REVIEW ARTICLE

Non-cardiovascular comorbidities in heart failure patients and their impact on prognosis

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ABSTRACT

With the aging of the population and improvement of life expectancy of patients with heart disease, there is an increase in non-cardiovascular (CV) comorbidities affecting chronic heart failure (HF) patients. The increased prevalence of different CV and non-CV comorbidities is a rising problem in the management of patients with HF, mostly because these comorbidities may lead to poor prognosis, increase of hospitalizations and mortality rate. Recently, important data from multicenter randomized studies point to diabetes mellitus or iron deficiency as new pharmacological targets, and this highlights the need of broad expertise for the 21st-century cardiologist. The management of HF should take into account non-CV comorbidities. In this review, we discuss novel aspects of non-CV comorbidities in HF patients and emphasize the impact on prognosis.

Key words: heart failure, chronic obstructive pulmonary disease, cardio-oncology, chronic kidney disease, diabetes

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INTRODUCTION

In industrialized countries, the prevalence of chronic heart failure (CHF) is estimated to be 1%–3% of the population, exceeding 30% in people over 85 years [1]. The increased prevalence of the different comorbidities leads to problems in the management of HF patients, mostly because these comorbidities may lead to poor prognosis, increased hospitalization and mortality rate. The correct management of comorbidities may be one of the strategies that reduce hospitalizations and death in this condition [2].

In heart failure (HF) patients, regardless of ejection fraction (EF), comorbidities can be divided into cardiovascular (CV) and non-CV.

Previous studies on outpatients with CHF showed that the highest prevalence among the non-CV comorbidities refers to iron deficiency (prevalence of 53%–65%), renal failure (prevalence of up to 55%), anemia (prevalence of up to 37%), diabetes mellitus (prevalence of between 23% and 47%), depression (prevalence of up to 61%), and chronic lung disease (prevalence of up to 63%) [1, 3, 4].

With the aging of the population, there is an increase in non-CV comorbidities affecting CHF patients [5]. In elderly patients with HF, the coexistence of non-CV comorbidities can exacerbate symptoms and signs of HF. This can hinder the diagnosis of HF and delay the prescription of appropriate therapies.

Among non-CV comorbidities, chronic obstructive pulmonary disease (COPD), diabetes mellitus, anemia, and obesity are more prevalent in HF with preserved ejection fraction (HFpEF) patients [6]. This underlines the possible role of non-CV comorbidities in the progression of HF in HFpEF and the importance of managing these comorbidities in HFpEF in order to slow HF progression and reduce rehospitalization rate and mortality.

Non-CV comorbidities are independent prognostic factors in HF populations regardless of EF and HF etiology

(ischemic vs. non-ischemic). Furthermore, the evaluation of the severity of these non-CV comorbidities could significantly worsen the prognosis in non-selected HF populations [7].

Among non-CV comorbidities, chronic renal failure, anemia and diabetes are the comorbidities most frequently associated with hospitalizations [8, 9].

In this review, we report an update on the non-CV comorbidities in patients with HF emphasizing the impact on the prognosis of HF patients.

METHODS

A focused literature search was performed on PubMed until November 2020, in order to identify relevant original research and review articles by using the following key words, alone or in combination: heart failure, chronic obstructive pulmonary disease, cancer, chronic kidney disease, obstructive and central sleep apnea, diabetes, hypothyroidism and hyperthyroidism, hyperuricemia, vitamin D deficiency, anabolic hormones, iron deficiency, depression, cognitive impairment. Only articles in English were selected for this review, focusing on the most consistent, recent, and relevant trials and original papers, preferentially involving humans. Titles and abstracts from these searches were reviewed, full-text articles were obtained for relevant manuscripts, and reference lists were reviewed to identify additional manuscripts appropriate for the review.

CANCER AND HEART FAILURE

In the last few years, along with population aging, an important increase in the prevalence of cancer and HF has been reported [10]. Patients affected by HF show an increased risk of cancer (patients affected by HF carry a 68% higher risk of cancer diagnosis) and their prognosis is worse compared with cancer patients without HF [11]. Both these conditions may affect quality of life and, above all, prognosis. To date, most of the attention has been focused on the investigation of potential CV side effects of different antineoplastic regimens, including chemo-, radio- or immuno--therapy that may lead to the development of HF [12]. Indeed, antineoplastic drugs might induce left ventricular (LV) systolic dysfunction (as a reduction of left ventricular ejection fraction [LVEF] by more than 10 percentage points or a reduction under 50%) in up to 50% of patients [13]. However, besides chemotherapy-induced cardiotoxicity, we have to take into account other possible bidirectional interactions between HF and neoplastic diseases.

Recently, some authors speculated that HF per se may be a risk factor for developing tumors [14]. For example, recently diagnosed cancer patients may already have a history of LV dysfunction or HF, and this overlap of pathologies could make treatment of cancer patients and HF patients difficult. Patients affected by HF have a higher incidence of cancer compared to the general population [15]. Also, patients affected by HF and cancer have a poorer prognosis [16]. Even though the same risk factors (such as hypertension, obesity, diabetes and tobacco smoking) may be found in HF and in cancer patients; this similarity only in part can justify the close association between these conditions, such as hypertension, obesity, diabetes, and tobacco smoking [17]. In the last few years, some common molecular and pathophysiological mechanisms have been demonstrated among cancer patients and HF.

SLEEP-DISORDERED BREATHING

Sleep-related breathing (SBD) disorders are often present in patients affected by the high prevalence of SDB (47%–81%) [18] in HF with reduced ejection fraction (HFrEF) patients (obstructive sleep apnea [OSA] 29% and central sleep apnea [CSA] 31%) and in HFpEF (40% had OSA and 29% CSA) and are associated with poor prognosis. In particular, the *apnea*–hypopnea index (AHI; i.e., the number of apneas and hypopneas per hour of recording) is a powerful independent predictor of adverse outcome in clinically stable CHF [19]. OSA and CSA are related to the increased readmission in CHF [20, 21]. An increased risk of death was observed in patients affected by HFrEF with untreated OSA, independently of confounding factors [22].

Cheyne stokes respiration (CSR) is an abnormal pattern of breathing characterized by numerous central apneas alternating with hyperventilation. It is associated with a poor prognosis in patients with HF. Recently, in HFrEF patients, optimization of HF therapy with sacubitril/valsartan has affected phenotypic traits of CSR indicating improvements of hemodynamic parameters and chemosensitivity [23].

In HFrEF patients with predominantly CSA, enrolled in the SERVE-HF (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo-Ventilation in Patients with Heart Failure) trial [24], CV and all-cause mortality were more present in the auto-servo--ventilation subgroup [25]. Following these results in the last European Society of Cardiology (ESC) HF guidelines [1], adaptive servo-ventilation (ASV) is not recommended in HFrEF (Class of recommendation: III and Level of evidence: B). Results by a SERVE-HF substudy analysis showed that patients with HFrEF and CSA who experienced serious adverse events had longer CSR cycle length.

In hospitalized HF patients with moderate-to-severe sleep apnea, adding ASV to optimal medical therapy did not improve cardiovascular prognosis [26]. These results need further confirmatory data from ongoing studies. Among these ongoing studies, the retrospective FACE study was designed to evaluate the possible effect of adding ASV to standard care on morbidity and mortality in patients with different forms of HF distinguished according to the value of EF (HFpEF, mid-range, or HFrEF) who have SDB with an indication for ASV [27].

Phrenic nerve stimulation may be a promising treatment [28]. In our opinion, all HF patients should be screened for SDB.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease, a chronic inflammatory lung disease characterized by airflow limitation, is among the most common comorbidities in HF. The prevalence is similar within HFrEF and HFpEF (16% vs 14%) and ranges from 9% to 41% in European cohorts [29].

On the other hand, the prevalence of HF in COPD patients is high (from 20% to 70%) and often it is under-diagnosed and under-treated, with obvious prognostic implications [30]. COPD patients have a higher rate of hospitalization and death, coronary heart disease, stroke and CHF have been reported [31] as the most frequent causes.

Heart failure patients with COPD were older and presented with more comorbidities and lower exercise capacity [32]. The coexistence of COPD with HF is related to increased morbidity and mortality risk in both CHF [33] and acute HF (AHF) [34].

Issues regarding potential bronchoconstriction are the main reasons for the underutilization of β-blockers in these patients particularly after hospitalization for AHF or decompensation of HF [35]. HF guidelines stated that COPD "is not a contra-indication" to β-blocker therapy [1]. The benefits of the cardio-selective β-blockers in HF overcome any potential risk derived from the β-blocker use also in the case of patients with severe COPD [36].

Lung hyperinflation may play a pivotal role regarding cardiac chamber dimensions and cardiac dysfunction in patients affected by COPD. Hyperinflation (inspiratory capacity-to-total lung capacity ratio [IC/TLC], functional residual capacity, and residual volume) demonstrated stronger relation to cardiac dimensions than airway obstruction or diffusion capacity. IC/TLC correlated better with cardiac dimensions and was an independent predictor of cardiac dimensions [37]. The cardiac chambers dimensions decreased with increasing GOLD (Global Initiative for Obstructive Lung Disease) stage. There is an ongoing debate with conflicting results for the CV safety of drugs for COPD. Inhaled therapy with bronchodilators is the cornerstone of the COPD therapy. Bronchodilators include the long-acting β_2-agonists (LABA), long-acting muscarinic antagonist (LAMA), or a combination of LABA-LAMA. Bronchodilators reduce hyperinflation and improve breathlessness and cardiac output. Bronchodilators may prevent acute exacerbations of COPD, thus reducing the risk of CV events. Tiotropium, a LAMA, improves hyperinflation, CV responses to exercise in COPD patients [38], LV diastolic function in COPD patients [39] and it has been associated with decreased mortality (CV and no-CV) [40]. LV and right ventricular end-diastolic volume increase and LV and right ventricular stroke volume increase have been reported as effects of LABA-LAMA in COPD [41].

Lung-deflating medications (fluticasone furoate/vilanterol [ICS-LABA]) were proven to increase LV, right ventricle, and left atrium volumes [42]. Stone et al. [43] showed that right ventricular function remained unchanged.

Fluticasone/vilanterol/umeclidinium (ICS-LABA-LAMA) reduce all-cause mortality with lower rates of CV deaths [44]. Roflumilast, administered orally, indicated for frequent exacerbations of COPD, was related to the lower rate of CV events [45].

In our opinion, all HF patients should be screened for COPD, performing spirometry, a simple, cost-effective, non-invasive exam. Advances in COPD treatment could lead to a reduction of the readmissions in HF.

GLUCOSE METABOLISM DISORDERS

Diabetes mellitus (DM) is commonly reported in patients affected by HF and a strict bidirectional interaction exists between these two conditions. DM has a prevalence in HF that varies from 10% to 30% in outpatients and rises up to 40% in hospitalized patients with HF [46]. A state of insulin resistance, even in absence of overt DM, is frequently reported in HF, with a prevalence of about 70% [47]. On the other hand, LV dysfunction is a common finding in diabetic patients. Patients with DM are 2–5 times more likely to develop HF compared to the general population. In the Framingham Heart Study [48], HF was twice more common in men and 5 times more common in women with DM aged 45–74 years compared with similar non-diabetic controls. Older age, longer duration of DM, insulin therapy, and lower body mass index were identified as independent risk factors for the development of HF in DM patients.

In particular, diabetic patients may present with two different types of heart dysfunction. The first is a typical myocardial dysfunction secondary to coronary artery disease. The second is diabetic cardiomyopathy, a typical complication of DM, characterized by cardiac dysfunction that can be easily and simply assessed by echocardiography, and was reported for the first time in 1972 by Rubler et al. [49], describing post-mortem data of diabetic patients. In the last ESC Position Statement on the management of DM and HF [49], diabetic cardiomyopathy was defined as cardiac dysfunction occurring in diabetic patients in absence of coronary artery disease, relevant valvular heart disease, uncontrolled hypertension, or congenital heart disease. Two stages can be distinguished in diabetic cardiomyopathy: an early stage characterized by LV concentric hypertrophy increased filling pressures, and diastolic dysfunction, and a late stage characterized by progression of diastolic dysfunction, and systolic impairment. However, Seferovic et al. [49] recently proposed two different phenotypes of diabetic cardiomyopathy (a restrictive/HFpEF phenotype and a dilated/HFrEF phenotype) rather than two stages that belong to the same disease.

The pathophysiology of diabetic cardiomyopathy is still not clear and many hypotheses have been proposed. The main mechanisms are endothelial and microvascular dysfunction, excessive neurohormonal response, change in cardiac metabolism, accompanied by mitochondrial dysfunction, dysfunctional endoplasmic reticulum, and impaired calcium handling, all probably contributing to the

manifestation of diabetic cardiomyopathy and representing in the next future potential new therapeutic targets.

With regards to the long-term prognostic impact of the coexistence of DM and HF, the ESC-HFA Registry [50] reported a higher cumulative incidence (all-cause death, CV death, and hospitalization for worsening HF) in HF outpatients with DM compared to non-diabetics even after adjustment for multiple risk factors. These data were confirmed by a recent meta-analysis including 381 725 patients with AHF and CHF [51]. The authors reported that the coexistence of DM and HF is related to a 30% increased risk of all-cause death, and a 35% increased risk of CV death and hospitalization during a 3-year follow-up. Looking at the parameters used in the multiparametric prognostic scores more frequently used in HF (Seattle Heart failure Model, MECKI score, HF-ACTION risk score) diabetes does not appear a determinant prognosticator. Moreover, in an analysis of the MECKI score database, that evaluated nearly 4000 HFrEF patients, a worse prognosis was demonstrated in diabetic patients with poor glycemic control (HbA_{1c} >8%), instead the presence of diabetic status and hypoglycemic drugs were not associated with prognosis after correction for various confounders [52]. Thus, probably, the population of diabetic patients cannot be considered as a unique entity, but it will be necessary to assess specific parameters, as glycemic control or drugs response, in order to appropriately evaluate every patient.

As for the treatment of HF in diabetic patients, the majority of the beneficial effects of HF treatments, reported in randomized controlled trials, are consistent with and without DM at baseline, thus the recommendations for the treatment of HF in the setting of DM are the same as in the general HF population.

Conversely, regarding the therapeutic approach to DM in HF patients, European guidelines [53] suggest the use of gliflozins as first choice, or as second choice in patients already taking metformin, starting from the excellent prognostic results of SGLT2-inhibitors in terms of prevention of HF-related events. Moreover, after the positive results in terms of CV protection derived by gliflozins, a busy trials schedule started to assess the benefit of gliflozins in patients affected by HF regardless of the presence of DM. The first study was the DAPA-HF trial [54], assessing the efficacy of dapagliflozin vs placebo in 4744 HFrEF patients on a primary composite outcome of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy) or CV death. In a follow-up of 18.2 months, and on top of HF therapy, the primary endpoint occurred in 386 (16.3%) dapagliflozin subjects and in 502 (21.2%) placebo patients with a relevant relative risk reduction of 26% and a number needed to treat of 21, and a 30% reduction of HF hospitalization with an 18% reduction in CV mortality. The recently published EMPEROR-Reduced [55] trial similarly assessed the effect of empagliflozin vs placebo in 3730 HFrEF subjects on a primary composite outcome of HF hospitalizations or CV death. During a follow-up of 16 months, in a sicker population, the trial reported an important reduction in the primary outcome (–25%) regardless of the presence or absence of diabetes, and confirmed a 30% reduction in HF hospitalizations, without a significant effect on CV death. International medical regulatory agencies approved the use of dapagliflozin for HFrEF patients regardless of the presence of DM. Thus gliflozins will be used as HF-specific drugs.

OTHER ENDOCRINE DISORDERS

Both HFpEF and HFrEF may coexist with other systemic conditions or even develop as possible consequences of such diseases. In particular, some endocrine disorders may have CV manifestations or may worsen a pre-existing HF.

Thyroid disease and HF

Besides their role in energetic homeostasis, thyroid hormones have a relevant impact on cardiac activity by acting on the cardiovascular system.

Hyperthyroidism, with excessive production of thyroid hormones leading to a hypermetabolic state and hemodynamic changes, is characterized by high cardiac output. HF with high cardiac output without heart disease could be secondary to the following factors: tachycardia, increased cardiac preload, decreased systemic vascular resistance, high ventricular filling pressure, raised pulmonary arterial pressure [56]. Furthermore, HF with low cardiac output in elderly patients with heart disease could be secondary to the following factors: increased cardiac preload, impaired LV filling, presence of atrial fibrillation, rapid ventricular rate, raised systemic vascular resistance, reduced contractile reserve.

Hypothyroidism is characterized by insufficient production of thyroid hormones. In this case, HF in patients with overt hypothyroidism or elderly patients with subclinical hypothyroidism could be secondary to the following factors: bradycardia, impairment of cardiac function (and systolic function and diastolic function), raised systemic vascular resistances, and arterial stiffness.

Both hyperthyroidism and hypothyroidism may affect patients with HFrEF. In particular, hyperthyroidism, especially in the acute setting, is a common trigger of exacerbation or acute decompensation of HF [57]. Although little is known on thyroid dysfunction in HFpEF, hypothyroidism is believed to be a negative prognostic factor in HFpEF [58].

Indeed, fT3, fT4, and TSH should be monitored every 6–12 months in patients affected by HF (every 3 months in patients treated with amiodarone). Hyperthyroidism and hypothyroidism are frequent complications of amiodarone use [59]. Two fundamental mechanisms are known as the cause of amiodarone-induced hyperthyroidism: increased synthesis of thyroid hormone due to iodide load (type 1), or destructive thyroiditis (type 2) [60]. Amiodarone-induced hypothyroidism is linked to the reduction in thyroid hormone secondary to intake of a large amount of iodine, and it is treated with T4.

Finally, euthyroid sick syndrome, known as "low-T3 syndrome" is another thyroid disorder often associated with HF. This condition is described by the presence of low T3 circulating levels. It was reported in patients with acute or chronic illness and can be induced by weight loss due to chronic caloric restriction. Patients with HF frequently present with low serum T3 levels, and this condition may negatively affect functional status and prognosis [61]. In particular, it is a strong predictor of death. The effect of T3 supplementation in HF patients with low T3 syndrome is not known.

Hyperuricemia

Hyperuricemia is a common metabolic alteration in both HFrEF and HFpEF and is both a comorbidity and a "biomarker". It could be secondary to the upregulation of the xanthine oxidase [62]. It is associated with a significant clinical impact on prognosis. Hyperuricemia independently predicted the risk of incident CHF events [63]. Hyperuricemia has a relevant association with poor outcomes in HF patients without chronic kidney disease (CKD) but not in those with CKD [64].

Despite concerns over febuxostat safety, the CARES [65] and FAST [66] trials showed its non-inferiority vs allopurinol regarding CV events and its use in patients with gout and at least one additional CV risk factor is not related to an increased risk of death compared with allopurinol.

The possible beneficial effects of xanthine oxidase inhibitors (allopurinol or febuxostat) on clinical outcome in HF are still unclear. Allopurinol did not improve the clinical status, exercise capacity, quality of life, or LVEF at 24 weeks in patients affected by HFrEF with elevated uric acid levels [67]. Instead, whether febuxostat compared to conventional treatment improves the clinical outcomes in CHF with hyperuricemia is being investigated by the LEAF-CHF trial [68].

Vitamin D deficiency

As demonstrated by cross-sectional and case-control studies, both vitamin D deficiency and increase in parathyroid hormone are related to increased prevalence of HF [69]. Furthermore, vitamin D deficiency can influence the onset and/or progression of HF and LV dysfunction. Indeed, vitamin D deficiency is related to more adverse prognosis in HF patients [70]. Until today there is no evidence for the impact of vitamin D supplementation on outcome improvement in HF patients [71, 72].

Anabolic hormones

Acromegalia is a disease characterized by increased and disproportionate production of growth hormone (GH) and, consequently, insulin-like growth factor-1 (IGF-1) and caused mostly by a GH-secreting pituitary adenoma [73]. It is frequently associated with CV manifestations including arterial hypertension, and congestive HF may represent a late manifestation of a typical cardiomyopathy characterized by biventricular hypertrophy, mainly involving the LV [74].

Some case reports bring evidence on the association between dilated cardiomyopathy and acromegalia [75]. On the other hand, a reduction of anabolic hormones, including GH and IGF-1, is common in chronic HFrEF and HFpEF and it is related to impaired functional capacity and clinical outcome [76]. Whether treatment of GH deficit could improve clinical outcome is still a matter of debate [77].

CHRONIC KIDNEY DISEASE

The heart and kidneys are strictly related. The dysfunction of one of these organs leads to poor prognosis through diverse mechanisms such as inflammation, oxidative stress, impaired hydro-saline homeostasis and diuretic resistance [78]. Renal dysfunction (RD) prevalence in HF ranges from 30% to 50% of patients [79]. However, the clinical scenario of RD in AHF and CHF should be highlighted. In the acute setting, both CKD and acute RD should be observed. CKD (defined as estimated glomerular filtration rate [GFR] <60 ml/min/m^2) in AHF represents a detrimental condition, related to poor prognosis [80]. Congestion is the essential hemodynamic determinant of renal function in HF [80–82]. Acute renal dysfunction in AHF recognizes different definitions according to cardiologists' and nephrologists' points of view. Indeed, Acute Kidney Injury Network criteria defined acute renal impairment as acute kidney injury according to the proportional increase in serum creatinine together with urine output reduction. Conversely, cardiologists defined renal deterioration as worsening renal function (WRF) considering serum creatinine increase ≥0.3 mg/dl or eGFR increase ≥20% or 25% with respect to baseline levels [83]. The differences regarding these definitions do not help physicians in renal impairment detection and management. The latest findings from HF studies suggest evaluating WRF in a specific clinical setting. For example, WRF due to aggressive diuretic therapy with effective decongestion seems to be related to a better prognosis than renal function in-hospital improvement with clinical congestion persistence. Due to these different conditions, WRF was classified as "true" and "pseudo" according to clinical deterioration and improvement, respectively [83]. The pathophysiological view of acute RD in AHF consists of two main mechanisms: hemodynamic derangement and neuro-hormonal overdrive. Reduced renal blood flow due to systolic and/or diastolic dysfunction and concomitant renal venous congestion represent the main actors of hemodynamic impairment. Reduced renal perfusion due to hemodynamic derangement contributes to increased sympathetic activity, renin–angiotensin–aldosterone system activation, and arginine–vasopressin release. These mechanisms contribute to aggravate the clinical status and prognosis of HF patients through vasoconstriction and water retention [79]. It appears mandatory to insert renal function evaluation in the clinical setting of HF patients, because of the benefits induced by decongestive thera-

pies. Conversely, patients with pre-existing CKD or chronic congestion develop "true" WRF with a worse outcome despite decongestive therapies [79].

Both CKD and sudden RD should be monitored in CHF patients. The decrease in cardiac output and thus renal blood flow is the main pathophysiological mechanisms involved. This condition is not sustained by the kidneys due to HF medication. Moreover, subclinical congestion, due to water and sodium retention leads to worse clinical condition and renal function [79]. All these alterations of the cardio-renal axis in a chronic setting contribute to worse the prognosis causing frequent hospitalization and mortality.

In conclusion, both CKD and WRF in acute and CHF are related to poor prognosis [84]. A specific approach should be considered due to the different clinical meanings of RD in different clinical settings of HF patients.

IRON DEFICIENCY IN HEART FAILURE

Anemia is a very common comorbidity in subjects affected by HFrEF and HFpEF [4]. It is justified in HF patients by nutritional deficiencies, loss of blood through the gastrointestinal system, reduced iron absorption, and reduced release of stored iron. It is an independent predictor of recurrent hospitalizations and it may negatively affect reduced exercise capacity and the quality of life. After the RED-HF trial [85] results (increasing hemoglobin to 12–13 g/dl with erythropoietin does not improve outcomes in HF patients with anemia) the focus has been shifted to the role of iron deficiency.

Iron deficiency (ID), frequent in patients with HF, is characterized by insufficient iron stores to meet the body requirements. There are different forms of ID: absolute and functional ID, both with or without anemia. In absolute ID, ferritin levels are <100 µg/ml. In functional ID, typical in chronic inflammatory diseases and CKD, ferritin is normal with a transferrin saturation <20%. This condition may increase hemodynamic instability, re-hospitalization, and mortality rates in patients with HF [86].

The results of the IRON-HF [87] and IRONOUT-HF [88] trials have demonstrated that oral iron supplementation is unsuccessful.

Ferric carboxymaltose (FCM) intravenous (IV) treatment seems to improve both ID and symptoms in HF patients. The FAIR-HF trial results demonstrated an improvement of functional class and a decreased impairment of renal function after 24 weeks of treatment with FCM [89]. The CONFIRM-HF trial [90] showed an exercise capacity improvement and a relevant decrease in the hospitalization rate after 12 months of FCM therapy in HF patients with ID and normal hemoglobin levels. Recently, Ponikowski et al. [91] demonstrated that FCM therapy was safe and able to decrease the risk of HF hospitalizations, without apparent effect on the risk of cardiovascular death, in stabilized patients after AHF with ID and LVEF <50%. Data from a substudy of the Myocardial-IRON trial [92] in patients with HFrEF with ID, showed FCM was related to short-term improvement in LVEF and right ventricular ejection fraction.

According to the latest ESC HF guidelines recommendations [1], all newly diagnosed HF patients should be routinely tested for ID and FCM IV the administration should be considered in HF patients (if serum ferritin <100 µg/l, or if ferritin between 100 and 299 µg/l and transferrin saturation <20%) in order to improve HF symptoms, and increase exercise capacity and the quality of life (Class recommendations: IIa, Level of evidence: A).

The ongoing FAIR-HF 2 trial (ClinicalTrials.gov Identifier: NCT03036462) was designed in order to further evaluate the possible benefit of IV iron in HF patients with ID. The IRON-CRT trial [93] will determine the effect of FCM on cardiac reverse remodeling and cardiac contractility in HFrEF patients. Furthermore, an ongoing FAIR-HFpEF trial (ClinicalTrials.gov Identifier: NCT03074591) will verify any benefits of IV iron in relation to survival in HFpEF patients. These results may suggest that ID could be a new therapeutic target for HF therapy.

DEPRESSION

Depression (also called major depressive disorder) is a mental disorder characterized by a persistent feeling of sadness and loss of interest. It may lead to different emotional problems. It is a common comorbidity in HF, above all in CHF and advanced HF. The prevalence rates are similar in studies of HFrEF and HFpEF (24% vs 25%) [94]. Depression is associated with poor prognosis (and all-cause mortality and rehospitalization) in both HFrEF and HFpEF [95]. Pharmacological therapy for depression in HF has not affected the prognosis [96]. Tricyclic antidepressants should be avoided because they might lead to significant hypotension, arrhythmias, and decompensation of HF [1]. The association between antidepressants and HF prognoses remains controversial. Recently, a meta-analysis demonstrated that patients with HF and depression taking antidepressants had increased risks of all-cause death and CV death. Compared with nonusers, the use of selective serotonin reuptake inhibitors, tricyclics, and selective serotonin reuptake inhibitors significantly increased the rate of all-cause death [97]. Instead, the combination of cognitive behavioral therapy with a selective serotonin reuptake inhibitors was reported as the best management of depression in HF patients in a position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association [98].

Recently, a reduction in depressive symptomatology in heart transplant waiting list patients treated with sacubitril/valsartan was demonstrated [99].

In HFpEF patients enrolled in the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial, randomization to spironolactone was related to a mild decrease in depressive symptoms [100].

Table 1. Key results of the studies about non-cardiovascular comorbidities in heart failure patients differentiating between acute heart failure and chronic heart failure and between heart failure with preserved ejection fraction and heart failure with reduced ejection fraction

Non-CV comorbidities		AHF	CHF	HFpEF	HFrEF
Cancer	**Prevalence:** The prevalence of 2 chronic diseases like cancer and HF usually increases with age. **Prognosis:** The presence of cancer obviously worsens the prognosis of HF patients, while CV diseases are the first non-cancer cause of death in cancer patients				
Obstructive sleep apnea	Prevalence prognosis	61% HR: 1.53 (time to death)	54% OR: 2.38 (increased risk readmission)	39.8% AHI ≥20/h 5 <AHI <20/h poor prognosis	29%
Central sleep apnea	Prevalence prognosis	21% HR: 1.61 (time to death)	27% AHI ≥30/h Poor prognosis	29.5% AHI ≥20/h 5< AHI <20/h poor prognosis	31% Rate ratio: 1.53 (cardiac readmission)
Chronic obstructive pulmonary disease	Prevalence prognosis	19.3% OR: 1.65 (in-hospital non-CV mortality)	15% HR: 1.37 (all-cause death)	14% HR: 1.6 (all-cause death)	16% HR: 1.25 (all-cause death)
Diabetes mellitus	Prevalence prognosis	39.1% HR: 1.77 (in-hospital mortality) HR: 1.16 (all-cause mortality) HR: 1.32 (re-hospitalization)	31.4% HR: 1.74 (all-cause death)	29.3% HR: 0,85 (all-cause death)	32.3% HR: 1.25 (all-cause death)
Hypothyroidism	Prevalence prognosis	7% (reported as thyroid disease)	9% HR: 1.31 (all-cause death) HR: 1.46 (HF hospitalization)	8% negative prognostic factor	10% HR: 1.58 (mortality)
Hyperthyroidism	Prevalence prognosis	7% (reported as thyroid disease)	3% HR: 1.16 (all-cause death) HR: 1.07 (HF hospitalization)	3%	4% HR: 1.85 (mortality)
Vitamin D deficiency	Prevalence prognosis		20< vitamin D <29 ng/ /ml 2.4% vitamin D <20 ng/ml 3.2% HR:1,52 (mortality)	HR: 1.55 (mortality) HR: 1.74 (CV hospitalization)	HR: 1.09 (death or HF hospitalization) HR: 1.10 (all-cause mortality)
Hyperuricemia	Prevalence prognosis	43% in HFrEF 57% in HFpEF HR: 1.48 in HFrEF HR: 2.38 in HFpEF (death or HF hospital)	39% in HFrEF 19.5% in HFpEF HR: 1.37 (all-cause death)	19.5% HR:1.98 (all-cause death)	39% HR: 1.35 (mortality)
Anabolic hormones depletion (focus on total testosterone and growth hormone deficiency)	Prevalence prognosis	—	GHD 30% Higher all-cause mortality Total testosterone HR: 0.929 (all-cause mortality)	45% of patients with 2 or more signs of hormone deficiency	Deficiencies in DHEAS, total testosterone, free testosterone, and IGF-1 (defined as serum levels at or below the 10th percentile)
Chronic kidney disease	Prevalence prognosis	26.3% OR: 2.34 (all-cause death)	41% HR: 1.5 (all-cause death) HR: 1.59 (HF hospitalization)	39% HR: 1.39 (mortality)	41% HR: 1.49 (mortality)
Iron deficiency	Prevalence prognosis	69%–75% (absolute ID) HR: 1.72 (higher risk of readmission)	42.5% HR: 1.42 (mortality)	58.4% (non-impact on death or hospitalization)	52.2%–65.1% HR: 0.043 (all-cause death) HR: 1.58 (death)
Depression	Prevalence prognosis	6.4%–12.3% HR: 1.43 (CV readmission and death)	21.5% OR: 2.23 (mortality at 1-year)	25% HR: 1.05 (CV hospitalization)	24% HR: 1.56 (death/CV hospitalization)

Abbreviations: AHF, acute heart failure; *AHI, apnea*–hypopnea index; CHF, chronic heart failure; CV, cardiovascular; DHEAS, dehydroepiandrosterone sulfate; GHD, growth hormone deficiency; HF, heart failure; HFpEF, heart failure with preserved ejection fraction, HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ID, iron deficiency; IGF-1, insulin-like growth factor-1; OR, odds ratio

According to the ESC HF guidelines recommendations [1], psychosocial intervention, behavior cognitive therapy and exercise training (low- to moderate-intensity aerobic training) might be helpful in patients with HFrEF and depression.

Table 1 summarizes the principal results of studies about non-CV comorbidities in HF patients about prevalence and prognosis of the comorbidities, differentiating between AHF and CHF and between HFpEF and HFrEF.

CONCLUSIONS

Comorbidities are very common in HF patients (HFrEF and HFpEF), with differences secondary to type of HF and sex. Non-CV comorbidities confer a relevant contribution to outcomes and in HFrEF and HFpEF. Recent data, derived by new trials, seem to suggest some comorbidities as new pharmacological targets in HF. The comprehensive management of patients affected by HF should include the management of comorbidities, with focus on to anemia and

iron deficiency, mental and behavioral disorders, diabetes mellitus, and respiratory diseases. The right treatment of these comorbidities may positively affect prognosis, hospitalization, and the health-related quality of life.

Article information

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