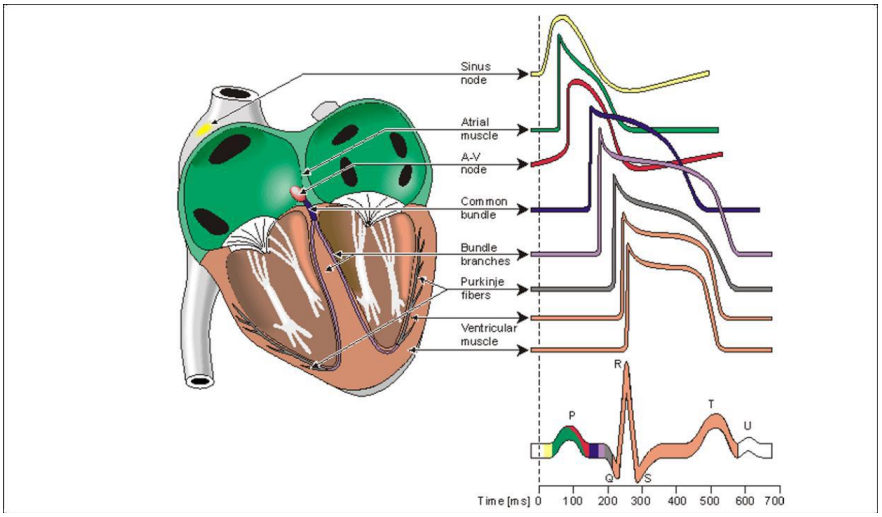

Figure 2: Showing Contraction of heart.

3.3 Dilated Heart

Dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) systolic dysfunction and LV enlargement, without abnormal loading conditions such as hypertension, valvular disease, or coronary artery disease (CAD) that could account for the myocardial abnormality.[39] The disorder is defined by an LV end-diastolic diameter (LVEDD) exceeding 2 standard deviations (SD) of the predicted values and an LV fractional shortening of less than 25% or an LV ejection fraction (EF) of less than 45%.[2] Predicted values are calculated using Henry's formula, corrected for age and body surface area, and expressed as a percentage of the predicted diameter as follows: The predicted LVEDD is calculated using the formula: (45.3 × body surface area^0.3) − (0.03 × age) − 7.2.[40] An LVEDD value greater than 112% (>2SD) is a diagnostic criterion for DCM, while a value greater than 117% (2SD + 5%) increases specificity. The prognosis for DCM patients has significantly improved over the past few decades due to advances in pharmacological and non-pharmacological treatments, earlier diagnosis through familial screening, pre-participation cardiac evaluation, and individualized long-term followup. As a result, survival rates without the need for heart transplantation have increased to over 80% at 8-year follow.[48]

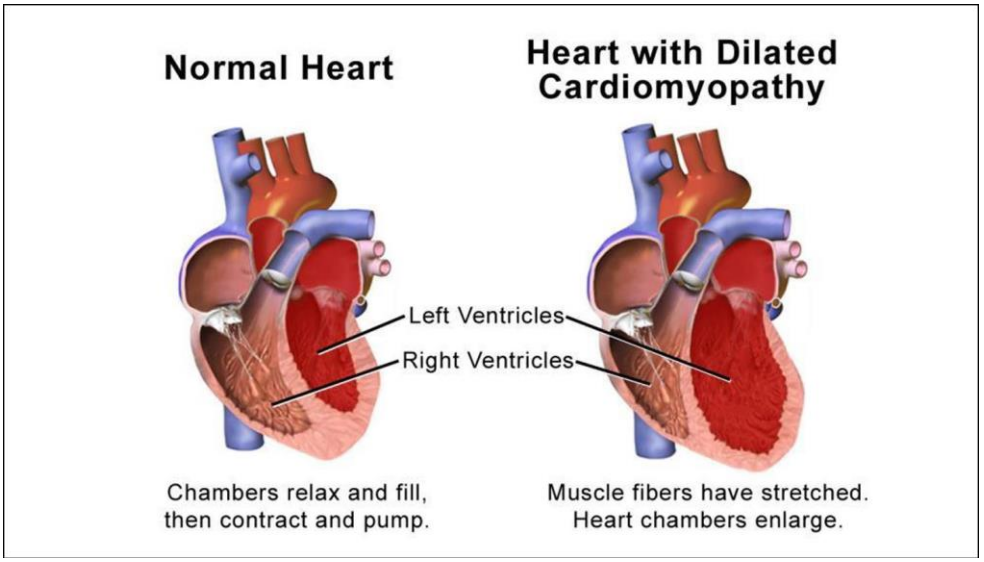

Figure 3: Dilated heart.

4. Sign & Symptom.[43]

4.1 Heart failure signs

- Edema/swelling
- Ankle/leg edema
- Palpitations
- Abdomen edema
- Irregular pulse
- Sudden weight gain
- Change in urine output compared with normal
- Low blood pressure or orthostatic blood pressure
- Heart rate <60/min or >120/min
- Whole-body edema
- Cool, pale, or mottled skin
- Weight loss.

4.2 Heart failure symptoms.[41]

- Shortness of breath; trouble breathing
- Exercise intolerance
- Orthopnea
- Profound fatigue with exertion or generalized weakness
- Dizziness/light-headedness
- Nausea/vomiting; diarrhoea or loss of appetite

- Paroxysmal nocturnal dyspnea
- Restlessness, confusion, or fainting
- Right-sided abdominal fullness, discomfort, or tenderness
- Severe cough
- Chest pain
- Wheezing.

5. Diagnosis of Acute Heart Failure

5.1 Role of clinical Assessment and history diagnosis tools

The management of patients with HF is strikingly heterogeneous across the world according to sociocultural disparities and differences in health-care systems. Many cardiology societies have endeavoured to increase awareness of HF among the population in different countries and to educate health-care professionals to improve the management of patients with HF. The following sections about diagnosis and treatment of AHF reflect current recommendations in high-income countries and may be substantially different from management standards in low-income or developing countries depending on local availability of resources.[20] Whereas loop diuretics to relieve congestion are inexpensive and widely available, disease-modifying drugs (particularly sacubitril (a neprilysin inhibitor)–valsartan (an angiotensin receptor blocker).[24] which promotes vasodilation and natriuresis, and sodium-glucose cotransporter 2 inhibitors, which reduce blood glucose levels in patients with diabetes mellitus and have also been shown to have beneficial effects in patients with HF).[22] and cardiac devices are usually available only in high-income areas. Furthermore, accurate diagnosis of the underlying cardiac diseases and specific treatments often require multimodal imaging techniques, as well as interventional and surgical procedures, which are mostly available in high-volume centres in developed countries.

5.2 Diagnostic method

5.2.1 Electrocardiogram

A 12-lead ECG should be conducted during the initial assessment of all patients with acute heart failure (AHF), and continuous monitoring of cardiac rhythm is recommended.

5.2.2 Chest X-ray

Chest X-ray is a standard diagnostic approach in hospitalized patients suspected of having acute heart failure (AHF). Cardiac enlargement and signs of pulmonary congestion (such as vascular redistribution, interstitial, alveolar, or pleural oedema) or other potential causes of

dyspnea, such as pulmonary disease, can be identified.[23]

5.2.3 Laboratory investigations

Standard biochemical tests that are typically conducted upon hospital admission encompass a complete blood count, blood glucose levels, urea and creatinine levels, BUN (blood urea nitrogen), estimated glomerular filtration rate (eGFR), electrolyte levels, liver enzyme levels, C-reactive protein levels, and, if available, thyroid stimulating hormone (TSH) levels.[24]

Screening and Prevention

By contrast, prevention of decompensation in patients with previously diagnosed HF is of major importance. Hospital readmissions are frequent — in particular during the first months after hospital discharge for AHF — and are associated with adverse outcomes and relevant health-care expenditure.[10] Residual congestion and lack of disease-modifying treatment implementation before hospital discharge have been associated with worse post-discharge outcomes.[25,26] Patient education and empowerment may play a crucial part: patients should understand the importance of compliance with medical treatment, be able to recognize symptoms or signs of worsening HF.[25]

6. Management of Acute heart Failure

6.1 Pre-hospital early management

There is a growing body of evidence that delayed treatment delivery is associated with poor outcomes in AHF102. For this reason, current guidelines advocate a ‘time-to-treatment’ concept, similar to those for acute myocardial infarctions or cerebrovascular accidents, and recommend early initiation of treatment in patients with AHF, optimally before hospital admission.[1,7,24] When the clinical diagnosis of AHF is straightforward, intravenous treatment (mostly vasodilators and/or diuretics) based on the clinical phenotype and involved pathophysiology should be delivered without waiting for additional testing. Diuretics are mainly used in the presence of fluid retention, whereas vasodilators are administered to reduce filling pressures and modulate ventricular–vascular coupling in the presence of fluid redistribution and preserved systolic blood pressure (>110 mmHg; caution should be used if the systolic blood pressure is 90–110 mmHg).[1,2] The use of vasodilators is recommended by current guidelines.[1,2]

6.2 In-hospital management

Individuals with AHF are at risk of death not only from cardiovascular failure but also from

the consequences of organ dysfunction due to congestion and hypoperfusion; thus, it is imperative that the treatment strategy addresses both these issues. Despite the fact that there is little evidence from randomized controlled trials that tackling congestion improves survival, the effect of diuretics on symptoms and organ congestion are evident. Once oxygen saturation has been restored the initial treatment goals in patients presenting with AHF consist of achieving decongestion without residual fluid retention, optimizing perfusion pressures to preserve organ perfusion and maintaining or initiating disease-modifying oral therapies directed towards neurohumoral activation, as these medications also increase diuretic response and improve long-term survival.[27,28]

Special considerations in Acute Heart Failure

7.3.1 Acute treatment

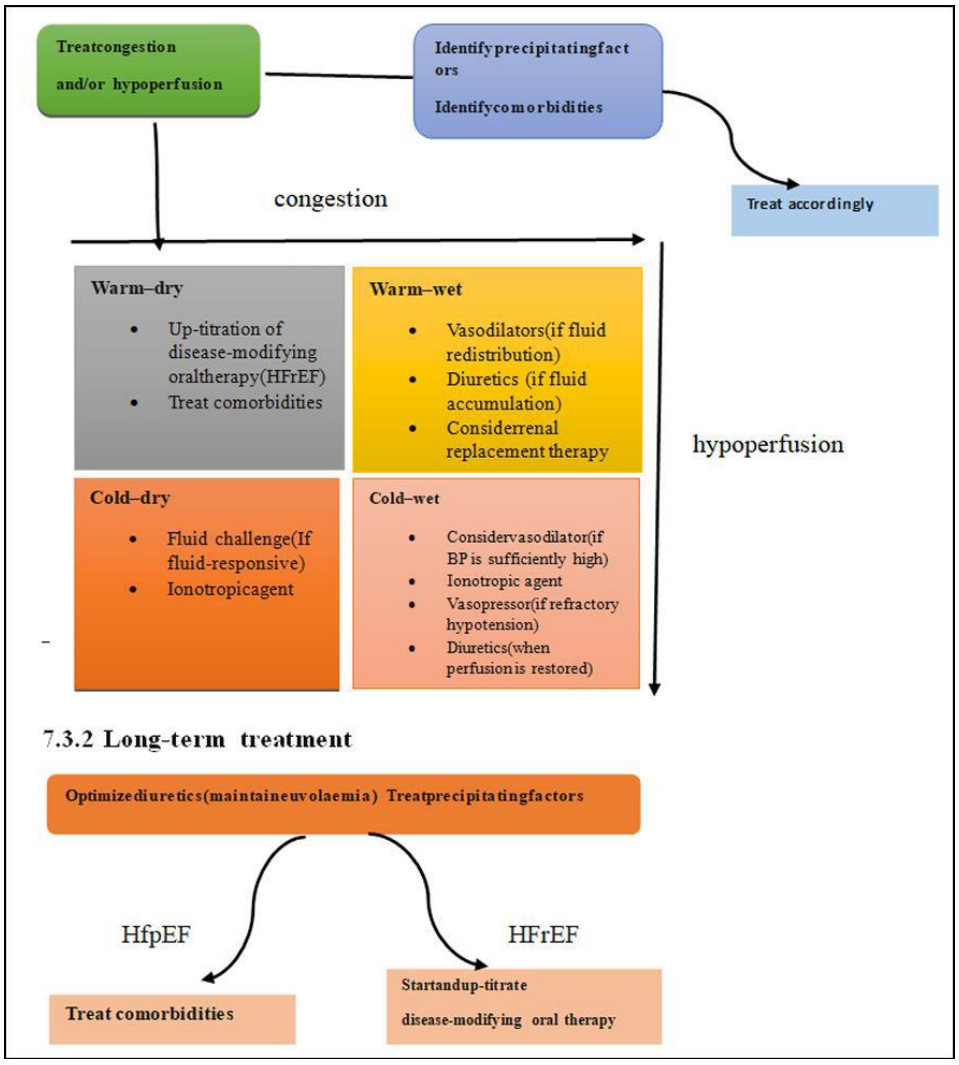

Figure 4: Proposed management algorithm for patients with AHF.

Decongestive therapy: As patients with AHF present with a similar congestion profile irrespective of their LVEF.[23] the decongestive therapy is similar in patients with HFrEF or HFpEF.[1] The decongestive treatment should be tailored according to the haemodynamic phenotype loop diuretic administration generally indicates an inadequate response to diuretics.[20]

7.4. Long-term management

7.4.1. IN HOSPITAL MANAGEMENT

7.4.1.1. Management goals and pre-discharge management

Individuals who survive the first episode of AHF are at increased risk of experiencing another episode.[10] Thus, the management goals include improving survival and reducing the risk of hospital readmission due to subsequent episodes of AHF. Ensuring that the individual's condition is sufficiently stabilized for a safe hospital discharge is the central element of pre-discharge management. Patients with AHF are considered ready for discharge after achieving adequate decongestion and stable renal function on guideline-directed oral therapy.[1]

7.4.1.2. Post-discharge management

In addition to continued supervised medical therapy, post-discharge management should incorporate efforts to improve symptoms and quality of life (QOL), delay disease progression and attempt to triage and prognosticate using a risk assessment framework to prevent hospital readmission and death. Generally, post-discharge prognostic tools are prediction models that take several patient clinical variables (for example, age, vital signs during hospitalization, laboratory data and comorbidities) into account and relate them to 30-day and 1-year mortality. Regardless of the time period considered, patients with AHF remain at persistently high risk of rehospitalization and death.[30]

8. Quality of life in patients with AHF

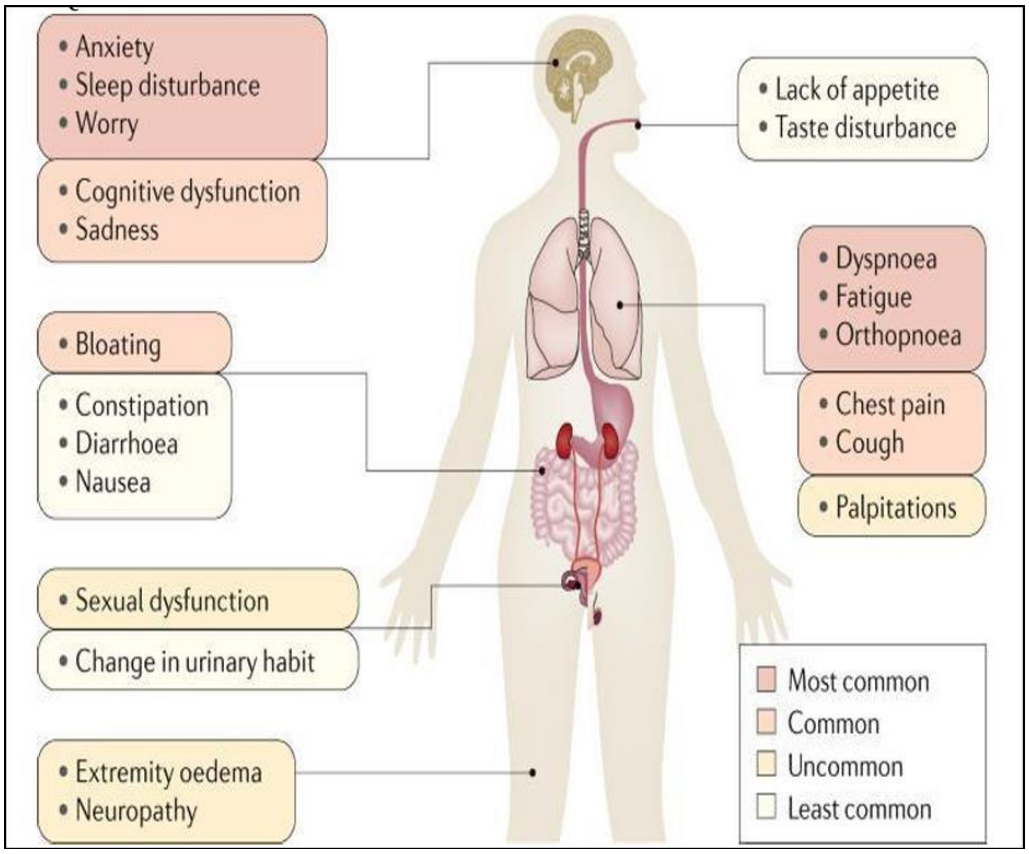

Figure 5: Quality of life in patients with AHF.[35]

Individuals suffering from acute heart failure (AHF) and chronic heart failure (HF) contend with a multitude of physical and psychological symptoms that detrimentally impact their quality of life (QOL).[44] Dyspnea, fatigue, dry mouth, orthopnea, sleep disturbances, and difficulty concentrating are widespread, distressing, and burdensome symptoms, which are indicative of diminished quality of life within this demographic. Depression is a more prevalent condition among individuals with heart failure compared to the general population, with at least 20% of heart failure patients meeting the diagnostic criteria for major depression.[45] The prevalence rates of depression in the heart failure population show significant variation, spanning from 9% to 60%.[46] This wide range is believed to primarily stem from variances in the methods used for outcome assessment, such as interviews versus self-reported questionnaires, as well as differences in the severity of heart failure at the time of evaluation. Patients with heart failure who experience more severe depression demonstrate elevated levels of healthcare utilization, increased rates of rehospitalization, and higher mortality rates. Clinicians often face challenges in distinguishing symptoms stemming from heart failure and those arising from depression, underscoring the essential requirement for a practical and

standardized approach to assessing quality of life in routine clinical practice.[44] Apart from the physiological changes experienced by patients with acute heart failure (AHF), the stressors inherent in the acute care setting can worsen both physical and psychological impairments, potentially resulting in additional deterioration in quality of life (QOL).[46] Hospitalized elderly patients with acute heart failure (AHF) experience significantly greater symptom burden and poorer quality of life (QOL) compared to age-matched cohorts with stable heart failure with preserved ejection fraction (HFpEF) and stable heart failure with reduced ejection fraction (HFrEF).[44] In a prospective, extensive, multicentre, and multidimensional evaluation involving 27 hospitalized patients aged 60 years or older with acute decompensated heart failure (ADHF), compared to three age-matched outpatient cohorts with stable heart failure, it was found that 78% of the ADHF group exhibited cognitive impairment, and 30% had depressive symptoms.[45] Surprisingly, only 11% had been previously diagnosed with depression, indicating significant under-recognition of depression within this population. In a sex-stratified examination of numerous large international studies on chronic heart failure (HF), it was noted that women experienced significantly poorer disease-specific and general quality of life (QOL) compared to men.[44,45]

9. Treatment

9.1 Diuretics

The impact of diuretic therapy on glomerular filtration rate (GFR) can vary significantly among patients with heart failure (HF). For certain individuals, diuretics may elevate serum creatinine levels by reducing cardiac filling pressure and cardiac output. However, others may not undergo alterations in left ventricular end-diastolic pressure, cardiac output, or serum creatinine levels. In certain patients, diuretic therapy leads to a decline in serum creatinine levels due to the restoration of left ventricular filling and function.[34]

9.2 Renin-angiotensin-aldosterone-system antagonists

Whether heart failure or renal insufficiency is the primary condition, the renin-angiotensinaldosterone system (RAAS) instigates the progression of the other disease by triggering the activation of angiotensin II and reactive oxygen products. Oxidative damage is regarded as one of the contributing factors in the development of cardiorenal syndrome (CRS).[34] In the majority of acute heart failure (AHF) patients, the initiation of RAAS antagonists leads to a decrease in glomerular filtration rate (GFR), although a moderate increase may also be noted in certain individuals. Analyses examining the effects of RAAS

antagonists in heart failure (HF) patients with chronic renal diseases have concluded that the benefits of these drugs are not influenced by renal dysfunction.[30] However, there may be a higher incidence of hyperkalemia and worsening renal function.

9.3 Vasodilators

The positive effects of intravenous vasodilators on renal function and mortality have not been conclusively confirmed. In the ADHERE registries, encompassing approximately 100,000 acute heart failure (AHF) patients, renal dysfunction occurred more frequently in patients who received vasodilators in conjunction with intravenous diuretic treatment.[33]

9.4 Inotropic drugs

Inotropic agents are not commonly employed except for specific acute heart failure (AHF) patients or those with cardiogenic shock. Their role in treating cardiorenal syndrome (CRS) remains uncertain. Inotropic medications are anticipated to enhance renal function by boosting renal blood flow and potentially reducing renal venous pressure. However, evidence supporting this expectation was only noted in patients who received dopamine. Dopamine doses that enhance blood flow are less than 3 µgr/kg/min, and this effect is believed to rely on the dilation dopamine induces in both large and small resistant renal vessels. However, the clinical efficacy and safety of dopamine in patients with cardiorenal syndrome (CRS) could not be demonstrated.[35]

9.5 Ultrafiltration

Ultrafiltration is typically utilized in acute heart failure (AHF) patients who exhibit resistance to diuretics and/or renal dysfunction. According to current international guidelines, ultrafiltration may be considered if urine output remains below 20 mL/h despite standard treatment for acute pulmonary edema; however, its effectiveness and safety are not sufficiently understood.[33]

9.6 Vasopressin antagonists (Aquauretics)

In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) study, urine output was elevated in patients administered tolvaptan, and the increase in serum creatinine (0.03 mg/dL versus 0.08 mg/dL) was statistically significant compared to placebo, though it remained clinically insignificant. Trials examining the role of tolvaptan in cardiorenal syndrome (CRS) are on going.[36]

9.7 Adenosine-A1 receptor antagonist

The PROTECT study examined the effects of rolofylline, an adenosine-A1 receptor antagonist, in hospitalized patients with acute heart failure (AHF) and renal dysfunction**.** The incidence of cardiovascular endpoints and renal dysfunction was comparable between patients receiving the selective adenosine A1 receptor antagonist and those receiving placebo. Additionally, neurological adverse events such as stroke and seizures were common among patients administered rolofylline.[36]

9.7 Serelaxin

In studies conducted in acute heart failure (AHF) patients with serelaxin, there was no rise in new-onset renal failure, and adverse events associated with renal dysfunction occurred less frequently compared to placebo. Patients necessitated reduced administration of intravenous diuretics and vasoactive drugs. The ongoing phase 3 RELAX-2 study is anticipated to provide more comprehensive insights into the utilization of serelaxin in patients with cardiorenal syndrome (CRS).[37]

10. Challenges and Future Directions Barriers to early Diagnosis for Acute Heart failure

The findings from our investigation conducted among residents of a major metropolitan area in central New England shed light on the clinical manifestations linked to decompensated heart failure.[38] Additionally, our study examines the correlation between these indicators and patients' demographic details, clinical profiles, treatment approaches, and immediate prognoses. Our findings indicate that a considerable number of heart failure patients exhibit various acute signs and symptoms, with the majority experiencing breathlessness and congestion-related signs rather than those indicating low cardiac output.[39] Nonetheless, around 40% of patients reported having only two or fewer typical symptoms of heart failure. Patients who reported fewer symptoms related to heart failure tended to be older and more frequently female.[38] They were also less prone to have significant concurrent comorbidities and were less often receiving effective cardiac treatments. The presentation of symptoms was consistent among patients whether they had an initial or previously documented episode of heart failure. This consistency was observed whether we analysed the five most common symptoms reported by patients or all 14 acute signs and symptoms that were examined. The detailed analysis of various symptoms, the duration of delay in seeking medical attention, and the connection between acute symptoms and medical interventions and hospital outcomes in hospitalized individuals with decompensated heart failure has not been thoroughly explored in

existing published literature.[40] Previous studies, which adopted a methodology akin to the one employed in our current investigation, reviewed data from hospital medical records. These studies found that the frequency and nature of symptoms reported by patients with acute heart failure were comparable to those observed in our population-based study. For instance, in a study analyzing the medical records of 753 hospitalized patients with heart failure at a Veteran's Administration hospital, the predominant symptoms reported by patients upon admission were dyspnea, edema, and fatigue.[38] These results imply that the lack of administration of effective cardiac medications to these patients might result in higher short-term mortality rates within this relatively overlooked patient population characterized by fewer acute symptoms. Several hypotheses can be proposed to explain the findings we have observed. Patients who report fewer acute symptoms may have encountered prolonged delays in hospital presentation, presented with more atypical symptoms, and experienced greater diagnostic uncertainty, potentially resulting in delays in receiving appropriate treatment and higher mortality rates.[38]

11. CONCLUSIONS

The findings from this population-based study indicate that individuals experiencing acute heart failure exhibit numerous signs and symptoms of decompensation. Patients who report fewer symptoms typically belong to older age groups, are more likely to be female, have fewer concurrent medical conditions, receive lower prescriptions for heart failure therapy, and experience poorer short-term outcomes compared to those reporting multiple acute symptoms. These results indicate that healthcare providers should prioritize monitoring and implementing targeted therapeutic approaches in patients with acute heart failure who present fewer symptoms of decompensation. SGLT2 inhibitors, as a group, have represented a significant advancement in treating HFpEF recently and currently stand as the only medications supported by concrete evidence for benefit in this condition. However, evidence for mortality benefit and reducing major adverse cardiovascular events (MACE) remains insufficient. One could posit that attaining symptom alleviation and reducing hospitalizations represents a crucial milestone in managing HFpEF. This achievement would undoubtedly alleviate patient symptoms, reduce morbidity, enhance quality of life, and alleviate financial and healthcare burdens. Another perspective suggests that due to the brief duration of follow-up in clinical trials, the disparity in mortality and MACE may not have been significant. It's posited that with longer patient follow-up, significant benefits in hard endpoints could potentially be achieved. However, such extrapolation should be approached with caution.

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