Heart Failure Reviews (2025) 30:715–734
https://doi.org/10.1007/s10741-025-10497-z

CONSENSUS ARTICLE

Worsening heart failure: progress, pitfalls, and perspectives

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Accepted: 11 February 2025 / Published online: 20 February 2025

Abstract
For most patients with chronic heart failure (HF), the clinical course of the disease includes periods of apparent clinical stability punctuated by episodes of clinical deterioration with worsening signs and symptoms, a condition referred to as worsening heart failure (WHF). Over time, episodes of WHF may become more frequent, and patients may enter a cycle of recurrent events associated with deterioration in their quality of life and functional capacity, hospitalizations, and ultimately death. WHF is apparently an old concept but seems to have acquired new boundaries in terms of definition and clinical and prognostic value due to the fast-paced evolution of the HF treatment landscape and the emergence of new drugs in this setting. As a result, the management of WHF is being reshaped. In the present paper, a group of HF experts gathered to discuss the concept, prevention, detection, and treatment of WHF.

Keywords Chronic heart failure · Emerging treatment · Expert consensus · Guideline-directed medical therapy · Management · Vericiguat · Worsening heart failure

Introduction

Chronic heart failure (HF) is associated with a high risk of morbidity, mortality, and healthcare resource use and currently represents a substantial public health problem [1]. It has been considered a global health problem, and its prevalence and burden are increasing in both high- and middle-income countries [2, 3]. Although it is acknowledged that the global prevalence of HF in the general adult population is increasing, prevalence data in the literature have remained relatively unchanged at 1–3% for several years, based on estimates from old studies, meta-analyses, and/or specific or subpopulations [2]. About 6.7 million Americans over the age of 20 have HF, a figure that is expected to increase to 8.5 million by 2030 [4]. A similar trend is observed in Europe [2, 3, 5]. In fact, one in every four people is estimated to develop HF during their lifetime [4]. These numbers will predictably rise in the coming years due to the increasing longevity of the population and the availability of better diagnostic tools and medical treatments.

In Portugal, an initial estimate from the EPICA study reported an overall prevalence of chronic HF of 4.36% [6], a re-estimate based on the EPICA study and considering only the aging of the population and data from the 2011 census by Statistics Portugal indicated an increase in HF prevalence in the country of 30% by 2035 and 33% by 2060 [7], and the most recent estimate from the 2023–2024 population-based PORTHOS study showed a prevalence of 16.5% in the Portuguese population aged ≥ 50 years (mostly HF with preserved ejection fraction [HFpEF; 15.2%] and increasing with age [30.7% in people aged ≥ 70 years]) [8, 9]. The disease represents a significant social and economic burden for the country [10, 11]. It accounts for 2.6% of the total public health expenditure due to direct and indirect costs [10], similar to what has been reported in the literature for healthcare systems around the world [12–14]. These costs are also expected to increase in the future [10]. Inpatient treatments represent the most important component of the economic burden of HF, being responsible for at least half and up to 80% of the total costs of HF treatment [10, 12–14]. Considering population aging over a 22-year horizon, the deaths and burden of HF are expected to reach 8,112 deaths and 27,059 disability-adjusted life years (DALYs) lost in 2036, mainly driven by the increase of years of life lost [11]. In addition, HF also takes a high toll on patients' lives, as documented by quality of life (QoL) studies and surveys [15–17].

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Despite advances in HF therapy over the past decades, HF is still associated with a dismal prognosis. Mortality rates are high independently of LVEF [18]. The risk of cardiovascular death appears to be significantly higher in HFrEF compared to HFpEF. Conversely, the risk of non-cardiovascular death seems to be higher in HFpEF [19–22].

Although most patients with chronic HF under guideline-directed medical therapy (GDMT) can remain hemodynamically stable and oligo-symptomatic for months to years [23], they still carry ahigh residual risk of clinical deterioration and death [23]. In fact, for most patients, the clinical course of HF includes periods of apparent clinical stability punctuated by episodes of clinical deterioration with worsening signs and symptoms, a condition referred to as worsening heart failure (WHF) [23–25]. Over time, episodes of WHF may become more frequent and patients enter a cycle of recurrent events [23], associated with the deterioration of their QoL and functional capacity, as well as the occurrence of hospitalizations and death.

WHF is apparently an old concept but seems to have acquired new boundaries in terms of definition and clinical and prognostic value. The evolution of the HF treatment landscape with the emergence of new drugs has prompted this change and reshaped the management of WHF. However, although currently recognized as a relevant clinical phase with significant health, societal, economic, and prognostic impact, there is still debate around the definition of WHF [26, 27]. This definition is evolving, but WHF remains poorly characterized and lacks real-world data regarding incidence, characteristics, and outcomes. The current knowledge is mostly retrieved from randomized controlled trials, which included highly selected patient populations, or few real-world studies, which are either retrospective, not primarily focused on WHF, or conducted in specific patient subgroups [28].

In the present paper, a group of HF experts gathered to discuss the concept, prevention, detection, and treatment of WHF.

Worsening heart failure – a specific phase in the continuum of HF

WHF is defined by escalating signs and symptoms of HF in patients with chronic HF despite optimal therapy, also implying the need for urgent therapy escalation [29–31]. It is not synonymous with decompensated HF but may culminate in a fully decompensated clinical picture if not early identified and timely treated [30]. However, establishing a clear definition of WHF is challenging, as evidenced on the recent clinical consensus statement of the European Society of Cardiology (ESC) [21]. This document excludes from the definition patients with comorbidities as the primary cause of WHF [26], and in addition to worsening signs and symptoms of HF in patients with preexisting disease despite stable optimized background therapy, the definition of WHF comprises the need for HF therapy intensification, usually with loop diuretics. Conversely, it excludes cases of (i) new-onset, or ‘de novo’ HF (therapy-naïve patients) and (ii) concomitant factors (such as comorbidities and/or poor treatment compliance) as the primary cause of WHF signs, symptoms, and hemodynamic state in a patient with preexisting HF.

According to this definition, progression of underlying myocardial and/or valvular disease seems to be the only precursor of a WHF event. However, in real life, there are common precipitants for WHF, such as infection, arrhythmia, myocardial ischemia, uncontrolled hypertension, and renal failure, among many others [32–34], which can undoubtedly contribute to the condition. Also, the consideration of ‘optimized background therapy’ appears to be outside the context of the real-world practice. Are patients with WHF truly optimized? What should the definition of 'optimized therapy' be? Should it be the maximum tolerated therapeutic dose for each recommended drug for each patient plus the adequate device therapy? In clinical practice, this therapy optimization falls short of what is recommended, as shown in HF registries [32, 35, 36].

WHF is increasingly acknowledged as a specific phase in the natural course of chronic HF that marks its progression and anticipates a substantially worse prognosis [1, 30]. Its occurrence should raise awareness of the fact that the patient is gradually clinically deteriorating and will require additional treatment [37]. Several studies have documented the higher risk of death and HF hospitalizations of patients with versus without WHF, including the MADIT-CRT trial [38] and the PARADIGM-HF trial [39].

WHF and the setting of care

The management of WHF has traditionally been hospital-based, with the need for intravenous (i.v.) diuretic therapy [2, 40–44].Observations that an increasing proportion of patients with WHF also carried a worse prognosis [38, 39] despite being managed as outpatients [40, 45–48] led to a shift in this paradigm and supported a definition of WHF independent of the site of care [26, 29].

In line with this, the definition of WHF currently encompasses three possible care settings: the outpatient setting, usually at the HF clinic; the Emergency Department (ED); and hospitalization, when patients are admitted for i.v. therapy or other specific treatments [26].

Accumulating data in patients with HF with reduced ejection fraction (HFrEF) suggest that WHF without hospitalization is associated with a high rate of clinical events but a lower risk of death compared to WHF that needs to be managed in the hospital [42, 48–50]. Inpatients with HFpEF,

the PARAGON-HF trial showed that patients with a first episode of WHF managed in the hospital had higher rates of subsequent death than those managed in an urgent HF visit, and both had higher rates of death than patients not experiencing WHF [51].

WHF should be distinguished from acute HF, as they have a significantly different prognosis. In fact, distinguishing between them has implications for risk stratification. Although sometimes used interchangeably, these are distinct entities, with WHF specifically referring to the clinical course of patients with chronic, preexisting HF, and acute HF being a much broader entity that includes both the first manifestation of'de novo' HF and chronic decompensated HF. In addition, acute HF has a distinct set of clinical presentations (such as right ventricular failure, acute pulmonary edema, and cardiogenic shock [52]) and requires hospitalization, while WHF can also be managed in the outpatient setting in many cases [41, 53–56]. WHF should also be differentiated from decompensated HF, a threshold within WHF for the use of additional intensified rescue therapies beyond the standard GDMTs [57].

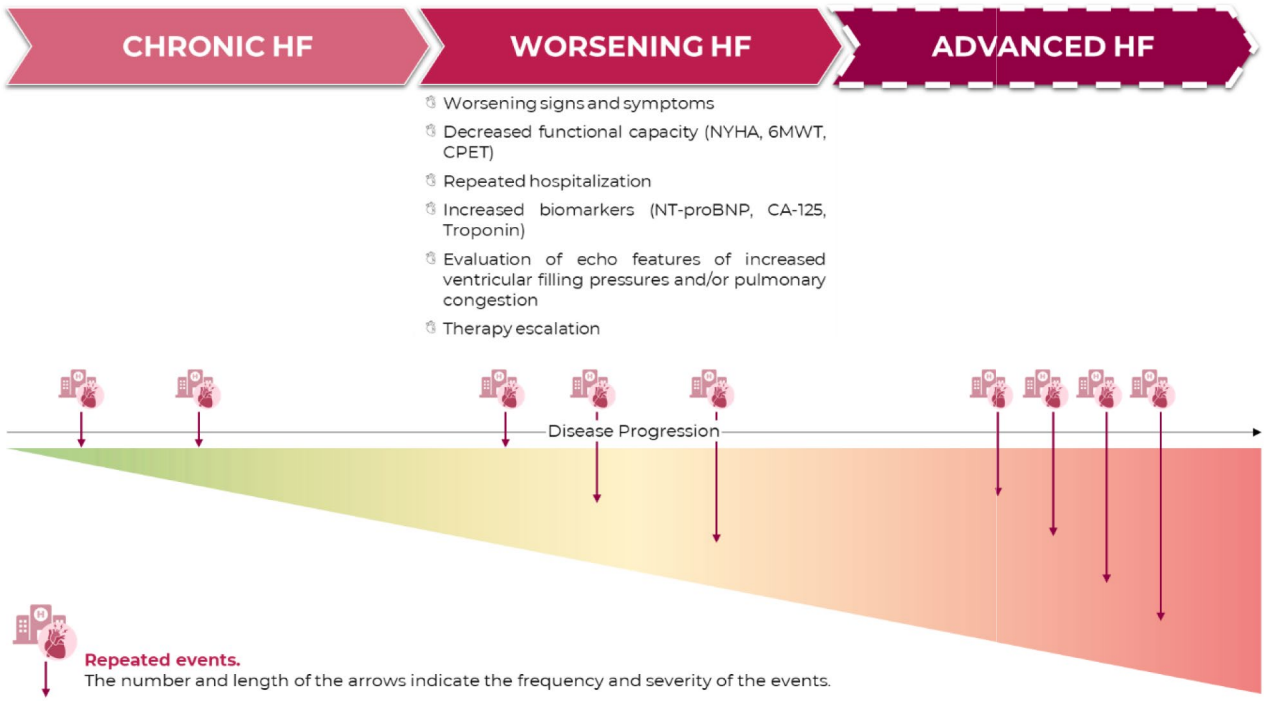
WHF should be considered the beginning of a distinct high-risk phase in HF and its definition should be revised [30]. This expert panel therefore proposes an understanding of the HF continuum to guide management in clinical practice (Fig. 1):

6MWT, 6-min walking test; CA-125, cancer antigen 125; CPET, cardiopulmonary exercise test; ED, Emergency Department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

How to prevent and/or detect early

Early prevention and detection are the cornerstones of WHF management.

The pathophysiology of WHF is linked to increasing ventricular filling pressures irrespective of the left ventricular ejection fraction (LVEF) [58–60]. Congestion can build up slowly over days to weeks, preceding overt decompensation



6MWT, 6-min walking test; CA-125, cancer antigen 125; CPET, cardiopulmonary exercise test; ED, Emergency Department; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

Fig. 1 WHF as a specific high-risk phase in the HF continuum. Repeated events include hospitalizations, ED visits, and unscheduled day hospital visits. The advanced HF phase is represented by dotted lines, as not all patients with WHF progress to an advanced state

[59, 60], with hypoperfusion and end-organ injury/dysfunction potentially also present [52, 61, 62].

The underlying hemodynamic changes that lead to decompensated HF cannot be accurately detected by an isolated clinical finding or by physical assessment alone [63, 64]. Several congestion scores combining different clinical markers have been proposed, but they are more often used as prognostic rather than diagnostic tools [63, 64]. Exercise tests (as the 6-min walking test [6MWT] or the cardiopulmonary exercise test [CPET]) and patient-reported outcome measures (PROMs; such as the Kansas City Cardiomyopathy Questionnaire [KCCQ]) can also be used as objective measurements of WHF and can be more accurate than the NYHA class alone [26, 65–67]. For instance, the 6MWT is widely used for the tight follow-up of congestion in pulmonary arterial hypertension patients [68].

Several biomarkers have been shown to be clinically useful in the management of patients with WHF [26, 52, 69–71]. Some authors proposed that an asymptomatic increase in N-terminal pro-B-type natriuretic peptide (NT-proBNP) or an increase in troponin could be useful in detecting subclinical worsening without overt worsening signs and symptoms [30, 72, 73]. Also subclinical worsening of congestion (evaluated by increasing pulmonary artery pressure), magnitude of asymptomatic change in filling pressure, and bioimpedance, among others, could act as potential markers of worsening biology [30]. However, there are caveats in such approaches as these biomarkers can vary significantly (up to 25%) without correlation with left ventricular filling pressures. Additionally, biomarker-based strategies failed to demonstrate a clear benefit in comparison with standard-of-care management [74].

Although several risk scores have been developed to predict the development of WHF or mortality in patients with chronic HF [75, 76], there are currently no widely validated risk scores for patients with a recent episode of WHF.

Remote hemodynamic monitoring through implantable devices has a major impact on the management of HF patients. The CHAMPION trial demonstrated the benefit of pulmonary artery pressure-guided HF monitoring with the CardioMEMS® system in patients with high-risk and advanced HF by showing a significant reduction in HF-related hospitalizations at 6 months and during the entire follow-up [77, 78]. A subsequent meta-analysis including CHAMPION and other four implantable hemodynamic monitoring trials across a range of ejection fractions showed that this approach was effective in reducing WHF events in patients with HFrEF (HR 0.75, 95% CI 0.66−0.86) [79]. Its effect in patients with HFpEF remains uncertain [79].

The benefits of noninvasive telemonitoring in the early identification of HF decompensation and consequent reduction of HF hospitalization and cardiovascular (CV) mortality have not been fully demonstrated, so a tailored use of remote monitoring should be applied [80, 81]. Noninvasive home telemonitoring involves periodic self-measurement by patients – typically on a daily basis – of various biodata, including vital signs, weight, and electrocardiogram, according to a defined plan. These data are then transmitted remotely to healthcare providers for review [82, 83]. While the use of noninvasive telemonitoring is appealing and user-friendly, its effectiveness depends on timely review of the transmitted data, ideally on the same day, which requires a 24/7 telemedicine service. Alerts are generated when a patient's biodata exceed specific cut-offs, prompting medical intervention to determine appropriate management and prevent WHF. Despite the potential of noninvasive telemonitoring, clinical trials have shown mixed results regarding its efficacy. While some studies suggest clinical benefit [80, 84], its role in the management of patients with HF remains controversial. International guidelines currently do not recommend the routine use of telemonitoring due to inconsistent evidence [85, 86].

The detection of WHF in clinical practice should ultimately rely on a set of clinical parameters, biomarkers, and imaging markers, depending on the severity of the patient's clinical status, the care setting, and the local logistics. In the outpatient setting, hemodynamically stable HF patients might benefit from follow-up according to self-monitoring (weight, signs, and symptoms) and local protocols [87, 88]. This will include periodic evaluation through PROMs (validated HF questionnaires), exercise tests (e.g., 6-min walking test), echocardiographic study (evaluating simple metrics as inferior vena cava diameter, jugular venous pressure, renal venous pressure, VEXUS, and E/e´ ratio), lung ultrasonography (lung B-lines), and some biomarkers (e.g., NT-proBNP, troponin, and CA-125 levels), as symptoms/signs of WHF sometimes may go unnoticed or appear late [26, 30, 65–67, 72, 73, 89, 90]. These evaluations are also important at predischarge to determine the next therapeutic strategy (namely the diuretic regimen), but also to individualize the different HF phenotypes that require different GDMT to be initiated prior to discharge: either the four pillars (angiotensin receptor/neprilysin inhibitors [ARNi]/angiotensin-converting enzyme inhibitors [ACEi], beta-blockers, mineralocorticoid receptor antagonists [MRA], sodium-glucose co-transporter 2 inhibitors [SGLT2i]) for HFrEF; or SGLT2i for HFpEF or HF with mildly reduced ejection fraction (HFmrEF) [26, 85, 91]. Importantly, finerenone, a nonsteroidal MRA, has recently been shown to be a disease-modifying drug in HFmrEF and HFpEF in the FINEARTS-HF study [92] and, although not yet included in the guidelines, should be considered as a pivotal therapy in those populations.

In addition, and according to the patient's characteristics, individualized tests may be required during follow-up. Remote (noninvasive or invasive) monitoring, including device-based (e.g., CardioMEMS® or OptiVol methodology), may also be helpful in several HF settings to reduce hospitalizations [78, 81, 93–96].

Importantly, given the high prevalence of HF, particularly HFpEF [8, 9], which is steadily increasing in the community, the implementation of these recommendations requires specialized structures supported by multidisciplinary teams and integrated HF programs that provide timely access to medical care (outpatient diagnosis and treatment) and prevent hospitalizations. To this day, the implementation of HF Clinics – with a special emphasis on day hospitals, specialized centers focused on the comprehensive management of HF – remains an organizational challenge, as they require significant resources, including trained personnel and proper infrastructures, as well as sustainable funding models [97, 98].

Based on this body of evidence, the following measures are proposed to detect and prevent WHF in HFrEF, HFmrEF, and HFpEF in clinical practice (Fig. 2):

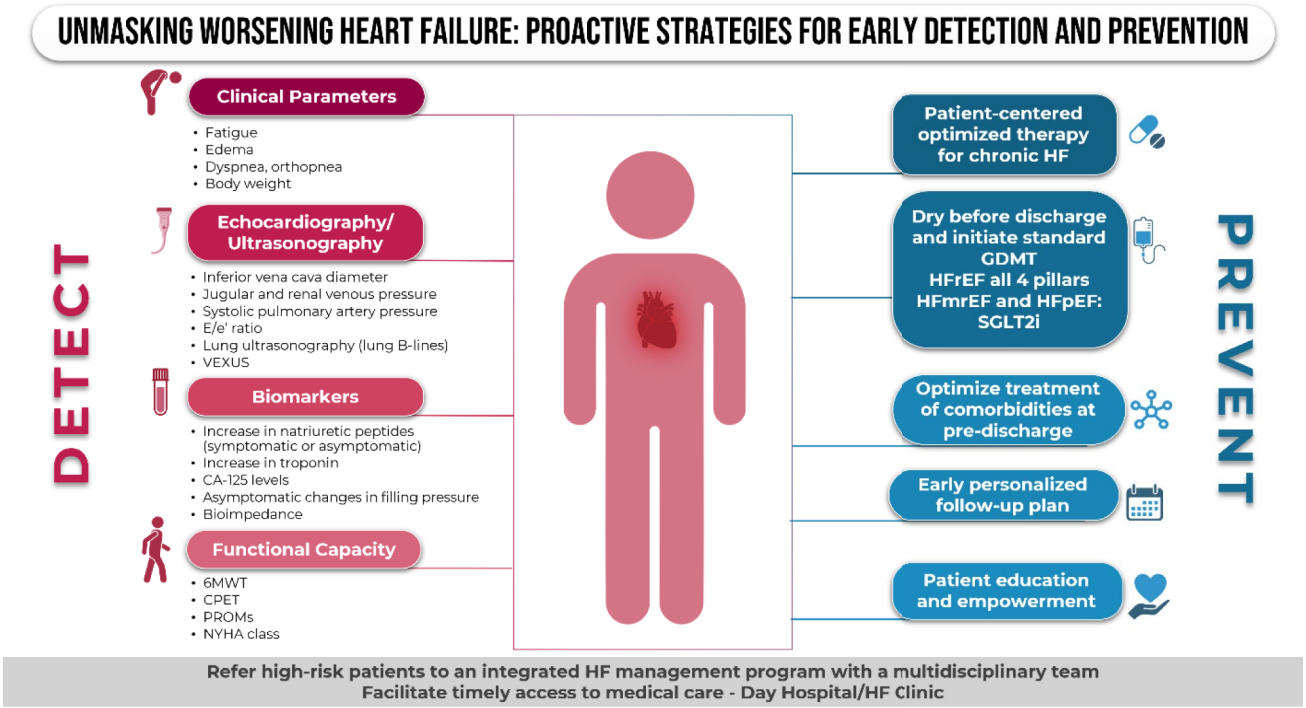
6MWT, 6-min walking test; CA-125, cancer antigen 125; CPET, cardiopulmonary exercise test; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; PROMs, patient reported outcomes measures; SGLT2i, sodium-glucose co-transporter 2 inhibitors; VEXUS, venous excess ultrasonography.

How to treat early

Upon a WHF event, beyond the use of i.v. or/and higher oral dose diuretics, an optimized pharmacological strategy should be defined for each individual patient. Although evidence is still accumulating, some novel agents appear to have beneficial effects on CV outcomes in this HF population (Table 1).

WHF treatment – from concept to clinical practice

Several systems and mechanisms are recognized as critically pathogenic in HF and have been implicated in the



6MWT, 6-min walking test; CA-125, cancer antigen 125; CPET, cardiopulmonary exercise test; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; PROMs, patient reported outcomes measures; SGLT2i, sodium-glucose co-transporter 2 inhibitors; VEXUS, venous excess ultrasonography

Fig. 2 Measures for early detection and prevention of WHF in HFrEF, HFmrEF, and HFpEF

Table 1 Chronic HF clinical trials that included patients with WHF

Clinical trial	Study arms	HF pathway targeted	Study population	Proportion of patients with a history of WHF at baseline	WHF outcomes of interest
Analysis of **MADIT-CTR** (Skali H et al. 2014 [38])	Cardiac resynchronization therapy vs. control	–	1820 patients with LVEF ≤ 0.30	• Prior HF hospitalization: - 45% of patients with an inpatient HF event - 48% of patients with an outpatient HF event	• 2.9% of patients with non-fatal outpatient WHF and 18.1% with non-fatal inpatient WHF • Risk of death in patients with hospitalization for WHF and treated for WHF as outpatients (vs. no WHF events): HR 12.4, 95% CI 9.1–16.9 and HR 10.7, 95% CI 6.1–18.7
PARADIGM-HF (McMurray JJV et al. 2014 [107] and Okumura N et al. 2016 [39])	Sacubitril/valsartan vs. enalapril	RAAS	8399 patients with HFrEF	• Prior HF hospitalization: 62.3% vs. 63.3% in McMurray JJV et al	• First hospitalization for WHF: 12.8% vs. 15.6% Manifestations of WHF: - outpatient intensification of HF therapy: 4% - ED visit for HF: 1% - hospitalization for WHF as first non-fatal event: 13% • Mortality rates after each event: 32%, 31%, and 37%, respectively • Risk of death (vs. no events): HR 4.8, 95% CI 3.9–5.9 for outpatient intensification of therapy; HR 4.5; 95% CI 3.0–6.7 for ED visit; HR 5.9, 95% CI 5.2–6.6 for hospitalization for WHF

Table 1 (continued)

Clinical trial	Study arms	HF pathway targeted	Study population	Proportion of patients with a history of WHF at baseline	WHF outcomes of interest
PARAGON-HF (Solomon SD et al. 2019 [110] and Vaduganathan M et al. [51])	Sacubitril/valsartan vs. valsartan	RAAS	4796 patients with HFpEF (LVEF ≥ 45%)	• Hospitalization for HF: 47.2% vs.49.0%	• 18.4% of patients had a first WHF event • 7.5% of patients experiencing a first WHF had an urgent HF visit and 92.5% of patients had a HF hospitalization as first event • Rate of death in patients with a first WHF event (vs. no events): 19.2 per 100 patient-years, 95% CI 16.9−21.8 after a HF hospitalization; 10.1 per 100 patient-years, 95% CI 5.4−18.7 after an urgent HF visit • Risk of death after an urgent HF visit lower than after a HF hospitalization: HR 0.52, 95% CI 0.27−0.97; $p = 0.04$ • Rate of subsequent WHF events (CV death + any HF event) similar not significantly different after an urgent HF visit (55 per 100 patient-years, 95% CI 42−72) and a HF hospitalization (68 per 100 patient-years, 95% CI 63−73); $p = 0.39$
Pooled analysis of **PARAGON-HF** and **PARAGLIDE-HF** (Vaduganathan M et al. 2023 [111])	Sacubitril/valsartan vs. valsartan	RAAS	Patients with HFmr/pEF (LVEF > 40% in PARAGLIDE-HF and ≥ 45% in PARAGON-HF)	• Two pooled analyses: - 1088 patients with recent WHF (during or within 30 days of a WHF event) in the first analysis - the entire population of 5262 patients from both trials in the second analysis	• Significant reduction of total WHF events and CV death with sacubitril/valsartan vs. valsartan in the first analysis (event rate 27.5 vs. 34.5 per 100 patient-years; RR 0.78, 95% CI 0.61–0.99; $p = 0.042$) and in the second analysis (event rate 14.5 vs. 16.8 per 100 patient-years; RR 0.86, 95% CI 0.75–0.98; $p = 0.027$)

Table 1 (continued)

Clinical trial	Study arms	HF pathway targeted	Study population	Proportion of patients with a history of WHF at baseline	WHF outcomes of interest
DAPA-HF (McMurray JJV et al. 2019 [108] and Docherty K et al. 2020 [42])	Dapagliflozin vs. placebo	SGLT2	4744 patients with HFrEF	• Hospitalization for HF: 47.4% vs. 47.5%	• Unplanned HF hospitalization or urgent visit requiring i.v. therapy for HF: 10% vs. 13.7% • Hospitalizations for HF: 9.7% vs. 13.4% (HR 0.70, 95% CI 0.59–0.83) • Urgent HF visits: 0.4% vs. 1.0% (HR 0.43, 95% CI 0.20–0.90) • 12.7% and 8.6% of patients had outpatient WHF leading to therapy intensification in McMurray JJV et al. and Docherty K et al., respectively • 0.7% and 0.4% of patients had an urgent HF visit requiring i.v. therapy in McMurray JJV et al. and Docherty K et al., respectively • 11.6% and 10.3% of patients had WHF hospitalization in McMurray JJV et al. and Docherty K et al., respectively • 6.2% of patients had CV death as first WHF event • Adjusted risk of death from any cause (vs. no events): HR 2.67, 95% CI 2.03–3.52 after an outpatient WHF; HR 3.00, 95% CI 1.39–6.48 after an urgent HF visit; HR 6.21, 95% CI 5.07–7.62 after a HF hospitalization
EMPEROR-REDUCED (Packer M et al. 2020 [109])	Empagliflozin vs. placebo	SGLT2	3730 patients with HFrEF	• Hospitalization for HF in ≤ 12 months: 31.0% vs.30.7%	• Hospitalization for WHF: 13.2% vs. 18.3% (HR 0.69. 95% CI 0.59–0.81)

CI confidence interval, *CV* cardiovascular, *ED* Emergency Department, *HF* heart failure, *HFmrEF* heart failure with mildly reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HR* hazard ratio, *i.v.* intravenous, *LVEF* left ventricular ejection fraction, *NM* not mentioned, *RAAS* renin–angiotensin–aldosterone system, *SGLT2* sodium-glucose cotransporter 2, *RR* rate ratio, *WHF* worsening heart failure

progression of WHF(reviewed in [26]). The autonomic nervous system, the renin–angiotensin–aldosterone system (RAAS), the natriuretic peptide system, and the guanylate cyclase system represent critical regulatory pathways in HF [99–105], and the burden of the disease can only be reduced through a holistic approach targeting the several systems. This is particularly true in high-risk HF patients, as those with a recent WHF episode[106].

Treatment strategies for WHF have been investigated in both WHF-dedicated and non-dedicated trials and are briefly reviewed in Table 1.

Data on WHF retrieved from chronic HF trials

Although not having WHF as an inclusion criterion, some HF trials have enrolled patients with WHF and studied their outcomes, providing some insights into this specific patient population (Table 1). However, it should be noted that these trials have used different definitions of WHF.

Data on WHF retrieved from dedicated WHF trials

To date, only a reduced number of trials have looked specifically into the outcomes of patients with WHF. The increasing recognition of WHF as a specific phase in the course of chronic HF has spurred the development of dedicated WHF trials, with a growing body of evidence showing the benefit of GDMT in the management of outpatient WHF events. Three agents have been investigated in this setting: vericiguat, sotagliflozin, and omecamtiv mecarbil (Table 2).

Vericiguat

Despite the well-established benefit of RAAS inhibitors, beta-blockers, MRA, and SGLT2i in the treatment of chronic HF, patients with WHF continue to suffer from an unacceptable rate of events. A long and well-established line of research has demonstrated that the impairment of the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate (NO-sGC-cGMP) system is associated with important deleterious effects on the CV and renal systems [112]. Oxidative stress and endothelial dysfunction impair the production of nitric oxide and therefore soluble guanylate cyclase activity, which ultimately leads to cyclic guanosine monophosphate (cGMP) deficiency [113, 114]. Vericiguat is an oral soluble guanylate cyclase stimulator that activates the NO-sGC-cGMP system and may therefore improve and even reverse the alterations seen in the heart (by reducing myocardial stiffening, fibrosis, and ventricular hypertrophy and remodeling), kidneys (by decreasing fibrosis and improving renal blood flow), and systemic and pulmonary vessels (by enhancing endothelial function and reducing vasoconstriction) [115, 116].

After a long development program that began more than 20 years ago and included the SOCRATES-REDUCED trial [117], which showed a dose-dependent effect in HFrEF patients, the efficacy of vericiguat in the treatment of WHF was investigated in the VICTORIA trial. The trial enrolled 5050 patients with symptomatic chronic HFrEF and HF with mildly reduced EF (LVEF cut-off under 45%) and evidence of WHF, defined as HF hospitalization within the 6 months before randomization or receiving IV diuretic therapy without hospitalization within the previous 3 months [118]. In the study, the primary endpoint, a composite of CV death and hospitalization for HF, occurred in 35.5% of the vericiguat group and 38.5% of the control group, representing a significant relative risk reduction of 10% in favor of vericiguat (HR 0.90, 95% CI 0.82–0.98), which translated into an absolute risk reduction of 4.2 events per 100 patient/year. This high event rate in the placebo group highlighted the high-risk profile of the WHF patient. Regarding the secondary endpoints, vericiguat showed a significant reduction in total HFH (HR 0.91, 95% Cl 0.84–0.99) and the composite of HFH or all-cause mortality (HR 0.95, 95% Cl 0.84–1.07), but failed to meet the endpoint of CV death. Importantly, patients could be included with an eGFR above 15 mL/min/1.73 m^2, and no significant interaction with renal function was noted.

In terms of safety, vericiguat was well tolerated, with a similar overall frequency of adverse events and adverse events related to renal function or electrolyte balance compared to placebo. Systolic blood pressure showed a slight decline in the first 16 weeks and then returned to baseline, with a mean reduction of systolic blood pressure of 1–2 mmHg vs placebo. Importantly, symptomatic hypotension was similar among groups (9.1% in the vericiguat group versus 7.9% of the patients in the placebo group, P = 0.12), as it was syncope (4.0% in the vericiguat group versus 3.5% in the placebo group, p = 0.30).

Data from the pivotal VICTORIA trial showed the benefit of increasing soluble guanylate cyclase activity with vericiguat in patients with chronic HF with a recent decompensation and led to its inclusion in the treatment armamentarium for patients with HFrEF by the ESC and the American College of Cardiology (ACC)/American Heart Association (AHA) in addition to the other four mainstays of treatment, with a class IIb indication[26, 52, 91, 119, 120].

The early post-discharge period, also called the "vulnerable phase", has high mortality and hospital readmission rates, highlighting the need fora therapeutic approach of early and simultaneous (or rapid sequence initiation) of foundational therapies [24].The benefits of such a strategy were demonstrated in the STRONG-HF trial, where rapid, simultaneous up-titration of GDMTs and close follow-up were associated with a significant reduction of all-cause death or HF readmissions and increased patient QoL [121].

Table 2 Clinical trials that focused on patients with WHF

Clinical trial	Study arms	HF pathway targeted	Study population	WHF definition	WHF outcomes of interest
VICTORIA (Armstrong PW et al. 2020 [118])	Vericiguat vs placebo	Guanylate cyclase system	5050 patients with HFrEF and WHF	HF hospitalization in the previous 3 months or 3 – 6 months, or receipt of i.v. diuretic therapy without hospitalization in the previous 3 months	Death from CV causes or first HF hospitalization: 35.5% with vericiguat vs. 38.5% with placebo (HR 0.90, 95% CI 0.82–0.98; p = 0.02) Death from CV causes: 16.4% vs. 17.5% (HR 0.93, 95% CI 0.81–1.06) HF hospitalization: 27.4% vs. 29.6% (HR 0.90, 95% CI 0.81–1.00) Total HF hospitalizations (first and recurrent events): 38.3 events per 100 patient-years vs. 42.4 events per 100 patient-years (HR 0.91, 95% CI 0.84–0.99; p = 0.02) Death from any cause or first HF hospitalization: 37.9% vs. 40.9% (HR 0.90, 95% CI 0.83–0.98; p = 0.02) Death from any cause: 20.3% vs. 21.2% (HR 0.95, 95% CI 0.84–1.07; p = 0.38)
Analysis of **VICTORIA** (Lam et al. 2021 [50])	Vericiguat vs placebo	Guanylate cyclase system	5050 patients with HFrEF and WHF	HF hospitalization in the previous 3 months or 3 – 6 months, or receipt of i.v. diuretic therapy without hospitalization in the previous 3 months 67% of patients less than 3 months from index HF hospitalization (11% in-hospital), 17% 3 – 6 months from index HF hospitalization, 16% within 3 months of outpatient WHF	Rate of CV death or HF hospitalization per 100 patient-years: - HF hospitalization < 3 months: 40.9 - HF hospitalization 3 – 6 months: 29.6 - Outpatient WHF: 23.4 Adjusted risk of CV death or HF hospitalization vs. outpatient WHF: - HF hospitalization < 3 months: HR 1.48, 95% CI 1.27–1.73 - HF hospitalization 3 – 6 months: not significantly different (adjusted p = 0.25)

Table 2 (continued)

Clinical trial	Study arms	HF pathway targeted	Study population	WHF definition	WHF outcomes of interest
SOLOIST-WHF (Bhatt DL et al. 2021) [122]	Sotagliflozin vs. placebo	SGLT2	1222 patients with type 2 diabetes mellitus and HFr/pEF hospitalized for WHF	Hospitalization due to the presence of signs and symptoms of HF and treatment with i.v. diuretic therapy	Rate of total number of CV deaths, hospitalizations, and urgent HF visits per 100 patient-years: 51.0 with sotagliflozin vs. 76.3 with placebo (HR 0.67, 95% CI 0.52–0.85; $p < 0.001$) Rate of hospitalizations or urgent HF visits: 40.4 vs. 63.9 (HR 0.64, 95% CI 0.49–0.83; $p < 0.001$) Rate of death from CV causes: 10.6 vs. 12.5 (HR 0.84, 95% CI 0.58–1.22: $p = 0.36$) Rate of death from any cause: 13.5 vs. 16.3 (HR 0.82, 95% CI 0.59–1.14)
GALACTIC-HF (Teerlink JR et al. 2021 [124])	Omecamtiv mecarbil vs. placebo	Cardiac myosin	8256 patients with HFrEF	HF hospitalization at the time of enrollment or HF hospitalization or urgent ED visit for HF within 1 year prior to screening	Rate of first HF event (hospitalization or urgent HF visit) or death from CV causes per 100 patient-years: 24.2 with omecamtiv mecarbil vs. 26.3 with placebo (HR 0.92, 95% CI 0.86–0.99; $p = 0.03$) Rate of death from CV causes per 100 patient-years: 10.9 vs. 10.8 (HR 1.01, 95% CI 0.92–1.11; $p = 0.86$) Rate of first HF hospitalization per 100 patient-years: 18.0 vs. 19.1 (HR 0.95, 95% CI 0.87–1.03) Rate of death from any cause per 100 patient-years: 14.4 vs. 14.4 (HR 1.00, 95% CI 0.92–1.09)

Table 2 (continued)

Clinical trial	Study arms	HF pathway targeted	Study population	WHF definition	WHF outcomes of interest
Analysis of **PIONEER-HF** (Morrow DA et al. 2019 [125])	Sacubitril-valsartan vs. enalapril	RAAS	881 patients with HFrEF	Hospitalization for acute decompensated HF	Rate of CV death or rehospitalization for HF: 5.8% vs. 8.6% (HR 0.67, 95% CI 0.40–1.11) Rate or rehospitalization for HF: 5.1% vs. 7.0% (HR 0.72; 95% CI 0.42–1.25) Total number of rehospitalizations for HF: 41 vs. 64 events (RR 0.64; 95% CI 0.42–0.97; p = 0.037)
Analysis of **EMPULSE** (Voors AA et al. 2022[126])	Empagliflozin vs placebo	SGLT2	530 patients with HFmr/rEF	Hospitalization for acute HF and treatment with i.v. furosemide or equivalent	Rate of CV death or WHF event until end-of-trial visit: 12.8% vs. 18.5% (HR 0.69; 95% CI 0.45–1.08) Number of events per 100 patient-years: 55.01 vs. 80.45 Greater absolute change in KCCQ-TSS: −4.45 points; 95% CI 0.32–8.59 Win ratio: 1.36 (95% CI 1.09–1.68; p = 0.0054). Empagliflozin superior in 53.9% vs. placebo superior in 39.7%

CI confidence interval, *CV* cardiovascular, *ED* Emergency Department, *HF* heart failure, *HFmrEF* heart failure with mildly reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HR* hazard ratio, *i.v* intravenous, *KCCQ-TSS* Kansas City Cardiomyopathy Questionnaire Total Symptom Score, *LVEF* left ventricular ejection fraction, *RAAS* renin–angiotensin–aldosterone system, *RR* rate ratio, *SGLT2* sodium-glucose cotransporter 2, *WHF* worsening heart failure

However, the implementation of GMDT remains suboptimal. Therefore, vericiguat could be offered as a pillar after a WHF event to better control the progression of HF. As these challenging patients often suffer from impaired kidney function, hyperkalemia, and hypotension, the favorable tolerability profile of vericiguat is of particular interest for this subset of patients.

Sotagliflozin

Sotagliflozin is a SGLT2i with a dual-receptor binding affinity for SGLT1 and SGLT2. After SGLT2i have shown efficacy in reducing the risk of hospitalizations for HF and all-cause and CV death among patients with stable HFrEF in several studies, including DAPA-HF [108]and EMPEROR-REDUCED[109], a third agent in this class, sotagliflozin, was investigated when initiated shortly after a WHF event in the SOLOIST-WHF trial [122]. This randomized, placebo-controlled, phase 3trial evaluated sotagliflozin in diabetic patients with HFr/pEF recently hospitalized for WHF [122]. The primary endpoint was a composite of death from CV causes and hospitalizations or urgent care visits for HF. Study results showed a lower rate of primary endpoint events in the sotagliflozin arm (51.0 per 100 patient-years) compared to the placebo arm (76.3 per 100 patient-years; HR 0.67, 95% CI 0.52–0.85; $p < 0.001$), indicating the benefit of sotagliflozin in the treatment of WHF in patients with either reduced or preserved ejection fraction (the latter comprising 21% of the study population) when administered soon after a decompensated HF event.

Omecamtiv mecarbil

Omecamtiv mecarbil is a selective cardiac myosin activator that prolongs the duration of left ventricular systole without the undesirable secondary effects of altered calcium homeostasis and without changing the velocity of pressure development, improving cardiac function in patients with chronic HFrEF [123].

Its potential effects in the treatment of WHF were assessed in the randomized, placebo-controlled, phase 3 GALACTIC-HF trial, in which omecamtiv mecarbil was associated with an 8% lower relative risk of the composite primary endpoint of time to CV death or first HF event [124]. The trial showed that, in patients with HFrEF who were either hospitalized at the time of enrolment for a primary HF reason or had a hospitalization or ED admission for HF within 1 year before screening, omecamtiv mecarbil added to GDMT significantly lowered the incidence of a HF event or death from CV causes (HR 0.92; 95% CI 0.86–0.99; $p = 0.025$).Although the effect of omecamtiv mecarbil was generally consistent across subgroups, a possible interaction was seen with ejection fraction at baseline. In fact, although there was no benefit of this agent on the primary composite outcome for patients with a median LVEF > 28% (HR 1.04; 95% CI 0.94–1.16), a 16% lower risk was observed for patients with a median LVEF ≤ 28% (HR 0.84; 95% CI 0.77–0.92). Of note, omecamtiv mecarbil has been associated with an increase in troponin levels as a result of the drug's effect on myocardial workload [124].

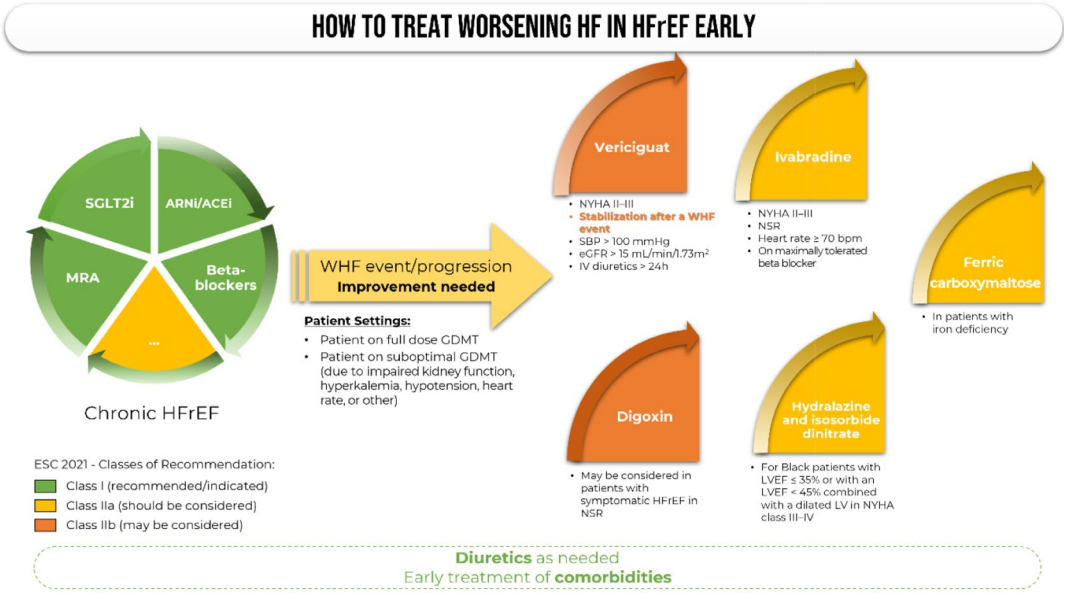
As of December 2024, the incorporation of omecamtiv mecarbil into clinical practice guidelines is pending further validation and regulatory approval.

In addition to providing evidence of the benefit of treating WHF with GDMT, the VICTORIA, SOLOIST-WHF, and GALACTIC-HF trials consistently documented these patients' high risk, by reporting a higher rate of the composite primary endpoint of CV death and HF hospitalization in the control group. Compared with other HFrEF landmark trials (38.5%, 39.1%, and 76.3% in the VICTORIA, GALACTIC-HF, and SOLOIST-WHF trials vs. 26.5%, 21.2%, and 24.7%, in the PARADIGM-HF, DAPA-HF, or EMPEROR-REDUCED trials) [107–109, 118, 122, 124].

Given the challenges of keeping patients in the recommended GDMT uptake, the optimal therapeutic strategy (including therapy initiation and uptitration) should be tailored to each patient according to his/her characteristics and tolerability, as well as vital signs, renal function, electrolytes, and comorbidities. In this assessment, monitoring parameters such as blood pressure, heart rate, renal function, and potassium levels may be relevant for therapy initiation and uptitration [52].

Extensive data support the use of quadruple therapy and innovative drugs for the treatment of HFrEF and SGLT2i for the treatment of HFmrEF and HFpEF, but the uptake of GDMT remains low due to tolerability issues, economic constraints, and limited drug access [127]. In addition, physician inertia and lack of patient compliance also contribute to the suboptimal use of GDMT. A tailored approach for patients with WHF, taking into account the impact of tolerability and other issues, is essential for the optimization and full implementation of GDMT. In the STRONG-HF trial, patients readily accepted an intensive treatment strategy of rapid pre-discharge initiation of all treatment pillars and subsequent titration of GDMT during frequent post-discharge follow-up with monitoring of clinical status and laboratory values with serial measurements of NT-proBNP, as it reduced symptoms, improved QoL, and reduced the risk of all-cause death or HF readmission compared with usual care [121].

In addition, after a WHF event, a single treatment adjustment, such as oral diuretics, disease-modifying drugs for HFrEF, HFmrEF, or HFpEF, or drugs to treat comorbidities (especially relevant for WHF in HFpEF), is often not sufficient and urgent i.v. treatment is required (e.g. i.v. diuretics, commonly used for decongestion in all HF phenotypes).



ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor neprilysin inhibitor; bpm, beats per minute; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LV, left ventricle; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter inhibitor; NSR, normal sinus rhythm; WHF, worsening heart failure.

Fig. 3 Proposal for early pharmacological management of WHF in HFrEF. Color code for classes of recommendation: green for class of recommendation I; yellow for class of recommendation IIa; orange for class of recommendation IIb (based on the 2021 ESC Guidelines [52])

Other treatments, such as i.v. administration of intermittent doses of levosimendan to reduce plasma NT-proBNP, worsening health-related QoL, and hospitalizations for HF, in outpatients with advanced chronic HFrEF on a trajectory to either definitive intervention by heart transplantation or left ventricular assist device implantation, or a palliative care pathway, are also required [128, 129]. The HF day hospital plays a critical role in improving access to care, providing timely outpatient i.v. treatment, reducing hospitalizations and associated costs, and improving patient QoL.

In line with this, a framework for the management of patients with HFrEF experiencing WHF is proposed, emphasizing the urgency of managing congestion and precipitants and initiating quadruple medical therapy along with additional medications to mitigate residual clinical risk (Fig. 3). Conversely, treatment options for HFpEF remain limited, with only SGLT2 inhibitors recommended as class IA therapies. In both cases, it is essential to prioritize early management of comorbidities and diuretic use in this patient population.

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor neprilysin inhibitor; bpm, beats per minute; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LV, left ventricle; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter inhibitor; NSR, normal sinus rhythm; WHF, worsening heart failure.

Lastly, beyond pharmacological therapy, the guidelines recommend optimization of GDMT inpatients with HFrEF with severe secondary mitral regurgitation either with surgery, in patients with an indication for coronary artery bypass grafting (CABG), or with transcatheter edge-to-edge repair (TEER) in patients who meet the COAPT (Cardiovascular Outcomes Assessment of the Mitra Clip Percutaneous Therapy for HF Patients With Functional Mitral Regurgitation) trial inclusion criteria [27, 52, 130], as well as cardiac resynchronization therapy (CRT) or implantable cardioverter-defibrillator (ICD) if indicated[131, 132].

Conclusions

WHF marks the beginning of a high-risk phase in the clinical course of HF, but is not recognized or treated promptly, leading to impaired QoL and functional capacity and poor outcomes.

After careful consideration of all the evidence gathered and presented in this article, the expert panel highlights the following key messages:

- Although recognized as a relevant clinical phase with significant health, social, economic, and prognostic impact, there is no consensus among experts on the definition of WHF. In addition, the condition remains poorly characterized and lacks real-world data.
- The definition of WHF should be revised and clearly established, although it is acknowledged that the concept of WHF is difficult to delimitate and define in the journey of patients living with chronic HF.
- The concept of 'optimized background therapy' for these patients is still not implemented in clinical practice. It should also be clearly defined and incorporated into the usual management of these patients.
- Early prevention and detection are the cornerstones of WHF management. Detection of WHF in clinical practice should rely on clinical parameters, imaging markers, biomarkers, and assessment of the patient's functional capacity according to the severity of his/her clinical status, care setting, and local logistics. Prevention of WHF should be based on patient-centered optimized therapy for chronic HF, a "dry before discharge" strategy, early initiation of the four pillars of treatment for HFrEF and SGLT2i for HFpEF, and elaboration of a tailored follow-up plan and patient education and empowerment.
- Some novel agents have shown benefit on CV outcomes in patients with WHF and should be included in their management as part of standard GDMT.
- The uptake of GDMT remains low due to tolerability issues, economic constraints, and limited drug access and should be optimized and fully implemented as it is critical to improve the outcomes of patients with WHF.
- Referral of high-risk HF patients to HF clinics with day hospitals, multidisciplinary teams, and integrated programs must be a priority.

Acknowledgements The authors acknowledge the medical writing assistance provided by Joana Cavaco-Silva, Ph.D. (jo.cvsilva@gmail.com).

Author contributions All authors contributed equally to this article through conceptualization, literature search, data analysis, drafting, and critical revision of the work.

Funding Medical writing assistance provided by Joana Cavaco Silva, Ph.D., from ScienceCircle - Scientific and Biomedical Consulting (jo.cvsilva@gmail.com), was funded by Bayer AG.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical standards The manuscript does not contain clinical studies or patient data.

Competing interests CF received consultancy fees, grants, and speaker's honoraria from Astra Zeneca, Bayer, Bial, Boehringer Ingelheim, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Servier, and CSLVifor. RB received speaker, advisory board, and grant funding fees from AstraZeneca, Bayer, Bial, Boehringer Ingelheim, Lilly, Menarini, Merck, MSD, Novartis, Pfizer, Servier Portugal, and Vifor Pharma. FF received consultant fees from Bayer, AstraZeneca, Boehringer Ingelheim, and Medinfar. BM received consultant or speaking fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Servier, Novartis, Vifor pharma, and Viatris. JP received speaker and consultant fees from Astra Zeneca, Bayer, Bial, Boehringer-Ingelheim, Lilly, Merck, Novartis, Pfizer, Roche diagnostics, Servier, and CSL Vifor. PMS received consultant or speaking fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, and Pfizer. JSC received research, consultant, or speaking fees from AstraZeneca, Bayer, Bial, Boehringer Ingelheim, Eli Lilly, Novartis, Pfizer, Servier, and Vifor Pharma. DB received consultancy fees and lectures or scientific meeting sponsorship from Alnylam, AstraZeneca, Bayer, Bial, Boehringer Ingelheim, Novartis, and Pfizer.

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