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Review

Heart Failure in Elderly People: From Pathophysiology to Diagnosis and Management

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Abstract

As the older population increases, there is an increase in age-related chronic diseases, especially heart failure. It affects 25% of over 75-year-old outpatients and represents the leading cause of hospitalization and death in older people. This review aimed to point out the main characteristics concerning heart failure in older people, taking into account clinical symptoms, diagnosis, and treatment. An extensive search on heart failure was made on PubMed and Google, using the keywords older people, heart failure, epidemiology, diagnosis, clinical symptoms, and pharmacological approach. Our results underline how heart failure in older patients is a complex and multifaceted reality that requires a multidimensional assessment to frame the patient correctly, resolve the acute episode, and set a targeted

therapeutic, pharmacological, and non-pharmacological approach, without neglecting the psychogeriatric aspect. The latter must be aimed at reducing the relapse rate and preserving functional autonomy and quality of life, decreasing the rate of re-hospitalization and institutionalization, the length of hospitalization, and improving predictive outcomes.

Keywords
Older people; heart failure; epidemiology; diagnosis; clinical symptoms and pharmacological approach

1. Introduction and Epidemiology

As the older population increases, there is an increase in age-related chronic diseases, especially heart failure (HF) [1].

Diagnosis of heart failure affects 25% of outpatients over 75 years of age [2] and represents the main cause of hospitalization and death in older people, as well as an important economic and social burden [3]. In Italy, in particular, heart failure is the cause of about 200,000 hospitalizations a year (88% of them regard people over 65), with an increasing trend [4].

The incidence and prevalence of HF strikingly increase with age. For example, data from the Framingham Heart Study have shown that annual rates of new HF events per 1000 person-years are 9.2 for white men aged 65 to 74, 22.3 for white men 75 to 84, and 43.0 for white men aged 85 years and over. Corresponding rates among white women are 4.7, 14.8, and 30.7 per 1000 person-years, respectively. Similar findings relating HF incidence rates with age have also been noted among more ethnically and racially diverse populations. HF incidence also varies by race, ethnicity, and socioeconomic factors [5].

Regarding the prevalence, a report from the American Heart Association in 2016 asserts that the proportion of adults with HF is 1.5% for men aged 40 to 59 years, 6.6% for men aged 60 to 79 years, and 10.6% for men 80 years and older. Corresponding proportions among women are 1.2%, 4.8%, and 13.5%, respectively. These data demonstrate that HF prevalence among women overcomes that of men in the oldest population [5].

The prevalence of heart failure varies between 1% and 3% in the general adult population in industrialized countries and is expected to increase substantially due to the availability of better diagnostic tools that ensure appropriate diagnoses and life-saving medical treatments that prolong life after its diagnosis [6].

Although the diagnosis of heart failure in old age has a high prevalence and incidence, as well as a high morbidity and mortality, diagnostic and therapeutic strategies for this population group are surprisingly lacking. Probably because older patients are often excluded from clinical trials concerning both diagnostic and therapeutic pathways, whether they are “fit” or frail and affected by comorbidity. [7, 8] Both cardiac and non-cardiac comorbidities are common in HF patients and are associated with adverse outcomes, such as reduced quality of life, hospitalizations, and fatal events [6].

Management of heart failure in old age is complicated by comorbidities: among them, diseases related to the cognitive-affective domain (cognitive deterioration, anxiety, depression, delirium) are

those that probably have the greatest impact, both from clinical as well as welfare and socio-economic point of view.

Furthermore, the literature suggests a close etiopathogenetic and outcome link between heart disease and psychogeriatric comorbidities [7, 8].

2. Classification and Definition

According to the 2021 ESC guidelines, heart failure is a clinical syndrome consisting of cardinal symptoms (e.g. dyspnoea and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral edema) due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise [9]. However, it can be difficult in older population to obtain an accurate clinical history, often complicated by confounding factors, such as comorbidities [10]. In addition, comorbidities associated with the reduced physical and functional activity of elderly and more fragile subjects can mask the typical symptoms and clinical signs of heart failure, such as dyspnea on exertion, easy fatigue, and lower extremity edema. For example, exertional dyspnea may not be reported because it is attributed to reduced physical activity or other comorbidities (i.e. chronic anemia, chronic obstructive pulmonary disease, or chronic renal failure) [11, 12].

Furthermore, it is important to emphasize that, in a situation of the reduced cardiac functional reserve, typical of older subjects, the onset of an acute pathological event can suddenly precipitate a case of latent and/or unrecognized heart failure.

Heart failure is divided into three different phenotypes depending on the left ventricular ejection fraction (LVEF) evaluated through echocardiography - Table 1.

Table 1 The table reports the three different phenotypes in heart failure based on echocardiographic assessment.

Type of HF	HFrEF	HFmrEF	HFpEF
	Symptoms and signs	Symptoms and signs	Symptoms and signs
Criteria	LVEF ≤ 40%	LVEF 41-49%	LVEF ≥ 50%
Criteria	-	-	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; LV = left ventricle.

Heart failure can also be divided into two categories according to a chronological criterion: chronic heart failure, in case the diagnosis has already been established or there is a gradual onset

of the clinical syndrome, or acute heart failure, in which the onset of symptoms and signs is sudden, requiring hospitalization and/or intravenous diuretic treatment.

The New York Heart Association (NYHA) functional classification is used to define the severity of symptoms, from the absence of symptoms (class I) up to the presence of symptoms at rest, associated with the inability to carry on any physical activity without discomfort [13].

As mentioned, the prevalence of heart failure increases with age, settling above 10% from age 70 upwards [9, 10].

LVpEF is the most frequently represented phenotype in the older population due to the paraphysiological aging processes of the cardiovascular system and concomitant diseases. Since the myocardium and the senile vascular tree, are more rigid and less elastic, they determine dysfunction in the diastolic phase of the cardiac cycle [10, 14]. In addition, heart failure with LVpEF affects women more than men, patients are often affected by hypertension, suffering from permanent atrial fibrillation, and comorbidities, which contribute to complicating the clinical syndrome [9]. All-cause mortality is generally higher in HFrEF than in HFpEF, demonstrating that, while the etiology of HFrEF is linked to organic heart disease, such as outcomes of ischemic heart disease, HFpEF is due to a paraphysiological process of aging, thus resulting in a better-tolerated chronicity [10].

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

3. Etiology and Pathophysiology

Complex interactions of the cardiovascular aging (excessive oxidative stress, chronic low-grade inflammation, limited endogenous regenerative capacity in response to injury, and the aging heart itself) process with risk factors (obesity, hypertension, and atherosclerosis), underlying heart conditions (ischemic heart disease, permanent atrial fibrillation, and hypertension), comorbidities (anemia, chronic kidney disease, diabetes, sarcopenia), and disease modifiers (sex, genes) contribute to the development of HF phenotype and outcome [10] (Figure 1).

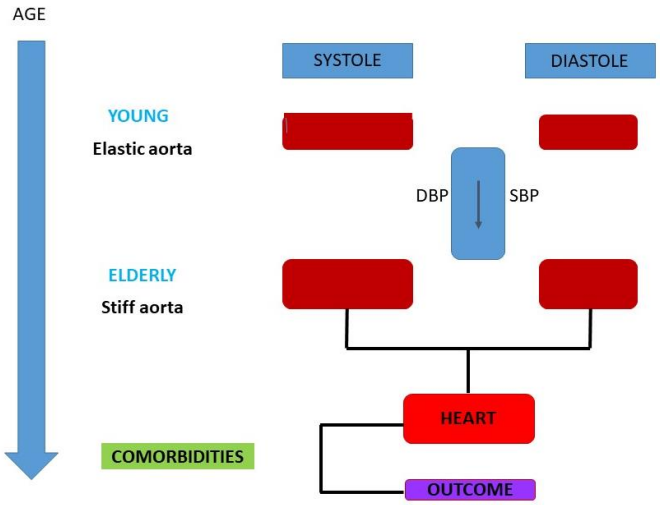

Figure 1 Association between cardiac aging and the onset of heart failure and its progression. SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, LV: Left Ventricular, LA: left Atrial.

3.1 Biomolecular Modification

The major implicated processes are excessive oxidative stress and chronic low-grade inflammation superimposed on the limited cardiac regeneration capacity [15]. Further biological aging as cellular senescence, reduced stress resistance, genomic instability, telomere attrition, reduced proteostasis, stem cell dysfunction, and/or epigenetic modifications can contribute to the heart failure onset [16]. Aged cardiomyocytes show abnormalities in mitochondrial structure (enlarged organelles, matrix derangement, and loss of cristae) and increased generation of free radicals, major drivers of cardiomyocyte senescence [17]. This determines disturbance in calcium signaling due to changes in the type 2 ryanodine receptor (RyR2) and the sarcoplasmic reticulum Ca^{2+} ATPase pump (SERCA) [18]. At the same time, autophagic and proteasomal degradations, their catabolic defensive mechanisms, decline with age [17]. In this context, there are a lot of covalent cross-linked protein aggregates, leading to detrimental effects [17]. A chronic pro-inflammatory status is a characteristic feature of aging. This chronic low-grade inflammation occurring in the absence of overt infection has been defined as “inflammaging”, and represents a significant risk factor for morbidity and mortality in the elderly [19]. Potential mechanisms of inflammaging include genetic susceptibility, central obesity, increased gut permeability, changes to microbiota composition, cellular senescence, oxidative stress caused by dysfunctional mitochondria, chronic infections, and immune cell dysregulation [20]. Also, sirtuin proteins are impaired in aged hearts and are critical to maintaining redox homeostasis via regulating substrate metabolism and inflammation, thus preserving cardiac function under stress [Sirtuin1 (SIRT1) and Sirtuin3 (SIRT3)] [21].

Myocardial fibrosis is typical of an aging heart: fibrotic tissue is stiffer and less compliant, resulting in subsequent cardiac dysfunction and increased risk of HF [22]. Angiotensin II acts as a pro-inflammatory molecule and pro-fibrotic agent. The binding of angiotensin II to AT1 is followed by intracellular free radical generation that contributes to tissue damage by promoting mitochondrial dysfunction [23].

3.2 Aging Heart

In healthy individuals, aging results in an increase in the incidence of left ventricular (LV) hypertrophy, decline in LV diastolic function, left atrial (LA) dilation, preservation of left ventricular ejection fraction (LVEF), decline in exercise capacity, and an increase in the prevalence of atrial fibrillation (AF) [5]. All of these factors can potentially lead to heart failure in elderly persons. There is also the reduction in maximal heart rate, caused by the decreased intrinsic heart rate and chronotropic responsiveness to beta-adrenergic stimulation, due to deficits in intracellular signaling to impaired G-protein coupling of receptors to adenyl-cyclase, as well as to reductions in the amount and/or activation of adenyl-cyclase [24]. In contrast, the activity of the sympathetic nervous system increases with aging [25]. As a result, maximum heart rate (HR) declines almost linearly with age, often denoted by the formula: maximum HR = 220 - age; peak contractility also declines with age [22]. The reduction in maximal heart rate and the reduction in LV stroke volume despite the higher LV filling pressure due to the decreased LV relaxation and compliance, result in aging-induced diminished maximal cardiac output, culminating in a compromised cardiac reserve capacity [26]. Furthermore, chronotropic incompetence has been detected in more than 30% of patients with

HFpEF (Heart Failure with preserved ejection fraction), and abnormal heart rate recovery is also frequent, affecting approximately 20% of patients [27].

Left Atrial (LA) volume and function are affected by age: maximal and minimal volume increase, LA enlargement is a marker of chronically elevated LV filling pressures and is frequently present in patients with HFpEF. In the early stages of HFpEF, the LA is able to compensate for LV diastolic dysfunction, acting through its reservoir function to store blood without untoward elevation in LA pressure, then facilitating LV filling through its booster function. However, with prolonged or more advanced LV dysfunction, LA dilation and dysfunction progress, and are associated with pulmonary hypertension and right ventricular dysfunction [28]. This progression is strongly tied to the development of atrial fibrillation (AF), which may be considered an electrical biomarker of LA myopathy [29]. LA dysfunction and loss of atrioventricular synchrony with atrial fibrillation are associated with limitations in cardiac output at rest and with activity, as well as the development of mitral regurgitation due to annular dilatation [30].

Pulmonary artery pressure and vascular resistance mildly increase with normal aging, likely secondary to increased pulmonary arterial stiffness [31]. Between 50–80% of patients with HFpEF have pulmonary hypertension (PH), initially caused by passive transmission of elevated downstream LA pressure. However, with chronic, sustained exposure to elevated LA pressure, pulmonary vascular remodeling often develops, resulting in an increase in pulmonary vascular resistance [32]. Patients with this precapillary component to PH display poorer exercise capacity, a unique hemodynamic signature characterized by right heart failure and left heart underfilling, and an increased risk of hospitalization and death [33].

Finally in 2008, Tanskanen & coworkers observed studies that approximately 25% of all adults over 85 years of age have acquired wild-type transthyretin-related cardiac amyloidosis [34]. Deposing amyloid fibrils in the extracellular matrix increases ventricular wall thickness and myocardial stiffness [35]. Cardiac amyloidosis is significantly underdiagnosed and increasingly recognized as a cause of heart failure with preserved ejection fraction [36].

3.3 Aging and Vascular Sistem

In the elderly, the elastic components of the aortic media suffer from progressive fragmentation and breakdown and are partially replaced by highly cross-linked collagen leading to stiffening, dilation, and elongation of the aorta. This condition is based on a general increase in the intimal-medial thickness of medium-sized arteries. In the stiffened aorta, systolic pressure and LV afterload rise, leading to LV hypertrophy and increased myocardial oxygen demand, whereas aortic diastolic pressure decreases, resulting in perfusion-metabolism mismatch and myocardial ischemia [37]. A stiff aorta also transmits greater pulsatile energy to the microcirculation, which may lead to peripheral organ damage and contribute to the development of isolated systolic hypertension, which is extremely common in the elderly [38].

3.4 Risk Factors and Lifestyle Influences

Hypertension, ischemic heart disease, and obesity (especially visceral adiposity) always precede the development of HF and are associated with an increased HF incidence [39]. Also, sedentary behavior, smoking, and dietary patterns affect cardiovascular aging [40, 41].

Therefore, changes related to other systems must be considered, which contributes to complicating the management of heart failure in a synergistic way. The reduction in hepatic and renal function, and decrease in lean mass in favor of fat mass, significantly change the pharmacokinetic and pharmacodynamic parameters, with important therapeutic implications.

Comorbidities and polypharmacy are other important aspects that can exacerbate heart failure. Furthermore, physical deconditioning and a situation of frailty and/or disability that can mask or delay the diagnosis should also not be forgotten [14] - Figure 2.

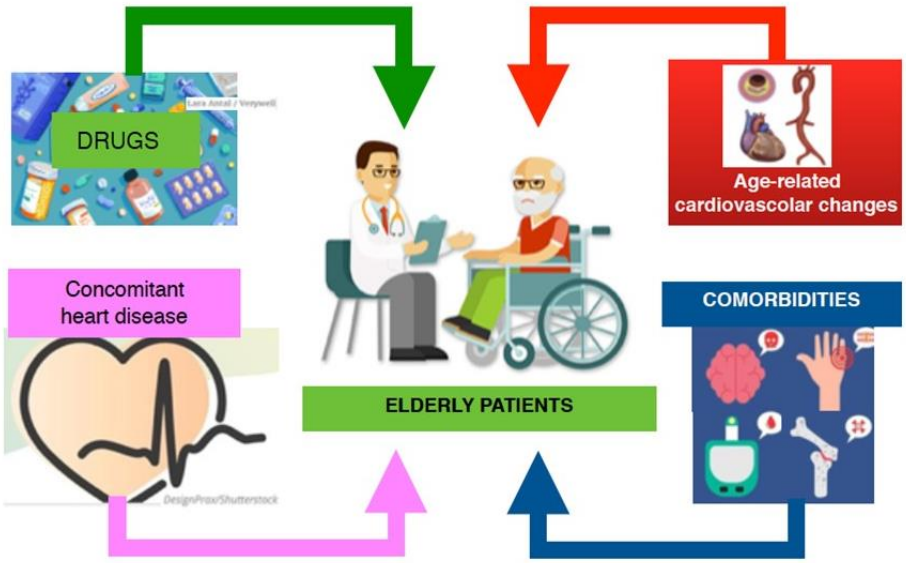

Figure 2 Older persons are more prone to heart failure due to complex inks between age-related cardiovascular changes comorbidities and polytreatment.

In particular, comorbidities represent the worsening and further complexity in managing acute or chronic heart failure and, furthermore, a significant financial burden [14]. Indeed, days of hospitalization often increase, requiring more care and rehabilitation complexity and a considerable social burden. There is often a loss of self-sufficiency and institutionalization, sometimes definitive [14]. Patients with heart failure have a higher prevalence of many chronic conditions [42]. Comorbidities affecting older people, in addition to those causing the etiology of heart failure, such as atrial fibrillation, arterial hypertension, and ischemic heart disease, were found to be sarcopenia, anemia, cognitive impairment, depressive syndrome, and delirium [42].

Changes in lean mass are a frequent critical determinant in the pathophysiology and progression of heart failure. The relationship between sarcopenia and heart failure is twofold: the first can be considered one of the most important causes of poor physical performances and reduced cardiorespiratory ability in older people, whereas heart failure can induce sarcopenia through common pathogenetic pathways, such as hormonal changes, malnutrition and physical inactivity, and mechanisms that influence each other - Figure 3.

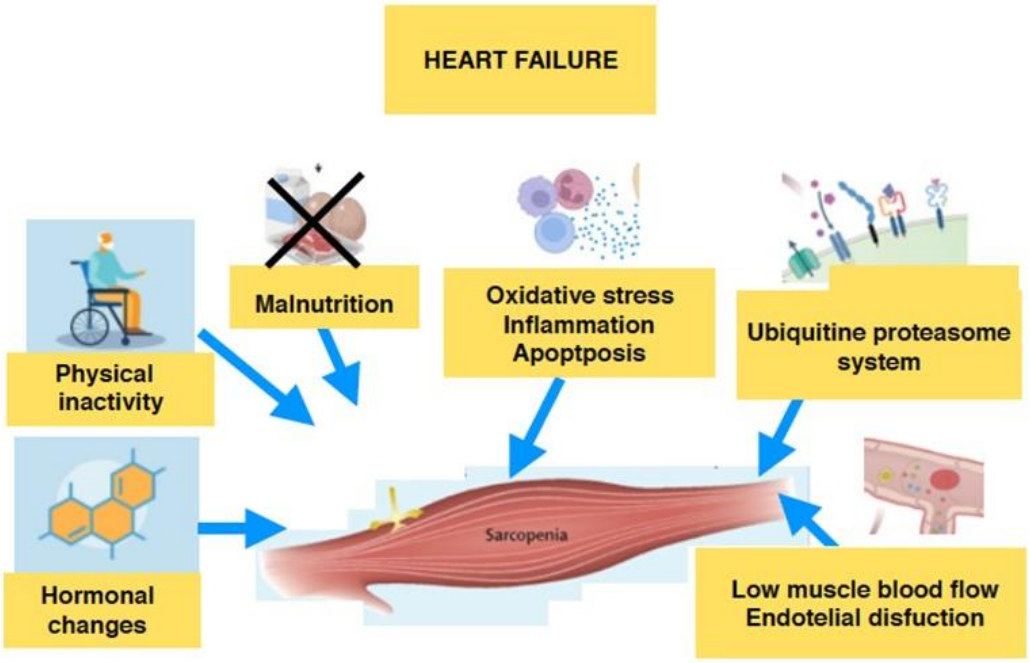

Figure 3 Factors related to heart failure, potentially leading to sarcopenia.

Paradoxically, sarcopenia is associated with a non-functional hypertrophic myocardium, in which contractility is less effective in the pump effect. First-line pharmacological agents for treating heart failure, physical activity, and nutritional interventions may offer a prognostic advantage in sarcopenic patients regardless of outcomes [43]. Therefore, correct multidimensional management of cardiac and sarcopenic pathology can lead to an improvement in prognostic expectations. Iron deficiency is also one of the conditions most frequently linked to heart failure. It occurs in approximately 50% of patients with stable heart failure, regardless of left ventricular function. In fact, in addition to cardiac dysfunction and reduced cardiac output, which are obviously required for defining HF, age-related muscle decline overlapping with "cardiac skeletal myopathy" may be considered the most important cause of low physical performance and reduced cardiorespiratory fitness in older patients with HF [16]. Closely related to sarcopenia is frailty, defined as "a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes" [44]. Frailty can predict worse clinical- and patient-oriented outcomes among older adults in general, and adults with HF in particular [45]. The prevalence of frailty among HF outpatients ranges from 19% to 52% according to the Fried frailty phenotype [46]. Among HF subtypes, the prevalence of frailty ranges from 50% to 94% among adults with HFpEF [47] and is higher than HFrEF (Heart Failure with reduced Ejection Fraction) [46]. The interrelationships between neurohormonal dysregulation, inflammation, and skeletal muscle dysfunction have been proposed as underlying pathogenic mechanisms of frailty, which have been noted to also parallel the pathogenesis of HF [48]. Chronic HF accelerates the aging-associated decline in muscle mass with relative preservation or accumulation of adipose tissue, leading to higher rates of sarcopenic obesity than with aging alone, and is also associated with abnormal muscle composition (i.e., high levels of intermuscular adipose tissue, shift in fiber type, reduced capillary density) that contributes to impaired mitochondrial function in skeletal muscle, reduced exercise capacity, and physical frailty [49]. The relation

between frailty and HF is bidirectional: higher frailty contributes to worse physical functional status, cognitive impairment, and quality of life in patients with HF through upregulation of pro-inflammatory pathways and lower tolerance to physiological stressors [47]. On the other side, these chronic processes may be exacerbated by an acute rise in inflammatory cytokines, due to an acute stressor and to the consequences of hospitalization for acute heart failure, which promote muscle loss as well as adipocyte proliferation and lipid accumulation, which may further impair muscle function and recovery and contribute to sustained, prolonged global decline in functional status through local and systemic inflammatory and metabolic pathways [50]. This may contribute to hospital-associated functional decline and a "post-hospital syndrome", such as in those cases following the resolution of decompensated HF when patients continue to have marked impairments in physical function and a higher burden of frailty [51]. Frail patients with HF have a higher symptom burden, (in particular dyspnea), 75% worse sleep disturbances and depressive symptoms, and worse quality of life [36]. Among clinical outcomes, a meta-analysis showed that patients with HF and frailty, determined by using the Fried phenotype, had a 57% higher risk of hospitalization and 80% higher risk of mortality than non-frail patients [52]. Indeed, in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, cohort patients with HFpEF and a high Frailty Index (FI) versus a low FI (>0.5 vs. <0.3) had markedly higher risk of HF hospitalization and all-cause mortality [53, 54]. Frailty assessment may identify patients with HF who are at higher risk of disability and adverse clinical outcomes at each stage of the disease manifestation, and it may facilitate targeted interventions that reduce frailty burden and improve outcomes.

The iron deficit in elderly patients affected by heart failure is another important issue. Indeed, it is often associated with anemia, which overlaps with heart failure, resulting in less tolerance to effort, deconditioning, and dyspnea, with an inevitable worsening of performance and increased morbidity and mortality [43]. Anemia is also common in patients with chronic kidney disease (CKD) and congestive heart failure (CHF), an association known as cardio-renal anemia syndrome (CRAS), leading to a significantly increased risk of death [55]. Among the possible mechanisms responsible for anemia, the decrease in erythropoietin levels, the activation of the renin-angiotensin-aldosterone system, the systemic inflammation, and the increases in hepcidin levels (the primary regulator of iron absorption) have been shown to amplify anemia, CHF, and CKD severity and worsen patients' outcomes [55].

Various studies have established that parenteral iron supplementation is an important complement to improving prognosis, well-being, and physical performance [43]. Intravenous iron preparations, in the first-line ferric carboxymaltose, as demonstrated in previous clinical trials, have shown a superior clinical effect compared to oral iron preparations. Indeed, they can improve the New York Heart Association functional class, 6 min walk test distance, peak oxygen consumption, and quality of life and exercise capacity in patients with ID and systolic heart failure [54, 56]. However, the definitive relationship of iron supplementation with mortality and morbidity in heart failure patients needs further validation in ongoing and future large-scale, randomized prospective trials [56]. Although the current guidelines for treating chronic and acute heart failure acknowledge the importance of iron deficiency correction and recommend intravenous iron supplementation, iron deficiency remains frequently undertreated and underdiagnosed in chronic heart failure [55, 56].

Cognitive decline is one of the most common comorbidities during senescence and has important repercussions from a prognostic point of view, therapeutic compliance, and intensity of care. They also contribute to disability in patients with chronic heart failure, affecting 25-50% of subjects [57]. Literature data support that cardiac dysfunction causes a pathological alteration of cerebral blood flow, thus predisposing to cognitive decline. Chronic regional hypoperfusion of strategic brain areas is one of the postulated mechanisms underlying this condition. Microvascular damage can also further compromise cognitive domains due to uncontrolled cardiovascular risk factors and a chronic inflammatory state - Figure 4.

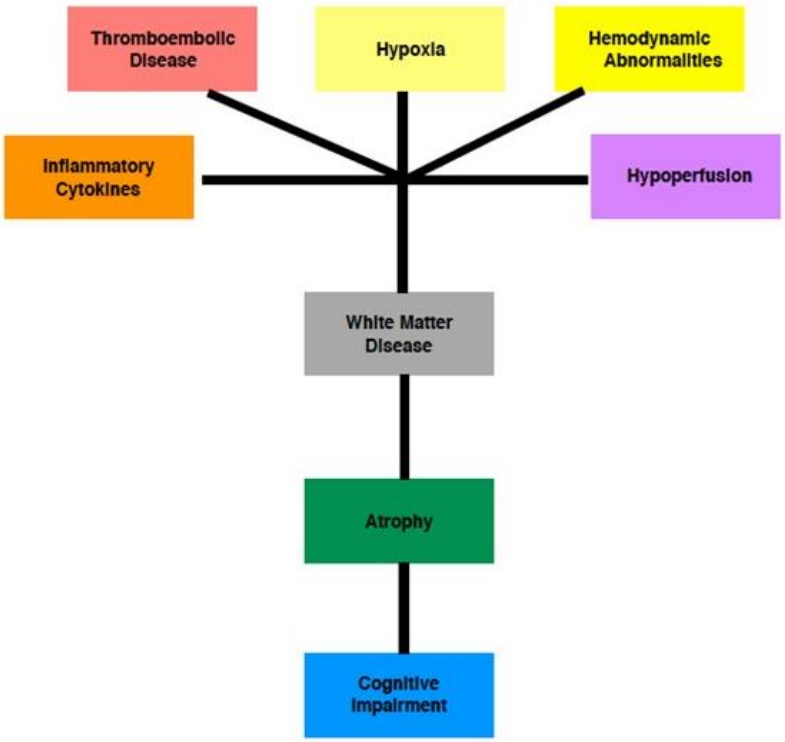

Figure 4 Pathophysiological pathways linking heart failure to the development of cognitive impairment.

In addition, 25-75% of cognitive impairment cases were observed in subjects with heart failure with reduced ejection fraction (HFrEF), characterized by more deficits in executive and verbal functions [57]. In the heart failure with preserved ejection fraction (HFpEF) phenotype, on the other hand, currently, there are few studies evaluating the different cognitive characteristics. The Hoorn study has shown that diastolic dysfunction was associated with low scores on attentional skills and executive functions [8]. There are many predictive factors for the development of cognitive impairment in patients with heart failure, such as advanced age and low education, but more related to the disease are functional decline, reduced ejection fraction, high NT-pro-BNP values, atrial fibrillation, renal failure, and low blood pressure - Table 2 [57].

Table 2 Predictors of cognitive decline in heart failure [57].

Predictors of cognitive decline in heart failure
• Functional decline
• Reduction of LVEF
• Increase of BNP
• Atrial Fibrillation
• Increase of BMI and waist circumference
• Anemia and chronic kidney disease
• Hypotension
• COPD

BMI = Body Mass Index; BNP = Brain Natriuretic Peptides; COPD = Chronic Obstructive Pulmonary Disease.

Functional impairment linked to heart failure and cognitive disease is associated with a worse prognosis and an increase in mortality, and also with an increase in disability, hospitalization rate, and definitive institutionalization, with severe consequences on social and welfare costs. Another aspect to focus is the relationship between heart failure and cognitive impairment and lack of diagnostic accuracy. It inevitably has repercussions on pharmacological and non-pharmacological treatment, preventing functional decline and progression of the disease, with worsening of primary and secondary outcomes.

Delirium is a common syndrome in patients with acute heart failure and chronic decompensated heart failure: a 2011 study [57] found that 17% of patients hospitalized for heart failure had this syndrome during hospitalization (data likely underestimated). Furthermore, it is associated with a threefold increase in mortality at 60 days, a longer length of hospitalization, and is independently associated with an increased risk of re-hospitalization at 30 and 90 days, as well as of developing a major neurocognitive disorder [58-61].

An acute confusional state causes an increase in heart rate, natriuretic peptides, and activation of the renin-angiotensin-aldosterone system, which is an important element underlying the change in metabolism and cerebral perfusion [62]. Furthermore, a systemic inflammatory state due to heart failure influences the cognitive structure, through interaction between neurons and glial cells mediated by inflammatory cytokines [63], and it has also been found that plasma level of catecholamines on hospital admission is more elevated in people with heart failure and delirium. The latter data suggest that beta-blocker treatment in patients with heart failure could reduce the risk of delirium [64]. The latest data suggest that beta-blocker treatment in heart failure patients could reduce the risk of delirium [64]. As already known, the precipitating factors of an acute confusional state are electrolyte changes, renal failure, and poly-treatment with increased risk of interactions, hypoxia, malnutrition, bladder catheterization, and frequent use of venous lines. Drugs such as warfarin and digoxin (although less used in current clinical practice), furosemide, and nitrates, may have anticholinergic effects, and increase the risk of delirium, as well as beta-blockers, non-dihydropyridine calcium antagonists, amiodarone. Furthermore, drugs used for the management of delirium (typical and atypical neuroleptics) can influence QTc interval on electrocardiogram and this fact might have consequences on a compromised myocardium [65].

Pathophysiology that links cognitive impairment, delirium ("simple" and related to dementia), and heart failure are common, with important consequences on outcomes. Therefore, a correct diagnosis of these conditions and a careful study of their connections are essential to set up a correct pharmacological and non-treatment, to minimize iatrogenic effects and improve the prognosis [66].

Depression as a comorbidity of heart failure is an important reality and has a prevalence of 30% it has important prognostic, diagnostic, and therapeutic compliance repercussions [67].

Symptoms related to heart failure (asthenia, easy fatigue, and dyspnoea), drug effects (frequent urination from diuretic therapy limiting social relationships), and side effects (gynecomastia linked to anti-aldosteronism, with consequences on the perception of one's body in males or sexual dysfunction secondary to beta-blockers which can also lead to insomnia or depressive symptoms) increase the risk of developing an anxiety-depressive syndrome [68].

Depressive symptoms, on the other hand, such as increased fatigue, lack of motivation, reduced physical activity, and use of consoling substances (alcohol, smoking, food) determine reduced therapeutic compliance with a worsening prognosis [68].

An increase in inflammatory cytokines was also observed in this clinical association. Stressful factors are highly represented in the psychogeriatric setting of depressed elderly people, but also patients suffering from heart failure. The stress response mediated by the hypothalamic-pituitary-adrenocortical axis, highly stimulated in this population, determines an increase in cortisol, which acts negatively on cardiovascular risk factors. It causes increased blood pressure, hyperglycemia, insulin resistance, and, through the aldosterone effect, cardiac remodeling with worsening of function (fibrosis, non-functional hypertrophy of myocytes) [68].

Furthermore, depression is linked to increased proinflammatory cytokines, interleukin-1 (IL-1), interleukin-6 (IL-6), C reactive protein, and fibrinogen. In particular, IL-6 is one of the most powerful stimulators of the hypothalamus-pituitary-adrenal axis and causes a chronic increase in cortisol levels. This leads to alterations in down-regulation and inhibition of receptors for glucocorticoids, and consequently, chronic hypercortisolism which in turn enhances the secretion of proinflammatory cytokines with a vicious and deleterious circle on the functionality of mood and cardiovascular system [69].

SSRIs have been shown to have a good therapeutic response and a good tolerability, however, in these patients, it is remarkable to set up a multimodal approach [69].

Depressive syndrome and other psychogeriatric comorbidities are strongly represented in older patients with heart failure. These diseases have a common pathophysiological pattern, with repercussions in prognosis, therapeutic compliance, and quality of life. Therefore making a correct diagnosis of both cardiovascular and psychogeriatric disease is essential, to prepare a correct treatment, optimize prognosis, and minimize iatrogenic effects as much as possible.

Another important issue in elderly patients with HF is self-care [70], Despite the high frequency of HF in elderly people, few studies described self-care in this population. The possible barriers to self-care emerged from a literature search including 28 studies were depression and the presence of peripheral arterial disease. A positive effect on self-care was male gender, number of cardiologist referrals, and self-efficacy. Interestingly, a telemonitoring intervention was used in multiple studies to enhance self-care. Conversely, few studies described the possible relationship between cognitive functioning and self-care. Furthermore, no strong evidence supported the relationship between self-care and health outcomes, i.e. readmission rate [70].

4. Diagnosis

Making an early diagnosis as soon as possible is important to improve prognosis. It is based on clinical evaluation to identify the typical signs and symptoms of heart failure, associated with laboratory tests (the measurement of natriuretic peptides) and instrumental tests, such as ECG and echocardiogram [9].

A normal electrocardiogram (ECG) makes the diagnosis of heart failure unlikely [13]. ECG can show alterations such as atrial fibrillation, Q waves, ventricular hypertrophy, and enlarged QRS complexes suggestive of organic heart disease.

The dosage of natriuretic peptides is recommended when available [9]. A plasma B-type natriuretic peptide (BNP) assay <35 pg/mL, N-terminal pro-B-type natriuretic peptide (NT-proBNP) <125 pg/mL, or mid-regional pro-atrial natriuretic peptide (MR-proANP) <40 pmol/L makes the diagnosis unlikely [71].

Plasma concentration of natriuretic peptides is recommended at the beginning of the diagnostic process as it has a high sensitivity, but a non-optimal specificity, contributing, with its negativity, to exclude the diagnosis of heart failure. Furthermore, their plasma dosage has a diagnostic value, an important prognostic significance [72], and guides further cardiac diagnostic investigations [73].

However, it should be emphasized that several conditions can cause an increase in natriuretic peptides, including advanced age, atrial fibrillation, and acute and chronic renal failure [74] - Table 3.

Table 3 Causes of increased natriuretic peptides [9, 74].

Cardiac	Heart failure Acute coronary syndrome Pulmonary thromboembolism Myocarditis Left ventricular hypertrophy Hypertrophic-restrictive cardiac disease Valvulopathies Congenital heart disease Atrial and ventricular arrhythmias Cardiac contusions Cardioversions, shock ICD (implantable cardioverter- defibrillators) Cardiac surgery interventions Pulmonary hypertension
Not cardiac	Old age Cerebral ischemic stroke Subarachnoid hemorrhage Acute and chronic renal failure Hepatic insufficiency Paraneoplastic syndromes Chronic Obstructive Pulmonary Disease Sepsis

	Anemia
	Widespread burns
	Severe endocrinological changes (thyrotoxicosis)

Furthermore, they can be falsely reduced in obese subjects [74].

The problem of dosage of natriuretic peptides in older population was discussed and evaluated in a recent Position Paper of the European Society of Cardiology; it was proposed to use a higher cut-off of NT-proBNP in ruling-out heart failure diagnosis in older people [75] (Table 4).

Table 4 NT-proBNP levels recommended for the diagnosis of acute heart failure [73, 75].

	Cut-off levels (pg/mL) NT-pro-BNP		
Patient with acute dyspnea	Age <50 years	Age between 50-75 years	Age >75 years
Unlikely HF	<300		
Gray area	300-450	300-900	300-1800
Probable HF	>450	>900	>1800

HF: Heart Failure

However, the prognostic value remains important in later life, as evidenced by Vergaro and coworkers [76] as regards HFrEF.

Finally, a transthoracic echocardiogram is a cornerstone in heart failure diagnosis because it assesses cardiac function. It provides examination of LVEF, and also information on the size of heart chambers, characteristics of ventricular hypertrophy, global and segmental kinesis, the function of the right ventricle, presence of pulmonary hypertension and/or valvulopathies and parameters of ventricular dysfunction [75, 77].

5. Pharmacological Treatment

Heart failure treatment differs according to the value of the ejection fraction. Indeed, it differs in the case of reduced or preserved ejection fraction.

5.1 HFrEF - Heart Failure with Reduced Ejection Fraction

Pharmacotherapy is the cornerstone of treatment for HFrEF. There are three major goals of treatment for patients with HFrEF: reduction in mortality, prevention of recurrent hospitalizations due to worsening HF, and improvement in clinical status, functional capacity, and quality of life. Therapy should be up-titrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible) before deeming it insufficient and considering the use of devices (ICD, PM). Furthermore, it must always be accompanied by non-pharmacological interventions to correct lifestyles. Modulation of the renin-angiotensin-aldosterone and sympathetic nervous systems with angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA) has been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF. The triad of an ACE-I/ARNI, a beta-blocker, and an MRA are recommended as cornerstone

therapies for these patients unless the drugs are contraindicated or not tolerated. It is recommended the use of ARNI as a replacement for ACE-I in suitable patients who remain symptomatic on ACE-I, beta-blocker, and MRA therapies. However, an ARNI may be considered a first-line therapy instead of an ACE-I. Angiotensin-receptor blockers (ARBs) still have a role in those who are intolerant to ACE-I or ARNI. The sodium-glucose cotransporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin added to treatment with ACE-I/ARNI/beta-blocker/MRA reduced the risk of CV death and worsening HF in patients with HFrEF. Unless contraindicated or not tolerated, dapagliflozin or empagliflozin are recommended for all patients with HFrEF already treated with an ACE-I/ARNI, a beta-blocker, and an MRA, regardless of whether they have diabetes or not [7, 8]. Furthermore, SGLT2 inhibitors have shown particular efficacy in patients with frailty, with more improvements in those with the worst frailty index [7, 8, 78]. Diuretics deserve a separate mention. Loop diuretics are recommended to reduce the signs and/or symptoms of congestion in patients with HFrEF. Diuretic treatment aims to achieve and maintain euvolemia with the lowest diuretic dose. The quality of the evidence regarding diuretics is poor and their effects on morbidity and mortality have not been studied in randomized studies. However in patients with HFrEF, loop and thiazide diuretics appear to reduce the risk of death and worsening HF, they also improve exercise capacity. Of note, ARNI, MRAs, and SGLT2 inhibitors may also possess diuretic properties, therefore, an optimal chronic therapy with these drugs can reduce the use of diuretics. Other drugs such as digoxin and ivabradine may find indications in particular conditions, for example in patients intolerant to standard therapy. The use of digoxin in older patients requires carefulness and attention, because of the possible interactions with other drugs and the possible risk of intoxication in people affected with renal failure [79]. Other molecules are being studied and have given promising results that will lead them to be associated with the standard therapy for HFrEF in the future. Some patients require the use of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy to treat arrhythmic events when they occur [9].

The lack of studies in the real world with older patients who are not involved enough is a possible misleading factor.

5.2 HFmrEF - Heart Failure with Mildly Reduced Ejection Fraction

Patients with HFmrEF have, on average, features that are more similar to HFrEF than HFpEF, however, they have lower mortality than those with HFrEF, more akin to those with HFpEF. As in other forms of HF, diuretics should be used to control congestion. ACE-I, ARBs, beta-blockers, MRA, and ARNI can be considered to reduce the risk of hospitalization and death, however, there are no studies performed exclusively in patients with HFmrEF that scientifically support these treatment indications [9].

5.3 HFpEF - Heart Failure with Preserved Ejection Fraction

To date, no treatment has been shown to convincingly reduce mortality and morbidity in patients with HFpEF, although improvements have been seen for some specific phenotypes of patients. However, none of the large randomized controlled trials conducted in HFpEF has achieved their primary endpoints. Hospitalizations for HF were reduced by candesartan and spironolactone and there was a trend towards reduction with sacubitril/valsartan, but these are hypothesis-generating findings only. Studies are also underway that could lead to a redefinition of HFpEF in the future and

have therapeutic implications. Without recommendations regarding disease-modifying therapies, treatment should be aimed at reducing symptoms of congestion with diuretics. Loop diuretics such as furosemide at different dosages are preferred, although thiazide diuretics may be useful for managing hypertension. Reducing body weight in obese patients and increasing exercise may further improve symptoms and exercise capacity and should therefore be considered in appropriate patients. It is important to identify and treat the underlying risk factors, etiology, and coexisting comorbidities in HFpEF (e.g. hypertension, coronary artery disease (CAD), amyloidosis, atrial fibrillation, and valvular heart disease) [9].

6. Conclusions

As discussed, heart failure in older patients is a complex syndrome with high incidence and prevalence in the over-65-year-old population, which requires careful assessment in acute situations and timely planning and follow-up in chronicization and dehospitalization.

In our hospital (Geriatrics Ward Hospital Maria Vittoria-Birago di Vische in Turin), during the first three months of 2022 we found 32% of NYHA class III-IV patients hospitalized with a primary or secondary diagnosis of heart failure. The mean age was 88.5 years, 52% were female, 62.5% had a preserved ejection fraction, and they had at least 4 comorbidities (including neurocognitive disorder, iron deficiency anemia, chronic kidney failure, sarcopenia, diabetes mellitus, arterial hypertension, chronic obstructive pulmonary disease (COPD), atrial fibrillation), taking at least five different kinds of drugs. These results are similar to what the literature reported [14], but also highlight how elderly subjects hospitalized for heart failure are usually very old, and complex, as they are comorbid and poly-treated. Among patients admitted to our division, 73% presented acute respiratory failure requiring oxygen therapy, on admission to the emergency room, and 8.2% needed non-invasive ventilation. NT-pro-BNP values were higher than 4000 pg/ml at the time of diagnosis and never reached normal values, despite clinical stabilization and resolution, underlining how these subjects present advanced heart failure, comorbidities influencing natriuretic peptides kinetics, and a poor prognosis in the short-medium period, in terms of exacerbation, mortality, and re-hospitalization rate.

It is important to underline that about 48% of hospitalized subjects presented at least one hospitalization in the previous six months for acute heart failure and only 2% were enrolled in a specialist cardiological follow-up.

The mean length of hospitalization of our subjects was about 18 days, burdened by the onset of intercurrent complications, such as delirium, infectious episodes, and adverse events related to drug therapy such as orthostatic hypotension (secondary to the attempt to maximize therapy and deconditioning), hyperkalemia, worsening of renal function.

Therapeutic optimization in the elderly is a sensitive topic in this population. As already pointed out, first because this population is often excluded from clinical trials and then because it is very difficult to titrate drugs up to the recommended dosage and manage multiple classes of drugs without interactions and side effects, affecting clinical stability and quality of life [80-85].

In addition, a complex poly-treatment, which requires proper administration and careful follow-up about side effects, requires compliance and attention from the caregivers of our patients which is not always possible. Therefore, in our population we observed that no subject, despite the

advanced degree of heart failure, could reach the specific maximal therapy, even taking at least five classes of drugs at discharge.

From a functional point of view, most of the patients on entering the ward were dependent on ADL and IADL (on average three functions lost) and during hospitalization, the aim was to recover the maximum possible autonomy, through a short path of motor reactivation and cardiovascular reconditioning. Approximately 54% of hospitalized subjects were discharged to a post-acute care facility at discharge.

These data, though partial and incomplete, further underline how heart failure in older patients is a complex and multifaceted reality that requires a multidimensional assessment that aims to frame the patient correctly to resolve the acute episode and set a targeted both pharmacological and non-pharmacological treatment, without neglecting the psychogeriatric aspect, which presents not only a common pathophysiological pattern but also important repercussions in terms of prognosis, costs, and patient well-being. The latter must be aimed at reducing the relapse rate and preserving functional autonomy and quality of life, to reduce the rate of re-hospitalization and institutionalization, the length of hospitalization, and the improvement of prognostic outcomes.

The assessment and the multidimensional geriatric approach during hospitalization are fundamental. Another priority aspect is the territorial outpatient management of the subject with heart failure. It must be aimed at preventing acute events and therefore hospitalization in frail, comorbid subjects, but also fit elderly people. In addition, it must also be addressed to careful follow-up to reduce the re-hospitalization and institutionalization rate, to maintain autonomy and quality of life, and optimize and correctly manage the complex therapy of heart failure and its comorbidities. All this complexity can be managed only in a collaboration between the holistic geriatric approach and the specialist cardiology one to organize dedicated diagnostic-therapeutic paths at an intra-hospital and territorial level - Figure 5 [79, 82, 83, 85].

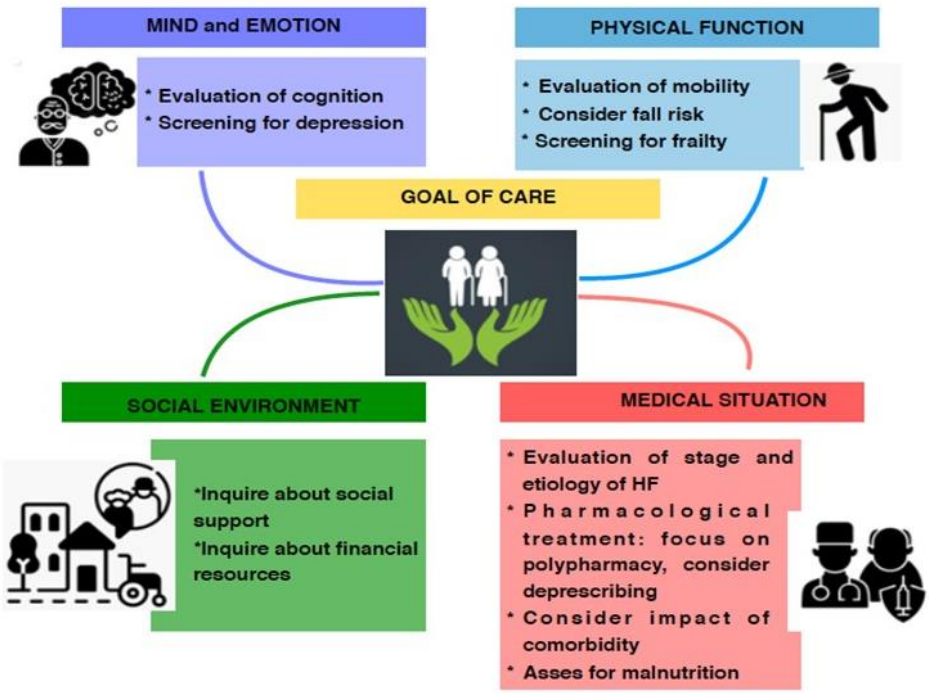

Figure 5 Multidimensional assessment of the elderly with heart failure.

Author Contributions

Study concept and design: Elisa, Martinelli, Antonino Maria Cotroneo. Acquisition of data: Elisa Martinelli, Angelo Di Stefano, Pasqualina Sapone, Pietro Gareri and Antonino Maria Cotroneo. Drafting of the manuscript: Elisa Martinelli, Angelo Di stefano, Pasqualina Sapone, Rosaria Carlucci, Pietro Gareri, and Antonino Maria Cotroneo. Critical revision of the manuscript for important intellectual content: Elisa Martinelli, Angelo Di Stefano, Pietro Gareri, Pasqualina Sapone, Rosaria Carlucci, Massimo Brandino, Ettore Maina, Sara Piscioneri, Giada Cagnoli, Antonino Maria Cotroneo.

Competing Interests

There are no conflicts of interest to declare. We received no support from industry or organizations which may have influenced this work, and there were no study sponsors involved.

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