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CONSENSUS STATEMENT

Worsening of chronic heart failure: definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association of the European Society of Cardiology

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Episodes of worsening symptoms and signs characterize the clinical course of patients with chronic heart failure (HF). These events are associated with poorer quality of life, increased risks of hospitalization and death and are a major burden on healthcare resources. They usually require diuretic therapy, either administered intravenously or by escalation of oral doses or with combinations of different diuretic classes. Additional treatments may also have a major role, including initiation of guideline-recommended medical therapy (GRMT). Hospital admission is often necessary but treatment in the emergency service or in outpatient clinics or by primary care physicians has become increasingly used. Prevention of first and recurring episodes of worsening HF is an essential component of HF treatment and this may be achieved through early and rapid administration of GRMT. The aim of the present clinical consensus statement by the Heart Failure Association of the European Society of Cardiology is to provide an update on the definition, clinical characteristics, management and prevention of worsening HF in clinical practice.

Keywords Worsening heart failure • Hospitalization • Emergency department visits • Outpatients • Intensification of oral therapy • Prognosis

Preamble

The clinical course of heart failure (HF) is characterized by episodes of worsening symptoms and signs.[1–3] These episodes of worsening HF (WHF) are followed by an increased risk of hospitalizations and death and are a major burden on the health-care system, because of their frequency, urgency and prognostic impact.[1,3–5] Their prevention is a major target of current treatment of HF. The aim of the present clinical consensus statement by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) is to provide an update on the definition and clinical characteristics of WHF and summarize recent findings for the management and prevention of WHF in clinical practice.

Definition and classification

Definition

Worsening HF can be defined as worsening symptoms and signs of HF in patients with pre-existing HF, requiring intensification of treatment, most often diuretic therapy. It requires a prior diagnosis of HF, excluding episodes of new-onset HF. Cases where poor adherence to treatment, rather than decompensation of pre-existing HF, is the cause of worsening symptoms and signs are also excluded (*Table 1*). The need for intensification of HF therapy is an essential component of our definition of WHF. Worsening HF must be kept distinct from acute HF which is a much broader entity including also new-onset HF as well as different clinical presentations such as acute pulmonary oedema, right ventricular failure and cardiogenic shock.[1] When the term of WHF is used the focus is, instead, on the clinical course of the patient with chronic, pre-existing HF. We provide here an in-depth review of this topic with focus on findings with implications for clinical practice.

Clinical presentations

Episodes of WHF can have different clinical presentations depending on precipitating factors, comorbidities, speed of deterioration, severity, symptoms and clinical signs (e.g. worsening peripheral oedema, increasing exertional breathlessness, orthopnoea). Clinical presentation dictates the urgency and site of care (*Figure 1*). Sites of care include the following:

(1) Hospitalization: patients with WHF are often hospitalized for urgent assessment, intravenous (IV) medications and other specific treatments. Hospitalization remains the most frequent clinical event for WHF.
(2) Emergency department (ED) visit: patients present at the ED for worsening signs/symptoms, receive IV therapy, generally loop diuretics, and are discharged without hospitalization.
(3) Ambulatory treatment: either as outpatients receiving IV therapy in an outpatients setting or as outpatients treated with an escalation of their oral diuretic therapy.

The common feature of all these WHF events is the need for an urgent re-evaluation of the patient because of worsening symptoms or signs. Most patients with severe WHF are currently admitted to hospital for IV diuretic therapy.[6–8] However, managing patients in day-care facilities, outpatient clinics and in the community is becoming more frequent both because patients are increasingly seeking alternatives to hospital admission (which will depend on service availability, symptom severity and acuity, distance from the clinic/hospital, patients' decisions, physicians' advice) and hospitals are seeking to reduce admissions and use alternative resources more cost-efficiently.

Although new-onset HF may be considered as WHF, too, the present document is focused only on WHF occurring in patients with a previous diagnosis of HF, i.e. worsening of pre-existing chronic HF. Worsening HF may also occur while patients are hospitalized and similarly lead to the initiation or escalation of IV treatment, generally with diuretics and/or inotropes.[9,10] These episodes are also associated with subsequent poorer outcomes and their reduction may be major target of treatment.[9] Their consideration goes beyond the aims of this clinical consensus statement and they have been extensively reviewed elsewhere.[9]

Table 1 Definition, pathophysiology and site of care of worsening heart failure

	Includes	Excludes
Definition	• Worsening symptoms and signs of HF • Requiring intensification of treatment, generally including diuretic therapy • Occurring in patients with pre-existing HF	• New-onset HF • Episodes with concomitant factors, including comorbidities and/or poor compliance, as primary cause
Pathophysiology	• Disease progression • Congestion	• Precipitating factors as main cause
Site of care	• Hospital • Emergency department • Ambulatory – with IV therapy – with escalation of oral therapy	• Episodes requiring no changes in HF treatment

HF, heart failure; IV, intravenous.

Epidemiology and outcome

Hospitalizations

Worsening HF is a common cause of urgent hospitalizations in adults.[11–17] Many, likely most, patients with HF will be hospitalized for WHF at some time.[14,17,18] Hospitalization rates for WHF vary depending on many factors including national customs, socio-economic factors and the availability of out-of-hospital management resources.[17,19–21] An example of how extrinsic factors may influence hospitalizations rates has been the impact of COVID-19 lockdown which has reduced dramatically admissions for HF.[22–26]

Patients hospitalized for WHF have a substantial increase in rehospitalization rates and mortality compared to those who remain clinically stable (*Table 2*).[27,28] In the US, among patients hospitalized for worsening of HF with reduced ejection fraction (HFrEF) between 2007 and 2018, the rates of in-hospital mortality, 30-day mortality and 30-day HF readmission were 4.0%, 8.2% and 9.8%, respectively.[18] In the ESC HFA Long-Term Registry, in-hospital mortality was 3.4%, 2.1% and 2.2% in patients with HFrEF, HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF), respectively. One-year mortality rates were 22, 17, and 17 per 100 patient-years and HF rehospitalization rates 29, 19 and 17 per 100 patient-years, respectively. All-cause rehospitalization rates were 48, 35, and 42 per 100 patient-years in HFrEF, HFmrEF, and HFpEF, respectively.[29] Many readmissions after a HF hospitalization are primarily for reasons other than HF, including infection and renal dysfunction, often with HF as a secondary diagnosis. HF increases patients' fragility, making them more susceptible to and exacerbating the effects of comorbidities.

In the large National Cardiovascular Data Registry PINNACLE database, 17% of the patients developed WHF within 18 months following initial diagnosis of HFrEF and their 2-year mortality and 30-day rehospitalization rates were 22.5% and 56%, respectively.[30] Kimmoun *et al.*[11] analysed all studies published from 1980 to 2017 regarding acute HF, including 285 studies representing 15 million of patients. Total mortality and non-elective rehospitalizations rates were 7% and 24% and of 18% and 46%, at 30 days and 1 year, respectively, after the acute HF event. A decline in all-cause deaths, likely related with the implementation of neurohormonal antagonists, with stable rehospitalization rates was found in the last decades.

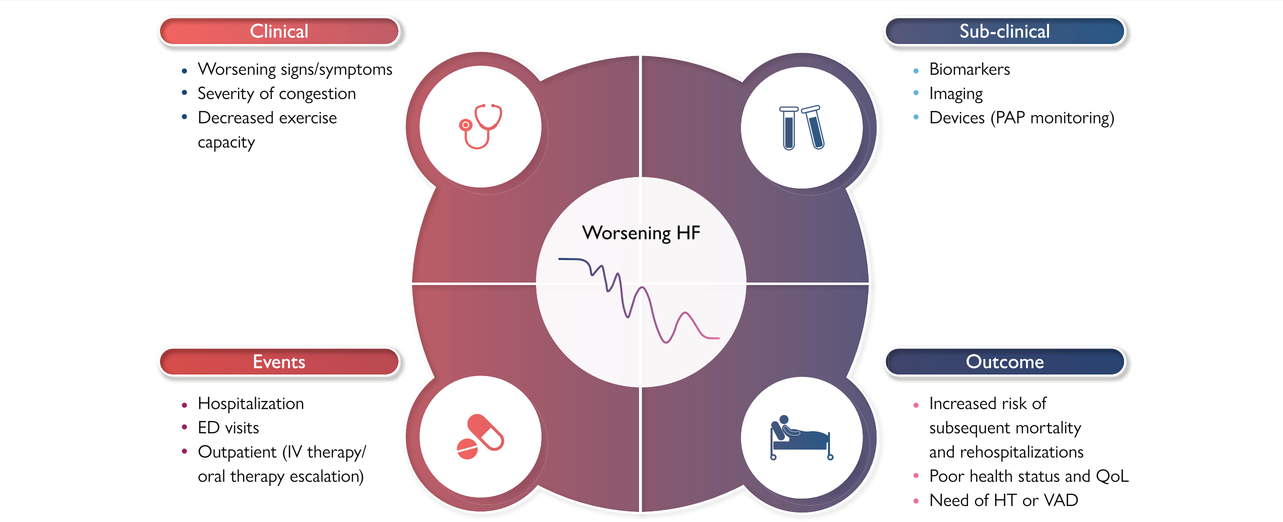

Figure 1 The four domains of a patient with an episode of worsening heart failure (HF). ED, emergency department; HT, heart transplantation; IV, intravenous; PAP, pulmonary artery pressure; QoL, quality of life; VAD, ventricular assist device. [Correction added on 14 June 2023, after first online publication: Figure 1 has been updated in this version.]

Table 2 Summary of studies reporting clinical outcomes in patients experiencing worsening heart failure

Author, year	Study population	WHF definition	All-cause mortality, HR (95% CI)	All-cause mortality, rates	Other outcomes
Randomized clinical trials					
Solomon *et al.*,[28] 2007	7572 patients from the CHARM programme	1455 (19%) had HF hospitalization	Unadjusted HR 4.55 (4.11–5.03); adjusted HR 3.15 (2.83–3.50) compared to those never hospitalized	–	–
Skali *et al.*,[32] 2014	1820 patients from MADIT-CRT	52 (2.9%) patients experienced non-fatal outpatient WHF and 331 (18.2%) non-fatal inpatient WHF	HR 10.7 (6.1–18.7) for outpatient WHF; HR 12.4 (9.1–16.9) for inpatient WHF, compared with non WHF events	Rates per 100 p/y: - Inpatient WHF, 18.5 - Outpatient WHF, 15.9 - Non-WHF, 1.5	–
Okumura *et al.*,[6] 2016	8399 patients from PARADIGM-HF	In an examination of first non-fatal events, 1107 patients (13.2%) were hospitalized for WHF; 78 (1.0%) had an ED visit; 361 (4.3%) had outpatient intensification of therapy	- Inpatient WHF, HR 5.9 (5.2–6.6) - ED visit, HR 4.5 (3.0–6.7) - Outpatient WHF, HR 4.8 (3.9–5.9) compared to patients without WHF events	Rates per 100 p/y: - Inpatient WHF, 33.4 (30.3–36.8) - ED visit, 25.1 (16.9–37.5) - Outpatient WHF, 27.2 (22.7–32.7) - No WHF events, 5.9 (5.6–6.3)	Rate of CV death per 100 p/y: - Inpatient WHF, 30.3 (27.4–33.6) - ED visit, 19.9 (12.7–31.2) - Outpatient WHF, 22.1 (18.0–27.0) - No WHF, 4.6 (4.2–4.9)
Docherty *et al.*,[8] 2020	4744 patients from DAPA-HF	First episode of WHF: –407 (8.6%) outpatient augmentation of therapy; –20 (0.4%) urgent HF visit with IV therapy; –489 (10.3%) HF hospitalization	- Outpatient WHF, adjusted HR 2.67 (2.03–3.52) - Urgent HF visit, adjusted HR 3.00 (1.39–6.48) - Inpatient WHF, adjusted HR 6.21 (5.07–7.62), in comparison with no WHF events	–	–
Lam *et al.*,[35] 2021	5050 patients from VICTORIA	3378 (67%) were randomized less than 3 months from index HFH (11% in-hospital), 871 (17%) within 3 to 6 months of HFH, and 801 (16%) within 3 months of outpatient WHF	–	–	Rates of CV death or HFH per 100 p/y: - HFH <3 months, 40.9 - HFH 3 to 6 months, 29.6 - Outpatient WHF: 23.4 Adjusted HR, 1.48 (1.27–1.73), for HFH <3 months vs. outpatient WHF; no significant difference between HFH 3 to 6 months and outpatient WHF (adjusted $p = 0.25$)
Vaduganathan *et al.*,[36] 2021	4796 patients from PARAGON-HF	884 experienced a first episode of WHF, of which 66 (7.5%) were urgent HF visits and 818 (92.5%) were HFH	HR 0.52 (0.27–0.97) for an urgent HF visit compared with HFH	Rates per 100 p/y: - HFH, 19.2 (16.9–21.8) -Urgent HF visit, 10.1 (5.4–18.7) -No WHF, 4.0 (3.6–4.4)	–
Registries					
Butler *et al.*,[30] 2019	11 064 patients with incident HFrEF from the National CV Data Registry PINNACLE	1851 (17%) developed WHF	–	Subsequent 2-year mortality rate, 22.5% Mean survival time using Kaplan–Meier estimate, 19.7 ± 0.2 months	56% of patients were rehospitalized within 30 days of the WHF event
Ferreira *et al.*,[34] 2019	2516 patients with WHF from BIOSTAT-CHF	1694 inpatient WHF, 822 outpatient WHF	–	–	Rate of the composite of all-cause death or HFH per 100 p/y: - Inpatients, 33.4 (31.1–35.9) - Outpatients, 18.5 (16.4–21.0) Adjusted HR 1.24 (1.07–1.43) for inpatients vs. outpatients
Butt *et al.*,[14] 2020	17 176 patients with a first HFH in 2013–2015 from the Danish nationwide registries	8860 (51.6%) patients were admitted with new-onset HF and 8316 (48.4%) with worsening of CHF	Unadjusted HR 1.37 (1.31–1.44); adjusted HR 1.22 (1.16–1.28) compared with new-onset HF	In-hospital mortality, 6.9% in patients with WHF	- Unadjusted HR for all-cause death or HFH: 1.54 (1.48–1.60); adjusted HR 1.37 (1.31–1.43) - Unadjusted HR for HF readmission: 2.13 (2.01–2.27); adjusted HR 1.81(1.69–1.93); - Unadjusted HR for any readmission 1.34 (1.29–1.39); adjusted HR 1.18 (1.13–1.22) compared with new-onset HF
Madelaire *et al.*,[37] 2020	74 990 Danish patients diagnosed with HF from 2001 to 2016	- 53 794 (71.7%) no WHF - 4517 (6.0%) outpatient event - 3160 (4.2%) hospitalized for WHF - 942 (1.6%) with both events	Adjusted HR for 1-year death: - Outpatient WHF HR, 1.75 (1.66–1.85) - Inpatient WHF, HR 2.28 (2.16–2.41) compared with non-WHF events	1-year mortality: - 18.0% after an outpatient event - 22.6% after HF hospitalization - 10.4% for non-WHF	–

Table 2 (Continued)

Author, year	Study population	WHF definition	All-cause mortality, HR (95% CI)	All-cause mortality, rates	Other outcomes
Greene et al.,[18] 2021	22 677 patients with HFrEF hospitalized between 2007 and 2018 in US	8621 (38%) had *de novo* HF and 14 056 (62%) had worsening CHF	–	Rates of in-hospital mortality and 30-day mortality were 4.0% and 8.2%, respectively in patients with WHF	Rates of 30-day HF readmission and 30-day all-cause readmission were 9.8% and 15.1% in patients with WHF
Kimmoun et al.,[11] 2021	Systematic review including 285 AHF studies (15 million patients) from 1980 to 2017	–	–	Total 30-day and 1-year all-cause death rates were 7% (6–8) and 24% (23–26), respectively	Total 30-day and 1-year all-cause non-elective readmission rates were 18% (16–19) and 46% (41–51), respectively
Agarwal et al.,[13] 2021	8 273 270 HF hospital admissions from 2010 to 2017 from US	–	–	–	- Rates per 1000 adults for HF readmissions: 1.0 in 2010, 0.9 in 2014 and 1.1 in 2017 - All-cause 30-day readmissions: 0.8 in 2010, 0.7 in 2014 and 0.9 in 2017
Labrosciano et al.,[15] 2021	Patients >18 years hospitalized with HF from 2010 to 2015 in Australia and New Zealand	–	–	Out of 153 592 patients, 16 442 (10.7%) died within 30 days of admission (6.6% in hospital and 4.1% after discharge)	Out of 148 704 patients, 33 158 (22.3%) had at least one unplanned readmission within 30 days of discharge
Shah et al.,[33] 2022	2661 US patients hospitalized for HF from ASCEND-HF	AT 30-day follow-up: - 193 patients (7%) had ED visit and discharge - 459 patients (17%) had HFH - 2009 patients (76%) had neither urgent visit	Adjusted HRs for 150-day mortality: - HR 2.41 (1.85–3.12) for HFH vs. no WHF -HR 1.39 (0.88–2.18) for ED discharge vs. no WHF - HR 0.58 (0.36–0.92) for ED discharge vs. HFH	Rates of death during the subsequent 150 days: - 21.0% (17.5–25.0) for patients with HFH - 11.4% (7.7–16.8) for patients discharged from the ED - 8.0% (6.9–9.3) for patients without WHF	–
Ambrosy et al.,[7] 2022	103 138 patients with HF from 2010 to 2019 from Kaiser Permanente Northern California (KPNC)	126 008 WHF episodes, including 34 758 (27.6%) outpatient encounters, 28 301 (22.5%) ED visits/observation stays, and 62 949 (50.0%) hospitalizations		30-day rates of all-cause death: 14.1% for inpatient WHF vs. 5.0% for patients with ED visits vs. 3.0% for outpatients WHF	- 30-day rates of hospitalization for WHF: 12.4% for inpatient WHF vs. 10.6% for patients with ED visits vs. 8.2% for outpatients WHF - 30-day rates of all-cause hospitalization: 20.8% for inpatient WHF vs. 16.7% for patients with ED visits vs. 13.7% for outpatients WHF
Kaplon-Cieslicka et al.,[29] 2022	5951 participants in the ESC HF Long-Term Registry hospitalized for AHF	–	–	- In-hospital mortality: 3.4% in HFrEF, 2.1% in HFmrEF, and 2.2% in HFpEF - 1-year mortality rates: 22, 17, and 17 per 100 p/y, respectively	- HF rehospitalization rates: 29, 19 and 17 per 100 p/y in HFrEF, HFmrEF and HFpEF, respectively. - All-cause rehospitalization rates: 48, 35, and 42 per 100 p/y, in HFrEF, HFmrEF, and HFpEF, respectively
Hariharaputhiran et al.,[16] 2022	283 048 patients hospitalized for HF from 2008 to 2017 in Australia and New Zealand	–	–	48.3% (48.1–48.5) were surviving by 3 years, 34.1% (33.9–34.3) by 5 years and 17.1% (16.8–17.4) by 10 years (median survival 2.8 years)	–

AHF, acute heart failure; CHF, chronic heart failure; CI, confidence interval; CV, cardiovascular; ED, emergency department; HF, heart failure; HFH, heart failure hospitalization; 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; IV, intravenous; p/y, patient-years; WHF, worsening heart failure.

Outpatient treatment of worsening heart failure

Data from clinical trials

Val-HeFT (Valsartan Heart Failure Trial) was one of the first trials to include WHF as an outcome, including the administration of IV inotropic or vasodilator therapy for at least 4 h.[31] A secondary analysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial was the first to show the prognostic impact of outpatient WHF events.[32] In this study, risk of death was higher both in patients with a hospitalization for WHF and in those who were treated for WHF as outpatients, compared to that of patients without HF events (hazard ratio [HR] 12.4, 95% confidence interval [CI] 9.1–16.9 for patients hospitalized for WHF and HR 10.7, 95% CI 6.1–18.7 for those treated for WHF as outpatients).[32]

The poor outcome of WHF events without hospitalization was confirmed by subsequent analyses of other clinical trials (*Table 2*). In the PARADIGM-HF (Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ACEI [angiotensin-converting enzyme inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, among 8399 patients, 361 (4.3%) had outpatient intensification of HF therapy, 78 (1.0%) had an ED visit, and 1107 (13.2%) had HF hospitalizations. The risk of subsequent death, compared to patients without HF events, was similar after each manifestation of WHF: outpatient intensification of HF therapy (HR 4.8; 95% CI 3.9–5.9); ED visit (HR 4.5; 95% CI 3.0–6.7); HF hospitalizations (HR 5.9; 95% CI 5.2–6.6).[6]

Other studies showed that outpatients, compared to inpatients with WHF, had a lower risk of clinical events, though still significantly higher than that of outpatients.[33] In a pre-specified analysis of the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, Docherty *et al.*[8] examined the frequency and significance of different types of WHF. Among the 4744 randomized patients, 8.6% of patients were treated by an outpatient augmentation of oral treatment, 0.4% with an urgent HF visit with IV therapy and 10.3% had a HF hospitalization. The adjusted risk of death from any cause (in comparison with no event) was lower for outpatient WHF (HR 2.67, 95% CI 2.03–3.52) or an urgent HF visit (HR 3.00, 95% CI 1.39–6.48) compared to a HF hospitalization (HR 6.21, 95% CI 5.07–7.62). BIOSTAT-CHF (The BIOlogy Study to TAilored Treatment in Chronic Heart Failure) included 2516 patients with worsening signs and symptoms of HF, of whom 1694 were managed as inpatients and 822 as outpatients. Inpatients had higher rates of the primary outcome of death or HF hospitalization with an incidence rate per 100 person-years of 33.4 (95% CI 31.1–35.9) for inpatients vs. 18.5 (95% CI 16.4–21.0) for outpatients (adjusted HR 1.24, 95% CI 1.07–1.43).[34]

Among patients with worsening chronic HF in the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial, those randomized within 3 months of HF hospitalization had an approximately two-fold higher risk of cardiovascular death or HF hospitalization than those with an outpatient WHF event without hospitalization, even after adjusting for relevant covariates, background therapy, and laboratory tests. This risk was further increased in those randomized within 1 month of HF hospitalization (>40 events per 100 patient-years) or among patients randomized within their index hospitalization (>50 events per 100 patient-years).[35]

The significance of ambulatory WHF episodes was more recently evaluated in patients with HFpEF enrolled in the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction) trial. Of 884 first WHF events, 66 (7.5%) were urgent HF visits. Regardless of the treatment setting, patients with a first episode of WHF had higher rates of subsequent death: 19.2 per 100 patient-years for those who had a HF hospitalization and 10.1 per 100 patient-years for those who had urgent HF visit, compared with 4.0 per 100 patient-years in those who did not experience WHF. Patients whose first episode of WHF was an urgent visit had similar age, comorbidities, baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP), and Meta-Analysis Global Group in Chronic Heart Failure risk scores to those in whom the first HF event was a hospitalization.[36]

Data from registries

Registries have confirmed that treatment of WHF with intensification of outpatient oral diuretic therapy or outpatient IV loop diuretic administration is occurring in an increasing proportion of patients. In an analysis of the nationwide Danish registry, among 74 990 outpatients with HF, there were 9 per 100 person-years who had intensification of diuretic therapy. One-year mortality was 18.0% after outpatient intensification of diuretic therapy, 22.6% after HF hospitalization, and 10.4% for matched controls with neither events.[37] In US, among 3426 outpatients with chronic HFrEF enrolled in the CHAMP-HF (Change the Management of Patients with Heart Failure) registry, intensification of oral diuretics occurred in 796 (23%) patients. Patients with a diuretic dose increase had a significantly higher number of HF hospitalizations (rate ratio 2.53, 95% CI 2.10–3.05), ED visits (rate ratio 1.84, 95% CI 1.56–2.17), and home health visits (rate ratio 1.88, 95% CI 1.39–2.54), compared with patients with no increase in diuretic dose.[38] Ambrosy *et al.*[7] described the incidence of WHF events across the care continuum from ambulatory encounters to hospitalizations. A total of 126 008 WHF episodes were identified, including 27.6% outpatient encounters, 22.5% ED visits/observation stays, and 50.0% hospitalizations. Thirty-day mortality rates ranged from 3.0% for outpatient encounters to 5.0% for ED visits and up to 14.1% for HF hospitalizations. The 30-day rate of hospitalizations for WHF ranged from 8.2% for outpatient encounters to 12.4% for hospitalizations.[7]

Pathophysiology

An increase in intracardiac pressures plays a pivotal role in the pathophysiology of WHF, irrespective of left ventricular ejection fraction (LVEF), and precedes overt decompensation.[39,40] Hypoperfusion and end-organ injury and dysfunction may also be present.[1,41,42] Among patients hospitalized with WHF in the ESC HFA HF registry, 9.9% were ‘dry-warm’, 70% were ‘wet-warm’, 20% were 'wet-cold', and 0.4% were 'dry-cold'.[43] Congestion may reduce absorption of guideline-recommended medical therapies (GRMT) and loop diuretics, further worsening HF.[44] Congestion usually presents with variable degrees of bilateral lower limb oedema and substantial weight gain. On the other hand, a significant proportion of patients hospitalized for decompensated HF display only minor increases in body weight (<1 kg) before hospital admission.[45] In these patients, congestion may be precipitated by fluid redistribution, rather than accumulation, with pulmonary congestion being the main clinical sign.[42] Sympathetic stimulation induces a transient vasoconstriction leading to a sudden displacement of volume from the splanchnic and peripheral venous system to the pulmonary circulation. Being maladaptive volume redistribution a leading cause of WHF, splanchnic nerve modulation has been identified as a potential target for patients with WHF.[46,47]

An important contributor of a recurrent WHF event after discharge is residual congestion that can be clinically overt or subclinical. Precipitating factors leading to WHF include non-adherence to diet (i.e. salt restriction) or medications.[48] Comorbid conditions, either cardiovascular (myocardial ischaemia, atrial fibrillation, valvular heart disease) or non-cardiovascular (lung and renal disease, sleep-disordered breathing, iron deficiency, thyroid disorders) or other precipitant factors (i.e. infections) can contribute to the development of WHF and may require a specific treatment.[49–51] Greene *et al.*[5,52] have proposed that congestion and HF symptoms entirely explicable by failure to take medication or an undercurrent non-HF event such as acute coronary syndrome should not be included in the definition of WHF as they do not primarily reflect an alteration in the HF process but rather a second insult. There is logic to this proposal and it is close to the practice adopted by many clinical event committees in defining a WHF event.

Early detection

Clinical signs and risk scores

Physical examination cannot accurately detect the underlying haemodynamic changes that lead to WHF.[53] Several congestion scores including symptoms (dyspnoea, orthopnoea, fatigue) and signs of HF (rales, peripheral oedema, jugular vein distension, hepatomegaly, weight gain) have been proposed and may be useful in different settings/moments of the patients' journey.[53] Patient-reported outcomes (e.g. Kansas City Cardiomyopathy Questionnaire [KCCQ]) or exercise tests (e.g. 6-min walking test, cardiopulmonary exercise test) may be more accurate and objective measurements of WHF than New York Heart Association (NYHA) class alone.[54–56] In a pre-specified pooled analysis of VITALITY-HFpEF (eValuate the effIcacy and safeTy of the orAL sGC stImulator vericiguaT to improve phYsical functioning in activities of daily living in patients with Heart Failure and preserved Ejection Fraction), any degree of worsening from baseline on the KCCQ physical limitation score (PLS) (worsening in ≥1 response category) suggested a deterioration in patients with HFpEF.[57] Development of exercise intolerance is a marker of HF progression (*Figure 1*).

Several HF risk scores are available for patients with chronic HF to predict development of WHF or mortality,[58,59] whereas, to date, no largely validated risk scores have been developed for patients with a recent episode of WHF. The COACH (Comparison of Outcomes and Access to Care for Heart Failure) trial has recently demonstrated that a previously derived and validated point-of-care tool for risk stratification (EHMRG30-ST), including clinical and laboratory variables, combined with the provision of standardized transitional care may enable physicians to make informed decisions about appropriate care settings and may enhance safety by reducing discharge from ED of high-risk patients presenting with WHF and improve efficiency by reducing admission of lower-risk patients.[60]

Biomarkers

Changes in plasma concentrations of biomarkers may detect congestion and WHF at an earlier stage so that prompt treatment may prevent hospitalization.[1,61–63] The increase in NT-proBNP concentrations may be similar regardless of site of care (urgent visit vs. HF hospitalization).[36] Although serial measurements of natriuretic peptide plasma concentrations may identify patients with WHF at an earlier stage,[64] strategies based on measurements of NT-proBNP levels to guide therapy have failed to show advantages compared with usual care in prospective randomized trials.[65,66] However, in the most recent STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial, serial measurements of NT-proBNP, along with physical examination and assessment of symptoms and signs of congestion, during frequent follow-up visits to optimize GRMT for HF, were used to rapidly implement GRMT in patients with a recent hospitalization for HF (*Table 3*).[67]

Multiple mechanisms cause the release of high-sensitivity cardiac troponin in patients with HF (*Table 3*).[61,68–70] Elevated NT-proBNP and troponin identified patients with HF at increased risk of major events with a significant incremental value compared with clinical parameters alone in recent trials.[71,72]

In BIOSTAT-CHF carbohydrate antigen 125 (CA-125) was the strongest single biomarker to distinguish WHF requiring hospitalization from worsening HF in chronic outpatients, with a C-index of 0.71.[73] Higher levels of CA-125 were positively associated with measures of peripheral congestion. Furthermore, CA-125 remained independently associated with a higher risk of clinical outcomes, even beyond a pre-defined risk model and clinical surrogates of congestion.[63,70,74,75] Biologically active adrenomedullin (bio-ADM) was the strongest predictor of a clinical congestion score.[76] Also, albuminuria resulted a marker of systemic congestion in these patients, being associated with other markers of congestion (e.g. NYHA functional class, higher concentrations of bio-ADM, CA-125, and NT-proBNP at baseline) and less with indices of renal function.[77] Among 4268 patients with HFrEF from studies that assessed soluble suppression of tumorigenicity 2 (sST2) for risk prediction in chronic HF, sST2 yielded strong, independent predictive value for all-cause and cardiovascular mortality, and hospitalization for WHF.[78] In patients admitted due to acute HF, sST2 at discharge predicted the risk of rehospitalizations.[79]

Worsening renal function is common in patients presenting with WHF due to an increase in central venous pressure,

Table 3 Pathophysiological mechanisms, outcome and clinical utility of several biomarkers in patients with worsening heart failure

Biomarker	Pathophysiological mechanisms	Outcome	Clinical utility	Ref.
NPs	Related to increased left ventricular myocardial wall stress and intracardiac pressure, activation of neuro-endocrine-immune system.	Admission/discharge/follow-up levels of NPs are diagnostic of HF and predict prognosis. Serial changes have prognostic value.	- Of help for the diagnosis of WHF above all if an increase is detected with serial measurements - More related with left ventricular dysfunction - High prognostic value - Serial measurements of NT-proBNP, along with clinical evaluation, during frequent follow-up visits were used to rapidly implement GRMT in patients with a recent hospitalization for HF in STRONG-HF	1,36,62,64–67
cTn	Related to increased left ventricular wall tension, subendocardial hypoperfusion, inflammation, neuro-hormonal activation, supply–demand mismatch, cytotoxicity, cellular necrosis, apoptosis or autophagy, and possibly exocytosis of cytosolic contents.	Associated with poor outcomes and ventricular remodelling. Combined with NT-proBNP may identify patients at higher risk with incremental value beyond clinical parameters.	- To exclude the presence of type 1 MI or other acute triggers for HF (beyond the definition of WHF). - Prognostic assessment.	61,63,68,69,71,72
CA-125	Related to systemic congestion and inflammation (synthesized by mesothelial cells in response to an increase in hydrostatic pressures and/or inflammatory mediators).	Associated with a higher risk of all-cause mortality and the combined all-cause death and hospitalization for HF.	- Associated with systemic congestion. - Prognostic assessment – CA125-guided therapy was associated with a reduction of 1-year death/AHF-related risk.	73–75
Bio-ADM	Related to congestion (ADM expression is stimulated by volume overload). Vasodilatory peptide hormone that regulates endothelial function/stabilizes endothelial barrier function.	Associated with increased risk of all-cause mortality and the combined all-cause mortality and HF hospitalization.	- Subclinical detection of congestion. - Prognostic assessment.	76
sST2, GDF-15, galectin-3	Markers of inflammation and/or fibrosis.	Prognostic value in AHF (admission and discharge sST2).	- Possible prognostic assessment.	61,78,79
Kidney markers (e.g. eGFR, NGAL, miRNA, cystatin C)	WRF is common in patients presenting with WHF due to an increase in central venous pressure, leading to raised renal interstitial pressures, and neurohormonal activation.	The prognostic value of WRF is critically dependent on concomitant congestion and it may be associated with better outcome when occurring in patients with decongestion and a good diuretic response, representing a sign of adequate decongestion.	Kidney function is a major comorbidity and determinant of medical therapy.	61,68,81–83,85
Albuminuria	Related to congestion.	Associated with increased risk of mortality and HF (re)hospitalization.	Prognostic assessment.	77
Procalcitonin	Released directly by endotoxins or indirectly via cytokines (e.g. interleukin-6) during bacterial infections.	–	Differential diagnosis of HF (vs. pneumonia and infections).	61

AHF, acute heart failure; bio-ADM, biologically active adrenomedullin; CA-125, carbohydrate antigen 125; cTn, cardiac troponin; CV cardiovascular; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; GRMT, guideline-recommended medical therapy; HF, heart failure; MI, myocardial infarction; miRNA, microRNA; NGAL, neutrophil gelatinase-associated lipocalin; NPs, natriuretic peptides; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity 2; WHF, worsening heart failure; WRF, worsening renal function.

leading to raised renal interstitial pressures and neurohormonal activation.[80–82] In a post-hoc analysis of the PARAGON-HF trial, patients who experienced an HF hospitalization during follow-up had an accelerated decline in estimated glomerular filtration rate (eGFR) both in the 12 months before and in those following HF hospitalization, compared with a stable eGFR trajectory in those without HF hospitalization.[83] The prognostic value of worsening renal function is, however, critically dependent on concomitant congestion and it may be associated with better outcome when occurring in patients with decongestion and a good diuretic response, representing a sign of adequate decongestion.[81,82,84,85] Other biomarkers that can be useful in the management of patients with WHF are enlisted in *Table 3*.

Imaging

Echocardiography provides a thorough assessment of signs of congestion, including inferior vena cava diameter, pulmonary artery pressure, estimates of ventricular filling pressure and diastolic function such as the E/e' ratio. Ultrasound may also measure lung B-lines, jugular vein diameter, and intra-renal venous flow, which may be also useful for the early detection of subclinical congestion.[86–88] About a half of ambulatory patients without clinical signs of congestion had ultrasound markers of congestion, which were associated with elevated natriuretic peptides and an adverse prognosis.[89] These measures may be useful for physicians to choose and monitor their management choices (e.g. in-hospital admission; IV diuretic administration, oral diuretic escalation, GRMT up-titration). More specifically, the technique of lung ultrasound represents a helpful non-invasive method to detect changes in pulmonary congestion and to assess residual congestion (and pleural effusion) either pre-discharge or in the routine care of ambulatory patients with chronic HF, identifying those at increased risk for adverse events.[90]

Devices

Implantable haemodynamic monitoring systems enable daily transmission of snapshot recordings to remote healthcare providers, obviating the need for in-person visits and facilitating home telemonitoring. They can therefore detect WHF when still subclinical, allowing prompt adjustment of therapy to prevent WHF events.[91–93] The CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial showed a significant reduction in HF hospitalizations for patients in NYHA class III who were managed with CardioMEMS, a wireless implantable pulmonary artery pressure sensor.[91] Decreases in HF hospitalizations with CardioMEMS were mainly related to frequent medication adjustments with significant increases in the doses of diuretics, vasodilators, and neurohormonal antagonists.[94] Neutral results from the larger haemodynamic GUIDE-HF (GUIDEed management of Heart Failure) trial, including also NYHA class II patients, might be partially explained by the interference of the COVID-19 pandemic.[95] Furthermore, the observed mean reduction in pulmonary pressure with CardioMEMS monitoring was only slightly higher than for the control group, suggesting that a more aggressive treatment was needed. Even if more changes in diuretics with pulmonary artery pressure monitoring occurred, it is unclear if the cumulative dose increased. Systemic arterial pressure and renal function were not monitored, and this might have hampered effective pharmacological management. Also, the GUIDE-HF trial enrolled a substantial proportion of patients with baseline pressures in the target range with a limited possibility of short-term gain, and with a low risk of HF events. SIRONA was a first-in-human multicentre clinical study combining the commercially available Cordella Heart Failure System and the investigational Cordella Sensor to provide pulmonary artery pressure, weight, blood pressure, heart rate and oxygen saturations to patients and physicians through a remote monitoring system in ambulatory symptomatic HF patients (NYHA class III). The study showed that implantation of the Cordella Sensor was feasible and safe with excellent accuracy of the Cordella Sensor pulmonary artery pressure measurements, compared to fluid-filled catheter at 3-month follow-up.[96,97] Patients that could benefit from haemodynamic monitoring system implantation are those with NYHA class ≥III, with an increased risk of WHF events or with a recent episode of WHF, displaying high pulmonary artery pressure at baseline.

Cardiac resynchronization therapy and the implantable cardioverter-defibrillator offer diagnostic features that allow monitoring of several variables, including intrathoracic impedance used to measure changes in thoracic fluid content, intracardiac pressures, heart rate variability, patients' physical activity level, and arrhythmias.[98] In a systematic review and meta-analysis of randomized controlled trials comparing device-based remote monitoring strategies for congestion-guided HF management versus standard therapy, a strategy of congestion-guided HF management significantly reduced the primary outcome of all-cause death and hospitalizations for HF and the results were mainly driven by a reduction in the risk of hospitalizations for HF. Conversely, a strategy of impedance-guided management did not reduce the risks of all-cause death, HF hospitalizations, and the composite of both compared to standard therapy.[93] Telemonitoring systems that allow daily recording of HF symptoms and daily measurements of blood pressure or weight might early detect episodes of WHF. Whether telemonitoring improves clinical outcomes in selected populations needs further confirmation.[99,100]

Treatment

Site of care

Management of WHF has traditionally been hospital-based, but the increasing prevalence of HF and the costs of HF on healthcare systems led to the need and the development of different opportunities other than long hospital stays (*Figure 2*).[17,44,101]

In the COACH trial, patients judged as at low risk were discharged early with early discharge defined as either discharge directly from the ED or discharge after an observation period in the hospital of up to 3 days. Patients who were discharged early were given access to standardized transitional care in the Rapid Ambulatory Program for Investigation and Diagnosis of Heart Failure (RAPID-HF) clinic. The RAPID-HF clinic was staffed by a nurse

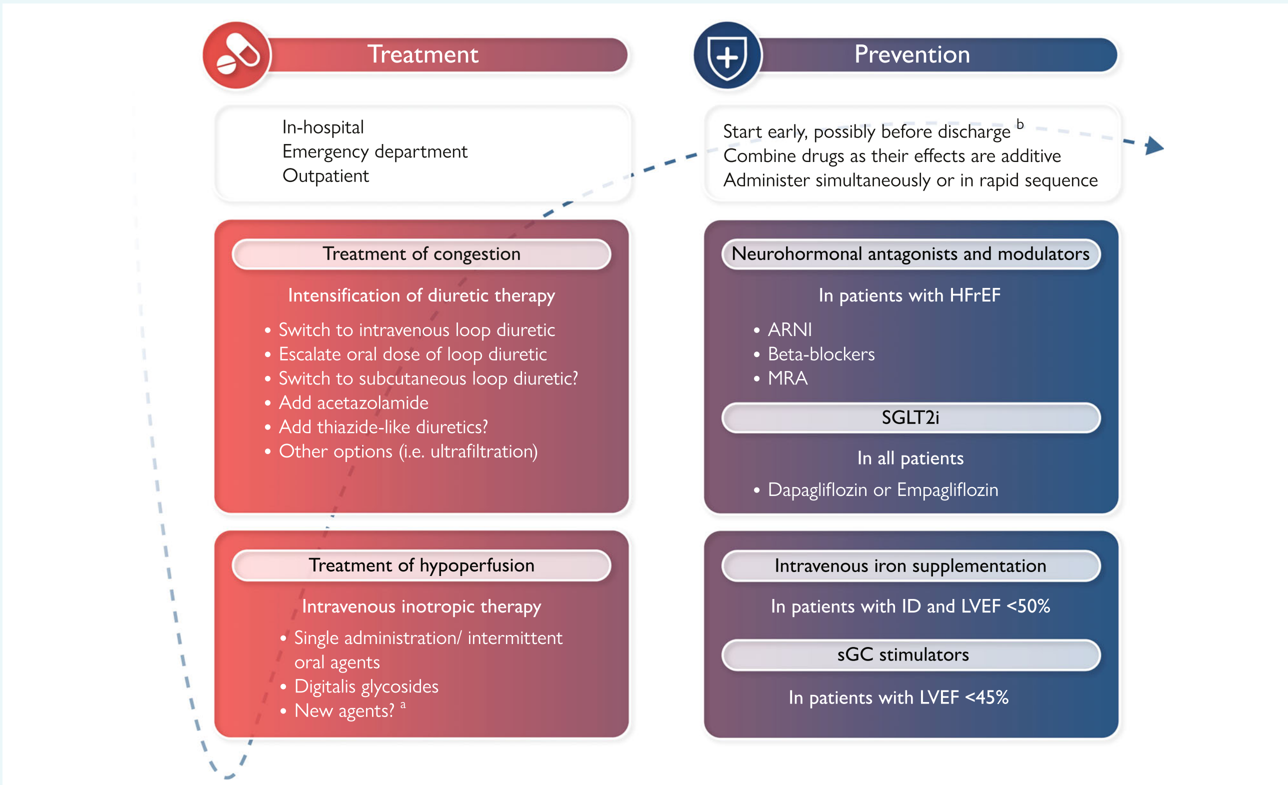

Figure 2 Treatment and prevention of worsening heart failure. [a]Treatment with new agents, including myotropic agents, is pending approval by the regulatory authorities. [b]Data on early initiation and administration are available for neurohormonal antagonists and modulators, sodium–glucose contransporter 2 inhibitors (SGLT2i) and ferric carboxymaltose.[51,124,129,144,145] [c]Replacement of angiotensin-converting enzyme inhibitor (ACEI) with angiotensin receptor–neprilysin inhibitor (ARNI) is advised in patients previously on ACEI.[1,146] ID, iron deficiency; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; sGC, soluble guanylate cyclase. [Correction added on 14 June 2023, after first online publication: Figure 2 has been updated in this version.]

and supervised by a cardiologist, and the clinic provided outpatient care for up to 30 days after discharge from the ED or hospital. This strategy proved to be safe and effective for the treatment of these patients.[60] Door-to-furosemide time, defined as the time from patient arrival at the ED to the first IV furosemide injection, should be shortened. Early and aggressive treatment of congestion is crucial for patients with WHF in order to reduce duration of hospitalization, avoid in-hospital WHF and early readmissions and improve outcome.[102] Patients presenting with signs of hypoperfusion and low cardiac output, low oxygen saturation levels (i.e. peripheral oxygen saturation <92%) and/or symptoms at rest (NYHA class IV) must be managed in hospital.

In-hospital treatment

Medical treatment of patients with WHF requiring hospitalization is codified in the 2021 ESC guidelines.[1] The previous algorithm for the management of diuretic therapy[103] can be adapted following the recent results from ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload). ADVOR assessed the use of IV acetazolamide compared to placebo in addition to furosemide in patients admitted with acute HF and volume overload. Acetazolamide is a carbonic anhydrase inhibitor that reduces sodium reabsorption in the proximal tubular and may improve diuretic efficiency when added to loop diuretics.[104] Patients receiving the IV combination of furosemide and acetazolamide had a greater incidence of successful decongestion within 3 days, which did not translate into better outcome, at least for mortality.[105] Importantly, patients enrolled in ADVOR did not receive other proximal tubular diuretics, like sodium–glucose cotransporter 2 (SGLT2) inhibitors, although these drugs have a different mechanism of action.

In a pre-specified analysis of the EMPULSE (EMPagliflozin in patients hospitalized with acUte heart faiLure who have been StabilizEd) trial on decongestion-related endpoints, Biegus and colleagues showed that empagliflozin started orally 3 days after hospital admission led to greater improvement in congestion compared with furosemide alone after hospital discharge, as early as at day 15, and was associated with higher probability of clinical benefit at day 90.[104,106] In the absence of data regarding the combination of these three class of drugs, Mebazaa *et al.*[104] proposed the association of acetazolamide and SGLT2 inhibitors with furosemide in different time periods during an acute HF hospitalization and post-discharge (IV acetazolamide from admission to day 3 and an SGLT2 inhibitor from day 3 and on). The prospective, double-blind, placebo-controlled CLOROTIC (Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure) trial randomized patients with acute HF to receive hydrochlorothiazide (HCTZ) or placebo in addition to IV furosemide. HCTZ was associated with greater weight loss and diuretic response but not with a significant improvement in patient-reported dyspnoea. A decline in renal function occurred more frequently among patients treated with HCTZ versus placebo.[107]

Emergency department visit

Not all patients who present to the ED due to WHF require hospitalization.[20,33] Patients considered at low-risk profile after ED evaluation could be discharged home, or managed for 24 to 48 h in an ED-based observation unit.[60,108] A large proportion of patients experience improvement in dyspnoea and/or a complete resolution of symptoms within 24 h of IV therapy (e.g. diuretics, vasodilators) during their ED stay. This strategy requires transition to outpatient care with a close follow-up.[108]

Outpatient intravenous or subcutaneous diuretic therapy

A practical guide for the outpatient management of worsening chronic HF (including both ambulatory IV diuretics in a day-hospital setting and 'hospital at home' or 'home hospitalization') has recently been published.[44] The cornerstone of WHF treatment is IV loop diuretic since congestion is crucial in the pathophysiology of WHF. Diuretic sessions usually consist in a 3–6 h IV diuretic infusion. Doses of loop diuretics depend on the oral diuretic maintenance dose. Assessment of treatment response (including diuresis, urinary sodium, clinical decongestion, electrolytes, biomarkers and/or ultrasound) is of utmost importance. Initial experiences of ambulatory IV diuretic treatment have been published.[109,110] Subcutaneous formulation of furosemide might be particularly useful for home treatment.[111]

Outpatient intensification of oral treatment

Intensification of oral diuretic therapy in ambulatory patients with chronic HF and evidence of worsening includes (i) initiation of a loop diuretic in patients who were not previously treated; (ii) change to a total daily dose of loop diuretic higher than their previous total daily dose; and (iii) short-term addition of a diuretic with a different mechanisms of action (e.g. thiazides, metolazone). Thiazide-like diuretics, namely oral metolazone (2.5 to 5 mg), can be used in patients with advanced HF with diuretic resistance in a sequential nephron blockade or in those with eGFR <30 ml/min/1.73 m^2. This approach requires a closer monitoring of serum potassium and sodium concentrations.[101]

Change from furosemide to either bumetanide or torasemide may also be considered.[37,38] Of note, the TRANSFORM-HF (Torasemide Comparison With Furosemide for Management of Heart Failure) trial, enrolling patients discharged after a hospitalization for HF, failed to show a significant difference in all-cause mortality over 12 months with torasemide compared to furosemide.[112]

Frequent flyers

Patients with WHF that progress to advanced HF, presenting with refractory symptoms and signs of congestion despite high doses of oral loop diuretics and optimal medical therapy, may represent one of the main target population for the treatment with IV diuretics in the outpatient setting (day hospital or 'hospital at home' settings). Indeed, these patients spend a substantial amount of time in hospital ('frequent flyers'). In these patients intermittent treatment with inotropic agents has been proposed while, also, considering them for advanced treatments.[113,114] Recurrent worsening episodes can be the preamble to lack of response to GRMT and, thus, trigger candidacy to heart transplantation, durable mechanical circulatory support and palliative care. Data from retrospective studies showed that ambulatory patients with advanced HF (INTERMACS profiles 4–7) might benefit from long-term mechanical circulatory support even more than those with cardiogenic shock (INTERMACS 1–2) or inotrope-dependent (INTERMACS 3) due to the lower risk of complications.[113,115,116] The ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device [LVAD] and Medical Management) trial evaluated HeartMate II LVAD support versus optimal medical management in ambulatory NYHA functional class IIIB/IV patients meeting indications for LVAD destination therapy but not dependent on IV inotropic support. Overall, LVAD support prolonged survival and improved health status, but was associated with a higher risk of adverse events and hospitalizations. Then, the HeartMate III LVAD has been associated with a lower risk of adverse events compared to the HeartMate II pump, possibly widening the indications to LVAD.[113,117] As for the recommendations to heart transplantation, we refer to HF guidelines.[1]

Prevention

Guidelines recommend ACEI, ARNI, mineralocorticoid receptor antagonists, beta-blockers and SGLT2 inhibitors to reduce the risk of HF hospitalizations and death (*Figure 2*).[1,118] Recent analyses show the efficacy of GRMT also for the prevention of outpatient WHF events, including emergency visits with IV diuretic administration and outpatient visits followed by diuretic dose intensification.[6,119–122] In PARADIGM-HF, the benefit of sacubitril/valsartan over enalapril was similar to the primary outcome for the expanded composite outcome including outpatient intensification of HF therapy, ED visits, HF hospitalizations and cardiovascular deaths (HR 0.79; 95% CI 0.73–0.86) with consistent effects across the different components.[6] In PARAGON-HF, enrolling patients with HFpEF, cardiovascular death and HF hospitalizations and episodes of WHF outside of the hospital setting were similarly reduced by sacubitril/valsartan versus valsartan (HR 0.87, 95% CI 0.75–1.005 and HR 086, 95% CI 0.75–0.99, respectively).[36] PARAGLIDE-HF, a multicentre, double-blind, randomized, controlled trial testing safety, tolerability and efficacy of sacubitril/valsartan versus valsartan in patients with LVEF >40% enrolled within 30 days of a WHF event, will add data for the treatment of these patients.[123]

Randomized controlled trials have shown that SGLT2 inhibitors reduce all WHF events with a similar efficacy on HF hospitalizations as well as on outpatient events.[8,120–122,124,125] The benefits of SGLT2 inhibitors on clinical outcome and quality of life are additive to those of the other GRMT[126–128] and are significant also in patients randomized during a HF hospitalization or within 30 days of it.[124,129] Similar to what shown also with the other GRMT,[130–132] the beneficial effects on outcome of SGLT2 inhibitors become significant early after their initiation with, therefore, a strong rationale for their early initiation after a WHF episode.[120,133–135]

Administration of ferric carboxymaltose is advised according to guidelines and recent trials in patients with iron deficiency and LVEF <50% to reduce the risk of HF rehospitalizations and improve symptoms and quality of life.[1,51,136]

Finally, the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial included patients with LVEF<45%, NYHA class II–IV, elevated natriuretic peptide concentrations and WHF, defined as a HF hospitalization within 6 months before randomization or an episode of decompensation with outpatient treatment with IV furosemide 3 months before randomization.[137,138] These criteria yielded a very high risk study group with an annualized event rate of the primary endpoint of cardiovascular death or HF hospitalizations of 37.8 versus 33.6 events per 100 patient-years with placebo and vericiguat, respectively. The 10% relative risk reduction of the primary endpoint (HR 0.90, 95% CI 0.82–0.98) therefore corresponded to a 3.7 absolute risk reduction, similar in magnitude to that of previous trials.[138,139] The benefit of vericiguat did not differ significantly across the spectrum of risk in WHF and the range of times from WHF to randomization.[35] Based on these results, vericiguat administration should be advised, in addition to the four pillars of HFrEF therapy, in patients symptomatic and with LVEF <45% after a WHF event (*Figure 2*).[1,118,140,141]

Besides, exercise rehabilitation seems to reduce the risk of further HF events among older, frail patients hospitalized for decompensated HF, especially in those who are highly adherent to the exercise programme.[140,142,143]

Future directions

Further epidemiology data seem necessary to better understand the size of the problem of WHF and its impact in healthcare resources. This seems particularly warranted since more patients are now treated in an outpatient setting and the new medications should have a major effect on the patients' clinical course.

There is a compelling need to prevent or reduce the occurrence of WHF in order to improve outcomes for patients with HF and to reduce the pressure on healthcare resources. Biomarkers, imaging techniques and devices enable early detection of congestion and identify patients at risk of WHF. However, convincing evidence from randomized, prospective trials showing a favourable effect on outcome with the use of any of these tools is lacking. The best strategies for relieving congestion with diuretic agents, in terms of dose, combinations and mode of administration require further research. Mechanisms leading to decompensation are still incompletely understood and should probably be better characterized. Finally, we have new and effective treatments to reduce or prevent WHF and it is time to develop implementation strategies to ensure they are used effectively.

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References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**:4–131.
2. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. 2021;**23**:352–80.
3. Butler J, Braunwald E, Gheorghiade M. Recognizing worsening chronic heart failure as an entity and an end point in clinical trials. *JAMA*. 2014;**312**:789–90.
4. Greene SJ, Mentz RJ, Felker GM. Outpatient worsening heart failure as a target for therapy: a review. *JAMA Cardiol*. 2018;**3**:252–9.
5. Greene SJ, Bauersachs J, Brugts JJ, Ezekowitz JA, Lam CSP, Lund LH, et al. Worsening heart failure: nomenclature, epidemiology, and future directions: JACC review topic of the week. *J Am Coll Cardiol*. 2023;**81**:413–24.
6. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, et al.; PARADIGM-HF Investigators and Committees. Importance of clinical worsening of heart failure treated in the outpatient setting: evidence from the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF). *Circulation*. 2016;**133**:2254–62.
7. Ambrosy AP, Parikh RV, Sung SH, Tan TC, Narayanan A, Masson R, et al. Analysis of worsening heart failure events in an integrated health care system. *J Am Coll Cardiol*. 2022;**80**:111–22.
8. Docherty KF, Jhund PS, Anand I, Bengtsson O, Bohm M, de Boer RA, et al. Effect of dapagliflozin on outpatient worsening of patients with heart failure and reduced ejection fraction: a prespecified analysis of DAPA-HF. *Circulation*. 2020;**142**:1623–32.
9. Butler J, Gheorghiade M, Kelkar A, Fonarow GC, Anker S, Greene SJ, et al. In-hospital worsening heart failure. *Eur J Heart Fail*. 2015;**17**:1104–13.
10. Gualandro DM, Puelacher C, Chew MS, Andersson H, Lurati Buse G, Glarner N, et al.; BASEL-PMI Investigators. Acute heart failure after non-cardiac surgery: incidence, phenotypes, determinants and outcomes. *Eur J Heart Fail*. 2023;**25**:347–57.
11. Kimmoun A, Takagi K, Gall E, Ishihara S, Hammoum P, El Beze N, et al. Temporal trends in mortality and readmission after acute heart failure: a systematic review and meta-regression in the past four decades. *Eur J Heart Fail*. 2021;**23**:420–31.
12. Lawson CA, Zaccardi F, Squire I, Ling S, Davies MJ, Lam CSP, et al. 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study. *Lancet Public Health*. 2019;**4**:e406–20.
13. Agarwal MA, Fonarow GC, Ziaeian B. National trends in heart failure hospitalizations and readmissions from 2010 to 2017. *JAMA Cardiol*. 2021;**6**:952–6.
14. Butt JH, Fosbol EL, Gerds TA, Andersson C, McMurray JJV, Petrie MC, et al. Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: insights from a nationwide cohort. *Eur J Heart Fail*. 2020;**22**:1777–85.
15. Labrosciano C, Horton D, Air T, Tavella R, Beltrame JF, Zeitz CJ, et al. Frequency, trends and institutional variation in 30-day all-cause mortality and unplanned readmissions following hospitalisation for heart failure in Australia and New Zealand. *Eur J Heart Fail*. 2021;**23**:31–40.
16. Hariharaputhiran S, Peng Y, Ngo L, Ali A, Hossain S, Visvanathan R, et al. Long-term survival and life expectancy following an acute heart failure hospitalization in Australia and New Zealand. *Eur J Heart Fail*. 2022;**24**:1519–28.
17. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2023;**118**:3272–87.
18. Greene SJ, Triana TS, Ionescu-Ittu R, Shi S, Guerin A, DeSouza MM, et al. Patients hospitalized for de novo versus worsening chronic heart failure in the United States. *J Am Coll Cardiol*. 2021;**77**:1023–5.
19. Seferović PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, et al. The Heart Failure Association Atlas: heart failure epidemiology and management statistics 2019. *Eur J Heart Fail*. 2021;**23**:906–14.
20. Storrow AB, Jenkins CA, Self WH, Alexander PT, Barrett TW, Han JH, et al. The burden of acute heart failure on U.S. emergency departments. *JACC Heart Fail*. 2014;**2**:269–77.
21. Blecker S, Ladapo JA, Doran KM, Goldfeld KS, Katz S. Emergency department visits for heart failure and subsequent hospitalization or observation unit admission. *Am Heart J*. 2014;**168**:901–8.e1.
22. Andersson C, Gerds T, Fosbol E, Phelps M, Andersen J, Lamberts M, et al. Incidence of new-onset and worsening heart failure before and after the COVID-19 epidemic lockdown in Denmark: a nationwide cohort study. *Circ Heart Fail*. 2020;**13**:e007274.
23. Cannata A, Bromage DI, Rind IA, Gregorio C, Bannister C, Albarjas M, et al. Temporal trends in decompensated heart failure and outcomes during COVID-19: a multisite report from heart failure referral centres in London. *Eur J Heart Fail*. 2020;**22**:2219–24.
24. Cox ZL, Lai P, Lindenfeld J. Decreases in acute heart failure hospitalizations during COVID-19. *Eur J Heart Fail*. 2020;**22**:1045–6.
25. Frankfurter C, Buchan TA, Kobulnik J, Lee DS, Luk A, McDonald M, et al. Reduced rate of hospital presentations for heart failure during the COVID-19 pandemic in Toronto, Canada. *Can J Cardiol*. 2020;**36**:1680–4.
26. Konig S, Hohenstein S, Meier-Hellmann A, Kuhlen R, Hindricks G, Bollmann A, et al. In-hospital care in acute heart failure during the COVID-19 pandemic: insights from the German-wide Helios hospital network. *Eur J Heart Fail*. 2020;**22**:2190–201.
27. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014;**63**:1123–33.
28. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, et al.; Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;**116**:1482–7.
29. Kaplon-Cieslicka A, Benson L, Chioncel O, Crespo-Leiro MG, Coats AJS, Anker SD, et al.; Heart Failure Association (HFA) of the European Society of

Cardiology (ESC) and the ESC Heart Failure Long-Term Registry Investigators. A comprehensive characterization of acute heart failure with preserved versus mildly reduced versus reduced ejection fraction – insights from the ESC-HFA EORP Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2022;**24**:335–50.
30. Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, et al. Clinical course of patients with worsening heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;**73**:935–44.
31. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;**345**:1667–75.
32. Skali H, Dwyer EM, Goldstein R, Haigney M, Krone R, Kukin M, et al. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. *Eur J Heart Fail*. 2014;**16**:560–5.
33. Shah A, Mentz RJ, Sun JL, Rao VN, Alhanti B, Blumer V, et al. Emergency department visits versus hospital readmissions among patients hospitalized for heart failure. *J Card Fail*. 2022;**28**:916–23.
34. Ferreira JP, Metra M, Mordi I, Gregson J, Ter Maaten JM, Tromp J, et al. Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study. *Eur J Heart Fail*. 2019;**21**:112–20.
35. Lam CSP, Giczewska A, Sliwa K, Edelmann F, Refsgaard J, Bocchi E, et al.; VICTORIA Study Group. Clinical outcomes and response to vericiguat according to index heart failure event: insights from the VICTORIA trial. *JAMA Cardiol*. 2021;**6**:706–12.
36. Vaduganathan M, Cunningham JW, Claggett BL, Causland FM, Barkoudah E, Finn P, et al. Worsening heart failure episodes outside a hospital setting in heart failure with preserved ejection fraction: the PARAGON-HF trial. *JACC Heart Fail*. 2021;**9**:374–82.
37. Madelaire C, Gustafsson F, Stevenson LW, Kristensen SL, Kober L, Andersen J, et al. One-year mortality after intensification of outpatient diuretic therapy. *J Am Heart Assoc*. 2020;**9**:e016010.
38. Khan MS, Greene SJ, Hellkamp AS, DeVore AD, Shen X, Albert NM, et al. Diuretic changes, health care resource utilization, and clinical outcomes for heart failure with reduced ejection fraction: from the Change the Management of Patients with Heart Failure Registry. *Circ Heart Fail*. 2021;**14**:e008351.
39. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation*. 2008;**118**:1433–41.
40. Van Aelst LNL, Arrigo M, Placido R, Akiyama E, Girerd N, Zannad F, et al. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. *Eur J Heart Fail*. 2018;**20**:738–47.
41. Mentz RJ, O'Connor CM. Pathophysiology and clinical evaluation of acute heart failure. *Nat Rev Cardiol*. 2016;**13**:28–35.
42. Tomasoni D, Lombardi CM, Sbolli M, Cotter G, Metra M. Acute heart failure: more questions than answers. *Prog Cardiovasc Dis*. 2020;**63**:599–606.
43. Chioncel O, Mebazaa A, Maggioni AP, Harjola VP, Rosano G, Laroche C, et al.; ESC-EORP-HFA Heart Failure Long-Term Registry Investigators. Acute heart failure congestion and perfusion status – impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2019;**21**:1338–52.
44. Girerd N, Mewton N, Tartiere JM, Guijarro D, Jourdain P, Damy T, et al. Practical outpatient management of worsening chronic heart failure. *Eur J Heart Fail*. 2022;**24**:750–61.
45. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. *Circulation*. 2007;**116**:1549–54.
46. Fudim M, Ganesh A, Green C, Jones WS, Blazing MA, DeVore AD, et al. Splanchnic nerve block for decompensated chronic heart failure: splanchnic-HF. *Eur Heart J*. 2018;**39**:4255–6.
47. Fudim M, Ponikowski PP, Burkhoff D, Dunlap ME, Sobotka PA, Molinger J, et al. Splanchnic nerve modulation in heart failure: mechanistic overview, initial clinical experience, and safety considerations. *Eur J Heart Fail*. 2021;**23**:1076–84.
48. Tromp J, Beusekamp JC, Ouwerkerk W, van der Meer P, Cleland JGF, Angermann CE, et al. Regional differences in precipitating factors of hospitalization for acute heart failure: insights from the REPORT-HF registry. *Eur J Heart Fail*. 2022;**24**:645–52.
49. Pagnesi M, Adamo M, Sama IE, Anker SD, Cleland JG, Dickstein K, et al. Impact of mitral regurgitation in patients with worsening heart failure: insights from BIOSTAT-CHF. *Eur J Heart Fail*. 2021;**23**:1750–8.
50. Metra M, Jankowska EA, Pagnesi M, Anker SD, Butler J, Dorigotti F, et al.; AFFIRM-AHF Investigators. Impact of ischaemic aetiology on the efficacy of intravenous ferric carboxymaltose in patients with iron deficiency and acute heart failure: insights from the AFFIRM-AHF trial. *Eur J Heart Fail*. 2022;**24**:1928–39.
51. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, et al.; AFFIRM-AHF Investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;**396**:1895–904.
52. Greene SJ, Butler J, Fonarow GC. In-hospital initiation of quadruple medical therapy for heart failure: making the post-discharge vulnerable phase far less vulnerable. *Eur J Heart Fail*. 2022;**24**:227–9.
53. Girerd N, Seronde MF, Coiro S, Chouihed T, Bilbault P, Braun F, et al.; INI-CRCT, Great Network, and the EF-HF Group. Integrative assessment of congestion in heart failure throughout the patient journey. *JACC Heart Fail*. 2018;**6**:273–85.
54. Butler J, Shahzeb Khan M, Lindenfeld J, Abraham WT, Savarese G, Salsali A, et al. Minimally clinically important difference in health status scores in patients with HFrEF vs HFpEF. *JACC Heart Fail*. 2022;**10**:651–61.
55. Savarese G, Lindenfeld J, Stolfo D, Adams K, Ahmad T, Desai NR, et al. Use of patient-reported outcomes in heart failure: from clinical trials to routine practice. *Eur J Heart Fail*. 2023;**25**:139–51.
56. Del Buono MG, Arena R, Borlaug BA, Carbone S, Canada JM, Kirkman DL, et al. Exercise intolerance in patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;**73**:2209–25.
57. Butler J, Spertus JA, Bamber L, Khan MS, Roessig L, Vlajnic V, et al.; VITALITY-HFpEF Study Group. Defining changes in physical limitation from the patient perspective: insights from the VITALITY-HFpEF randomized trial. *Eur J Heart Fail*. 2022;**24**:843–50.
58. Codina P, Lupón J, Borrellas A, Spitaleri G, Cediel G, Domingo M, et al. Head-to-head comparison of contemporary heart failure risk scores. *Eur J Heart Fail*. 2021;**23**:2035–44.
59. Alvarez-Garcia J, Ferrero-Gregori A, Puig T, Vazquez R, Delgado J, Pascual-Figal D, et al.; Investigators of the Spanish Heart Failure Network (REDINSCOR). A simple validated method for predicting the risk of hospitalization for worsening of heart failure in ambulatory patients: the Redin-SCORE. *Eur J Heart Fail*. 2015;**17**:818–27.
60. Lee DS, Straus SE, Farkouh ME, Austin PC, Taljaard M, Chong A, et al.; COACH Trial Investigators. Trial of an intervention to improve acute heart failure outcomes. *N Engl J Med*. 2023;**388**:22–32.
61. Meijers WC, Bayes-Genis A, Mebazaa A, Bauersachs J, Cleland JGF, Coats AJS, et al. Circulating heart failure biomarkers beyond natriuretic peptides: review from the Biomarker Study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). *Eur J Heart Fail*. 2021;**23**:1610–32.
62. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail*. 2019;**21**:715–31.
63. Nunez J, de la Espriella R, Rossignol P, Voors AA, Mullens W, Metra M, et al. Congestion in heart failure: a circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology. *Eur J Heart Fail*. 2022;**24**:1751–66.
64. Israr MZ, Salzano A, Yazaki Y, Voors AA, Ouwerkerk W, Anker SD, et al.; BIOSTAT-CHF Consortium. Implications of serial measurements of natriuretic peptides in heart failure: insights from BIOSTAT-CHF. *Eur J Heart Fail*. 2020;**22**:1486–90.
65. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2017;**318**:713–20.
66. Stienen S, Salah K, Moons AH, Bakx AL, van Pol P, Kortz RAM, et al. NT-proBNP (N-terminal pro-B-type natriuretic peptide)-guided therapy in acute decompensated heart failure: PRIMA II randomized controlled trial (can NT-ProBNP-guided therapy during hospital admission for acute decompensated heart failure reduce mortality and readmissions?). *Circulation*. 2018;**137**:1671–83.
67. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022;**400**:1938–52.
68. Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, et al.; RELAX-AHF Investigators. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. *J Am Coll Cardiol*. 2013;**61**:196–206.
69. Januzzi JL Jr, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *Eur Heart J*. 2012;**33**:2265–71.

70. Nunez J, Llacer P, Garcia-Blas S, Bonanad C, Ventura S, Nunez JM, et al. CA125-guided diuretic treatment versus usual care in patients with acute heart failure and renal dysfunction. *Am J Med*. 2020;**133**:370–80.e4.
71. Januzzi JL Jr, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, et al.; EMPEROR-Preserved Trial Study Group. Prognostic implications of N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin T in EMPEROR-Preserved. *JACC Heart Fail*. 2022;**10**:512–24.
72. Januzzi JL Jr, Zannad F, Anker SD, Butler J, Filippatos G, Pocock SJ, et al.; EMPEROR-Reduced Trial Committees and Investigators. Prognostic importance of NT-proBNP and effect of empagliflozin in the EMPEROR-Reduced trial. *J Am Coll Cardiol*. 2021;**78**:1321–32.
73. Davison BA, Senger S, Sama IE, Koch GG, Mebazaa A, Dickstein K, et al. Is acute heart failure a distinctive disorder? An analysis from BIOSTAT-CHF. *Eur J Heart Fail*. 2021;**23**:43–57.
74. Nunez J, Bayes-Genis A, Revuelta-Lopez E, Ter Maaten JM, Minana G, Barallat J, et al. Clinical role of CA125 in worsening heart failure: a BIOSTAT-CHF study subanalysis. *JACC Heart Fail*. 2020;**8**:386–97.
75. Nunez J, de la Espriella R, Minana G, Santas E, Llacer P, Nunez E, et al. Antigen carbohydrate 125 as a biomarker in heart failure: a narrative review. *Eur J Heart Fail*. 2021;**23**:1445–57.
76. Ter Maaten JM, Kremer D, Demissei BG, Struck J, Bergmann A, Anker SD, et al. Bio-adrenomedullin as a marker of congestion in patients with new-onset and worsening heart failure. *Eur J Heart Fail*. 2019;**21**:732–43.
77. Boorsma EM, Ter Maaten JM, Damman K, van Essen BJ, Zannad F, van Veldhuisen DJ, et al. Albuminuria as a marker of systemic congestion in patients with heart failure. *Eur Heart J*. 2023;**44**:368–80.
78. Emdin M, Aimo A, Vergaro G, Bayes-Genis A, Lupon J, Latini R, et al. sST2 predicts outcome in chronic heart failure beyond NT-proBNP and high-sensitivity troponin T. *J Am Coll Cardiol*. 2018;**72**:2309–20.
79. Aimo A, Vergaro G, Ripoli A, Bayes-Genis A, Pascual Figal DA, de Boer RA, et al. Meta-analysis of soluble suppression of tumorigenicity-2 and prognosis in acute heart failure. *JACC Heart Fail*. 2017;**5**:287–96.
80. Girerd N. Worsening renal function precedes and follows worsening heart failure. *Eur J Heart Fail*. 2022;**24**:1915–7.
81. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, et al. Evaluation of kidney function throughout the heart failure trajectory – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2020;**22**:584–603.
82. Mullens W, Martens P, Testani JM, Tang WHW, Skouri H, Verbrugge FH, et al. Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2022;**24**:603–19.
83. Chatur S, Vaduganathan M, Peikert A, Claggett BL, McCausland FR, Skali H, et al. Longitudinal trajectories in renal function before and after heart failure hospitalization among patients with heart failure with preserved ejection fraction in the PARAGON-HF trial. *Eur J Heart Fail*. 2022;**24**:1906–14.
84. Emmens JE, Ter Maaten JM, Matsue Y, Figarska SM, Sama IE, Cotter G, et al. Worsening renal function in acute heart failure in the context of diuretic response. *Eur J Heart Fail*. 2022;**24**:365–74.
85. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 2012;**5**:54–62.
86. Pellicori P, Platz E, Dauw J, Ter Maaten JM, Martens P, Pivetta E, et al. Ultrasound imaging of congestion in heart failure: examinations beyond the heart. *Eur J Heart Fail*. 2021;**23**:703–12.
87. Platz E, Lewis EF, Uno H, Peck J, Pivetta E, Merz AA, et al. Detection and prognostic value of pulmonary congestion by lung ultrasound in ambulatory heart failure patients. *Eur Heart J*. 2016;**37**:1244–51.
88. Čelutkienė J, Lainscak M, Anderson L, Gayat E, Grapsa J, Harjola VP, et al. Imaging in patients with suspected acute heart failure: timeline approach position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2020;**22**:181–95.
89. Pellicori P, Shah P, Cuthbert J, Urbinati A, Zhang J, Kallvikbacka-Bennett A, et al. Prevalence, pattern and clinical relevance of ultrasound indices of congestion in outpatients with heart failure. *Eur J Heart Fail*. 2019;**21**:904–16.
90. Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. *Eur J Heart Fail*. 2017;**19**:1154–63.
91. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al.; CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. 2011;**377**:658–66.
92. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *Lancet*. 2021;**398**:991–1001.
93. Zito A, Princi G, Romiti GF, Galli M, Basili S, Liuzzo G, et al. Device-based remote monitoring strategies for congestion-guided management of patients with heart failure: a systematic review and meta-analysis. *Eur J Heart Fail*. 2022;**24**:2333–41.
94. Costanzo MR, Stevenson LW, Adamson PB, Desai AS, Heywood JT, Bourge RC, et al. Interventions linked to decreased heart failure hospitalizations during ambulatory pulmonary artery pressure monitoring. *JACC Heart Fail*. 2016;**4**:333–44.
95. Cleland JGF, Pellicori P. To master heart failure, first master congestion. *Lancet*. 2021;**398**:935–6.
96. Mullens W, Sharif F, Dupont M, Rothman AMK, Wijns W. Digital health care solution for proactive heart failure management with the Cordella Heart Failure System: results of the SIRONA first-in-human study. *Eur J Heart Fail*. 2020;**22**:1912–9.
97. Latib A, Hashim Mustehsan M, Abraham WT, Jorde UP, Bartunek J. Transcatheter interventions for heart failure. *EuroIntervention*. 2023;**18**:1135–49.
98. van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G, et al.; DOT-HF Investigators. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. *Circulation*. 2011;**124**:1719–26.
99. Galinier M, Roubille F, Berdague P, Brierre G, Cantie P, Dary P, et al.; OSICAT Investigators. Telemonitoring versus standard care in heart failure: a randomised multicentre trial. *Eur J Heart Fail*. 2020;**22**:985–94.
100. Koehler J, Stengel A, Hofmann T, Wegscheider K, Koehler K, Sehner S, et al. Telemonitoring in patients with chronic heart failure and moderate depressed symptoms: results of the Telemedical Interventional Monitoring in Heart Failure (TIM-HF) study. *Eur J Heart Fail*. 2021;**23**:186–94.
101. Zsilinszka R, Mentz RJ, DeVore AD, Eapen ZJ, Pang PS, Hernandez AF. Acute heart failure: alternatives to hospitalization. *JACC Heart Fail*. 2017;**5**:329–36.
102. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J Am Coll Cardiol*. 2017;**69**:3042–51.
103. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;**21**:137–55.
104. Mebazaa A, Solal AC, Colombo PC. Assessing and treating congestion in acute decompensated heart failure: are we seeing the light at the end of the tunnel? *Eur Heart J*. 2023;**44**:51–3.
105. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al.; ADVOR Study Group. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med*. 2022;**387**:1185–95.
106. Biegus J, Voors AA, Collins SP, Kosiborod MN, Teerlink JR, Angermann CE, et al. Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. *Eur Heart J*. 2023;**44**:41–50.
107. Trulls JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Snchez-Marteles M, Conde-Martel A, et al.; CLOROTIC Trial Investigators. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J*. 2023;**44**:411–21.
108. Collins SP, Pang PS, Fonarow GC, Yancy CW, Bonow RO, Gheorghiade M. Is hospital admission for heart failure really necessary? The role of the emergency department and observation unit in preventing hospitalization and rehospitalization. *J Am Coll Cardiol*. 2013;**61**:121–6.
109. Buckley LF, Carter DM, Matta L, Cheng JW, Stevens C, Belenkiy RM, et al. Intravenous diuretic therapy for the management of heart failure and volume overload in a multidisciplinary outpatient unit. *JACC Heart Fail*. 2016;**4**:1–8.
110. Buckley LF, Stevenson LW, Cooper IM, Knowles DM, Matta L, Molway DW, et al. Ambulatory treatment of worsening heart failure with intravenous loop diuretics: a four-year experience. *J Card Fail*. 2020;**26**:798–9.
111. Gilotra NA, Princewill O, Marino B, Okwuosa IS, Chasler J, Almansa J, et al. Efficacy of intravenous furosemide versus a novel, pH-neutral furosemide formulation administered subcutaneously in outpatients with worsening heart failure. *JACC Heart Fail*. 2018;**6**:65–70.
112. Mentz RJ, Anstrom KJ, Eisenstein EL, Sapp S, Greene SJ, Morgan S, et al.; TRANSFORM-HF Investigators. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: the TRANSFORM-HF randomized clinical trial. *JAMA*. 2023;**329**:214–23.
113. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;**20**:1505–35.
114. Gustafsson F, Damman K, Nalbantgil S, Van Laake LW, Tops LF, Thum T, et al. Inotropic therapy in patients with advanced heart failure. A clinical consensus

statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2023;**25**:457–68.
115. Jorde UP, Kushwaha SS, Tatooles AJ, Naka Y, Bhat G, Long JW, et al.; HeartMate II Clinical Investigators. Results of the destination therapy post-Food and Drug Administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol*. 2014;**63**:1751–7.
116. Boyle AJ, Ascheim DD, Russo MJ, Kormos RL, John R, Naka Y, et al. Clinical outcomes for continuous-flow left ventricular assist device patients stratified by pre-operative INTERMACS classification. *J Heart Lung Transplant*. 2011;**30**:402–7.
117. Gustafsson F, Rogers JG. Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes. *Eur J Heart Fail*. 2017;**19**:595–602.
118. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;**145**:e895–e1032.
119. McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, et al.; DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail*. 2019;**21**:665–75.
120. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, et al.; EMPEROR-Preserved Trial Study Group. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-Preserved trial. *Circulation*. 2021;**144**:1284–94.
121. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al.; EMPEROR-Reduced Trial Committees and Investigators. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Circulation*. 2021;**143**:326–36.
122. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al.; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;**387**:1089–98.
123. Mentz RJ, Ward JH, Hernandez AF, Lepage S, Morrow DA, Sarwat S, et al. Rationale, design and baseline characteristics of the PARAGLIDE-HF trial: sacubitril/valsartan vs valsartan in HFmrEF and HFpEF with a worsening heart failure event. *J Card Fail*. 2023;**29**:922–30.
124. Cunningham JW, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS, et al. Dapagliflozin in patients recently hospitalized with heart failure and mildly reduced or preserved ejection fraction. *J Am Coll Cardiol*. 2022;**80**:1302–10.
125. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al.; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;**384**:117–28.
126. Docherty KF, Jhund PS, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *Eur Heart J*. 2020;**41**:2379–92.
127. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al.; EMPEROR-Reduced Trial Committees and Investigators. Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Eur Heart J*. 2021;**42**:671–80.
128. Verma S, Dhingra NK, Butler J, Anker SD, Ferreira JP, Filippatos G, et al.; EMPEROR-Reduced Trial Committees and Investigators. Empagliflozin in the treatment of heart failure with reduced ejection fraction in addition to background therapies and therapeutic combinations (EMPEROR-Reduced): a post-hoc analysis of a randomised, double-blind trial. *Lancet Diabetes Endocrinol*. 2022;**10**:35–45.
129. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;**28**:568–74.
130. Bedrouni W, Sharma A, Pitt B, Lam CSP, Ni J, Ferreira JP, et al. Timing of statistical benefit of mineralocorticoid receptor antagonists among patients with heart failure and post-myocardial infarction. *Circ Heart Fail*. 2022; **15**:e009295.
131. Krum H, Roecker EB, Mohacsi P, Rouleau JL, Tendera M, Coats AJ, et al.; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS study. *JAMA*. 2003;**289**:712–8.
132. Lam PH, Packer M, Fonarow GC, Faselis C, Allman RM, Morgan CJ, et al. Early effects of starting doses of enalapril in patients with chronic heart failure in the SOLVD treatment trial. *Am J Med*. 2020;**133**:e25–31.
133. Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. *JAMA Cardiol*. 2021;**6**:499–507.
134. Rao VN, Murray E, Butler J, Cooper LB, Cox ZL, Fiuzat M, et al. In-hospital initiation of sodium-glucose cotransporter-2 inhibitors for heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2021;**78**:2004–12.
135. Tomasoni D, Fonarow GC, Adamo M, Anker SD, Butler J, Coats AJS, et al. Sodium-glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail*. 2022;**24**:431–41.
136. Jankowska EA, Kirwan BA, Kosiborod M, Butler J, Anker SD, McDonagh T, et al. The effect of intravenous ferric carboxymaltose on health-related quality of life in iron-deficient patients with acute heart failure: the results of the AFFIRM-AHF study. *Eur Heart J*. 2021;**42**:3011–20.
137. Butler J, Usman MS, Anstrom KJ, Blaustein RO, Bonaca MP, Ezekowitz JA, et al. Soluble guanylate cyclase stimulators in patients with heart failure with reduced ejection fraction across the risk spectrum. *Eur J Heart Fail*. 2022;**24**: 2029–36.
138. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al.; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;**382**:1883–93.
139. Butler J, Anstrom KJ, Armstrong PW. Comparing the benefit of novel therapies across clinical trials: insights from the VICTORIA trial. *Circulation*. 2020;**142**:717–9.
140. Tomasoni D, Adamo M, Bozkurt B, Heidenreich P, McDonagh T, Rosano GMC, et al. Aiming at harmony. Comparing and contrasting international HFrEF guidelines. *Eur Heart J Suppl*. 2022;**24**:L20–8.
141. Rao VN, Diez J, Gustafsson F, Mentz RJ, Senni M, Jankowska EA, et al. Practical patient care considerations with use of vericiguat after worsening heart failure events. *J Card Fail*. 2023;**29**:389–402.
142. Nelson MB, Gilbert ON, Duncan PW, Kitzman DW, Reeves GR, Whellan DJ, et al. Intervention adherence in REHAB-HF: predictors and relationship with physical function, quality of life, and clinical events. *J Am Heart Assoc*. 2022;**11**:e024246.
143. Pandey A, Kitzman DW, Nelson MB, Pastva AM, Duncan P, Whellan DJ, et al. Frailty and effects of a multidomain physical rehabilitation intervention among older patients hospitalized for acute heart failure: a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2023;**8**:167–76.
144. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al.; OPTIMIZE-HF Investigators and Coordinators. Carvedilol use at discharge in patients hospitalized for heart failure is associated with improved survival: an analysis from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2007;**153**: 82.e1-11.
145. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al.; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;**380**:539–48.
146. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;**371**:993–1004.