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REVIEW

Heart failure: an update from the last years and a look at the near future

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Abstract

In the last years, major progress occurred in heart failure (HF) management. Quadruple therapy is now mandatory for all the patients with HF with reduced ejection fraction. Whilst verciguat is becoming available across several countries, omecamtiv mecarbil is waiting to be released for clinical use. Concurrent use of potassium-lowering agents may counteract hyperkalaemia and facilitate renin–angiotensin–aldosterone system inhibitor implementations. The results of the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial were confirmed by the Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER) trial, and we now have, for the first time, evidence for treatment of also patients with HF with preserved ejection fraction. In a pre-specified meta-analysis of major randomized controlled trials, sodium–glucose co-transporter-2 inhibitors reduced all-cause mortality, cardiovascular (CV) mortality, and HF hospitalization in the patients with HF regardless of left ventricular ejection fraction. Other steps forward have occurred in the treatment of decompensated HF. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR) trial showed that the addition of intravenous acetazolamide to loop diuretics leads to greater decongestion vs. placebo. The addition of hydrochlorothiazide to loop diuretics was evaluated in the CLOROTIC trial. Torasemide did not change outcomes, compared with furosemide, in TRANSFORM-HF. Ferric derisomaltose had an effect on the primary outcome of CV mortality or HF rehospitalizations in IRONMAN (rate ratio 0.82; 95% confidence interval 0.66–1.02; P = 0.070). Further options for the treatment of HF, including device therapies, cardiac contractility modulation, and percutaneous treatment of valvulopathies, are summarized in this article.

Keywords Heart failure; HFmrEF; HFpEF; HFrEF; Diagnosis; Prognosis; Treatment; SGLT2 inhibitors; Acute HF

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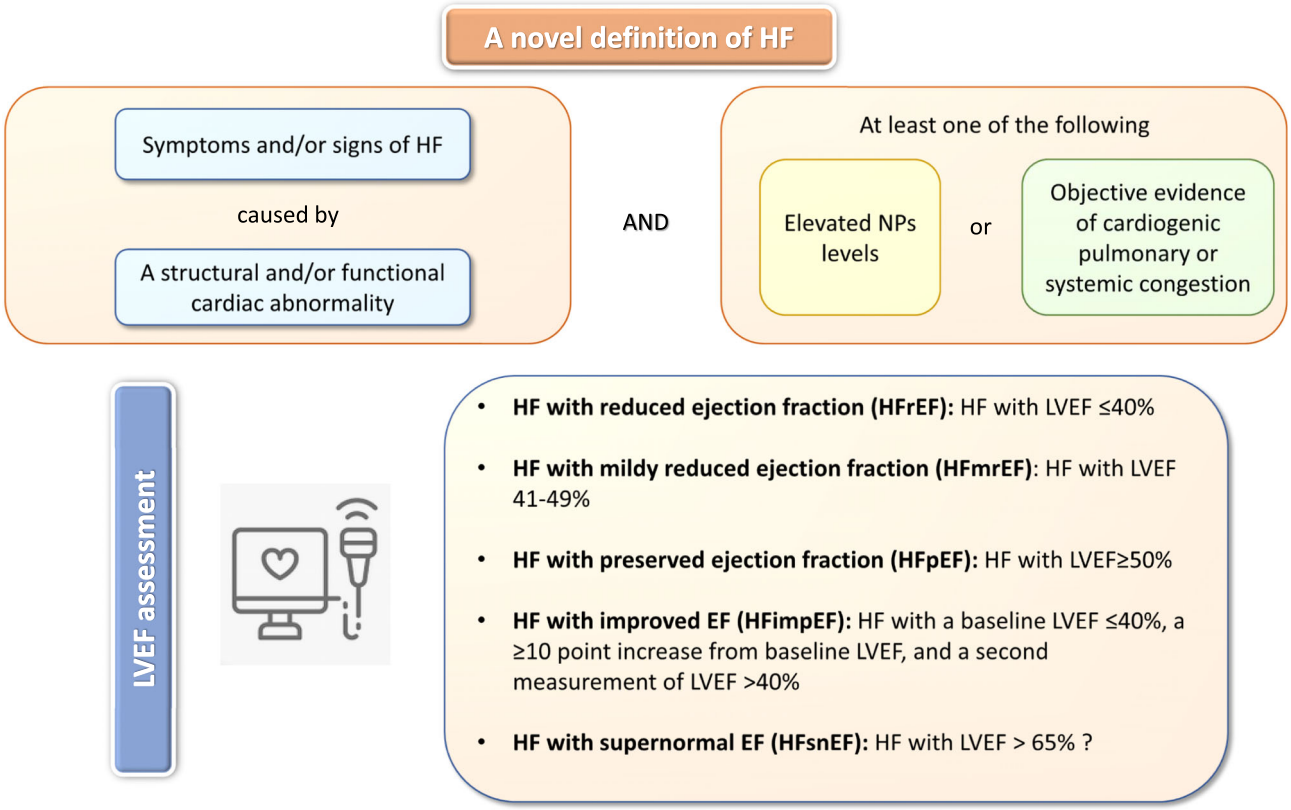
Introduction

Heart failure (HF) is a major health and economic challenge worldwide. In this article, we aim to summarize the most recent findings and advances in the field of HF.

Universal definition of heart failure

The Heart Failure Society of America (HFSA), the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), and the Japanese Heart Failure Society (JHFS) proposed the universal definition of HF. HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide (NP) levels and/or objective evidence of pulmonary or systemic congestion.[1] According to left ventricular (LV) ejection fraction (EF) (LVEF), patients with HF are classified into those with reduced EF (HFrEF, EF $\leq$ 40%), mildly reduced EF (HFmrEF, EF 41–49%), preserved EF (HFpEF, EF $\geq$ 50%), and improved EF (HFimpEF, baseline EF $\leq$ 40%, a $\geq$10-point increase in EF, and a second EF $>$ 40%)[1–3] (*Figure 1*).

Figure 1 A novel definition of heart failure (HF) (modified from Bozkurt *et al.*[1]). LVEF, left ventricular ejection fraction; NPs, natriuretic peptides.



Epidemiology

Due to population growth and ageing, the total number of HF patients continues to rise. It is estimated that 64.3 million people live with HF worldwide. In developed countries, the prevalence of known HF is generally estimated at 1–2% of the general adult population.[2,4] Groenewegen *et al*. estimated a more realistic prevalence of 4.2% with HF that remains undetected in over half of the cases.[2,4]

An alarming rise in relatively young people and in countries with low socio-demographic index is probably related to an increase in risk factors.[5,6] In addition, there has been a clear transition towards HFpEF due to an improvement in the recognition of the disorder but also its relationship to obesity and the ageing of the population.[4,7–10] HF is still burdened by high morbidity and mortality.[11–13]

Sex differences

Sex-based differences exist among patients with HF.[14–19] Women with known or suspected coronary artery disease are at a higher risk of new-onset HF,[20] but they are generally older than men at the time of diagnosis, more frequently develop HFpEF, and seem to have a better prognosis than men, even after age adjustment.[21,22] A systematic review of randomized controlled trials, including 183 097 patients with HFrEF, showed that women were under-enrolled in most of the studies, representing about a quarter of the patients.[23] Several studies investigated interactions between sex and treatment effects.[15,24–26]

Diagnosis and prognosis

Electrolytes

Both hypokalaemia and hyperkalaemia have been associated with worse prognosis.[27,28] Cooper *et al*. showed a U-shaped relationship between serum potassium levels and mortality risk in 13 015 patients with HFrEF from the Swedish Heart Failure Registry.[29] Hyperkalaemia (together with elevated plasma volume) is a sign of instability after a recent hospitalization,[30] and it is a frequent cause of renin–angiotensin–aldosterone system inhibitor (RAASi) discontinuation.[31] However, an analysis from the ESC–HFA–EURObservational Research Programme (EORP) Heart Failure Long-Term Registry showed that hyperkalaemia was no lon-

ger associated with mortality after adjusting for RAASi discontinuation, suggesting that hyperkalaemia may be a risk marker for RAASi discontinuation rather than a risk factor for worse outcomes.[32,33] These data were then confirmed in the Observational study from the Stockholm CREAtinine Measurements (SCREAM) project 2006–18.[34] About half of the HF patients also present hyperuricaemia, a prognostic ominous factor in HFrEF.[35] In the Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) trial, serum uric acid (UA) was an independent predictor of poor outcome also in HFpEF. Sacubitril/valsartan reduced serum UA levels and the need for UA-related drugs with an improvement of outcomes.[36] Similarly, in the Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF), compared with placebo, dapagliflozin reduced UA and improved outcomes irrespective of UA concentration.[37]

Biomarkers

Biomarkers are needed for the management of patients with HF.[38–42] Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are related with left intracardiac filling pressures and pulmonary capillary wedge pressures (PCWP).[43] Cardiac troponin (Tn) has a central role in the prognostic evaluation of HF patients.[44] In the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), increasing levels of high-sensitivity cardiac Tn T were associated with higher rates of comorbidities [i.e. diabetes mellitus (DM) and atrial fibrillation (AF)], more advanced New York Heart Association (NYHA) functional class, decreased renal function, higher concentrations of NP, and worse clinical course.[45] The combination of NT-proBNP and cardiac Tn improves HF risk prediction in overweight and obese individuals.[46]

Several other biomarkers are under study and have already demonstrated a diagnostic and prognostic role, including soluble suppression of tumourigenesis-2 (sST2), galectin-3, and GDF-15, markers that are associated with inflammatory disease and fibrosis,[47] bio-adrenomedullin (bio-ADM), a possible marker of congestion,[48,49] circulating dipeptidyl peptidase 3 (cDPP3),[50,51] a protease involved in angiotensin II and enkephalin degradation,[52] carboxy-terminal propeptide of procollagen type I (PICP),[53] fibroblast growth factor 23 (FGF23),[54] antigen carbohydrate 125 (CA125),[55,56] cystatin C,[47] serum and urine neutrophil gelatinase-associated lipocalin (NGAL),[57] and urine peptides.[58]

Imaging

The role of imaging in the management of HF is well established.[59–63] The Copenhagen City Heart Study investigated the prognostic value of two-dimensional speckle tracking echocardiography in the general population. Overall, 4013 citizens were included. Whole wall and epi-myocardial global longitudinal strain (GLS) were found to be detrimental in differentiating between ischaemic and non-ischaemic aetiology[64] to assess diastolic function[65] and to be significant predictors of outcome [a composite of incident HF or cardiovascular (CV) death] in males, whereas no GLS parameter was useful in females,[66] and also able to improve diagnosis. In a larger cohort of 117 275 subjects being followed up with echocardiography, even modest LVEF changes over time had a significant impact on prognosis with an increase from 12% to 29% of 5 year all-cause mortality among subjects with the smallest to the largest decrease in LVEF (from <5 to >30 units).[67] Several ultrasound methods allow the detection of elevated intracardiac pressures and/or fluid overload, including imaging of the heart, lungs (B-lines), kidneys (intrarenal venous flow), and venous system (inferior vena cava and internal jugular vein diameter).[68] Among 238 subjects with at least one risk factor for HF, subclinical congestion assessed by inferior vena cava diameter, jugular vein distensibility ratio, and the number of B-lines at lung ultrasound was detected in 30%.[69] LVEF remains a major determinant of prognosis.[63] Systolic time intervals can be reliably quantified by conventional echocardiography. Patients with HFrEF displayed shorter LV ejection times reflecting an impairment in LV contractility.[70] Longer systolic ejection times were independently associated with improved outcome in HFrEF but not in HFpEF patients.[71,72]

'Atrial disease', also referred as atrial failure or myopathy, represents an intersection of subclinical structural, electrophysiological, and functional changes that affect the atria and has an important diagnostic and prognostic role, above all in patients with HFpEF.[2,73,74] Left atrial (LA) reservoir and pump strain are associated with LV filling pressure and may contribute to the limitation of exercise capacity in the patients with HF.[75,76] LA size predicted 4 year mortality also in HF patients with mitral regurgitation (MR) treated by percutaneous repair.[77]

Machine learning and risk prediction

Machine learning procedures have been successfully used to guide diagnosis,[78] therapeutic strategies,[79] and prognosis.[80] Using a machine learning algorithm, Adler *et al*. proposed a novel mortality risk score that was then successfully validated across the LVEF categories.[81,82] A machine learning approach was also useful to stratify patients, namely, those with HFpEF, into different clusters with different outcomes.[38,81–85]

Treatment of heart failure with reduced ejection fraction

Pharmacological therapies

Pharmacotherapy is the cornerstone of treatment for HFrEF and is based on combined administration of drugs acting through different pathways.[2,86–88] However, implementation of the so-called guidelines directed medical treatment (GDMT) remains suboptimal in a large proportion of patients.[14,89–95] In a multinational observational study, using healthcare databases in Sweden, the United Kingdom, and the United States, among new users of HFrEF drugs, over 12 month follow-up, target doses of angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), beta-blockers, and angiotensin receptor–neprilysin inhibitors (ARNIs) were achieved in 15%, 10%, 12%, and 30% of patients, respectively. Treatment discontinuation was frequently observed occurring in 55% of the patients on ACEi, 33% of those on ARB, 40% of those on mineralocorticoid receptor antagonist (MRA), and, importantly as ACEi/ARB discontinuation might have been related to the initiation of ARNI, 27% of those on ARNI.[96] Another recent analysis of Medicare beneficiaries in the United States showed that 34% did not have an active sacubitril/valsartan prescription at Day 180 after its initiation with Black race, comorbidities, and the start early after a hospitalization as factors increasing the likelihood of early discontinuation.[97] Several strategies have been proposed for the implementation of GDMT, including rapid sequencing and patient profiling.[98–102]

Neurohormonal modulators

The interaction between different drugs has therefore a major role for their tolerance and the implementation of GDMT. Use of sacubitril/valsartan (when compared with enalapril) did not lead to greater discontinuation or dose down-titration of other key GDMT and promoted sustained MRA use in follow-up.[101] Initiation of sacubitril/valsartan as first-line therapy in *de novo* HF patients was safe.[103] Further benefits of ARNI on liver function have been highlighted.[104] On the other hand, sacubitril/valsartan failed to improve exercise capacity compared with enalapril in two small randomized controlled trials, the ACTIVITY-HF and OUTSTEP-HF trials.[105–107] In 2021, the results of PARADISE-MI trial were published.[108–111] Sacubitril/valsartan did not significantly reduce the rate of CV death or incident HF in patients with LVEF $\leq$ 40% and/or pulmonary congestion following acute myocardial infarction (AMI), compared with ramipril.[111] However, in a *post hoc* analysis of the PARADISE-MI trial using the win ratio, sacubitril/valsartan was superior to ramipril among high-risk survivors of AMI.[112]

Finerenone is a novel nonsteroidal, selective MRA.[113,114] FIDELIO-DKD and FIGARO-DKD trials demonstrated that finerenone improved CV and kidney outcomes in patients with chronic kidney disease (CKD) and type 2 DM.[114–118] These positive results have been recently confirmed in the FIDELITY pooled analysis.[118] Further evidence on the efficacy and safety of finerenone compared with placebo in patients with HF and LVEF of 40% or greater is expected from the ongoing Finerenone Trial to Investigate Efficacy And Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF) study, which is currently recruiting (NCT04435626).

Sodium–glucose co-transporter-2 inhibitors

Sodium–glucose co-transporter-2 (SGLT2) inhibitors have a central role in the prevention and treatment of HF.[119–128] A recent meta-analysis of major randomized clinical trials (RCTs), including 71 553 participants with HF, CKD, or high-risk type 2 DM, showed that SGLT2 inhibitors reduced the risk of HF hospitalization by 31% and the composite outcome of CV death or HF hospitalization by 24%. Results were consistent across the broad spectrum of cardio-renal-metabolic risk, although those with established HF had the greatest absolute benefit.[129] Data from the Swedish Heart Failure Registry showed similar results with SGLT2i administration, leading to a 30% reduction of CV death/first HF hospitalization.[130] SGLT2 inhibitors reduced CV events regardless of several baseline characteristics, including NT-proBNP concentrations, body mass index (BMI), ischaemic vs. non-ischaemic aetiology, or the presence of chronic obstructive pulmonary disease.[131–136] Data on improvement in exercise capacity are still debated.[137] Tomasoni *et al*. reviewed growing evidence that support the early, upfront initiation of SGLT2is in both acute and chronic HF patients due to early benefits, with clinically meaningful reductions in clinical events that reach statistical significance within days to weeks, safety, and tolerability.[100,154,342,343]

Potassium-lowering agents

The DIAMOND trial, enrolling 1642 patients with HFrEF and current or a history of RAASi-related hyperkalaemia, showed that the use of patiromer was associated with significantly lower serum potassium levels at follow-up, fewer hyperkalaemia episodes, concurrent use of high doses of MRAs, and overall higher RAASi use compared with placebo.[138,139]

Soluble guanylate cyclase stimulators

Vericiguat, soluble guanylate cyclase stimulators, reduced the risk of CV death or HF hospitalization in patients with HFrEF and recently decompensated HF.[140,141] Benefits were consistent in those with and without AF and across the full range of estimated glomerular filtration rate (eGFR).[142,143] Vericiguat treatment was associated with reduction in inflammatory- and oxidative stress-related markers, such as high-sensitivity C-reactive protein and UA.[144]

Myosin activators

New insights from the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in HF (GALACTIC-HF) trial show the efficacy and safety of the selective cardiac myosin activator omecamtiv mecarbil in patients with severe systolic HF and with systolic blood pressure (BP) ≤100 mmHg.[145–150] In Multicenter Exercise Tolerance Evaluation of Omecamtiv Mecarbil Related to Increased Contractility in Heart Failure (METEORIC-HF) trial, omecamtiv mecarbil did not improve functional capacity in patients with HFrEF over 20 weeks.[151] This drug remains therefore indicated to improve patients' outcomes.[2] Danicamtiv is another selective myosin activator capable of improving LV and atrial contractility in experimental models and in a Phase 2a trial in patients with HFrEF.[152]

Possible future options

Transient receptor potential vanilloid 4 (TRPV4) channel regulates fluid exchange in the lungs. A novel transient TRPV4 antagonist (GSK2798745) was tested in a pilot randomized, placebo-controlled trial aimed at the reduction of lung water content.[153] The new drug was well tolerated and showed a trend towards improved gas transfer.[154] Mesenchymal autologous stem-cell therapy has had promising results in ischaemic cardiomyopathy and HF.[155,156] The Phase II CONCERT-HF trial demonstrated that the combination of mesenchymal stem cells and c-kit-positive cardiac cells was associated with further improvement in clinical outcome and quality of life (QoL).[157] Target therapies focusing on miRNA and plasma proteome may become a future perspective.[158,159]

Non-pharmacological therapies

Dietary interventions and exercise training

Dietary interventions are related to HF incidence and outcome.[160–162] A meta-analysis, including 122 RCTs and 176 097 participants, summarized and confirmed the impact of nutritional and dietary interventions on HF-related outcomes. Coenzyme Q10 was associated with lower all-cause mortality, whereas Mediterranean diet was related with a lower risk of developing HF.[162,163] A high-protein diet resulted in greater reductions in cardiometabolic risks relative to a standard-protein diet.[164] Ergoreflex is a cardiorespiratory reflex activated during physical effort. HF patients often develop skeletal myopathy, which is associated with increasing ergoreflex sensitivity and dyspnoea on effort. Exercise training represents a valuable strategy to reduce such sensitivity and increase exercise tolerance.[165–167]

Implantable defibrillator therapy

Sudden cardiac death (SCD) is a complication of HF.[168] Docherty *et al*. developed a risk model for SCD in ischaemic cardiomyopathy using data from the Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left Ventricular Dysfunction trial (CAPRICORN) and the Valsartan in Acute Myocardial Infarction Trial (VALIANT). This SCD risk score was superior to LVEF alone and might be useful in identifying patients for future trials testing treatments to prevent SCD early after AMI.[169] Current guidelines advise implantation of an implantable cardiac defibrillator (ICD) for SCD prevention in patients with a life expectancy of >1 year. An analysis, including 17 901 US veterans with HFrEF receiving a new ICD placement, showed that 1 year mortality was around 13%, suggesting the need of a better selection of patients. Age at implant was associated with higher rates of mortality.[170]

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) improves cardiac function and symptoms and reduces morbidity and mortality in an appropriately selected group of HF patients.[2,171] It may be a feasible treatment that can offer short-term and long-term clinical benefits for NYHA Class IV HF patients.[172] Nevertheless, up to two thirds of eligible patients are not referred for CRT.[173,174] A joint position statement from three ESC Associations, HFA, European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI), aimed at overcoming CRT under-utilization, improving patient selection, and implementing dedicated post-implant CRT care pathways.[174]

Cardiac contractility modulation

Cardiac contractility modulation (CCM) may improve functional capacity and reduce CV and HF hospitalizations.[175,176] A comprehensive meta-analysis of individual patient data from all known randomized trials has shown that CCM provides statistically significant and clinically meaningful benefits in measures of functional capacity and HF-related QoL.[177] Long-term effects of CCM were evaluated in a European prospective registry including 503 patients. CCM improved QoL, functional status, and LVEF. Furthermore, HF hospitalizations were reduced compared with before treatment.[178]

Percutaneous treatment of mitral regurgitation

Valvular heart disease is a major determinant of outcome in patients with HF.[74,179–183] Moderate-to-severe functional MR has a prevalence up to 41% in patients with worsening chronic or new-onset acute HF from the BIOSTAT-CHF study.[179] MR severity may dynamically change after a dedicated period of GDMT optimization.[184] Moreover, GDMT prescription is associated with higher 2 year survival after transcatheter edge-to-edge mitral valve repair (M-TEER) in HFrEF patients with functional MR.[185] M-TEER using a MitraClip device should be considered in selected HFrEF patients with secondary MR, not eligible for surgery, who fulfil the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) selection

criteria.[182,186,187] Residual MR 1+ after MitraClip was associated with reduced risk of 1 year mortality, compared with residual MR 2+ and 3/4+.[188,189] LA enlargement is a strong and independent predictor of adverse long-term outcome after M-TEER.[77,190] Among 221 patients with HFrEF and MR $\geq$ 3+ successfully treated with M-TEER, 40% had an improvement in right ventricular (RV) function, and this finding was independently associated with lower risk of death or heart transplantation (HTx) [hazard ratio (HR) 0.52; 95% confidence interval (CI) 0.29–0.94; P = 0.030].[191] In another cohort, more than one third of patients with secondary MR, undergoing successful M-TEER, experienced an improvement in tricuspid regurgitation (TR). A TR $\leq$ 2+ at short-term follow-up was independently associated with long-term mortality, whereas pre-procedural TR was not. Optimal M-TEER result and a small LA were among factors associated with a higher likelihood of TR $\leq$ 2+ after M-TEER.[192] Finally, mitral valve repair with MitraClip has positive clinical and echocardiographic impact in patients with functional MR 1 year after implantation. Preserved GLS and global constructive work values appeared to be associated with LV reverse remodelling post-intervention.[193]

In-hospital mortality after MitraClip procedure did not differ according to centre procedural volume, although patients treated in high-volume centres had a higher risk profile.[194] Novel percutaneous treatments of functional MR are currently studied.[195,196]

Percutaneous treatment of tricuspid regurgitation

Tricuspid regurgitation can be the cause or the consequence of RV dysfunction and HF.[2,197] In a large database of almost half-million US patients with HF, both prevalent TR and incident TR were independently associated with an increased risk of mortality at a median follow-up of 1.5 years.[180] Tricuspid valve surgery is recommended in patients with severe TR requiring left-sided cardiac surgery. It should be also considered in patients with moderate TR and tricuspid annulus dilatation requiring left-sided cardiac surgery and in symptomatic patients with isolated severe TR.[2] However, surgery in isolated TR is burdened by high in-hospital mortality. A new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery, the TRI-SCORE, has been proposed.[198]

Transcatheter tricuspid valve repair (TTVR) for severe TR was found to be safe and effective in different studies.[197,199,200] TTVR improved nutritional status, QoL, and outcome.[201] Actually, four devices have received the CE mark, that is, TriClip, PASCAL, TricValve, and Cardioband, addressing different mechanisms underlying TR.[197] Unterhuber *et al*. showed that outcome after TTVR was associated with pre-procedural cardiac index in a bimodal fashion with increased mortality for both patients in a low and high cardiac output (CO) state and highest overall mortality for patients with a high CO state phenotype.[202]

Heart failure with preserved ejection fraction

Epidemiology, clinical phenotypes, and pathophysiology

Heart failure with preserved ejection fraction is a heterogeneous syndrome with multiple aetiologies and phenotypes and accounts for more than half of the HF hospitalizations.[84,85,203–207] Kammerlander *et al*. investigated the prevalence of HFpEF following left-sided valve repair. Among 673 patients included, 67.4% fulfilled all criteria of HFpEF according to current guideline recommendations.[208] Three phenogroups of HFpEF were described among the participants to the TOPCAT trial.[85] Using unsupervised cluster analysis based on circulating biomarkers, Woolley *et al*. identified four distinct clusters of HFpEF with remarkable differences in clinical characteristics and outcomes, potentially reflecting different underlying pathophysiology.[84]

The role of DM and obesity in the pathogenesis of HFpEF has drawn significant attention in recent years.[203,209–213] CV effects of obesity may be driven by the distribution of fat, which can accumulate in the epicardial, visceral, and subcutaneous compartments.[214–216] Via adipokine-mediated inflammatory mechanisms, epicardial obesity might cause adverse myocardial remodelling in HF that was independently related with diastolic dysfunction, worse haemodynamic and metabolic profile, and worse survival.[217–219] However, also sarcopenia was an independent predictor of 1 year mortality in both HFpEF and HFrEF.[220]

Other mechanisms involved in the pathogenesis of HFpEF are venous dysfunction, endothelium-independent microvascular dysfunction, and subclinical inflammation.[221–224]

Diagnosis and prognosis

The diagnosis of HFpEF remains challenging.[225] The H_2FPEF and HFA-PEFF scores have been proposed and validated to solve the clinical dilemma of diagnosing HFpEF.[205,226–230] These scores also provided a prognostic significance.[231–233] Tomasoni *et al*. investigated the diagnostic and prognostic value of H_2FPEF and HFA-PEFF scores in patients with HFpEF caused by cardiac amyloidosis (CA). The HFA-PEFF score has a higher diagnostic utility compared with H_2FPEF score and holds independent prognostic value for all-cause mortality.[234] Exercise testing has also a central role to confirm the diagnosis of HFpEF.[235] Cardiopulmonary exercise test and echocardiographic parameters (i.e. LA size and function) allow the risk stratification of HFpEF patients.[60,73,74,76,236–239] Cardiac magnetic resonance (CMR) has a major role in the detection and quantification of myocardial fibrosis and adipose tissue,

two major determinants of the phenotype and outcomes of patients with HFpEF.[214,218]

Treatment

Sodium–glucose co-transporter-2 inhibitors

The EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial was the first trial proving benefits on major clinical endpoints in HFpEF. Empagliflozin reduced the composite endpoint of CV death or HF hospitalization in patients with LVEF $>$ 40% and NYHA Class II–IV, irrespective of DM history (HR 0.79; 95% CI 0.69–0.90; $P < 0.001$).[240] When compared with prior trials in HFpEF, the EMPEROR-Preserved cohort has a somewhat higher burden of comorbidities, lower LVEF, higher median NT-proBNP, and greater use of MRAs at baseline.[241] In a smaller randomized trial, enrolling 324 patients with HFpEF, dapagliflozin improved symptoms, QoL, and functional capacity compared with placebo.[242] In 2022, the results of the Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER) trial have been published.[243,244] Dapagliflozin reduced the combined risk of worsening HF or CV death among patients with symptoms and signs of HF, elevated concentrations of NT-proBNP, evidence of structural heart disease, and LVEF $>$ 40% compared with placebo (HR 0.82; 95% CI 0.73–0.92; $P < 0.001$).[244] Importantly, no appreciable difference was found in benefit among patients with an LVEF of 60% or more and those with an LVEF of $<$60%.

Vaduganathan *et al*. performed a pre-specified meta-analysis of DELIVER and EMPEROR-Preserved and subsequently included trials that enrolled patients with reduced LVEF (DAPA-HF and EMPEROR-Reduced) and those admitted to hospital with worsening HF, irrespective of LVEF (SOLOIST-WHF).[123] Among 12 251 participants from DELIVER and EMPEROR-Preserved, SGLT2 inhibitors reduced the composite endpoint of CV death or first hospitalization for HF (HR 0.80 [95% CI 0.73–0.87]) with consistent reductions in both components: CV death (0.88 [0.77–1.00]) and first hospitalization for HF (0.74 [0.67–0.83]). Among the 21 947 participants of five major trials, SGLT2is reduced the risk of CV death or HF hospitalization (0.77 [0.72–0.82]), CV death (0.87 [0.79–0.95]), first hospitalization for HF (0.72 [0.67–0.78]), and all-cause mortality (0.92 [0.86–0.99]). So, SGLT2 inhibitors reduced the risk of CV death and hospitalisations for HF in a broad range of patients with HF, supporting their role as a foundational therapy for HF, irrespective of LVEF or care setting.[123]

Other drugs

Inorganic nitrite improves peripheral and pulmonary components of oxygen (O_2) uptake during exercise in patients with HFpEF, including skeletal muscle conductance, peripheral O_2 kinetics, and lung gas diffusion.[245] HFpEF frequently coexists in patients with symptomatic AF and preserved EF. Dronedarone is associated with reduced CV events in patients with paroxysmal or persistent AF/atrial flutter and HF across the spectrum of LVEF, including those with HFpEF and HFmrEF.[246] Restoration and maintenance of sinus rhythm in patients with comorbid AF and HFpEF improve haemodynamic parameters, BNP, and symptoms associated with HFpEF.[247]

Device-based percutaneous treatments

The use of devices capable of creating interatrial shunts, to reduce LA pressure, represents a promising therapeutic option in patients with HFpEF. Most of the early trials demonstrate feasibility, safety, and effectiveness in reducing PCWP and improving patients' symptoms and QoL.[248–250] Of note, the Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE-LAP II), a randomized, blinded, sham-controlled trial, including patients with symptomatic HF, LVEF $\geq$ 40%, and PCWP during exercise of at least 25 mmHg, failed to demonstrate difference between groups for the primary hierarchical composite endpoint (win ratio 1.0 [95% CI 0.8–1.2]; $P = 0.85$).[251]

Splanchnic nerve modulation

Approximately 60–70% of blood volume resides in the venous circulation, and up to 20–50% is in the high capacitance, highly innervated, veins of the splanchnic compartment. Sympathetic stimulation causes their constriction or shifting blood to the heart with a rise in intracardiac pressure. Splanchnic nerve modulation is proposed to inhibit such effect.[252,253] In a first series of patients with HFpEF, its favourable effects on exercise PCWP and an improvement in QoL are reported.[254–256]

Heart failure with supranormal ejection fraction

Left ventricular EF may have a U-shaped relationship with outcome, with patients with supranormal (sn) EF (HFsnEF) having a higher risk of events.[19,257–259] Overall, 2.5% of patients enrolled in the RELAX-AHF-2 trial had an LVEF $\geq$ 65%. These patients with HFsnEF, compared with HFpEF patients, were more often women, with higher prevalence of non-ischaemic HF, had lower levels of NPs and higher blood urea nitrogen plasma levels, and were less likely to be treated with beta-blockers. All-cause mortality was not statistically different between groups, although patients with HFsnEF had the highest numerical rate.[258] Another study investigated the prognostic implication of snLVEF as assessed by CMR and its inter-relationship with stroke volume. LVEF in the sn range was associated with a higher risk of adverse CV outcomes, particularly in those with lower stroke volume.[260]

Comorbidities

In a systematic review of HF trials, Khan *et al*. found that only 51% of HFrEF and 27% of HFpEF trials reported baseline comorbidities.[261] Cardiac and non-cardiac comorbidities, including ischaemic cardiomyopathy, AF, hypertension, hyperlipidaemia, DM, CKD, anaemia, and frailty, may influence the management of HF patients and are associated with outcome.[163,262–269] The FRAGILE-HF study was a prospective multicentre study investigating the prevalence, overlap, and prognostic implications of physical and social frailties and cognitive dysfunction in patients hospitalized with HF. Patients with a greater number of frailty domains had higher mortality and HF rehospitalization.[270] Furthermore, up to 30% of HF patients suffer from depression and even more have depressive symptoms.[271]

Anaemia and iron deficiency

Anaemia and iron deficiency (ID) are common in HF and are associated with prognosis.[272–274] Ferric carboxymaltose (FCM) has proven to improve QoL and outcome in patients with HF and ID.[275–277] However, data from the Swedish Heart Failure Registry showed that ID was screened only in about a quarter of the patients and only one in five patients received FCM when indicated.[278] Accurate diagnosis of ID remains controversial and not well established.[279] Sierpinski *et al*. quantified bone marrow iron stores in 30 patients with ischaemic HF and LVEF $\leq$ 45% and in 10 healthy subjects. They found that depleted iron stores in bone marrow have been found in most of patients with ischaemic HF with LVEF $\leq$ 45% (80%), regardless of concomitant anaemia. High serum soluble transferrin receptors reflecting depleted iron stores in bone marrow were the most accurate biomarker measured in peripheral blood, which strongly predicted increased mortality in this subset of patients.[280] In HFpEF, ID impacts prognosis but less exercise capacity.[275] Secondary analysis of DAPA-HF and EMPEROR-Reduced trials suggested that SGLT2i increased haematocrit and haemoglobin levels and reduced the rates of anaemia, compared with placebo likely through their anti-inflammatory effects.[281–283]

The effects of iron therapy in patients with ID were further evaluated in Effectiveness of Intravenous iron treatment vs. standard care in patients with heart failure and iron deficiency (IRONMAN), a prospective multicentre open-label, blinded-endpoint trial conducted across 70 UK hospitals enrolling 1137 adults with HF, LVEF $<$ 45%, and ID, only 14% hospitalized. Patients were assigned to intravenous (i.v.) ferric derisomaltose or not, in addition to standard HF care. Additional iron administrations were allowed if ID returned. During a median follow-up of 2.7 years, the primary outcome of HF hospitalisations and CV death occurred in 22.4 vs. 27.5 per 100 patient-years in the ferric derisomaltose vs. the usual care group [rate ratio (RR) 0.82; 95% CI 0.66–1.02; P = 0.070].[284] Consistently with AFFIRM-AHF, statistical significance was reached in a pre-specified COVID-19 sensitivity analysis (RR 0.76; 95% CI 0.58–1.00; P = 0.047), the reduction in the primary endpoint was driven by a reduction in HF hospitalizations, and QoL was also improved. Safety of iron therapy was also confirmed with fewer serious cardiac adverse events and no increase in infections or other untoward events with ferric derisomaltose. Compared with AFFIRM-AHF, these data were obtained with a longer follow-up and mainly in outpatients; no interaction with HF aetiology was found, differently from AFFIRM-AHF.[276,277,284]

Pulmonary hypertension

Patients with HF often present pulmonary hypertension (PH), which is mainly post-capillary. Some of them also develop a pre-capillary component, leading to a combined pre- and post-capillary PH.[285,286] RV dysfunction and PH are confirmed as major determinants of the poor prognosis of HF patients, including those with HFpEF.[287–291] In HFpEF and PH, diffuse RV fibrosis was described.[292]

COVID-19

The recent coronavirus disease 2019 (COVID-19) pandemic had a catastrophic impact on health systems worldwide.[293,294] Hospitalizations due to acute CV causes showed a significant reduction in the first pandemic period, leading to an increase in case severity and in-hospital mortality.[295–299]

A history of HF was associated with an increased risk of adverse outcome in COVID-19 patients.[300–302] The RAAS plays a key role in the pathophysiology of HF, and the angiotensin-converting enzyme 2 (ACE2) is the receptor for severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2). An increased susceptibility to COVID-19 infection has been hypothesized in patients treated with these drugs due to a higher expression of ACE2 mRNA.[303] However, real-world data did not support such hypothesis.[304] In a 1.4 million cohort from the Swedish National Patient Registry, use of RAASi was not associated with increased risk of hospitalization for or death from COVID-19.[305]

Nevertheless, COVID-19 infection may favour HF through several mechanisms that cause direct or indirect cardiac damage (i.e. fever, tachycardia, adrenergic stimulation, exaggerated inflammatory response, endotheliitis, and myocarditis).[301,306,307] In a large Spanish cohort of COVID-19 patients, NT-proBNP was frequently elevated even in the absence of clinical criteria for the diagnosis of HF. Moreover, NT-proBNP was independently associated with mortality after adjusting for relevant confounders, including chronic

HF and acute HF.[308–310] Lassen *et al*. compared echocardiographic findings in 91 consecutive patients hospitalized for COVID-19 with sex- and age-matched COVID-19-free subjects. Tn and NT-proBNP plasma levels and parameters of RV function were abnormal during hospitalization but improved during follow-up, whereas LV GLS remained abnormal also during follow-up.[311]

It has been hypothesized that COVID-19 might induce an HFpEF-like syndrome.[312] Hadzibegovic *et al*. showed that patients hospitalized for COVID-19 had a higher likelihood of presenting HFpEF, assessed by the HFA-PEFF score, compared with subjects with similar age, sex, and comorbidity status and without COVID-19.[313] Vascular and endothelial dysfunction, similar to that reported in untreated hypertensive patients, was observed at 4 month follow-up after COVID-19.[314]

Solid organ-transplanted recipients suffering from SARS-CoV-2 were reported to have up to 25% increased risk of death compared with matched controls.[315] Vaccines to prevent COVID-19 may have a reduced efficacy in immunocompromised patients. Among 42 HTx recipients, only 15% showed the presence of anti-spike immunoglobulin G (IgG) antibodies after the first dose of vaccine, and 36% of those who did not respond to the first dose of vaccine became anti-spike IgG seropositive after the second vaccination.[316]

Practical guidance was published in order to aid clinicians in the diagnosis and management of CV disease during COVID-19 pandemic.[317–319]

Advanced heart failure

Definition and prognosis

Many patients with HF progress into a phase of advanced HF, characterized by persistent symptoms despite maximal therapy.[320] The HFA-ESC advanced HF definition has been recently validated. The Italian HELP-HF registry enrolled consecutive patients with HF and at least one high-risk 'I NEED HELP' marker. Out of 4753 patients with HF screened, 1149 (24.3%) patients had at least one high-risk 'I NEED HELP' marker, and among them, 193 (16.8%) patients met the HFA-ESC advanced HF definition. The HFA-ESC advanced HF definition was associated with a higher risk of all-cause mortality or first HF hospitalization (adjusted HR 1.98; 95% CI 1.57–2.50; $P < 0.001$).[321] The efficacy and tolerability of GDMT in patients with the most advanced stages of HFrEF often remain unsettled.[150,322,323]

Therapy

Advanced therapeutic strategies including HTx, mechanical circulatory support (MCS) implantation, intermittent inotropes, and also end-of-life cares are often required in these patients.[324] Age and shock severity predict mortality in cardiac intensive care unit.[325]

Heart transplantation remains a limited therapeutic option due to the disproportion between donors and possible candidates needing the transplantation. The first case of genetically modified porcine-to-human cardiac xenotransplantation has been recently reported.[326]

Long-term MCS is a valid alternative in patients non-eligible to HTx or in those deteriorating while waiting for transplantation. However, MCS implantation is burdened by high costs and adverse events, limiting its use, and requiring restrictive clinical criteria as well.[327] The SweVAD study will compare survival, medium-term benefits, costs, and potential hazards with LV assist device (LVAD) vs. GDMT as destination therapy strategy in patients with advance HF ineligible for HTx.[328] The MOMENTUM 3 pivotal trial established superiority of the HeartMate 3 (HM3) LVAD, a fully magnetically levitated centrifugal-flow pump, over the HeartMate II axial-flow pump.[329] The primary results of accumulating HM3 LVAD experience suggest a lower adverse event burden and similar survival compared with the pivotal MOMENTUM 3 trial.[330] Conflicting data on fibrotic changes after LVAD support were reported.[331] A recent study showed that cardiac fibrosis was strongly increased in most failing hearts and even significantly increased during mechanical unloading.[332]

Sacubitril/valsartan initiation in patients with continuous-flow LVAD implant effectively reduces mean arterial pressure, a factor related to adverse events.[333]

Infections are common following LVAD implantation and predict adverse events.[334] The ARIES HM3 trial is an international, RCT to test the hypothesis that aspirin may be removed safely from the antithrombotic regimen with the HM3 LVAD to reduce bleeding risk.[335]

Palliative care

Quality of life is clinically relevant in patients with HF and has become a major endpoint for HF studies.[167,203,336–339] QoL in end-stage HF is even more important. As a consequence, the management of end-stage HF needs to include palliative care.[150,340] Sahlollbey *et al*. performed a meta-analysis of 10 RCTs showing that palliative care, compared with usual care, was associated with a reduction in HF hospitalization, with no clear adverse effect on survival, and a modest, though significant, improvement in QoL and symptoms in patients with advanced HF.[341]

Acute heart failure

Acute HF remains a life-threatening condition, burdened by high mortality.[9,342–345] A novel classification of acute HF has been provided in the latest ESC guidelines.[2] A study conducted in Australia and New Zealand showed that 1

out of 10 patients died within 30 days of their last HF hospitalization and 25% of patients required an unplanned rehospitalization.[346] In the BIOSTAT-CHF cohorts, acute HF inpatients displayed a higher 6 month mortality, compared with chronic outpatients with worsening HF (12.3% vs. 4.7%).[347]

Biomarkers, decongestion, and renal function

Higher levels of NT-proBNP at discharge, or an inadequate decline during hospitalization, confer higher risk of readmission and/or death within 180 days.[39,43] A practical approach would consider changes >30% of NT-proBNP as clinically relevant.[43] Also, high levels of bio-ADM levels at discharge are strongly associated with residual congestion in patients with acute HF.[48,348] An early re-evaluation (>10 days) with CA-125 measurement after an acute HF hospitalization may be useful in patient management.[55,56]

Other biomarkers are emerging. cDPP3 is a protease involved in angiotensin II and enkephalin degradation.[51] In patients with cardiogenic shock (CS), higher baseline cDPP3 levels were associated with increased short-term mortality and more severe organ dysfunction, and its rapid decrease within 24 h predicted a favourable outcome.[52] DPP3 administration in a mouse model induced myocardial depression and renal impairment, whereas DPP3 inhibition by a specific antibody normalized cardiac and kidney function with reduction in oxidative stress and inflammation.[50] Wettersten *et al*. evaluated the prognostic significance of serum and urine NGAL in 927 patients with acute HF. Serum NGAL outperformed urine NGAL but neither was superior to admission or peak serum creatinine for predicting adverse events.[57]

In an analysis of the RELAX-AHF-2 trial, worsening renal function (WRF), defined as a rise in serum creatinine ≥0.3 mg/dL, occurred in 28.2% of patients within the first 5 days of an acute HF hospitalization, with a higher incidence in those with a higher LVEF.[349] Measurement of natriuresis in patients hospitalized for acute HF early identifies high-risk patients with a poor diuretic response.[350] The Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure (PUSH-AHF) is a randomized, open-label controlled study aiming to enrol 310 acute HF patients in order to assess the efficacy of natriuresis-guided diuretic therapy. Patients will be randomized to either natriuresis-driven therapy or standard care, and the co-primary endpoints are 24 h urinary sodium excretion and 6 month all-cause mortality or first HF rehospitalization.[351]

Treatment

The prehospital patient pathway and healthcare organization play a significant role in the management of acute HF.[344,352] In 2022, the positive results of the Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR) trial have been published. The addition of acetazolamide (500 mg/day, i.v.) to loop diuretic therapy in patients with acute decompensated HF resulted in a greater incidence of successful decongestion, without differences in WRF, hypokalaemia, hypotension, and adverse event vs. placebo.[353] The addition of hydrochlorothiazide to loop diuretics was evaluated in the CLOROTIC trial.[354] Torasemide did not change outcomes, compared with furosemide, in TRANSFORM-HF[355,356] (*Figure 2*).

The EMPULSE trial randomized 530 patients hospitalized for acute HF, when clinically stable, to receive empagliflozin 10 mg once daily or placebo for up to 90 days. Empagliflozin provided a clinical benefit, defined as a hierarchical composite of death from any cause, number of HF events and time to first HF event, or a 5-point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days, as assessed using a win ratio (stratified win ratio 1.36; 95% CI 1.09–1.68; P = 0.0054).[357] In the EMPA-RESPONSE-AHF trial, empagliflozin increased fractional glucose excretion and plasma osmolality, without changes in fractional sodium and chloride excretion and urinary osmolality, and caused a temporary decline in eGFR.[358] An improvement in early decongestion has been confirmed in another study.[359] Optimization of treatment before or shortly after discharge remains a major goal in order to improve post-discharge outcomes in patients hospitalized for acute HF.[95,100,103,343,360] An intensive treatment strategy of rapid up-titration of GDMT and close follow-up after an acute HF admission reduced symptoms, improved QoL, and reduced the risk of 180 day all-cause death or HF readmission compared with usual care.[361]

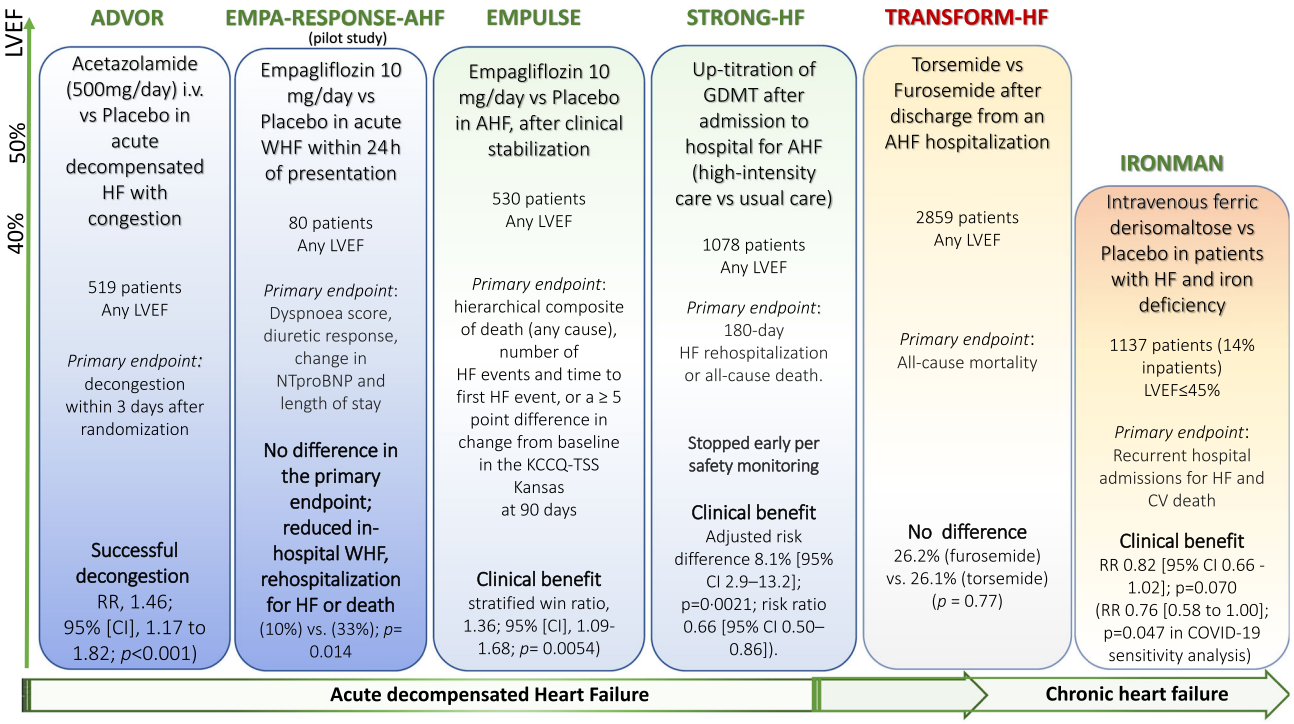
In a meta-analysis of six RCTs, including 11 359 patients treated with i.v. serelaxin or placebo within the first 16 h of acute HF admission, serelaxin administration was associated with a reduction in 5 day worsening HF, markers of renal dysfunction, NT-proBNP and Tn, and a favourable outcome.[362] In patients hospitalized for acute HF with reduced LVEF, a 24 h infusion of istaroxime improved parameters of diastolic and systolic cardiac function without major cardiac adverse effects.[363] The Phase 2a SEISMIC study, including patients with pre-CS, istaroxime improved BP and echocardiography measures related to HF (i.e. cardiac index, LA area, and LV end-systolic volume) and was well tolerated.[364]

Procalcitonin-guided initiation of antibiotic therapy did not improve clinical outcomes compared with standard of care in 742 patients admitted for acute HF.[365]

Cardiogenic shock

Cardiogenic shock is still burdened by an extremely poor prognosis.[366,367] Data from the Nationwide Readmis-

Figure 2 Recent completed trials in patients with heart failure (HF) [focusing on acute HF (AHF)]. CI, confidence interval; CV, cardiovascular; GDMT, guideline-directed medical therapy; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; RR, rate ratio; WHF, worsening heart failure.



sions Database showed that a regional 'hub-and-spoke' triage system, with direct admission to CS hubs or transfer to hubs, is associated with a lower mortality.[368] MCS may be useful in the management of CS. However, data from RCTs seem not to reflect real-world practice. Enrolment criteria from the main RCTs on MCS were applied to 1305 patients with CS admitted to a tertiary care hospital between 2009 and 2019. Only one third of this real-world population with CS was eligible for any trial. This was mostly due to the exclusion of CS not secondary to AMI, but even in a post-AMI CS scenario, only 65.4% of patients were eligible.[369]

Remote monitoring, telemedicine, and rehabilitation

Telemedicine and telemonitoring for HF patients have grown great interest, also driven by the need to find new management solutions in the era of COVID-19 pandemic.[317,370,371] Patients with depression have been excluded in most telemedicine studies. However, in a pre-specified analysis of the Telemedical Interventional Monitoring in Heart Failure (TIM-HF) trial, telemedicine significantly improved symptoms of depression and QoL over a period of 12 months in patients with chronic HF and moderate depression.[372] Available options to telemonitor patients include patient self-managed testing, wearable devices, technologies integrated into pacemakers and defibrillators, or arrhythmia monitoring systems.[160,373–375] Recently, implantable devices that can monitor pulmonary artery pressure have shown safety and have succeeded in reducing hospitalization rates in symptomatic HF patients.[376–378]

Cardiac rehabilitation (CR) is defined as a multidisciplinary programme that includes exercise training, cardiac risk factor modification, psychosocial assessment, and outcomes assessment. CR resulted in a reduction of HF-related hospitalizations and significant improvements in QoL, functional capacity, and exercise performance.[167,379,380] In the REHAB-HF trial, in a diverse population of older patients who were hospitalized for acute HF, an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical function domains resulted in greater improvement in physical function than usual care.[380] Several devices may be useful to monitor physical activity.[381]

Specific causes of heart failure

Cancer treatment

Cancer and HF have common pathways including inflammation, cellular metabolic changes, genetic predisposition, clonal haematopoiesis, and angiogenesis.[382–384] In a prospective study, patients with cancer, compared with healthy controls, were more likely to present premature ventricular contractions and non-sustained ventricular tachycardia.[385] HF can develop as a consequence of the toxic effects of anti-cancer therapy (cardiotoxicity).[383,386–388] In patients treated with immune checkpoint inhibitors (ICIs), pharmacovigilance data analysis reported an incidence of 4.2% of cardiac events, including myocarditis, which was often burdened by a high mortality.[389,390] The incidence of cardiac events was higher in those patients with dual ICI therapy. For this reason, a grading system for ICI myocarditis, based on endomyocardial biopsy, was developed.[391] New guidelines on cardio-oncology have been recently issued by the ESC.[392]

Cardiomyopathies

Cardiomyopathies are a heterogeneous cause of HF.[393–395] Electrocardiogram or clinical red flags can help identify specific forms.[396,397] Over the last years, improvement in survival was observed in patients with dilated cardiomyopathy (DCM), thanks to the efficacy of treatment and its implementation.[398] Withdrawal of HF drugs in patients with recovered DCM was associated with relapses in 44% of patients and with early ventricular remodelling, increase in myocardial mass, and decrease in GLS.[399,400]

Novel treatment strategies are being developed for hypertrophic cardiomyopathy, including mavacamten, a modulator of cardiac β-myosin, causing reversible inhibition of actin–myosin cross bridging, which now adds to septal reduction techniques, biventricular pacing, mitral valve surgical or percutaneous repair, and gene-based therapies.[401]

Cardiac amyloidosis

Increasing prevalence of CA is due to greater awareness and advances in diagnosis. Easily available echocardiographic red flags, when combined together, demonstrated good diagnostic accuracy.[402] CA often coexists with aortic stenosis (AS)[403–406] but also with mitral and tricuspid stenosis.[407] About 8–16% of patients with severe AS undergoing transcatheter aortic valve replacement have CA.[404]

Several measures, including a quantitation of disease severity by clinical and functional endpoints, biomarkers, imaging, and electrocardiographic parameters, should be used to detect disease progression and should be performed in a relatively short time frame (6–12 months) after diagnosis.[408,409] In a multicentre study including patients with immunoglobulin light chain (AL) or transthyretin (TTR) CA, both peak oxygen consumption (VO_2) $\leq$13 mL/kg/min and NT-proBNP $\geq$ 1800 ng/L were independently associated with a two-fold higher risk of the primary endpoint (death or HF hospitalization).[410]

Recent years saw the introduction of promising targeted therapies, which aim to interfere with the deposition of misfolded TTR at various stages of the cascade underlying TTR-CA progression. These include TTR tetramer stabilizers (tafamidis, diflunisal, and epigallocatechin-3-gallate), TTR silencers (inotersen and patisiran), and fibril disruptors (monoclonal antibodies, doxycycline, and tauroursodeoxycholic acid).[411–415]

Myocarditis

Acute myocarditis is an acute-onset inflammatory heart disease with heterogeneous clinical presentation, varying from chest pain, life-threatening ventricular arrhythmias, to CS.[416] Viral infections may be the cause of acute myocarditis with typical prodromic symptoms/signs (i.e. fever, flu-like symptoms, and sore throat).[417,418] The role of viral detection and immunomodulation in patients with acute lymphocytic myocarditis has been reviewed.[419] In an RCT, i.v. immunoglobulin did not improve systolic function or functional status in patients with parvovirus B19-related DCM compared with placebo.[420] Modulation of the acute defence reaction by eplerenone prevents cardiac disease progression in viral myocarditis.[421]

Conclusions

In recent years, there has been great progress in the treatment of HF. The 2021 ESC guidelines for the management of HF established the four pillars of HFrEF treatment with ACEis/ARNIs, beta-blockers, MRAs, and SGLT2is. These drugs should be started as soon as possible. The DIAMOND trial established the role of novel potassium binders, namely, patiromer, for the treatment of hyperkalaemia in order to reduce the rate of RAASi discontinuation. A major clinical need has been met in the last 2 years. With the results of

the EMPEROR-Preserved and DELIVER trials, SGLT2 inhibitors are the first class of drugs that demonstrated to improve prognosis in patients with HF and mildly reduced or preserved LVEF.

Conflict of interest

The authors declare no conflicts of interest as regard this article.

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