



## Review Article

# Heart Failure (HF): Recent innovations in clinical therapy and critical profiles of acute and chronic forms

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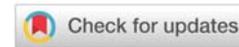
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## Abstract

**Background and objectives:** Heart failure is a pathological condition characterized by the inability of the heart to pump (cardiac output) an adequate amount of blood to meet the metabolic needs of the body or, at any rate, to be able to do so only at the expense of increased filling pressures in one or more cardiac chambers and the upstream venous circulation. The research group states here the primary objective of expanding the indications contained in the ESC 2021 with the results of the last year on the subject of treatment profiles, to facilitate a better understanding of the overall clinical picture and contribute to the next edition of the guidelines.

**Materials and methods:** Systematic literature review in the English language from January 1, 2021, to September 30, 2022, on PubMed/MedLine, Web on Science, and Cochrane archive. Our search strategy retrieved 8,317 articles. We excluded books and papers, meta-analyses, reviews, and systematic reviews and selected only 46 studies most significant about the clinical trial and randomized controlled trial.

**Results:** The recent ESC 2021 guidelines are accurate and timely, and have confirmed their usefulness from a functional perspective, including concerning certain aspects that were represented as a "grey area". Early risk prediction plays a key role in the subsequent management of patients, and to optimize risk prediction and intensity of management, one should take into account that: a) biomarkers have improved the understanding of the pathophysiology of heart failure and may therefore help to adjust the intensity of management in AHF; b) among the wide variety of biomarkers currently available, NT-proBNP and cTn seem the most promising in this indication; c) among the risk scores described, those combining demographic and clinical parameters with biomarkers in a model with routinely available rapid variables seem the most promising tools; d) in addition to biomarkers, age, systolic blood pressure, respiratory rate, oxygen saturation, creatinine, electrolytes, and blood urea nitrogen are the most commonly used predictor variables in the risk scores described; e) among the models selected, the MEESSEI-AHF risk score appears to be currently the most promising tool for predicting the risk of AHF; f) during the management of decompensated patients (and in later stages), the psychological aspect is completely ignored, thus promoting the worsening of psychological symptoms (the need is as evident during the acute episode as it is in the daily management of chronic heart failure).

**Conclusions:** The scientific literature search enriched the structure of ESC 2021, suggesting its implementation, with other findings related to new drug therapies such as Sotagliflozin, Hydrochlorothiazide Apabetalone, Alprostadil, Empagliflozin, Sacubitril/Valsartan, Dapagliflozin, Sodium-glucose co-transporter-2 inhibitors, and biomarkers such as Urinary sodium (UNa<sup>+</sup>), IL-6 levels and rh-brain natriuretic peptide (rhBNP), as well as the use of mindful breathing session, osteopathic manipulative treatment, electrical muscle stimulation, low-level tragus stimulation, venoarterial extracorporeal membrane oxygenation, oral nutritional supplements, and the correlative hypothesis between heart failure and intestinal dysbiosis, also concerning the psychological profile. However, these clinical studies suffer from some limitations that will necessarily have to be taken into account, such as the limited size of the population sample selected or the conflict of interest determined by the fact that some research is funded by the same pharmaceutical company producing the drug used that do not necessarily represent a negative limitation on the results obtained from studies.

## Background and objectives

### Definition

Heart failure is a pathological condition characterized by the inability of the heart to pump (cardiac output) an adequate amount of blood to meet the metabolic needs of the body or, at any rate, to be able to do so only at the expense of increased filling pressures in one or more cardiac chambers and the upstream venous circulation. Thus, circulatory failure secondary to noncardiac causes (e.g., hypovolemia caused by severe hemorrhage or dehydration) and circulatory congestion resulting from hypervolemia (as occurs in renal failure and states of water overload) cannot be included in the classic definition. Many heart diseases can lead to or evolve into a preclinical or clinical condition of heart failure, and the implementation of certain therapeutic measures can

in many cases prevent or delay its development. Moreover, it is possible to reduce the incidence of heart failure in the population also by preventing the development of heart diseases that are its potential causes (for example, ischemic heart disease and hypertension), through the control of risk factors that determine or aggravate them (for example, hypercholesterolemia, hypertriglyceridemia, excessive intake of sodium chloride, alcohol, drugs, smoking, and unhealthy dietary and lifestyle habits) [1].

### ACC/AHA Classification of heart failure into stages

Based on these considerations and the idea of a global approach to the problem of heart failure, aimed not only at treatment but also at prevention, a classification of heart failure into four stages has been proposed (Tables 1,2). The first two stages (A and B) include patients who have no

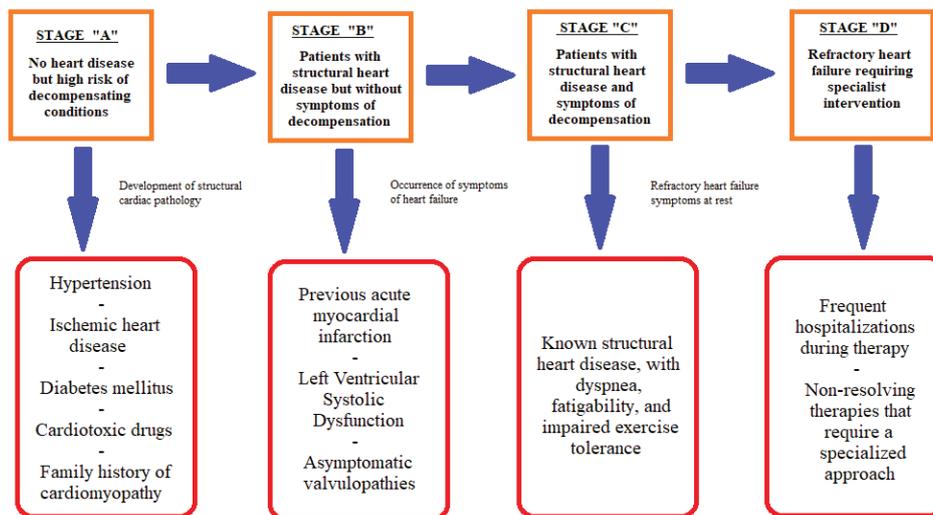


Table 1: ACC/AHA classification of heart failure into stages.

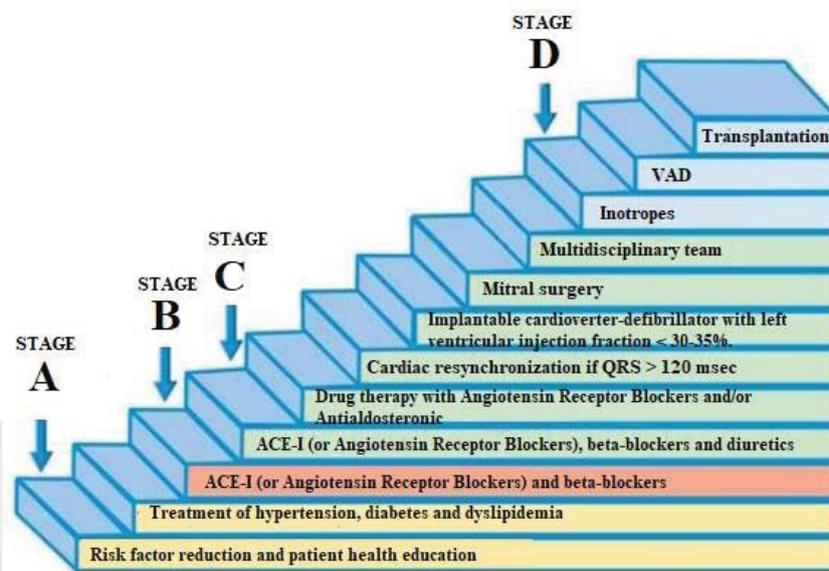


Table 2: Patient management according to the four stages.



evidence (clinical or subclinical) of decompensation, but in whom appropriate interventions may reduce the likelihood that they will develop heart failure in the future; the last two stages (C and D) include, conversely, patients with evidence of decompensation of increasing severity, who require specific types of treatment [2].

**Epidemiology**

Heart failure is a frequently encountered medical condition. In Europe, the prevalence ranges from 2 to 3%; therefore, approximately 15 million people are affected. A similar number of patients have left ventricular dysfunction in the absence of symptoms of heart failure. The incidence of decompensation in the population increases with age and doubles (or more) per decade from age 40 to 80. It is therefore likely to increase in the future, due both to the lengthening of the average life span of the population and, even more so, the increased life expectancy of patients with various forms of heart disease that can result in decompensation. In adulthood, decompensation is more frequent in men than in women, due to the higher prevalence of ischemic heart disease; however, the difference tends to disappear with the passing of the years [2].

**Etiology**

From a clinical point of view, it is useful to classify the causes of heart failure into two categories (Table 3): 1) underlying (responsible for the pathology); 2) precipitating or triggering (the clinical symptoms). In the first hypothesis (underlying causes), the main cause of myocardial contractility deficit (myocardial insufficiency) and other causes not originating directly from the insufficiency can be included. In the first case, we distinguish clinical causes that primitively involve the myocardium (myocarditis, cardiomyopathies, neuromuscular abnormalities, toxic substances such as cobalt and alcohol, and metabolic causes such as diabetes) from those that involve secondary involvement (ischemia infiltrative pathologies, inflammatory pathologies, systemic pathologies, mechanical alterations, uremia, myocardial depression secondary to drug use, genetic pathologies such as glycogenosis and chronic obstructive pulmonary disease); in the second case,

we distinguish instead the conditions that alter ventricular filling (rhythm alterations, myocardial restriction, pericardial constriction, aneurysm, and mitral or tricuspid stenosis) from those that force the heart to face pressure or volume load beyond its capacity (arterial hypertension, aortic stenosis, aortic insufficiency, and shunt). The second hypothesis (precipitating causes), i.e., the causes responsible for the deterioration of myocardial function, can be included those that have a cardiac origin (arrhythmias and negative inotropic drugs) from those that instead have an extracardiac origin (anemia, pregnancy, thyrotoxicosis, infections, pulmonary embolism, hypersodium, emotional stress, physical stress, lack of consistent adherence to drug therapy prescribed in cardiovascular disorders). Heart failure must be distinguished from other forms of circulatory failure (Table 4), in which the function of oxygen transport to tissues is impaired because of an alteration in one (or more) of the other components of the system (blood mass, oxygenated hemoglobin concentration, vascular bed). An example of a clinical picture of circulatory failure that cannot be attributed to myocardial or cardiac failure is, for example, hypovolemic shock from acute hemorrhage. In summary, it must be remembered that myocardial failure, cardiac failure, and circulatory failure are not synonyms, but concepts of increasing scope, each encompassing the preceding ones in a larger family [3].

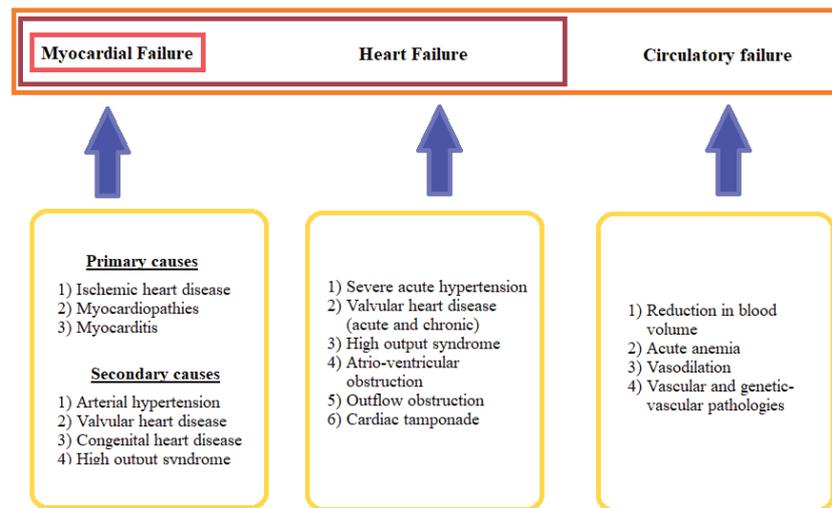
**Clinical types**

Based on symptomatology, the clinical forms of heart failure are divided into [1-3].

1. High and low output types, based on cardiac output. In most patients, cardiac output is reduced, or at least the heart is unable to increase it sufficiently during exercise. Low output hypotheses are all valvulopathy, cardiomyopathy, ischemic heart disease, pericardial disease, and hypertension, whereas high output hypotheses are sepsis, atrioventricular fistulas, hyperthyroidism, anemia, pregnancy, anaphylaxis, thiamine deficiency (or Beri-beri syndrome), and Paget's bone disease.

**Table 3:** Etiology of heart failure.

Etiology Heart Failure			
Underlying Causes			
Myocardial Failure	Primary Myocardial Involvement	Myocarditis, cardiomyopathies, neuromuscular abnormalities, such as cobalt and alcohol, and metabolic diabetes	toxic substances and metabolic causes such as diabetes
	Myocardial involvement secondary to extracardiac pictures or valvulopathy	Ischemia, infiltrative diseases, inflammatory diseases, systemic mechanical alterations, uremia, myocardial depression secondary to genetic diseases such as glycogenosis and chronic disease	diseases, drug use, obstructive pulmonary
Causes that do not directly originate from a deficit in myocardial contractility	Conditions that alter the ventricular filling	Rhythm alterations, myocardial restriction, pericardial constriction, aneurysm, and mitral or tricuspid stenosis	
	Conditions that force the heart to deal with a load of pressure or volume beyond its capacity	Arterial hypertension, aortic stenosis, aortic insufficiency, and shunts	
Precipitating Causes			
Cardiac origin	Arrhythmias and negative inotropic drugs		
Extracardiac origin	Anaemia, pregnancy, thyrotoxicosis, infections, pulmonary embolism, hypersodiemia, emotional stress, physical stress, consistent failure to adhere to prescribed drug therapy in	cardiovascular disorders	



**Table 4:** Relationship between myocardial, cardiac, and circulatory failure.

2. Acute or chronic type, based on the time it takes for adaptive mechanisms to set in and the speed of onset of the clinical picture. The chronic form generally originates from a myocardiopathy or valvulopathy (which is associated with slow clinical and hemodynamic deterioration and allows compensatory mechanisms to develop), whereas the acute form arises predominantly following a valvular rupture or acute myocardial infarction (which is associated with rapid clinical and hemodynamic deterioration).
3. Anterograde or retrograde type, based on ventricular incapacity. Specifically: in the anterograde form, the symptomatology is characterized by the ventricular inability to deliver sufficient blood to the arterial system, causing peripheral hypoperfusion (which also results in brain symptoms such as confusion, drowsiness, and agitation) and decreased renal perfusion (resulting in tubular reabsorption of water and sodium, oliguria and nocturia); in the retrograde form, the symptomatology is characterized by the inability of the ventricle to expel blood in sufficient quantity, causing an increase in upstream pressures and volumes, thus causing a state of venous congestion.
4. Left, right, or global type, based on location. In left heart failure, there is pulmonary congestion with dyspnea (which can be exertional, orthopneic, paroxysmal, at rest, and from acute pulmonary edema), whereas in right heart failure there is peripheral edema, hepatomegaly, gastrointestinal mucosal congestion, ascites, and increased jugular venous pressure (with turgor). However, the interdependence between the systemic and pulmonary circulation may also result in a global form, with an overlap in all or part of the two situations described (especially in the hypothesis of coronary atherosclerosis).
5. Systolic or diastolic type, based on the inability of the organ to work. In particular: in systolic heart failure

(by the way, the most frequent form) the inability of the ventricle to expel a sufficient amount of blood predominates (with a decrease in systolic volume and an increase in telediastolic volume); in diastolic heart failure (or heart failure with preserved ejection fraction), caused by fibrosis, increased filling pressures, cardiac ischemia, arterial hypertension, or tamponade, on the other hand, the ventricle is unable to release adequately and fill normally during diastole (while the ejection fraction remains normal).

6. Cardiac or cardiorenal type, based on organic involvement of the heart–renal axis. The cardiorenal syndrome is defined as the condition in which the failure of one of the two organs (heart–renal) causes the failure of the other, both in the acute and chronic form. There are five types: I, in which acute cardiac failure secondarily causes acute renal failure (acute cardiorenal syndrome); II, in which chronic cardiac failure secondarily causes chronic renal failure (chronic cardiorenal syndrome); III, in which acute renal failure secondarily causes acute cardiac failure (acute nephrocardiac syndrome); IV, in which chronic renal failure secondarily causes chronic cardiac failure (chronic nephrocardiac syndrome); V, in which the systemic condition (e.g., sepsis) causes cardiac and then renal failure (secondary cardiorenal syndrome).

### Diagnosis and criteria

Based on the history and objective examination, the healthcare professional can make the diagnosis of heart failure. However, the following instrumental and laboratory tests may facilitate the diagnostic workup [1–3]:

1. **Chest radiography:** Radiological changes may appear even before the symptoms and in case of increased capillary pressure, edematous formations are observed, septal (appearance of linear opacities called Kerley's lines), perivascular and peribronchial (loss

of definition and blurring of the profile of vessels and bronchi of medium caliber), subpleural (presence of lobar scissures) and alveolar-pulmonary (presence of bilateral infiltrate often central and “butterfly wings”).

2. **Hemogasanalysis:** We detect a depletion of muscle contractile capacity, with hypoventilation and CO<sub>2</sub> retention (hypoxemia and hypercapnia, associated in the latter case with poor prognosis and need for ventilatory support),
3. **Electrocardiogram:** To detect early arrhythmias of the heart rate and detect structural and functional pathologies.
4. **Laboratory analysis:** Brain Natriuretic Peptide (BNP) is a new-generation hormonal marker, although its specificity is not very high, it is sensitive if its values are normal.
5. **Colordoppler echocardiogram:** It has two purposes: to assess the etiology of decompensation and to monitor the effects of treatment. It is undoubtedly the test that contributes more than any other to identifying the causes of heart failure and assessing its severity. Easily performed, non-invasive, and risk-free, this examination allows the rapid identification of many of the cardiac pathologies (coronary, myocardial, valvular, and pericardial) that can cause heart failure. The echocardiogram allows, in particular, an adequate examination of the global and regional contractile function of the left ventricle and, albeit with less precision, of the right ventricle. In this regard, it allows easy calculation of left ventricular ejection fraction, which is the most important and widely used parameter in clinical practice to indicate the state of myocardial contractility and is also one of the most important prognostic parameters in heart patients. It expresses the percentage of blood ejected from the ventricle during systole on the total volume of blood it contains at the end of diastole and is obtained with the formula:  $[(\text{telediastolic volume} - \text{telesystolic volume}) / \text{total volume}] \times 100$ . Normally, FEVSn is between 60 and 75% and is still greater than 50%. Its reduction is greater than the impairment of global left ventricular contractility. Assessment of ventricular systolic function in patients with organic heart disease is extremely important because a subclinical reduction in left ventricular function often precedes symptoms and signs of decompensation. Therefore, its recognition may help prevent the progression to full-blown decompensation.
6. **Chromatography:** It should be performed in all cases in which the patient shows a left ventricular dysfunction of unknown origin, to exclude the presence of ischemic heart disease.

Based on the clinic, several criteria have been proposed for the diagnosis of heart failure [2,3]:

1. **Framingham criteria:** A distinction is made between major and minor criteria. In the first case, we find paroxysmal nocturnal dyspnea, distension of the neck veins, rales, cardiomegaly, acute pulmonary edema, III tone gallop rhythm, increased venous pressure (> 16 cm H<sub>2</sub>O) and hepatojugular reflux; in the second case, we find peripheral edema, nocturnal cough, dyspnea on exertion, hepatomegaly, pleural effusion, reduction of vital capacity by one-third of normal, tachycardia (heart rate > 120 bpm). Completing the clinical profile, in both hypotheses (major or minor) is any weight loss > 4.5 kg in 5 days in response to treatment. The diagnosis is considered certain in the presence of two major criteria or one major and two minor criteria.
2. **New York Heart Association (NYHA) criteria:** Thus, the major symptoms of heart failure involve respiratory function, muscle activity, diuresis, and brain function. The assessment of the level of physical activity that determines the appearance of symptoms (dyspnea and muscle fatigue in the first place) allows one to specify the degree of functional capacity of the patient, which is closely dependent on the severity of heart failure. This functional classification is based on the relationship between symptoms and physical activity. Thus: a) Class I: Patients without physical activity limitations. Habitual physical activity does not cause symptoms; b) Class II: Mild limitation of physical activity. The patient is asymptomatic at rest, but habitual physical activity causes symptoms; c) Class III: Severe limitation of physical activity. The patient is asymptomatic at rest, but even less than usual physical activity causes symptoms; d) Class IV: Inability to perform any physical activity without discomfort. The patient may present with symptoms of heart failure even at rest. The complaints increase if any physical activity is undertaken.

### Heart failure and respiratory function

Dyspnea is undoubtedly the most frequent and characteristic symptom of decompensation and consists of a feeling of difficulty in breathing associated with a sensation of air hunger or shortness of breath. It is a consequence of pulmonary congestion, which causes interstitial edema and therefore reduces the distensibility of the lungs and the oxygenation of the blood. This increases the work of the respiratory muscles, which may also be poorly oxygenated due to peripheral hypoperfusion, and contributes to the sensation of breathlessness. In mild or initial cases of decompensation, dyspnea occurs only with intense exertion, or otherwise under conditions requiring increased work and cardiac output. In some patients, in the early stages, a wheezing cough may be the dominant symptom. In more severe cases, dyspnea appears even during mild exertion and, in advanced cases, even at rest. In addition to exertion, in severe cases, dyspnea can appear by simply assuming the supine position, whereby the patient needs to assume or maintain an upright position to breathe normally (a condition called orthopnea). Therefore, when these patients go to bed they are forced to sleep with two or more pillows to avoid the appearance of dyspnea, and those



with greater heart failure are sometimes forced to spend entire nights sitting on the bed or in an armchair to avoid or contain dyspnea. The reason that the supine position facilitates the onset of dyspnea lies in the fact that it increases venous return to the heart, thereby facilitating pulmonary congestion. For similar reasons, patients with heart failure may experience sudden episodes of dyspnea during the night (paroxysmal nocturnal dyspnea). In addition to the supine position, other factors may contribute in this case to facilitate the appearance of dyspnea, such as a depression of the center of breath during sleep, which facilitates hypoxia, and the reduction of sympathetic tone, which deprives the myocardium of an important stimulus for its contractile efficiency. In these cases, the patient suddenly wakes up with a sensation of difficulty in breathing and a wheezing and sibilant breath, sometimes accompanied by a wheezing cough. Interstitial edema can compress the bronchioles, causing an increase in airway resistance (cardiac asthma). Typically, the patient sits up in bed with feet dangling or goes to the window in search of air. In mild cases, symptoms improve rapidly withstanding, while in more severe cases they improve only slowly or not at all without therapeutic intervention, especially if there is overt pulmonary edema, which occurs when the pulmonary congestion is such as to cause, in addition to interstitial edema, alveolar edema (see below, Acute pulmonary edema) [1].

### Heart failure and kidney function

In heart failure, alterations in diuresis are often typical. Diuresis is often contracted during the day, while it frequently improves at night (nocturia), forcing the patient to get up even several times for urination. This behavior derives from the fact that during daytime hours hypoperfusion of the kidney can be important (due to reduced cardiac output), so diuresis is reduced. At night, with the clinostat position, cardiac output increases as a result of the increased venous return; this results in increased renal perfusion, which also improves because of reduced vasoconstriction of the renal arterioles. In more advanced stages of decompensation, renal hypoperfusion becomes constant and produces oliguria (less than 500-600 mL in 24 hours), with increased blood nitrogen and creatinine values. When cardiac output is severely reduced, complete anuria results [2,3].

### Heart failure and cerebral activity

Cerebral activity symptoms of the altered cerebral function appear only in cases of severe reduction in cardiac output, particularly when severe cerebral vascular alterations coexist. Normally, cardiac output redistribution of cerebral blood flow protects the encephalon from hypoperfusion. When they occur, cerebral symptoms consist of memory loss, difficulty in concentrating, insomnia, and anxiety in chronic cases. In acute cases (pulmonary edema and cardiogenic shock), mental confusion, agitation, drowsiness, and eventually a comatose state is observed [2].

### Main pharmacological devices in the therapy of heart failure

Drug therapy is decided based on the type of heart failure

(whether acute or chronic) and the basis of the main effects, as shown in the following (Table 5):

### ESC 2021

During the 2021 edition of the recently concluded European Congress of Cardiology, the new European guidelines for the diagnosis and treatment of acute and chronic heart failure were finally awaited. The main novelties of these guidelines can be summarized in eight points [2,3]:

1. **Modification of criteria for chronic heart failure:** Compared with the previous guidelines, the classification of chronic heart failure has been modified based on left ventricular ejection fraction cut-offs, so that today it is defined if there is a reduced (< 40%), or moderately reduced (41% - 49%), or preserved (≥ 50%) fraction. Therefore, in the new classification, patients with a fraction of 40% have been included in

Table 5: Main pharmacological devices in the therapy of heart failure.

	Main pharmacological devices in the therapy of heart failure	
Chronic heart failure	Pharmacological devices	Main effects of heart failure
	ACE inhibitors and angiotensin II receptor antagonists Beta-blockers	1. Inhibition of the effects of angiotensin II
		2. Reduction of afterload
		3. Antiadrenergic effects
		4. Enhancement of adrenergic response
		5. Antiarrhythmic effect
	Nitrates	1. Peripheral venous vasodilation
		2. Preload reduction
	Hydralazine	1. Arteriolar vasodilation
	Loop diuretics and thiazides	1. Increased sodium and fluid excretion
2. Reduction in preload		
Antialdosteronics	1. Mild diuretic action	
	2. Potassium saving	
Digital glycosides	1. Positive inotropic activity	
	2. Heart rate reduction during atrial fibrillation	
Acute heart failure	Pharmacological devices	Main effects of heart failure
	Loop Diuretics	1. Increased sodium and fluid excretion
		2. Reduction in preload
	Nitrates	1. Peripheral venous vasodilation
		2. Preload reduction
	Sodium Nitroprusside	1. Arterial and venous vasodilation
		2. Reduction of preload and afterload
	Phosphodiesterase inhibitors	1. Positive inotropic activity
		2. Arterial vasodilator effect
	Sympathomimetic amines	1. Positive inotropic activity
2. Low-dose diuretic effect		
Digital glycosides	1. Positive inotropic activity	
	2. Heart rate reduction during atrial fibrillation	
Morphine	1. Peripheral venous vasodilation	
	2. Preload reduction	
	3. Pain relieving and sedative action	

the reduced fraction category and the category of heart failure with mid-range fraction has disappeared. This was driven on the one hand by the recognition that fraction is a variable with a continuous distribution, the measurement of which is highly subject to intra- and inter-operator variability, and on the other by retrospective analyses of several clinical trials that included patients with fractions between 40% and 49% and showed that these patients appear to benefit from the same therapies that are effective in patients with heart failure, suggesting that these patients are more similar to those with reduced fraction than to those with preserved fraction.

- 2. New drugs:** Based on the evidence from the DAPA-HF and EMPEROR-reduced clinical trials, dapagliflozin and empagliflozin, which act by blocking sodium-glucose co-transporter-2 (SGLT-2) at the proximal tubule, have been introduced as “disease-modifying” drugs for the treatment of decompensation with reduced fraction, regardless of the presence of diabetes, with a class IA recommendation. Indeed, in their respective registration studies, the two drugs were shown to significantly reduce (approximately 25%) the primary composite end-point of cardiovascular mortality and hospitalizations for heart failure in patients with a reduced fraction with and without diabetes. In addition, based on data from the VICTORIA trial, a new drug, Vericiguat (a soluble guanylate cyclase receptor stimulator), entered the guidelines for the first time. Vericiguat, in patients with symptomatic SCFEr despite the use of beta-blockers and renin-angiotensin-aldosterone system inhibitors, has been shown to reduce hospitalizations and cardiovascular mortality and is therefore indicated although with a class IIb.
- 3. First-line drug supplementation:** Concerning sacubitril-valsartan, the guidelines, while confirming the Class IB indication as a replacement for ACE inhibitor/sartan therapy in patients who are still symptomatic, for the first time recognize that sacubitril-valsartan can also be considered as first-line therapy, based on data from the PIONEER and TRANSITION trials.
- 4. New pharmacological strategies:** An important novelty is also represented by the overcoming of the previous strategy of implementing the therapy in progressive steps, which provided for the gradual addition, with progressive titration of beta-blockers, ACE inhibitors, antialdosteronic drugs, and possibly the replacement of ACE inhibitors/sartan with sacubitril-valsartan, in case of persistence of symptoms. The current strategy is to include all four categories of approved drugs (beta-blockers, ace-inhibitors/sartan/ARNIs, antialdosteronics, and glyphozines) in all patients with reduced fraction as soon as possible, which are considered the mainstays of heart failure therapy. In addition, for the first time, the guidelines recognize a role for beta-blockers, ace-inhibitors, sartans, and sacubitril-

valsartan in the treatment of SCFEr, conferring a class IIb indication (level of evidence C). This indication derives from the enhancement of subanalyses of several randomized trials that have demonstrated a possible clinical benefit of these categories of drugs in this range of FE. In particular, this indication was dragged by the compelling subanalysis of the PARAGON-HF trial in which sacubitril-valsartan reduced the composite end-point of cardiovascular death and hospitalizations for heart failure by 22% in patients with a fraction < 57%, with the more pronounced benefit of the more the fraction was reduced.

- 5. Phenotypic recognition:** Another important change in the patient approach proposed in the LGs is the recognition that the clinical phenotypes of decompensation with reduced fraction are multiple and therefore, once the four pillars of therapy have been implemented, further treatment approaches must be tailored to the specific clinical phenotype of the patient. Such personalization includes an indication for defibrillator implantation, resynchronization, ivabradine, ferrocaryxymaltose, digoxin, hydralazine, direct oral anticoagulants, coronary revascularization, aortic valve replacement, percutaneous treatment of mitral insufficiency, pulmonary vein isolation.
- 6. Electrical therapy:** As far as electrical therapy for heart failure is concerned, the guidelines have downgraded to IIa the indication for defibrillator implantation in primary prevention in patients with dilated cardiomyopathy of non-ischemic origin. This was based on the DANISH trial, which showed that the slight reduction in the risk of arrhythmic death achieved with the defibrillator in this population was not reflected in an improvement in total mortality. However, since non-ischemic dilated cardiomyopathy encompasses extremely heterogeneous clinical entities, implantation should be considered (class IIa) in those forms that present a greater arrhythmic risk per se (laminopathies, sarcoidosis, etc), in which the benefit of the defibrillator might be greater. Concerning resynchronization therapy, the new guidelines have confirmed that the greatest evidence of benefit is present in patients with left bundle branch block and QRS duration > 150 msec (Class IA), while in patients with QRS between 130 and 149 msec the evidence is less strong and therefore in this population there has been a down-grading of the indication to IIa.
- 7. Implementation of telemedicine and the follow-up tool:** Based on a network meta-analysis that included 53 randomized trials and an individual-patient-data meta-analysis of an additional 20 trials, which demonstrated a reduction in heart failure hospitalizations and mortality with the implementation of multidisciplinary heart failure management programs, the guidelines have assigned a Class IA recommendation to the implementation of these strategies. Multidisciplinary

programs should include not only, proper intra-hospital diagnosis and therapeutic implementation, but also adequate patient follow-up, first during the delicate transition phase after discharge (at 1-2 weeks) and then throughout the long trajectory of the natural history of heart failure. Long-term patient management models must include telemonitoring, patient and caregiver education in self-monitoring and diuretic therapy modulation, easy access to intensive care in case of clinical instability, cardiological rehabilitation, a structured integration of hospital care with territorial care, and accessibility to palliative care.

8. **Reclassification of acute heart failure (AHF):** ESC-2021 provides a new clinical classification based on four nosographic categories, united by the fact that patients with AHF require urgent evaluation and administration of therapies and procedures; this happens because this pathology is one of the main causes of hospitalization in individuals over the age of 65, with mortality ranging from 4% to 10%) and in fact, the severity and clinical outcome are determined by the complex interaction between the different factors, including patient comorbidities Table 6.

The diagnosis of AHF presupposes initial contact with the healthcare professional, to promptly identify the clinical signs, also with the aid of instruments, such as the electrocardiogram, echocardiography (heart-lung), and chest radiography (in the latter case, especially, if NP test is not available). Then if the diagnosis is uncertain, plasma NP levels (BNP or NT-proBNP or MR-proANP) should be measured; in fact, normal NP concentrations make the diagnosis of AHF unlikely (BNP < 100 pg/ml, NT-proBNP < 300 pg/ml and MR-proANP < 120 pg/ml) Table 7.

The clinical management of the patient with AHF can be divided into three phases (pre-hospital, in-hospital, and

pre-discharge), which have different objectives and require different approaches Table 8.

Four major clinical presentations can be described with possible overlaps between them [2,3]:

1. **Acute decompensated heart failure:** Acute decompensated heart failure (ADHF) is the most common form of AHF, accounting for 50-70% of presentations. It usually occurs in patients with a history of heart failure and previous cardiac dysfunction. Distinct from the acute pulmonary edema phenotype, it has a more gradual onset, and the main alteration is progressive fluid retention responsible for systemic congestion. Sometimes, congestion is associated with hypoperfusion. The objectives of treatment are the identification of precipitants, decongestion, and in rare instances, correction of hypoperfusion Table 9.
2. **Acute pulmonary edema:** Acute pulmonary edema is related to lung congestion. Clinical criteria for acute pulmonary edema diagnosis include dyspnoea with orthopnoea, respiratory failure (hypoxemia-hypercapnia), tachypnoea, > 25 breaths/min, and increased work of breathing. Three therapies should be commenced if indicated. First, oxygen, given as continuous positive airway pressure, non-invasive positive-pressure ventilation, and/or high-flow nasal cannula, should be started. Second, i.v. diuretics should be administered, and third, i.v. vasodilators may be given if systolic BP (SBP) is high, to reduce LV afterload. In a few cases of advanced heart failure, acute pulmonary edema may be associated with low cardiac output and, in this case, inotropes and vasopressors are indicated to restore organ perfusion Table 10.
3. **Isolated right ventricular failure:** RV failure is associated with increased RV and atrial pressure and systemic congestion. RV failure may also impair LV filling, and ultimately reduce systemic cardiac output, through ventricular interdependence. Diuretics are often the first option of therapy for venous congestion. Noradrenaline and/or inotropes are indicated for low cardiac output and hemodynamic instability. Inotropes reducing cardiac filling pressures may be preferred (i.e. levosimendan, phosphodiesterase type III inhibitors). Since inotropic agents may aggravate arterial hypotension, they may be combined with norepinephrine if needed Table 11.
4. **Cardiogenic shock:** Cardiogenic shock is a syndrome due to primary cardiac dysfunction that results in inadequate cardiac output, including a state of life-threatening tissue hypoperfusion, which can result in multiorgan failure and death. The cardiac insult that causes severe impairment of cardiac performance may be acute, as a result of acute loss of myocardial tissue (acute MI, myocarditis), or may be progressive as seen in patients with chronic decompensation who may experience a decline in disease stability as a result of the natural progression of advanced heart failure and/or specific precipitants. The diagnosis of cardiogenic shock

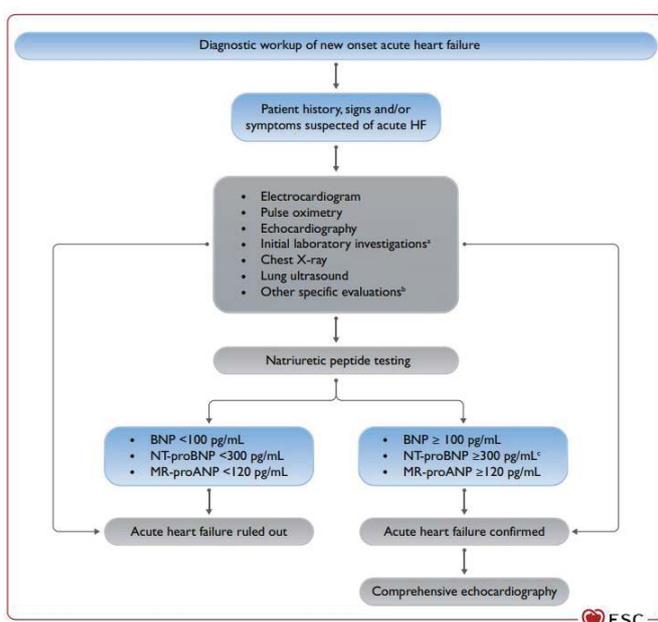


Table 6: Diagnostic workup of new-onset acute heart failure [2].



Exam	Time of measurement	Possible findings	Diagnostic value for AHF	Indication
ECG	Admission, during hospitalization, <sup>4b</sup> pre-discharge	Arrhythmias, myocardial ischaemia	Exclusion of ACS or arrhythmias	Recommended
Chest-X ray	Admission, during hospitalization <sup>a</sup>	Congestion, lung infection	Confirmatory	May be considered
LUS	Admission, during hospitalization, <sup>a</sup> pre-discharge	Congestion	Confirmatory	May be considered
Echocardiography	Admission, during hospitalization, <sup>a</sup> pre-discharge	Congestion, cardiac dysfunction, mechanical causes	Major	Recommended
Natriuretic peptides (BNP, NT-proBNP, MR-proANP)	Admission, pre-discharge	Congestion	High negative predictive value	Recommended
Serum troponin	Admission	Myocardial injury	Exclusion of ACS	Recommended
Serum creatinine	Admission, during hospitalization, <sup>a</sup> pre-discharge	Renal dysfunction	None	Recommended for prognostic assessment
Serum electrolytes (sodium, potassium, chloride)	Admission, during hospitalization, <sup>a</sup> pre-discharge	Electrolyte disorders	None	Recommended for prognostic assessment and treatment
Iron status (transferrin, ferritin)	Pre-discharge	Iron depletion	None	Recommended for prognostic assessment and treatment
TSH	Admission	Hypo- hyperthyroidism	None	Recommended when hypo- hyperthyroidism is suspected
D-dimer	Admission	Pulmonary embolism	Useful to exclude pulmonary embolism	Recommended when pulmonary embolism is suspected
Procalcitonin	Admission	Pneumonia	Useful for diagnosis of pneumonia	May be done when pneumonia is suspected
Lactate	Admission, during hospitalization <sup>a</sup>	Lactic acidosis	Useful to assess perfusion status	Recommended when peripheral hypoperfusion is suspected
Pulse oximetry and arterial blood gas analysis	Admission, during hospitalization <sup>a</sup>	Respiratory failure	Useful to assess respiratory function	Recommended when respiratory failure is suspected

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Table 7: Exams in acute heart failure [2].

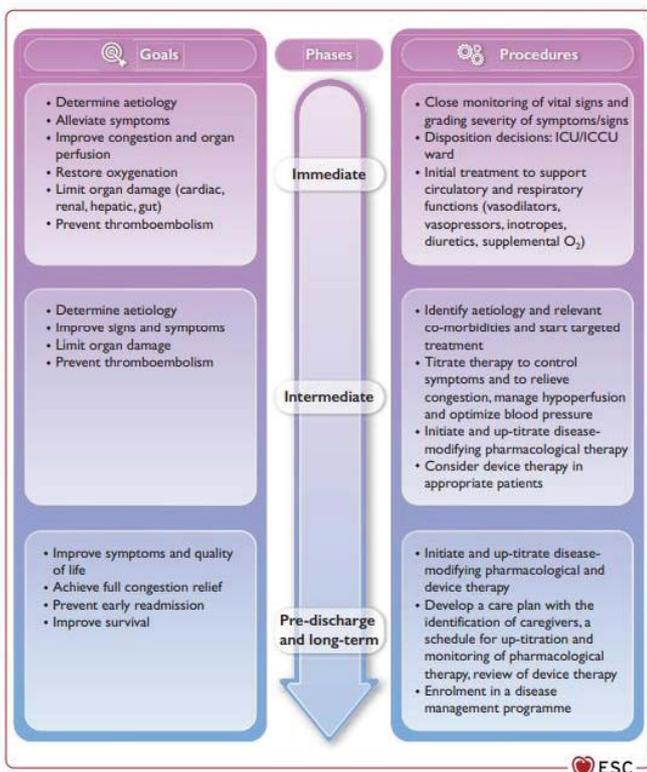


Table 8: Stages of management of patients with acute heart failure [2].

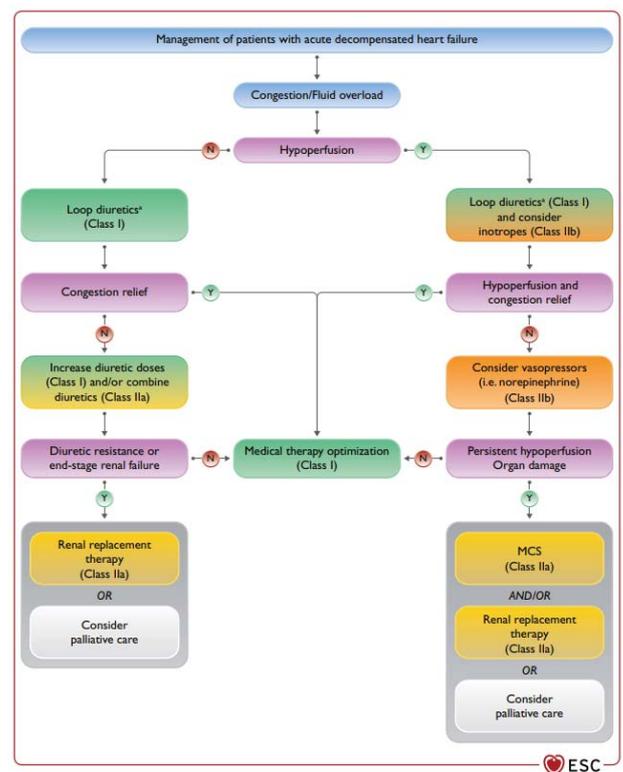


Table 9: Management of acute decompensated heart failure [2].

requires the presence of clinical signs of hypoperfusion, such as cold sweaty extremities, oliguria, mental confusion, dizziness, and reduced pulse pressure. In addition, biochemical manifestations of hypoperfusion, elevated serum creatinine, metabolic acidosis, and

elevated serum lactate are present and reflect tissue hypoxia and alterations in cellular metabolism leading to organ dysfunction. Of note, hypoperfusion is not always accompanied by hypotension, as the pressure can be preserved by compensatory vasoconstriction

(with/without pressor agents), albeit at the cost of impaired tissue perfusion and oxygenation Tables 12-14.

In the prehospital setting, patients with acute heart failure should benefit from noninvasive monitoring, including pulse

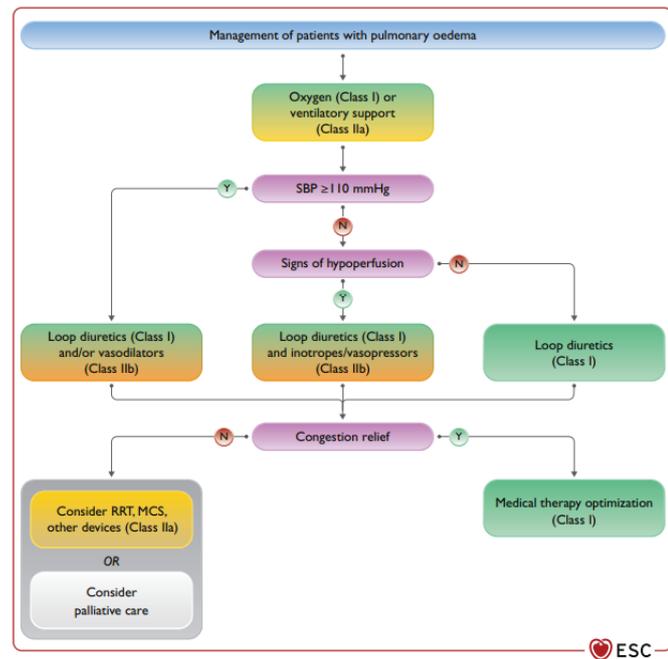


Table 10: Management of pulmonary edema [2].

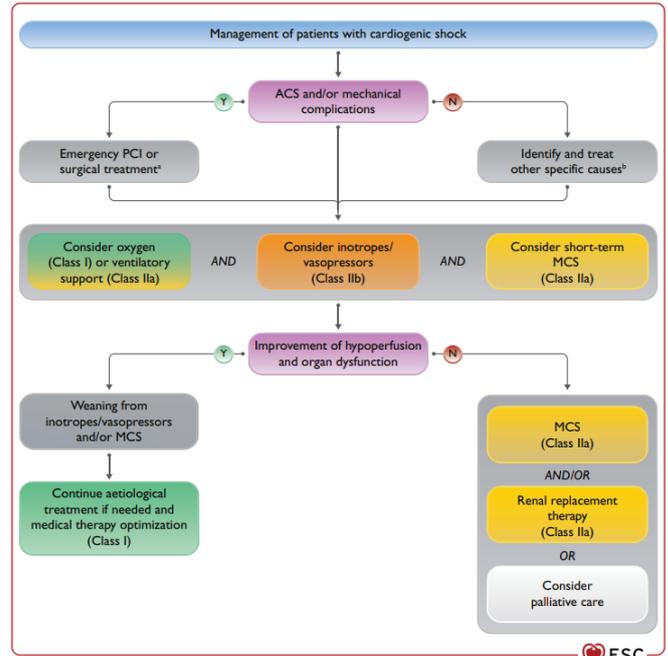


Table 12: Management of cardiogenic shock [2].

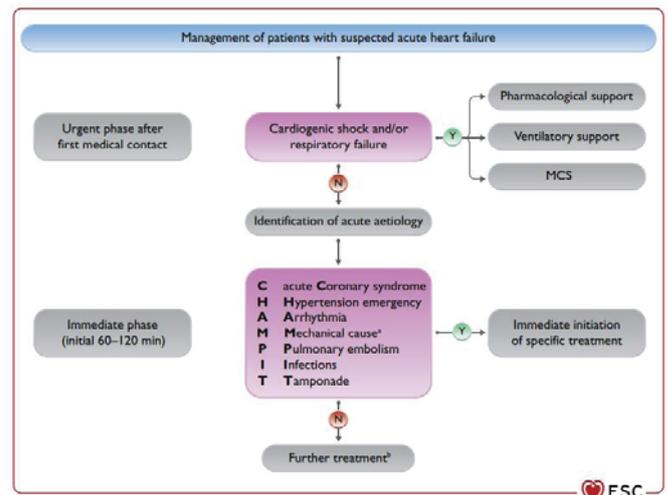


Table 13: Management of patients with suspected acute heart failure [2].

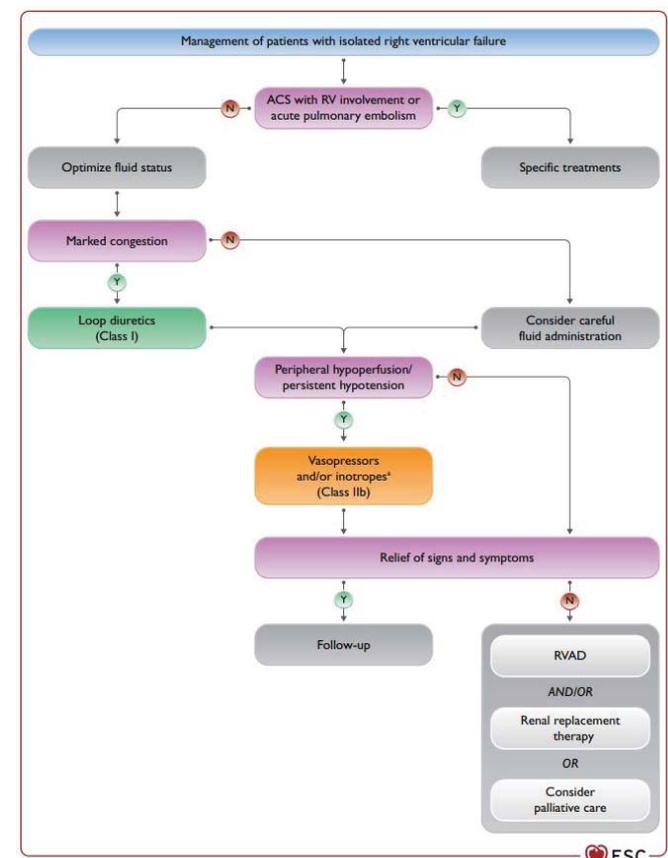


Table 11: Management of right ventricular failure [2].

oximetry, blood pressure, heart rate, respiratory rate, and a continuous ECG, triggered within minutes of patient contact and in the ambulance if possible. Oxygen therapy can be administered based on clinical judgment, while the search for specific causes (which include hypertension, arrhythmias, valve regurgitation, pulmonary embolism, and infections) must be the starting point to correctly determine the specific therapy [2,3].

1. **Oxygen therapy and/or ventilatory support:** In acute heart failure, oxygen should not be used routinely in nonhypoxemic patients, as it causes vasoconstriction and a reduction in cardiac output. Oxygen therapy is recommended in patients with acute heart failure and > 25 breaths/min, SpO<sub>2</sub> < 90%, or PaO<sub>2</sub> < 60 mmHg (to correct hypoxemia). During oxygen therapy, acid-base balance and SpO<sub>2</sub> should be monitored. Noninvasive



	Acute decompensated heart failure	Acute pulmonary oedema	Isolated right ventricular failure	Cardiogenic shock
<b>Main mechanisms</b>	LV dysfunction Sodium and water renal retention	Increased afterload and/or predominant LV diastolic dysfunction Valvular heart disease	RV dysfunction and/or pre-capillary pulmonary hypertension	Severe cardiac dysfunction
<b>Main cause of symptoms</b>	Fluid accumulation, increased intraventricular pressure	Fluid redistribution to the lungs and acute respiratory failure	Increased central venous pressure and often systemic hypoperfusion	Systemic hypoperfusion
<b>Onset</b>	Gradual (days)	Rapid (hours)	Gradual or rapid	Gradual or rapid
<b>Main haemodynamic abnormalities</b>	Increased LVEDP and PCWP <sup>a</sup> Low or normal cardiac output Normal to low SBP	Increased LVEDP and PCWP <sup>a</sup> Normal cardiac output Normal to high SBP	Increased RVEDP Low cardiac output Low SBP	Increased LVEDP and PCWP <sup>a</sup> Low cardiac output Low SBP
<b>Main clinical presentations<sup>1,446</sup></b>	Wet and warm OR Dry and cold	Wet and warm <sup>b</sup>	Dry and cold OR Wet and cold	Wet and cold
<b>Main treatment</b>	Diuretics Inotropic agents/vasopressors (if peripheral hypoperfusion/hypotension) Short-term MCS or RRT if needed	Diuretics Vasodilators <sup>b</sup>	Diuretics for peripheral congestion Inotropic agents/vasopressors (if peripheral hypoperfusion/hypotension) Short-term MCS or RRT if needed	Inotropic agents/vasopressors Short-term MCS RRT

LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; MCS = mechanical circulatory support; PCWP = pulmonary capillary wedge pressure; RV = right ventricular; RVEDP = right ventricular end-diastolic pressure; RRT = renal replacement therapy; SBP = systolic blood pressure.

<sup>a</sup>May be normal with low cardiac output.

<sup>b</sup>Wet and cold profile with need of inotropes and/or vasopressors may rarely occur.

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**Table 14:** Clinical presentations of acute heart failure [2].

positive pressure ventilation, either continuous positive airway pressure or pressure support, improves respiratory failure, increases oxygenation and pH, and decreases partial pressure of carbon dioxide (pCO<sub>2</sub>) and work of breathing. The fraction of inspired oxygen (FiO<sub>2</sub>) should be increased to 100%, if necessary, based on the level of oxygen saturation.

2. **Diuretics:** Intravenous diuretics are the cornerstone of treatment for AHF. They increase renal excretion of salt and water and are indicated for the treatment of fluid overload and congestion in most patients with AHF. Loop diuretics are commonly used because of their rapid onset of action and efficacy. However, data defining their optimal dosage, timing, and method of administration are limited. Diuretic treatment should be initiated with an initial intravenous dose of furosemide or an equivalent dose of bumetanide or torasemide, corresponding to 12 times the daily oral dose taken by the patient before admission. If the patient was not taking oral diuretics, a starting dose of 2040 mg furosemide or a bolus of 1020 mg intravenous torasemide may be used. Furosemide can be administered in 23 daily boluses or as a continuous infusion. Single bolus daily administrations are not recommended because of the possibility of post-dose sodium retention. With continuous infusion, a loading dose may be used to reach a steady state sooner. The diuretic response should be assessed shortly after initiation of diuretic therapy and can be evaluated by performing a urine sodium content measurement after 2 to 6 hours and/or measuring hourly urine output. A satisfactory diuretic response can be defined as a urine sodium content > 5070 mEq/L at 2 hours. If the diuretic response is inadequate, the

dose of intravenous loop diuretic may be doubled, with further evaluation of the diuretic response; if the diuretic response remains inadequate, concomitant administration of other diuretics acting at different sites, i.e., thiazides or metolazone or acetazolamide, may be considered. However, this combination requires careful monitoring of serum electrolytes and renal function. This strategy, based on the early and frequent assessment of diuretic response, allows treatment to be initiated with relatively low doses of loop diuretics, with frequent dose adjustments that may be less likely to cause dehydration and increased serum creatinine. The dose of loop diuretic should be progressively decreased when a significant negative fluid balance has been achieved. However, it should be emphasized that this algorithm is entirely based on expert opinion to date. Transition to oral treatment should be initiated when the patient's clinical condition is stable. It is recommended that after relief of congestion is achieved, oral loop diuretics be continued at the lowest possible dose to avoid congestion. Care must also be taken to prevent patients from being discharged from the hospital with persistent congestion, as this is a major predictor of increased deaths and rehospitalizations. Thus, care must be taken to achieve adequate decongestion and establish an appropriate long-term diuretic dose before discharge Table 15.

3. **Vasodilators:** Intravenous vasodilators, i.e., nitrates or nitroprusside, dilate venous and arterial vessels leading to a reduced venous return to the heart, reduced congestion, reduced afterload, increased stroke volume, and subsequent relief of symptoms. Nitrates act primarily on peripheral veins, whereas nitroprusside is

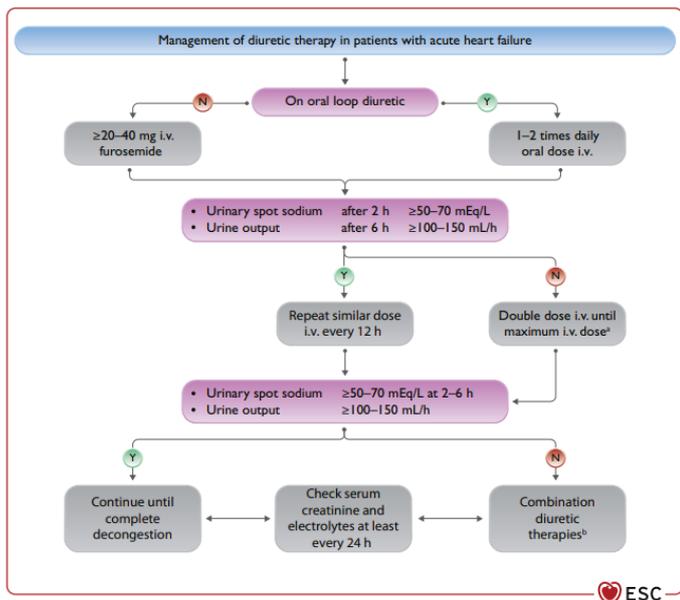


Table 15: Diuretic therapy (furosemide) in acute heart failure [2].

more of a balanced arterial and venous dilator. Because of their mechanisms of action, intravenous vasodilators may be more effective than diuretics in those patients whose acute pulmonary edema is caused by increased afterload and fluid redistribution to the lungs in the absence of minimal fluid accumulation. However, two recent randomized trials comparing usual care with early intensive and sustained vasodilation did not demonstrate a beneficial effect of intravenous vasodilators compared with high-dose diuretics. Thus, to date, no recommendation can be made in favor of a regimen based on vasodilator treatment over usual care. Intravenous vasodilators may be considered to relieve the symptoms of acute heart failure when blood pressure is > 110 mmHg. Nitrates are generally administered with an initial bolus followed by a continuous infusion. However, they can also be administered as repeated boluses. Nitroglycerin may be administered as 12-mg boluses in severely hypertensive patients with acute pulmonary edema. Care must be taken to avoid hypotension due to an excessive decrease in preload and afterload. For this reason, they should be used with extreme caution in patients with ventricular hypertrophy and/or severe aortic stenosis.

- Inotropes:** Inotropes are still necessary for the treatment of patients with low cardiac output and hypotension. They should be reserved for patients with left ventricular systolic dysfunction, low cardiac output, and low blood pressure (e.g., < 90 mmHg) resulting in poor vital organ perfusion. However, they should be used with caution by starting at low doses and increasing them with close monitoring. Inotropes, especially those with adrenergic mechanisms, may cause sinus tachycardia, increase ventricular rate in patients with atrial fibrillation, may induce myocardial ischemia and arrhythmias, and increase mortality. Levosimendan or phosphodiesterase type 3 inhibitors may be preferred to dobutamine for

patients on beta-blocker therapy because they act through independent mechanisms. Excessive peripheral vasodilation and hypotension may be major limitations of phosphodiesterase type 3 inhibitors or levosimendan, especially when given at high doses and/or when initiated with a bolus dose.

- Vasopressors:** La noradrenalina è sicuramente uno dei farmaci con maggiore azione vasoconstrictiva arteriosa periferica, ed è la scelta primaria nei pazienti con grave ipotensione, al fine di aumentare la perfusione agli organi vitali; tuttavia, però, questo determina un aumento del post-carico ventricolare sinistro, e pertanto è preferibile abbinare la norepinefrina e gli agenti inotropi, specialmente nei pazienti con insufficienza cardiaca avanzata e shock cardiogeno. Alcuni studi, sebbene con limitazioni, supportano l'uso della noradrenalina come prima scelta, rispetto alla dopamina (che aumenta gli episodi aritmici) o all'epinefrina (che aumenta gli episodi di shock refrattario e acidosi lattica) Table 16.
- Opiates:** Opioids relieve dyspnea and anxiety. They can be used as sedative agents during noninvasive positive pressure ventilation to improve patient adaptation. Dose-dependent side effects include nausea, hypotension, bradycardia, and respiratory depression. Retrospective analyses suggest that morphine administration is associated with increased frequency of mechanical ventilation, prolonged hospitalization, more intensive care unit admissions, and increased mortality. Therefore, routine use of opioids in acute heart failure is not recommended, although it may be considered in selected patients, particularly in severe/intractable pain or anxiety or as part of palliation.
- Digoxin:** Digoxin should be considered in patients with AF with a rapid ventricular rate (> 110 b.p.m.) despite beta-blockers. It can be administered in boluses of 0.25-0.5 mg IV if not used previously. However, in patients with comorbidities or other factors affecting digoxin metabolism (including other drugs) and/or in the elderly, the maintenance dose may be difficult to estimate theoretically, and measurements of serum digoxin concentrations should be performed.

Drug	Infusion rate
Dobutamine	2–20 µg/kg/min (beta+)
Dopamine	3–5 µg/kg/min; inotropic (beta+) >5 µg/kg/min: inotropic (beta+), vasopressor (alpha+)
Milrinone	0.375–0.75 µg/kg/min
Enoximone	5–20 µg/kg/min
Levosimendan	0.1 µg/kg/min, which can be decreased to 0.05 or increased to 0.2 µg/kg/min
Norepinephrine	0.2–1.0 µg/kg/min
Epinephrine	0.05–0.5 µg/kg/min

Table 16: Inotropes and/or vasopressors used to treat acute heart failure [2].

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8. **Thromboembolism prophylaxis:** Prophylaxis of thromboembolism with heparin (eg, low molecular weight heparin) or another anticoagulant is recommended unless contraindicated or unnecessary (because of existing treatment with oral anticoagulants).
9. **Short-term mechanical circulatory support:** In patients presenting with cardiogenic shock, short-term mechanical circulatory support may be necessary to increase cardiac output and support end-organ perfusion. High-quality evidence regarding outcomes, however, remains scarce. Therefore, the unselected use of mechanical circulatory supports in patients with cardiogenic shock is unsupported and these require specialized multidisciplinary expertise for implantation and management, similar to that outlined for advanced cardiology centers Table 17.

### Objectives

The present work intends to focus on the critical aspects related to the diagnostic profiles of heart failure, according to the most recent guidelines, to highlight possible criticalities and gaps not taken into account so far.

Based on what was introduced in the first paragraph of this

paper, the research group states here the primary objective of expanding the indications contained in the ESC 2021 with the results of the last year on the subject of treatment profiles, to facilitate a better understanding of the overall clinical picture and contribute to the next edition of the guidelines. Also, the ESC 2021 guidelines, as we will see, have definitively clarified the role of Heart Failure with Mid-Range Ejection Fraction (confirming the independence and nosographic importance) and the role of NT-proBNP (confirming the use and clinical utility). Excluded utility instead for the B-type natriuretic peptide (BNP).

### Materials and method

Systematic literature review: we conducted a systematic literature review, considering (inclusion criterion) articles published in the English language from January 1, 2021, to September 30, 2022, that is, all papers that were not considered by ESC 2021 on the topic of heart failure, and therefore all papers before the period and those not related to acute heart failure were excluded (exclusion criterion), to develop a search that could help us find answers to the questions in the objectives section. We performed the literature search in PubMed/MedLine, Web on Science, and Cochrane archive Table 18.

**Table 17:** Therapeutic profiles in acute heart failure.

Treatment	Criteria	Motivation	Potential exclusion assumptions
Oxygen therapy and ventilatory support	<ul style="list-style-type: none"> <li>✓ 25 breaths/min</li> <li>✓ SpO2 &lt; 90%</li> <li>✓ &lt; 60 mmHg</li> </ul>	Correcting hypoxemia	Excessive venous return
Diuretics	<ul style="list-style-type: none"> <li>✓ Venous Hypertension</li> <li>✓ Edema</li> <li>✓ Congestion</li> </ul>	Treatment of fluid overload and congestion	<ul style="list-style-type: none"> <li>✓ Kidney failure</li> <li>✓ Urinary tract obstructions</li> <li>✓ Hypotension</li> <li>✓ Coronary and/or cerebral stenosis</li> <li>✓ Gout</li> <li>✓ Diabetes</li> <li>✓ Hepatopathies</li> </ul>
Vasodilators	Venous Hypertension	Reduction of venous return and intravenous vasodilation. They are more effective than diuretics in those patients whose acute pulmonary edema is caused by increased afterload and redistribution of fluid to the lungs in the absence of minimal fluid accumulation. Care must be taken to avoid hypotension due to an excessive decrease in preload and afterload.	<ul style="list-style-type: none"> <li>✓ Hypotension</li> <li>✓ Ventricular hypertrophy</li> <li>✓ Severe aortic stenosis</li> </ul>
Inotropes	Hypotension as a result of left ventricular systolic dysfunction, low cardiac output, and low blood pressure (e.g., <90 mmHg) resulting in poor perfusion of vital organs	Treatment of low cardiac output and hypotension.	May cause sinus tachycardia, increase ventricular rate in patients with atrial fibrillation, may induce myocardial ischemia and arrhythmias, and increase mortality
Vasopressors	Venous Hypotension	Treatment of hypotension. A combination of norepinephrine and inotropic agents may be considered, especially in patients with advanced heart failure and cardiogenic shock	Excessive increase in left ventricular afterload
Opiates	Dyspnea and anxiety	Relieve symptoms of shortness of breath and anxiety	<ul style="list-style-type: none"> <li>✓ Respiratory Depressions</li> <li>✓ Bradycardia</li> <li>✓ Nausea</li> </ul>
Digoxin	Atrial fibrillation with rapid ventricular rate despite beta-blockers	Treatment of atrial fibrillation	<ul style="list-style-type: none"> <li>✓ Cardiac conduction block</li> <li>✓ Hypokalemia</li> <li>✓ Supraventricular arrhythmias, ventricular tachycardia, and ventricular fibrillation</li> <li>✓ Obstructive hypertrophic cardiomyopathy</li> </ul>

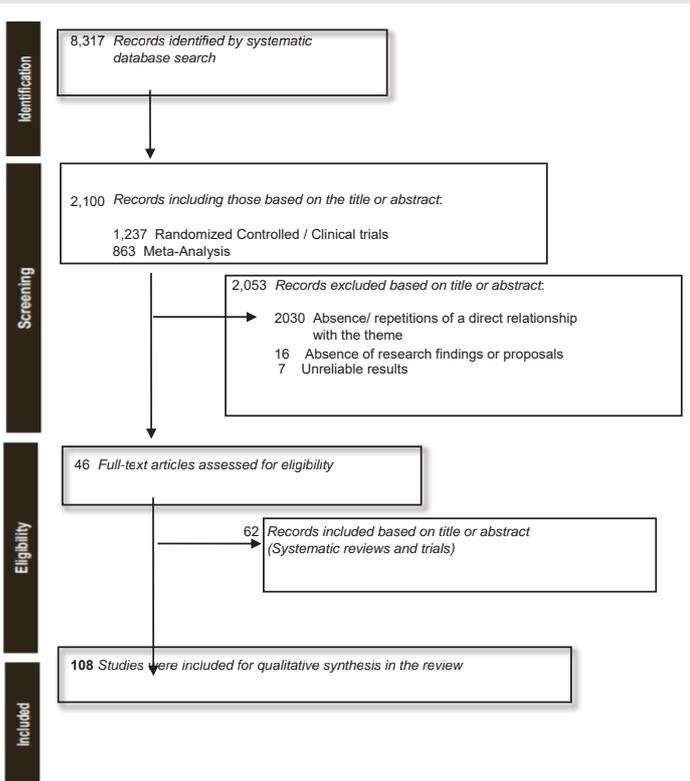


Table 18: PRISMA review.

## Results

### Introduction

Our search strategy retrieved 8,317 articles. We excluded books and papers, meta-analyses, reviews, and systematic reviews and selected only 46 studies most significant about the clinical trial and randomized controlled trial. An additional 62 manuscripts were then selected to complete related clinical profiles.

### New treatments and discoveries in heart failure

In particular, the following profiles emerge from the selected studies:

#### 1. Relative to therapies in heart failure patients

- In patients with diabetes and recent worsening of heart failure, therapy with sotagliflozin, initiated before or shortly after discharge, resulted in significantly fewer total deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure compared with placebo [4].
- Apabetalone treatment was associated with fewer hospitalizations for heart failure in patients with type 2 diabetes and recent acute coronary syndrome [5].
- Empagliflozin reduces the risk of hospitalization for heart failure in patients with type 2 diabetes and cardiovascular disease. We sought to elucidate the effect of empagliflozin as an add-on therapy on decongestion and renal function in patients with type 2 diabetes

admitted for acute decompensated heart failure. Empagliflozin achieved effective decongestion without an increased risk of worsening renal function as an add-on therapy in patients with type 2 diabetes with acute decompensated heart failure [6].

- Urinary sodium (UNa<sup>+</sup>) has emerged as a useful biomarker of poor clinical outcomes in acute heart failure (AHF). Here, we sought to evaluate: a) the usefulness of a single early determination of UNa<sup>+</sup> for predicting adverse outcomes in patients with AHF and renal dysfunction, and b) whether the change in UNa<sup>+</sup> at 24 hours ( $\Delta$ UNa<sub>24h</sub>) adds any additional prognostic information over baseline values. In patients with AHF and renal dysfunction, a single early determination of UNa<sup>+</sup>  $\leq$  50 mmol/L identifies patients with a higher risk of all-cause mortality and readmission. The  $\Delta$ UNa<sub>24h</sub> adds prognostic information over baseline values only when UNa<sup>+</sup> at admission is  $\leq$  50 mmol/L [7].
- Although elevated IL-6 levels were associated with higher all-cause mortality in acute HF, no independent association with this outcome was identified at baseline or 30-day measurements. In contrast with prior reports, we did not observe any impact of nesiritide over placebo on serial IL-6 levels [8].
- A study aimed to investigate the effects of baseline treatment for heart failure and sequential treatment with rh-brain natriuretic peptide (rhBNP) alone or the combination of rhBNP and sacubitril/valsartan. Cardiac structure, pulmonary artery pressure, inflammation, and oxidative stress in patients with acute heart failure were evaluated. Patients were therefore divided into 3 groups of 100 patients per group: the standard treatment group (treated with an angiotensin-converting enzyme inhibitor, a  $\beta$ -receptor blocker, and a corticosteroid antagonist), the rhBNP group (baseline treatment combined with rhBNP), and the sequential treatment group (baseline heart failure treatment combined with rhBNP followed by sacubitril/valsartan). Changes in NT-pro brain natriuretic peptide (BNP) levels, cardiac troponin T (cTnT) levels, cardiac structure, pulmonary artery pressure, and levels of inflammatory and oxidative stress factors were compared between the 3 groups at 1, 4, 12, and 36 weeks after treatment. The sequential treatment group showed superior results compared with the standard treatment group and the rhBNP group in terms of left atrium diameter, left ventricular end-diastolic volume, left ventricular ejection fraction, pulmonary artery pressure, NT-proBNP levels, and cTnT levels, which respond to damage to the structure of the heart and myocardium. This finding may be related to decreased levels of inflammatory factors and correction of the oxidative stress imbalance. Sacubitril/valsartan significantly reduced serum levels of inflammatory factors in patients with acute heart failure while decreasing levels of oxidant factors and increasing levels of antioxidant factors. These changes may be



one explanation for the improved cardiac structure and pulmonary artery pressure observed in the sequential treatment group [9].

- f) Treatment with sodium–glucose co–transporter–2 inhibitors induces an initial 3–5 ml/min/1.73 m<sup>2</sup> decline in the estimated glomerular filtration rate (eGFR). Although considered to be of hemodynamic origin and largely reversible, this ‘eGFR dip’ may cause concern in clinical practice, which highlights the need to better understand its incidence and clinical implications. In this post hoc analysis of the EMPA–REG OUTCOME trial, 6,668 participants randomized to empagliflozin 10 mg, 25 mg, or placebo with eGFR available at baseline and week four were categorized by initial eGFR change into three groups; over 10% decline (‘eGFR dipper’), over 0 and up to 10% decline (‘eGFR intermediate’), no eGFR decline (‘eGFR non–dipper’). Baseline characteristics of ‘eGFR intermediate’ and ‘eGFR non–dipper’ were generally comparable. An initial ‘eGFR dip’ was observed in 28.3% of empagliflozin versus 13.4% of placebo–treated participants; odds ratio 2.7 [95% Confidence Interval 2.3–3.0]. In multivariate logistic regression, diuretic use and higher KDIGO risk category at baseline were independently predictive of an ‘eGFR dip’ in empagliflozin versus placebo. The safety and beneficial treatment effects of empagliflozin on cardiovascular and kidney outcomes were consistent across subgroups based on these predictive factors. The initial ‘eGFR dip’ did not have a major impact on the treatment effect of empagliflozin on subsequent cardiovascular death, hospitalization for heart failure, and incident or worsening kidney disease. Thus, patients with type 2 diabetes with more advanced kidney disease and/or on diuretic therapy were more likely to experience an ‘eGFR dip’ of over 10% with empagliflozin, but the reduction in cardiovascular and kidney outcomes was not relevantly modified by such ‘eGFR dip.’ [10].
- g) Adding hydrochlorothiazide to the usual treatment of patients with acute decompensated heart failure did not cause a significant difference in daily body weight reduction compared to placebo. In an analysis adjusted to the dose of intravenous furosemide, adding HCTZ 50 mg to furosemide resulted in a significant synergistic effect on weight loss [11].
- h) Hospitalization for acute decompensated heart failure (ADHF) remains a major source of morbidity and mortality. The current study aimed to investigate the feasibility, safety, and efficacy of outpatient furosemide intravenous (IV) infusion following hospitalization for ADHF. The use of a standardized protocol of outpatient IV furosemide infusion for one month following hospitalization for ADHF was found to be safe and efficacious in reducing 30–day re–hospitalization [12].
- i) This study aimed to explore the rapid effects of dapagliflozin in heart failure with reduced ejection fraction (HFrEF). After 2 weeks, while multiple parameters

supported BP reduction and haemoconcentration with dapagliflozin, reduction in cardiac filling pressure, lung water, and functional improvement were not shown. Reduced ventricular ectopic burden suggests an early antiarrhythmic benefit. The small increase in troponin T and the reduction in the reactive hyperemia index warrant further mechanistic exploration in this treatment of proven mortality benefits in HFrEF [13].

- j) We sought to compare the effects of furosemide + hypertonic saline solution (HSS) treatment in patients with acute decompensated heart failure in comparison with furosemide alone and the response in a compensated state after an acute saline load about serum levels of heart failure biomarkers. Our findings concerning a comparable degree of reduction in the serum levels of three cardinal biomarkers indicate that a reduction in serum heart failure markers is not linked to a higher degree of congestion relief with a more rapid achievement of a clinical compensation state. This issue may have possible benefits on clinical practice concerning its therapeutic effects over and beyond the simple amelioration of clinical congestion signs and symptoms. Nevertheless, our findings of higher delta values after treatment with i.v. furosemide plus HSS indicates a possible higher efficacy using modulation of the stretching and fibrosis mechanisms [14].
- k) Associations between growth differentiation factor–15 (GDF–15), cardiovascular outcomes, and exercise capacity among patients with a recent hospitalization for heart failure (HHF) and heart failure with reduced ejection fraction (HFrEF) are unknown. We utilized data from the ‘Functional Impact of GLP–1 for Heart Failure Treatment (FIGHT) study to address these knowledge gaps. An increase in GDF–15 over 30 days among patients in HFrEF was independently associated with an increased risk of cardiovascular events and declining exercise capacity. These results support the value of longitudinal GDF–15 trajectory in informing the risk of heart failure disease progression [15].
- l) In older patients with hypertension, intensive treatment with a systolic blood–pressure target of 110 to less than 130 mm Hg resulted in a lower incidence of cardiovascular events than standard treatment with a target of 130 to less than 150 mm Hg [16].
- m) In patients stabilized during hospitalization for acute decompensated heart failure (HF), initiation of sacubitril/valsartan compared with enalapril decreased the risk of cardiovascular death or rehospitalization for HF without increasing the risk of adverse events. It is unknown whether potentially high–risk subpopulations have a similar risk–benefit profile. In high–risk subpopulations admitted for acute decompensated HF, treatment with sacubitril/valsartan after initial stabilization conferred a consistent reduction in cardiovascular death or rehospitalization for HF and was well tolerated [17].

n) Dapagliflozin administration in T2D (patients with type 2 diabetes) resulted in a both acute and chronic reduction in systolic blood pressure, a reduction in vasoconstrictors, and an increase in vasodilators. These changes may potentially contribute to its antihypertensive effects and its benefits in congestive cardiac failure [18].

### 2. Relative to therapies in patients with cardiorenal syndrome

In patients with acute heart failure, empagliflozin increased fractional glucose excretion and plasma osmolality, without affecting fractional sodium excretion or urine osmolality and caused a temporary decline in estimated glomerular filtration rate. This suggests that empagliflozin stimulates osmotic diuresis through increased glycosuria rather than natriuresis in patients with acute heart failure [19].

Ultrafiltration therapy is safe and can improve diuretic sensitivity in heart failure patients with reduced ejection fraction and diuretic resistance [20].

Although the reno-protective effects of sodium-glucose cotransporter 2 inhibitors are known in patients with heart failure or type 2 diabetes mellitus (T2DM), this effect has not been confirmed in patients with acute myocardial infarction (AMI). Empagliflozin prevented kidney function decline in patients with AMI and T2DM, especially those with baseline eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup>. Early administration of sodium-glucose cotransporter 2 inhibitors in these patients is considered desirable for renal protection [21].

### 3. Relative to psychological therapies in patients with heart failure

a) Standard treatment of heart failure includes pharmacotherapy and cardiac device implantation. However, supportive approaches in the management of dyspnea in heart failure are limited. A parallel-group, unblinded, randomized controlled trial of a single 20-minute mindful breathing session compared with standard care alone among patients hospitalized for moderate to severe dyspnea due to acute decompensated heart failure demonstrated a statistically significant reduction in dyspnea in the intervention group compared with the control group at minute 20, and therefore according to these results, it can be argued that a single 20-minute mindful breathing session is effective in reducing dyspnea for patients in acute decompensated heart failure [22].

b) Patients with chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) are at high risk of readmission after hospital discharge. There is conflicting evidence however on whether timely follow-up with a primary care provider reduces that risk. The objective of this study is to understand the perspectives of patients with COPD and CHF, and their caregivers, on the role of primary care provider follow-up after

hospital discharge. Patients and caregivers valued in-person follow-up with their primary care provider the following discharge from the hospital because of the trust established through pre-existing longitudinal relationships. Our results suggest policymakers should focus on improving rates of primary care provider attachment and systems supporting informational continuity [23].

### 4. Relative to therapies in patients with myocardial infarction

a) For patients with clinically defined heart failure following acute myocardial infarction, ramipril results in a sustained survival benefit and is associated with an extension of the life of up to 14.5 months for, on average, 13 months of treatment duration [24].

b) Myocardial infarction with non-obstructive coronary arteries (MINOCA) is common and occurs in 6-8% of all patients fulfilling the diagnostic criteria for acute myocardial infarction (AMI). This work describes the rationale behind the trial 'Randomized Evaluation of Beta Blocker and ACE-Inhibitor/Angiotensin Receptor Blocker Treatment (ACEI/ARB) of MINOCA patients' (MINOCA-BAT) and the need to improve the secondary preventive treatment of MINOCA patients. METHODS: MINOCA-BAT is a registry-based, randomized, parallel, open-label, multicenter trial with a 2:2 factorial design. The primary aim is to determine whether oral beta blockade compared with no oral beta-blockade, and ACEI/ARB compared with no ACEI/ARB, reduce the composite endpoint of death of any cause, readmission because of AMI, ischemic stroke, or heart failure in patients discharged after MINOCA without clinical signs of heart failure and with left ventricular ejection fraction  $\geq 40\%$ . A total of 3500 patients will be randomized into four groups; e.g. ACEI/ARB and beta blocker, beta blocker only, ACEI/ARB only, and neither ACEI/ARB nor beta blocker, and followed for a mean of 4 years. While patients with MINOCA have an increased risk of serious cardiovascular events and death, whether conventional secondary preventive therapies are beneficial has not been assessed in randomized trials. There is a limited basis for guideline recommendations in MINOCA. Furthermore, studies of routine clinical practice suggest that the use of secondary prevention therapies in MINOCA varies considerably. Thus results from this trial may influence future treatment strategies and guidelines specific to MINOCA patients [25].

c) In patients with symptomatic heart failure, sacubitril-valsartan has been found to reduce the risk of hospitalization and death from cardiovascular causes more effectively than an angiotensin-converting enzyme inhibitor. Trials comparing the effects of these drugs in patients with acute myocardial infarction have been lacking. Sacubitril-valsartan was not associated with a significantly lower incidence of death from cardiovascular causes or incident heart failure



than ramipril among patients with acute myocardial infarction [26].

- d) In patients with coronary heart disease (CHD), atrial fibrillation (AF) is associated with increased morbidity and mortality. We investigated the associations between clinical risk factors and biomarkers with incident AF in patients with CHD. In patients with optimally treated CHD, the incidence of new AF was 1.2% per year. Age, NT-proBNP as a marker of impaired cardiac function, and BMI were the strongest factors, independently and consistently associated with incident AF. Male sex and low physical activity may also contribute to the risk of AF in patients with CHD [27].
- e) Innate lymphoid cells type 2 (ILC2s) play critical homeostatic functions in peripheral tissues. ILC2s reside in perivascular niches and limit atherosclerosis development. ILC2s promote cardiac healing and improve the recovery of heart function after Myocardial Infarction (MI) in mice. Activation of ILC2 using low-dose IL-2 could be a novel therapeutic strategy to promote a reparative response after MI [28].
- f) Thyroid dysfunction contributes to adverse events in several types of cardiovascular diseases. The present study aims to determine whether thyroid status is associated with the prognosis of patients with acute myocardial infarction (AMI). Compared with euthyroid status, hypothyroid status has an independent predicting value for adverse cardiovascular events in AMI patients. Further investigations are required to illustrate whether treatment of thyroid dysfunction could improve the prognosis of AMI patients [29].
- g) Alprostadil can effectively dilate blood vessels, improve cardiac microcirculation, and reduce cardiac load. Tanshinone IIa injection can protect against atherosclerosis and reduce myocardial oxygen consumption. However, the effects of alprostadil combined with tanshinone IIa injection on microcirculation disorder, outcomes, and cardiac function in patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI) are still not fully clear. For AMI patients after PCI, alprostadil combined with tanshinone IIa injection can effectively improve microcirculation and ventricular remodeling, improve cardiac function and reduce the occurrence of MACEs. This combination can be widely used in clinical practice [30].
- h) It is unknown when to start anticoagulation after acute ischemic stroke (AIS) from atrial fibrillation (AF). Early anticoagulation may prevent recurrent infarctions but may provoke hemorrhagic transformation as AF strokes are typically larger and hemorrhagic transformation-prone. Later anticoagulation may prevent hemorrhagic transformation but increases the risk of secondary stroke in this time frame. I aimed to compare early anticoagulation with apixaban in AF patients with stroke

or transient ischemic attack (TIA) versus warfarin administration at later intervals. Early initiation of anticoagulation after TIA, small-, or medium-sized AIS from AF does not appear to compromise patient safety. The potential efficacy of early initiation of anticoagulation remains to be determined from larger pivotal trials [31].

#### 5. Relative to therapies in patients with COVID-19-related issues and vaccines in general

- a) Among patients hospitalized with mild to moderate COVID-19 and who were taking ACEIs or ARBs before hospital admission, there was no significant difference in the mean number of days alive and out of the hospital for those assigned to discontinue vs. continue these medications. These findings do not support routinely discontinuing ACEIs or ARBs among patients hospitalized with mild to moderate COVID-19 if there is an indication for treatment [32].
- b) In patients with high-risk cardiovascular disease, high-dose trivalent inactivated influenza vaccine, compared with standard-dose quadrivalent inactivated influenza vaccine, did not significantly reduce all-cause mortality or cardiopulmonary hospitalizations. Influenza vaccination remains strongly recommended in this population [33].

#### 6. Relative to therapies in patients with respiratory failure

- a) Respiratory failure during an index hospitalization for acute HF was associated with increased rehospitalization and all-cause mortality. The development of respiratory failure during an acute HF admission identifies a particularly vulnerable population, which should be identified for closer monitoring [34].
- b) Sigh is a cyclic brief recruitment maneuver: previous physiologic studies showed that its use could be an interesting addition to pressure support ventilation to improve lung elastance, decrease regional heterogeneity, and increase the release of surfactant. Among hypoxemic intubated intensive care unit patients, the application of sigh was feasible and without increased risk [35].
- c) Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) are characterized by severe symptom burden and common acute worsening episodes that often require hospitalization and affect prognosis. Although many studies have shown that person-centered care (PCC) increases self-efficacy in patients with chronic conditions, studies on patients with COPD and CHF treated in primary care and the effects of PCC on the risk of hospitalization in these patients are scarce. PCC using a combined digital platform and structured telephone support seems to be an option to increase the short-term self-efficacy of people with COPD and CHF. This study adds to the

knowledge of conceptual innovations in primary care to support patients with COPD and CHF [36].

- d) In patients presenting to the ED with acute cardiogenic pulmonary edema or decompensated COPD, hCPAP was non-inferior to fCPAP and resulted in greater comfort levels and lower intubation rate [37].
- e) In patients with heart failure (HF), the exhaled concentrations of hydrogen after a breath test (a non-invasive assessment of small intestinal overgrowth) have been related to HF severity and higher risk of adverse outcomes. Indeed, two intestinal bacterial metabolites—blood Trimethylamine N-Oxide (TMAO) and butyrate—have been related to a worse prognosis in HF. However, the relationship between the exhaled concentrations of hydrogen after a breath test and these two metabolites remains unknown. Thus, in this post-hoc analysis, we sought to evaluate whether these two metabolites are associated with the exhaled concentrations of hydrogen after a breath test in patients with a recent admission for HF. We included 60 patients with a recent hospitalization for HF. Cumulative hydrogen over time was integrated into a single measurement by the area under the concentration curve (AUC-H<sub>2</sub>). A linear regression multivariable analysis was used to evaluate the associations. A 2-sided p-value < 0.05 was considered to be statistically significant. The median (p<sub>25</sub>-p<sub>75</sub>) amino-terminal pro-brain natriuretic peptide, AUC-H<sub>2</sub>, TMAO, and Butyrate were 4789 pg/ml (1956-11149), 1615 (700-2585), 0.68 (0.42-1.12), and 0.22 ± 13, respectively. After multivariate adjustment, TMAO and butyrate were significantly associated with AUC-H<sub>2</sub> (p = 0.027 and p = 0.009, respectively). For TMAO, this association was positive, and for butyrate, negative. Bacterial-origin metabolites TMAO and Butyrate were independently related to AUC-H<sub>2</sub> in patients with a recent hospitalization for acute HF [38]. These results confirm the importance of the correlation between intestinal dysbiosis and heart failure [39].
- f) Acute respiratory distress syndrome (ARDS) is an increasingly common acute respiratory failure that seriously threatens people's health. ARDS has a case fatality rate of up to 40%. ARDS is a serious threat to the life safety of patients and their quality of life, causing a huge economic burden to individuals, families, and society. ARDS has become a large worldwide public health problem. Prone position ventilation (PPV) is an important auxiliary treatment for ARDS, which could improve oxygenation. However, PPV could cause Pressure injuries (PI) and other complications easily. We found that 45° PPV could reduce the incidence of PI, but lack of robust Evidence-based medicine evidence proving its efficacy. Therefore, we designed a randomized controlled trial to evaluate the efficacy of 45° PPV in the treatment of ARDS. 45° PPV may reduce the incidence of PI and improve oxygenation in patients with ARDS, which has important value in practical application [40].

## 7. Relative to therapies in cardiological patients and osteopathic manipulations, electrical muscle stimulation and other functions

- a) Osteopathic manipulative treatment modulates both the vascular and autonomic nervous system (ANS) in healthy volunteers. However, the acute and time-course effects of the OMT on patients with an overactive ANS remain unclear. Osteopathic manipulative treatment was effective at increasing brachial blood flow and stimulating the vagal system in patients with heart failure. Moreover, vascular changes seem to precede autonomic modulation [41].
- b) Reduced aerobic capacity and deconditioning contribute to morbidity and mortality in elderly acute heart failure (AHF) patients. Electrical muscle stimulation (EMS) is a suitable alternative to exercise in AHF. However, feasibility and efficacy are unknown in a real-world setting. Changes in 6-MWTD suggest the efficacy of EMS. Whereas all tolerated EMS well, the burden of study intervention was too high and resulted in a consent rate of < 50% and high dropouts, which limit the interpretability of our data. Less demanding EMS protocols are required to evaluate the full potential of EMS in elderly AHF patients [42].
- c) Older patients who are hospitalized for acute decompensated heart failure have high rates of physical frailty, poor quality of life, delayed recovery, and frequent rehospitalizations. Interventions to address physical frailty in this population are not well established. In a diverse population of older patients who were hospitalized for acute decompensated heart failure, an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical-function domains resulted in greater improvement in physical function than usual care [43].
- d) Autonomic dysregulation in heart failure with reduced ejection fraction plays a major role in endothelial dysfunction. Low-level tragus stimulation (LLTS) is a novel, noninvasive method of autonomic modulation. Our study demonstrated the beneficial effects of acute neuromodulation on macrovascular function. Larger studies to validate these findings and understand mechanistic links are warranted [44].
- e) Deterioration of nutritional status during hospitalization in patients with chronic heart failure increases mortality. Whether nutritional support during hospitalization reduces these risks, or on the contrary, may be harmful due to an increase in salt and fluid intake, remains unclear. Among hospitalized patients with chronic heart failure at high nutritional risk, individualized nutritional support reduced the risk for mortality and major cardiovascular events compared with standard hospital food. These data support malnutrition screening upon hospital admission followed by an individualized nutritional support strategy in this vulnerable patient population [45].



- f) Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is increasingly being used in circulatory failure. The main indications are cardiogenic shock, post-cardiotomy cardiac failure, and refractory cardiac arrest. However, VA-ECMO weaning is particularly challenging, and weaning failure is reported to be as high as 50%, with increased related mortality. Levosimendan is a novel long-acting effect indicator used in cardiogenic shock and terminal heart failure decompensation. Levosimendan use in VA-ECMO patients seems to reduce weaning failure regardless of the initial etiology and to reduce mortality when administered early after VA-ECMO initiation. However, studies are limited to retrospective analyses and reported case series. The WEANILEVO trial aims to evaluate whether the administration of levosimendan before VA-ECMO weaning is associated with reduced rates of weaning failure and recourse to other temporary circulatory support. Levosimendan use in VA-ECMO appears to be beneficial for reducing weaning failure and mortality. The results of WEANILEVO should significantly influence decisions regarding the use of levosimendan for VA-ECMO weaning [46].
- g) Oral Nutritional Supplements (ONS) are used to treat malnutrition and improve clinical outcomes in malnourished patients. Poor handgrip strength (HGS) is associated with an increased risk of mortality, disability, and other adverse health consequences. S-ONS provided during hospitalization and up to 90 days post-discharge improves HGS in malnourished older adults following cardiovascular and pulmonary events and may contribute to improvement in the patient's overall recovery [47].

### Heart Failure with mid-range ejection fraction

Heart failure with intermediate ejection fraction (HFmrEF) is a new category of heart failure (HF), between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Earlier studies were conducted primarily in HFrEF patients with a left ventricular ejection fraction (LVEF) of less than 35%–40%; later, HFpEF captured the spotlight of the research field, and studies focused on patients with HF symptoms but with an LVEF greater than 50%. As a result, a knowledge gap has arisen that includes LVEF between 40 and 49%. Current studies focusing on patients with HFmrEF are supporting the same conclusions or even have contradictory results. HFmrEF has a prevalence of 10–20% of patients with HF. HFmrEF has distinct but intermediate clinical, structural, and functional characteristics and intermediate outcomes compared to HFrEF and HFpEF [48]. However, there is still a large void of evidence regarding detailed hemodynamic features, long-term follow-up, and optimal treatment options for these patients, although the ESC 2021 guidelines confirm and solidify this distinction.

**Subsequent studies also confirm this direction, arguing that:**

1. The identification of high-risk heart failure (HF)

patients makes it possible to intensify their treatment; hs-cTnI levels  $\geq 17$  ng/l represent an independently increased risk of an adverse prognosis for patients with HFrEF and HFmrEF. Determining a patient's hs-cTnI level adds prognostic value to NT-proBNP and clinical parameters [49].

2. In the EMPA-REG OUTCOME trial, ejection fraction (EF) data were not collected. In the subpopulation with heart failure (HF), we applied a new predictive model for EF to determine the effects of empagliflozin in HF with predicted reduced (HF<sub>r</sub>EF) vs. preserved (HF<sub>p</sub>EF) EF vs. no HF. In EMPA-REG OUTCOME, one-third of the patients with HF had predicted HF<sub>p</sub>EF. The benefits of empagliflozin on HF and mortality outcomes were consistent in nonHF, predicted HF<sub>p</sub>EF, and HFmrEF/HFrEF [50].
3. Heart failure (HF) guidelines place patients into 3 discrete groups according to left ventricular ejection fraction (LVEF): reduced ( $< 40\%$ ), mid-range (40–49%), and preserved LVEF ( $\geq 50\%$ ). We assessed whether clinical phenol groups offer better prognostication than LVEF. Among patients hospitalized for HF, clinical phenotypes generated by unsupervised machine learning provided greater prognostic information for a composite of clinical endpoints at 6 and 12 months compared with LVEF-based categories [51].

### B-type natriuretic peptide (BNP) or NT-proBNP?

B-type natriuretic peptide (BNP) has favorable effects on left ventricular remodeling, including antifibrotic and antiapoptotic properties. We tested the hypothesis that infusion of BNP after an acute myocardial infarction would reduce left ventricular systolic and diastolic volumes and improve left ventricular ejection fraction compared with placebo. Infusion of BNP in patients with an anterior myocardial infarction did not affect parameters of left ventricular remodeling. Patients treated with BNP who had a baseline left ventricular ejection fraction of  $< 40\%$  had a trend towards reduced left ventricular infarction size compared with placebo. These results do not support the use of intravenous BNP in patients after recent myocardial infarction [52] as previously supported by other research [53].

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) aid in the diagnosis of heart failure (HF) and the determination of patient prognosis. In response to a myocardial wall stretching, pre-proBNP is synthesized and transformed into proBNP; which is further transformed into the biologically inactive fragment NT-proBNP and the biologically active fragment BNP. Because BNP and NT-proBNP are elevated in patients with HF, both are useful adjuncts to clinical evaluation. However, measurable concentrations of NT-proBNP are higher in plasma than BNP, necessitating different clinical cut-points; consequently, clinical guidelines give no guidance to clinicians or laboratories regarding the best natriuretic peptide to test for HF evaluation [54]. Despite widespread recognition that these tests are essentially clinically equivalent, no published

study has evaluated the diagnostic concordance between BNP and NT-proBNP to exclude or rule out HF at accepted cut points. To fill this gap in the literature, one study performed BNP and NT-proBNP testing on 3,029 BNP patient samples, assigning patients to two groups (acute HF and non-acute HF) It was found that there were frequent occasions when patients would be excluded for HF by one method and excluded for HF by the other; in addition, chronic kidney disease was found to have a profound negative impact on concordance between the two tests [55]. What this study, in short, highlights are the multiple biological and analytical complexities associated with natriuretic peptide immunoassays. There are multiple, well-known problems with the measurement of BNP and NT-proBNP in patient samples, including differences in protein glycosylation, half-life, renal clearance, biochemical diversity in HF patients, and variable antibody reactivity with the proBNP precursor [56].

Consequently, BNP and NT-proBNP are not interchangeable. However, further studies are needed to examine the diagnostic concentrations of natriuretic peptides, clearance patterns, and specificity of the assay for circulating forms. The differences between BNP and NT-proBNP at the biological level relate to the fact that one is biologically active as a hormone, BNP, whereas NT-proBNP is passively eliminated from the body and is not biologically active. Therefore, BNP has a much shorter half-life, and NT-proBNP has a longer half-life. NT-proBNP, as a result, circulates in higher concentrations in the bloodstream, which means, therefore, it is more likely to be more sensitive to detect earlier forms of heart failure because it circulates at somewhat higher levels. When you look at their diagnostic and prognostic capabilities, they are largely similar. But I would say that when we look at the value of these markers for patient management, for therapy monitoring, clearly NT-proBNP has substantially more data behind its use. Also, with the emergence of new therapies for heart failure, particularly the ARNi class of heart failure therapies, this class of drugs affects BNP concentrations because it blocks BNP breakdown, which means that BNP concentrations will increase substantially in patients treated with ARNis, whereas NT-proBNP values are not affected, as on the other hand already sustained in the past [57,58] and in the current future [59].

### **Mortality prediction in acute heart failure: scores or biomarkers? [60,61]**

Acute heart failure (AHF) is a complex and heterogeneous syndrome associated with an alarming increase in incidence and still unacceptably high rates of mortality and morbidity. Because this dismal outcome is at least in part due to a mismatch between the severity of AHF and the intensity of its management, both in the hospital and immediately after discharge, early and accurate risk prediction could contribute to more effective and risk-adjusted management. Biomarkers, in this role, are noninvasive and highly reproducible quantitative tools that have improved the understanding of the pathophysiology of AHF.

Better risk prediction using clinical risk scores or biomarkers could contribute to more effective risk-adjusted

management. Thus, high-risk patients could be transferred to an intensive care unit with continuous monitoring (marked in red), intermediate-risk patients could be admitted or treated temporarily in an intermediate care unit (marked in yellow), and low-risk patients could be safely discharged home with adapted outpatient follow-up (marked in green).

Early risk prediction plays a key role in the subsequent management of patients presenting with AHF, a heterogeneous syndrome associated with still unacceptably high rates of mortality and morbidity. To optimize risk prediction and intensity of management, clinicians should be aware of the following concepts:

- a) Biomarkers have improved understanding of the pathophysiology of heart failure and may therefore help to adjust the intensity of management in AHF.
- b) Among the wide variety of biomarkers currently available, natriuretic peptides can seem the most promising in this indication.
- c) As a heterogeneous syndrome with various phenotypes, a biomarker approach alone is insufficient for accurate risk prediction in AHF. Heart failure risk scores that combine several predictor variables are more promising to help clinicians make decisions and personalize the intensity of management.
- d) Among the risk scores described, those that combine demographic and clinical parameters with biomarkers in a model with routinely available fast variables seem the most promising tools for early and accurate risk stratification in the emergency department.
- e) For early risk stratification of patients with AHF in the emergency department, scores that have been specifically derived and validated in emergency department cohorts should preferably be used.
- f) In addition to biomarkers, age, systolic blood pressure, respiratory rate, oxygen saturation, creatinine, electrolytes, and blood urea nitrogen are the most commonly used predictive variables in the risk scores described.
- g) Among the selected models, the MEESSEI-AHF risk score currently appears to be the most promising tool for AHF risk prediction. This score was developed in the emergency department in a large derivation cohort, consists of fast and routinely available variables that show very accurate risk prediction, and has been externally validated in a country other than the one in which it was developed.

### **Psychological needs in patients with HF**

During the management of decompensated patients (and in later stages), the psychological aspect is completely ignored, with cardiological and systemic management of the HF sufferer being a priority [62], actually promoting a worsening



of psychological symptoms resulting from the traumatic event but also previous morbid conditions. The need is as evident during the acute episode as it is in the daily management of chronic heart failure.

The adverse clinical event determines a significant increase in anxiety symptomatology [63,64], capable of decompensating the patient or aggravating his or her psychopathological picture [65], whether neurotic [66], border [67-70], or psychotic [71,72].

It has been noted that, throughout the hospitalization period, the disease state is capable of generating marked anxiety and depressive symptoms [73,74], which are then capable of fostering or aggravating neurotic conditions from the traumatic cardiac event [75] such as obsessive and somatic disorders, avoidant behaviors, sleep-wake rhythm alterations, panic attacks, and behavioral addictions, to more or less structured suicidal ideations [76-83], as a result of one's emotional perception and one's ability to interpret the plane of reality [84-88].

Therefore, deepening the patient's inner human dimension is a fundamental clinical necessity, to ensure a holistic intervention capable of making him feel protected, especially after the traumatic cardiac event, with the help of a clinical psychological interview and, if necessary, a structured intervention with textual tools capable of investigating both the personality framework and its inner dimensions (ego

defense mechanisms and sexual matrix) [89-104], to foster in the patient the need to regain his human dimension of serenity and harmony [105-107].

## Discussion and study limitations

The ESC 2021 guidelines are a landmark in cardiology and represent the state of the art in science; therefore, the need to constantly update them represents a fundamental utility.

Already, the 2021 edition has introduced important innovations, especially in terms of changes in the criteria for chronic heart failure, in terms of the use of strategies and new pharmacological products and first-line drugs, in terms of phenotypic reconnaissance, in terms of electrical therapy, in terms of implementation of telemedicine and follow-up, and terms of reclassification of acute heart failure, but precisely based on what was introduced in the first paragraph of this paper, the research group states here the primary objective of expanding the indications contained in the ESC 2021 with the results of the last year on the subject of treatment profiles, to facilitate a better understanding of the overall clinical picture and contribute to the next edition of the guidelines.

Also, the ESC 2021 guidelines, as we will see, have definitively clarified the role of Heart Failure with Mid-Range Ejection Fraction (confirming the independence and nosographic importance) and the role of NT-proBNP (confirming the use and clinical utility). Excluded utility instead for the B-type natriuretic peptide (BNP) Table 19.

**Table 19:** Summary table of studies.

Author (Year)	Objectives	Type	Key Results and Conclusions
Bhatt DL, et al. [4]	Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure <sup>v</sup>	R: 1,222	In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo.
Boersma EM, et al. [19]	Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure	R: 76	In patients with acute HF, empagliflozin increased fractional glucose excretion and plasma osmolality, without affecting fractional sodium excretion or urine osmolality and caused a temporary decline in the estimated glomerular filtration rate.
Nicholls SJ, et al. [5]	Apabetalone and hospitalization for heart failure in patients following an acute coronary syndrome: a prespecified analysis of the BETonMACE study	R: 2,425	Apabetalone treatment was associated with fewer hospitalizations for heart failure in patients with type 2 diabetes and recent ACS. Future studies are warranted to define the potential for BET inhibition with apabetalone to prevent heart failure in patients with diabetes and ACS.
Leh-Ching NGD, et al. [22]	The Efficacy of a Single Session of 20-Minute Mindful Breathing in Reducing Dyspnea Among Patients With Acute Decompensated Heart Failure	R: 96	Both UC and BT with UC can reduce dyspnea and anxiety in patients admitted to ED with AHF. However, the effect of BT combined with UC was larger compared to UC only.
Wu J, et al. [24]	Long-term survival benefit of ramipril in patients with acute myocardial infarction complicated by heart failure	R: 603	For patients with clinically defined heart failure following AMI, ramipril results in a sustained survival benefit and is associated with an extension of the life of up to 14.5 months for, on average, 13 months of treatment duration.
Lopez RD, et al. [32]	Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19	R: 659	Among patients hospitalized with mild to moderate COVID-19 and who were taking ACEIs or ARBs before hospital admission, there was no significant difference in the mean number of days alive and out of the hospital for those assigned to discontinue vs continue these medications. These findings do not support routinely discontinuing ACEIs or ARBs among patients hospitalized with mild to moderate COVID-19 if there is an indication for treatment.
Vardeny O, et al. [33]	Effect of High-Dose Trivalent vs Standard-Dose Quadrivalent Influenza Vaccine on Mortality or Cardiopulmonary Hospitalization in Patients With High-risk	R: 5,260	In patients with high-risk cardiovascular disease, high-dose trivalent inactivated influenza vaccine, compared with standard-dose quadrivalent inactivated influenza vaccine, did not significantly reduce all-cause mortality or cardiopulmonary hospitalizations. Influenza vaccination remains strongly recommended in this population.



de la Espriella R, et al. [7]	Early urinary sodium trajectory and risk of adverse outcomes in acute heart failure and renal dysfunction	R: 160	n patients with AHF and renal dysfunction, a single early determination of UNa+ $\leq$ 50 mmol/L identifies patients with a higher risk of all-cause mortality and readmission. The $\Delta$ UNa24h adds prognostic information over baseline values only when UNa+ at admission is $\leq$ 50 mmol/L.
Perez AL, et al. [8]	Interleukin-6 and Outcomes in Acute Heart Failure	R: 883	Although elevated IL-6 levels were associated with higher all-cause mortality in acute HF, no independent association with this outcome was identified at baseline or 30-day measurements. In contrast with prior reports, we did not observe any impact of nesiritide over placebo on serial IL-6 levels.
Miller PE, et al. [34]	Association between Respiratory Failure and Clinical Outcomes in Patients with Acute Heart Failure	R: 8,296	Respiratory failure during an index hospitalization for acute HF was associated with increased rehospitalization and all-cause mortality. The development of respiratory failure during an acute HF admission identifies a particularly vulnerable population, which should be identified for closer monitoring.
Pang Z, et al. [9]	A study of the sequential treatment of acute heart failure with sacubitril/valsartan by recombinant human brain natriuretic peptide	R: 300	Sacubitril/valsartan significantly reduces the serum levels of inflammatory factors such as TNF- $\alpha$ in patients with acute heart failure while decreasing the levels of oxidizing factors such as MDA and XO and increasing the levels of antioxidants such as GSH-PX. These changes may explain why the sequential treatment group exhibited a better cardiac structure and better pulmonary artery pressure.
Kraus BJ, et al. [10]	Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial	R: 6,668	Treatment with sodium-glucose co-transporter-2 inhibitors induces an initial 3–5 ml/min/1.73 m <sup>2</sup> decline in the estimated glomerular filtration rate (eGFR).
Amatuzzi F, et al. [41]	Acute and Time-Course Effects of Osteopathic Manipulative Treatment on Vascular and Autonomic Function in Patients With Heart Failure	R: 20	Osteopathic manipulative treatment was effective at increasing brachial blood flow and stimulating the vagal system in patients with heart failure. Moreover, vascular changes seem to precede autonomic modulation.
Tamaki S, et al. [6]	Effect of Empagliflozin as an Add-On Therapy on Decongestion and Renal Function in Patients With Diabetes Hospitalized for Acute Decompensated Heart Failure	R: 59	In this exploratory analysis, empagliflozin achieved effective decongestion without an increased risk of worsening renal function as an add-on therapy in patients with type 2 diabetes with acute decompensated heart failure.
Piardi DS, et al. [11]	Effect of adding hydrochlorothiazide to the usual treatment of patients with acute decompensated heart failure	R: 50	Adding hydrochlorothiazide to the usual treatment of patients with acute decompensated heart failure did not cause a significant difference in daily body weight reduction compared to placebo.
Hamo CE, et al. [12]	OUTpatient intravenous LASix Trial in reducing hospitalization for acute decompensated heart failure	R: 100	The use of a standardized protocol of outpatient IV furosemide infusion for one month following hospitalization for ADHF was found to be safe and efficacious in reducing 30-day re-hospitalization.
Kitzman DW, et al. [213]	Physical Rehabilitation for Older Patients Hospitalized for Heart Failure	R: 349	In a diverse population of older patients who were hospitalized for acute decompensated heart failure, an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical-function domains resulted in greater improvement in physical function than usual care.
Hersberger L, et al. [45]	Individualized Nutritional Support for Hospitalized Patients With Chronic Heart Failure	R: 645	Among hospitalized patients with chronic heart failure at high nutritional risk, individualized nutritional support reduced the risk for mortality and major cardiovascular events compared with standard hospital food. These data support malnutrition screening upon hospital admission followed by an individualized nutritional support strategy in this vulnerable patient population.
Mauri T, et al. [35]	Sign-in Patients With Acute Hypoxemic Respiratory Failure and ARDS	R: 58	Among hypoxemic intubated ICU patients, the application of sigh was feasible and without increased risk.
Pfeffer MA, et al. [26]	Angiotensin Receptor-Nepriylsin Inhibition in Acute Myocardial Infarction	R: 5,661	Sacubitril-valsartan was not associated with a significantly lower incidence of death from cardiovascular causes or incident heart failure than ramipril among patients with acute myocardial infarction.
Tuttolomondo A, et al. [14]	Effects of intravenous furosemide plus small-volume hypertonic saline solutions on markers of heart failure	R: 141	Our findings concerning a comparable degree of reduction in the serum levels of three cardinal biomarkers indicate that a reduction in serum heart failure markers is not linked to a higher degree of congestion relief with a more rapid achievement of a clinical compensation state. This issue may have possible benefits on clinical practice concerning its therapeutic effects over and beyond the simple amelioration of clinical congestion signs and symptoms. Nevertheless, our findings of higher delta values after treatment with i.v. furosemide plus HSS indicates a possible higher efficacy using modulation of the stretching and fibrosis mechanisms.
Shen XL, et al. [20]	Safety and efficacy of ultrafiltration on heart failure patients with reduced ejection fraction and diuretic resistance	R: 148	Ultrafiltration therapy is safe and can improve diuretic sensitivity in heart failure patients with reduced ejection fraction and diuretic resistance.
Sharma A, et al. [15]	Growth differentiation factor-15, treatment with liraglutide, and clinical outcomes among patients with heart failure	R: 300	An increase in GDF-15 over 30 days among patients in HF $\text{rEF}$ was independently associated with an increased risk of cardiovascular events and declining exercise capacity. These results support the value of longitudinal GDF-15 trajectory in informing the risk of heart failure disease progression.
Ali L, et al. [36]	Effects of Person-Centered Care Using a Digital Platform and Structured Telephone Support for People With Chronic Obstructive Pulmonary Disease and Chronic Heart Failure	R: 222	PCC using a combined digital platform and structured telephone support seems to be an option to increase the short-term self-efficacy of people with COPD and CHF. This study adds to the knowledge of conceptual innovations in primary care to support patients with COPD and CHF.
Ellouze O, et al. [46]	Levosimendan in venoarterial ECMO weaning	R: 206	Levosimendan use in VA-ECMO appears to be beneficial for reducing weaning failure and mortality.



Adi O, et al. [37]	Helmet continuous positive airway pressure (hCPAP) to facemask continuous positive airway pressure (fCPAP) for the treatment of acute respiratory failure in the emergency department	R: 113	In patients presenting to the ED with acute cardiogenic pulmonary edema or decompensated COPD, hCPAP was non-inferior to fCPAP and resulted in greater comfort levels and lower intubation rate.
Griffiths S, et al. [23]	Role of the primary care physician follow-up post-hospital discharge in individuals admitted with chronic obstructive pulmonary disease or congestive heart failure	R: 16	Patients and caregivers valued in-person follow-up with their primary care provider the following discharge from the hospital because of the trust established through pre-existing longitudinal relationships. Our results suggest policymakers should focus on improving rates of primary care provider attachment and systems supporting informational continuity.
Zhang W, et al. [16]	Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension	R: 9,624	In older patients with hypertension, intensive treatment with a systolic blood-pressure target of 110 to less than 130 mm Hg resulted in a lower incidence of cardiovascular events than standard treatment with a target of 130 to less than 150 mm Hg.
Tomasdottir M, et al. [27]	Risk markers of incident atrial fibrillation in patients with coronary heart disease	R: 13,153	In patients with optimally treated CHD, the incidence of new AF was 1.2% per year. Age, NT-proBNP as a marker of impaired cardiac function, and BMI were the strongest factors, independently and consistently associated with incident AF. Male sex and low physical activity may also contribute to the risk of AF in patients with CHD.
Matheson EM, et al. [47]	Specialized oral nutritional supplement (ONS) improves handgrip strength in hospitalized, malnourished older patients with cardiovascular and pulmonary disease	Sys: 170	Current evidence suggests that cardiac cachexia and sarcopenia in patients with CHF are associated with greater severity of the disease and poor outcomes. Thus, early nutritional screening is essential.
Berg DD, et al. [17]	Efficacy and Safety of Sacubitril/Valsartan in High-Risk	R: 440	In high-risk subpopulations admitted for acute decompensated HF, treatment with sacubitril/valsartan after initial stabilization conferred a consistent reduction in cardiovascular death or rehospitalization for HF and was well tolerated.
Ghanim H, et al. [18]	Dapagliflozin reduces systolic blood pressure and modulates vasoactive factors	R: 52	Dapagliflozin administration in T2D resulted in a both acute and chronic reduction in systolic BP, a reduction in vasoconstrictors, and an increase in vasodilators. These changes may potentially contribute to its antihypertensive effects and its benefits in congestive cardiac failure.
Mozawa K, et al. [21]	Empagliflozin confers reno-protection in acute myocardial infarction and type 2 diabetes mellitus	R: 96	Empagliflozin prevented kidney function decline in patients with AMI and T2DM, especially those with baseline eGFR $\geq$ 60 mL/min/1.73 m <sup>2</sup> . Early administration of sodium-glucose cotransporter 2 inhibitors in these patients is considered desirable for renal protection.
Hubers SA, et al. [52]	B-type natriuretic peptide and cardiac remodeling after myocardial infarction	R: 58	Infusion of BNP in patients with an anterior myocardial infarction did not affect parameters of left ventricular remodeling. Patients treated with BNP who had a baseline left ventricular ejection fraction of <40% had a trend towards reduced left ventricular infarction size compared with placebo. These results do not support the use of intravenous BNP in patients after a recent myocardial infarction.
Yu X, et al. [28]	Innate Lymphoid Cells Promote Recovery of Ventricular Function After Myocardial Infarction	R: 64	ILC2s promote cardiac healing and improve the recovery of heart function after MI in mice. Activation of ILC2 using low-dose IL-2 could be a novel therapeutic strategy to promote a reparative response after MI.
Wang W, et al. [29]	Hypothyroidism is associated with clinical outcomes in patients with acute myocardial infarction	R: 431	Compared with euthyroid status, hypothyroid status has an independent predicting value for adverse cardiovascular events in AMI patients. Further investigations are required to illustrate whether treatment of thyroid dysfunction could improve the prognosis of AMI patients.
Lu Y, et al. [30]	Effects of alprostadil combined with tanshinone Ila injection on microcirculation disorder	R: 300	For AMI patients after PCI, alprostadil combined with tanshinone Ila injection can effectively improve microcirculation and ventricular remodeling, improve cardiac function and reduce the occurrence of MACES. This combination can be widely used in clinical practice.
Labovitz AJ, et al. [31]	Early Apixaban Use Following Stroke in Patients With Atrial Fibrillation	R: 120	Early initiation of anticoagulation after TIA, small-, or medium-sized AIS from AF does not appear to compromise patient safety.
Lokaj P, et al. [49]	Prognostic value of high-sensitivity cardiac troponin I in heart failure patients with mid-range and reduced ejection fraction	R: 520	hs-cTnI levels $\geq$ 17 ng/l represent an independently increased risk of an adverse prognosis for patients with HF <sub>rEF</sub> and HF <sub>mEF</sub> . Determining a patient's hs-cTnI level adds prognostic value to NT-proBNP and clinical parameters.
Savarese G, et al. [50]	Empagliflozin in Heart Failure With Predicted Preserved Versus Reduced Ejection Fraction	R: 7,001	In EMPA-REG OUTCOME, one-third of the patients with HF had predicted HF <sub>pEF</sub> . The benefits of empagliflozin on HF and mortality outcomes were consistent in nonHF, predicted HF <sub>pEF</sub> , and HF <sub>mEF</sub> /HF <sub>rEF</sub> .
Gevaert AB, et al. [51]	Clinical phenol groups are more effective than left ventricular ejection fraction categories in stratifying heart failure outcomes	R: 1,693	Among patients hospitalized for HF, clinical phenotypes generated by unsupervised machine learning provided greater prognostic information for a composite of clinical endpoints at 6 and 12 months compared with LVEF-based categories.
Coste J, et al. [53]	A Gray Zone Assigned to Inconclusive Results of Quantitative Diagnostic Tests	R: 699	The grey zone approach applied to the diagnosis of heart failure by a BNP might allow sensible cutoff values to be determined for clinical practice according to relevant subgroups of patients. The grey zone approach might be usefully applied to many other quantitative tests and clinical diagnostic or screening problems.
Farnsworth CW, et al. [55]	Diagnostic concordance between nt-pro-BNP and BNP for suspected heart failure	R: 2,729	The current cutoffs for diagnosing HF for NT-proBNP and BNP have a relatively low diagnostic concordance and correlation, particularly among patients with chronic kidney disease.



Bay M, et al. [57]	NT-proBNP: a new diagnostic screening tool to differentiate between patients with normal and reduced left ventricular systolic function	R: 2,193	A single measurement of NT-proBNP at the time of hospital admission provides important information about LVEF in unselected patients.
Yang Y, et al. [59]	Genetic association analysis of the cardiovascular biomarker	R: 4,331	In this family-based study of subjects with exceptional longevity, we identified several allelic variants in the BNP gene region associated with NT-pro-BNP levels and prevalent CVD.
Rossello X, et al. [61]	Article Navigation MEESSI-AHF risk score performance to predict multiple post-index events and post-discharge short-term outcomes	R: 7,755	The MEESSI-AHF risk score strongly predicts mortality outcomes in acute heart failure patients admitted to the emergency department, but the model performs poorly for outcomes involving hospital admission or emergency department revisit. There is a need to optimize this risk score to predict non-fatal events more effectively

## Conclusion

The ESC 2021 guidelines are a landmark in cardiology. The scientific literature search enriched the structure of ESC 2021, suggesting its implementation, with other findings related to new drug therapies such as Sotagliflozin, Hydrochlorothiazide, Apabetalone, Alprostadil, Empagliflozin, Sacubitril/Valsartan, Dapagliflozin, Sodium-glucose co-transporter-2 inhibitors, and biomarkers such as Urinary sodium (UNa<sup>+</sup>), IL-6 levels and rh-brain natriuretic peptide (rhBNP), as well as the use of mindful breathing session, osteopathic manipulative treatment, electrical muscle stimulation, low-level tragus stimulation, venoarterial extracorporeal membrane oxygenation, oral nutritional supplements, and the correlative hypothesis between heart failure and intestinal dysbiosis [39,108], also concerning psychopathological profiles.

However, these clinical studies suffer from some limitations that will necessarily have to be taken into accounts, such as the limited size of the population sample selected or the conflict of interest determined by the fact that some research is funded by the same pharmaceutical company producing the drug users that do not necessarily represent a negative limitation on the results obtained from studies.

## Data availability statement

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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