Heart failure in the last year: progress and perspective

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Abstract

Research about heart failure (HF) has made major progress in the last years. We give here an update on the most recent findings. Landmark trials have established new treatments for HF with reduced ejection fraction. Sacubitril/valsartan was superior to enalapril in PARADIGM-HF trial, and its initiation during hospitalization for acute HF or early after discharge can now be considered. More recently, new therapeutic pathways have been developed. In the DAPA-HF and EMPEROR-Reduced trials, dapagliflozin and empagliflozin reduced the risk of the primary composite endpoint, compared with placebo [hazard ratio (HR) 0.74; 95% confidence interval (CI) 0.65–0.85; P < 0.001 and HR 0.75; 95% CI 0.65–0.86; P < 0.001, respectively]. Second, vericiguat, an oral soluble guanylate cyclase stimulator, reduced the composite endpoint of cardiovascular death or HF hospitalization vs. placebo (HR 0.90; 95% CI 0.82–0.98; P = 0.02). On the other hand, both the diagnosis and treatment of HF with preserved ejection fraction, as well as management of advanced HF and acute HF, remain challenging. A better phenotyping of patients with HF would be helpful for prognostic stratification and treatment selection. Further aspects, such as the use of devices, treatment of arrhythmias, and percutaneous treatment of valvular heart disease in patients with HF, are also discussed and reviewed in this article.

Keywords Heart failure; Acute heart failure; HfpEF; HFrEF; Diagnosis; Treatment

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Introduction

Heart failure (HF) is a major health and economic burden worldwide.1–5 Because mortality remains high and the quality of life is poor, it is an area of active research.6–10 In this article, we update recent published data and findings.

Epidemiology: geographic and temporal trends

Data concerning the epidemiology of HF remain insufficient.11–13 The Heart Failure Association (HFA) Atlas is a novel European HF data set with a major aim to provide information about HF epidemiology, resource, and reimbursement policies for HF management.14

In a recent meta-analysis, Jones et al. presented long-term outcomes in 1.5 million ambulatory patients with chronic HF, including 60 non-interventional studies. Despite an improvement in 5 year survival rates between 1970–1979 and 2000–2009 from 29.1% to 59.7%, mortality rates remain unacceptably high and larger than for most types of cancer (Figure 1).11,15 Trends in HF hospitalizations from 2000 to 2014 were examined in Norway. Age-standardized rates of incident HF hospitalization declined on average 1.9% and 1.8% per year for men and women, respectively. Although mortality was reduced, HF rehospitalizations increased.16

Several studies have highlighted the regional heterogeneity of HF populations, patients’ characteristics, and outcomes.
with important implications for global trial design. Dewan et al. compared heart failure with reduced ejection fraction (HFrEF) patients enrolled in different continents in two large trials: Prospective comparison of angiotensin receptor neprilysin inhibitors (ARNI) with angiotensin-converting enzyme inhibitors to Determine Impact on Global Mortality and morbidity in HF (PARADIGM-HF) and Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE). They found that Asian patients were younger (55.0–63.9 years) than those in Western Europe (67.9 years) and North America (66.6 years). The adjusted risk of cardiovascular (CV) death was higher in many Asian countries, except Japan. Using Western Europe as the reference group, the adjusted hazard ratio (HR) for China, India, Thailand, and Japan was 1.89 (1.58–2.27), 1.76 (1.49–2.09), 1.87 (1.18–2.96), and 0.77 (0.53–1.12), respectively.

Prospective multinational data from Asia showed that heart failure with preserved ejection fraction (HFP EF) affects relatively young patients with high prevalence of co-morbidities, most commonly hypertension, anaemia, chronic kidney disease, diabetes, coronary heart disease, and atrial fibrillation (AF). Gender may also impact these international differences in HFrEF. Similar risk factors for incident HF were reported in the UK population. Novel risk factors for worse status continue to be discovered, including nutritional deficiencies even in the developed world.

Because outcomes are different worldwide, designing a risk prediction model remains challenging and might underestimate or overestimate mortality in some countries.

Specific phenotypes

Among the specific causes of HF, cardiomyopathies are a heterogeneous group of heart muscle diseases. Current knowledge regarding the incidence and prevalence of cardiomyopathies and HF has been summarized in a recent position paper by the HFA of the European Society of Cardiology (ESC). Genetic phenotyping of cardiomyopathies is helpful to understand the clinical course of the disease and to address aetiology-based therapy. Desmoglein-2 mutation carriers were found to be at high risk of end-stage HF compared with plakophilin-2 mutation carriers in arrhythmogenic right ventricular (RV) cardiomyopathy.

A specific phenotype of HF is that caused by amyloidosis. Cardiac amyloidosis is a peculiar cardiomyopathy, characterized by extracellular deposition of misfolded proteins that leads to increased biventricular wall thickness and increased myocardial stiffness. Different types of protein deposition cause different types of amyloidosis: light-chain amyloidosis and transthyretin amyloidosis are the most frequent, and the transthyretin stabilizer tafamidis has recently been introduced to improve the prognosis of affected patients. Amyloidosis may be a major cause of severe symptoms and poor outcomes. Transthyretin amyloidosis is an underdiagnosed cause of HF, especially in HFP EF, hypertrophic or restrictive cardiomyopathy, and aortic stenosis. Compared with wild-type transthyretin amyloidosis, transthyretin-related hereditary amyloidosis more often affects men and is characterized by an early onset with...
concomitant neurological involvement. Such patients need to be screened, and specific treatments can be considered.

Much recent interest has also focused on other cardiomyopathies including peripartum cardiomyopathy.

Co-morbidities

Co-morbidities play a major role in the clinical presentation and outcomes of HF. More than 70% of patients with HF are burdened by co-morbidities, and they have an independent effect on mortality.

Type 2 diabetes mellitus confers a greater risk of new onset HF, HF rehospitalization, and CV and all-cause mortality, particularly when patients require insulin treatment and/or have concomitant conditions.

Further common co-morbidities associated with HF are chronic kidney disease, chronic obstructive pulmonary disease, central nervous system abnormalities, sleep disordered breathing, iron deficiency, cancer, cachexia, muscle wasting (sarcopenia), and frailty. The prevalence of frailty is increased in HF and is associated with worse outcome. Its relation with outcome is independent from other variables in most of the studies. Frailty seems to be more common in HFpEF patients than in HFrEF due to the greater burden in cardiac and non-cardiac co-morbidities in the second condition. Recently, a new Frailty Score was developed by the HFA. It considers four main domains: clinical, physical–functional, cognitive–psychological, and social. Each domain covers different variables, including co-morbidities (clinical domain); cognitive impairment and mood disturbances, such as depression (cognitive–psychological); physical impairment, sarcopenia, or cachexia (functional); and isolation or the absence of a caregiver (social). This score should identify high-risk patients (Figure 2). The prognostic role of social and economic factors has been shown in recent studies, and also, sex differences are important to consider in the treatment of patients.

Heart failure and cancer

There is a complex and intriguing relationship between HF and cancer. On one hand, patients with HF have a higher occurrence of malignancy due to a combination of underlying shared mechanisms and risk factors. On the other hand, cancer patients frequently develop HF, due to cardiotoxicity. In breast cancer patients, increased levels of N-terminal pro B-type natriuretic peptide (NT-proBNP) and impaired global longitudinal strain (GLS) were found in 34% and 23% of the patients, respectively.

**Figure 2** The four main domains—clinical, physical–functional, cognitive–psychological, and social—defining Heart Failure Association Frailty Score. Reversible and/or treatable variables are identified by asterisks. ADL, activities of daily living; HF, heart failure; IADL, instrumental activities of daily living. From Vitale et al. 

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GLS and left ventricular ejection fraction (LVEF) declined with increasing cumulative anthracycline dose.\textsuperscript{94} Both left ventricular (LV) and RV GLS impairment predicted cardiotoxicity also in patients receiving trastuzumab.\textsuperscript{95} Also, plasma troponin levels may identify patients at higher risk of CV complications.\textsuperscript{96} In a recent experimental model, the protective effect of phenylalanine-butyramide against doxorubicin-induced cardiotoxicity has been shown.\textsuperscript{97}

**Diagnosis and prognosis**

New scores and risk prediction models are continuously developed to stratify risk in HF patients.\textsuperscript{98–101}

**Clinical signs**

Clinical signs have important prognostic value. Low systolic blood pressure and elevated heart rate are associated with poorer outcomes.\textsuperscript{102,103} The role of heart rate is controversial in patients with concomitant AF. No relation with outcomes was shown in one meta-analysis.\textsuperscript{104} A study by Sartipy et al., including HFrEF patients from the Swedish Heart Failure Registry, showed that in those with concomitant AF, higher heart rates were associated with poorer outcomes at short term (1 year) but had no prognostic value in the long term.\textsuperscript{105}

**Biomarkers**

Plasma levels of natriuretic peptides (NPs) are related with LV wall stress and are surrogates for intracardiac filling pressures. They are useful to discriminate HF from non-cardiac breathlessness in patients presenting to the emergency department. Lower levels of NPs have a very high negative predictive value for the diagnosis of HF. In patients with chronic HF, NPs may be persistently elevated, and an increase of 100% or more may suggest an acute decompensation.\textsuperscript{106,107} Moreover, sex and several co-morbidities may influence NP levels, requiring adjusted cut-off: for instance, obese patients have lower values of NT-proBNP.\textsuperscript{108} NPs, along with troponin, are the most useful biomarkers to predict outcomes in both chronic and acute HF to date.\textsuperscript{109–112} NT-proBNP is also predictive for non-CV death.\textsuperscript{113} The role of mid-regional proatrial natriuretic peptide has been recently investigated not only in the acute setting but also in chronic HF, and it has a diagnostic value similar to NT-proBNP.\textsuperscript{114}

An analysis of the Aliskiren Trial on Acute Heart Failure Outcome (ASTRONAUT) failed to show a role of plasma renin activity for the selection of patients with the highest likelihood to respond to aliskiren, even if it has a negative prognostic value.\textsuperscript{115,116} In PARADIGM-HF, elevated levels of growth factor 15 were associated with mortality and CV outcomes, though they were not changed by assigned treatment.\textsuperscript{117}

Given the central role of inflammation in the pathophysiology of HF, pro-inflammatory cytokines, including interleukin 6 (IL-6), raised interest in the scientific community.\textsuperscript{118–121} Over 50% of the patients with HFrEF in A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) had elevated IL-6 levels, associated with iron deficiency, AF, and poorer clinical outcome. IL-6 could become a potential therapeutic target, despite trials targeting another marker of inflammation, tumour necrosis factor alpha, were largely unsuccessful.\textsuperscript{122}

Circulating microRNAs continue to be of major interest. Different levels of plasma microRNAs could help in discriminating the aetiology behind HF (ischaemic vs. non-ischaemic).\textsuperscript{123} Such levels might change after treatment and could represent a tool to monitor patients’ clinical status, although evidence is lacking and further research is needed.\textsuperscript{124–126}

There is also increasing interest in biomarkers that may simultaneously be markers, disease process mediators, and therapeutic targets.\textsuperscript{127–129}

**The role of imaging, exercise testing, and invasive haemodynamic measurement**

Echocardiography allows the assessment of LV volumes and LVEF as well as an estimate of LV filling pressure, RV size and function, valvular disease, and pulmonary artery pressure.\textsuperscript{130,131} LV systolic ejection time (SET) is shorter in HF and is an independent predictor of incident HF (HR 1.07; 95% CI 1.02–1.14, per 10 ms decrease).\textsuperscript{132} Interestingly, a longer SET was associated with improved outcomes among HFrEF but not HFrEF patients. Hence, an increase in SET seems a promising pathway to improve systolic function in these patients.\textsuperscript{133}

Another major area of research regards the left atrium. Left atrial structure and function has been shown to predict outcomes in patients with HF and AF.\textsuperscript{134} Left atrial strain provided better diagnostic accuracy than conventional echocardiographic measures to discriminate HFrEF from non-cardiac causes of dyspnoea\textsuperscript{135} and was associated with impaired haemodynamics both at rest and during exercise.\textsuperscript{136,137}

Cardiac magnetic resonance (CMR) may be helpful in tissue characterization, detection, and quantification of myocardial fibrosis and adipose tissue, which are associated with HF development and progression.\textsuperscript{138,139} Myocardial adipose deposition and epicardial fat, both of which can be carefully measured by CMR, may play a major role in the development of HFrEF.\textsuperscript{138,140}
The 6 min walk test is a valid tool to assess exercise capacity. In BIOSTAT-CHF, both a reduced walked distance at baseline and a decline at 9 month follow-up were associated with a worse prognosis and were not modified by the up-titration of drugs. In the more recent PARADIGM-HF trial, sacubitril/valsartan was superior to enalapril in reducing the risks of death and of hospitalization for HF. A similar efficacy was shown in the reduction of recurrent events (Wei, Lin, and Weissfeld HR in the sacubitril/valsartan group 0.79; 95% CI 0.71–0.89). Moreover, treatment with sacubitril/valsartan allows a greater reduction in loop diuretic doses compared with enalapril. Results from the Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event (TRANSITION) study suggest that initiation of ARNI in HFrEF patients stabilized after an acute HF event, either in hospital or shortly after discharge, is feasible. De novo HFrEF patients had also major benefits compared with those with prior diagnosis, showing faster and greater decreases in NT-proBNP and high-sensitivity troponin T and lower rates of HF and all-cause rehospitalization.

In the ESC-EORP-HFA Heart Failure Long-Term Registry, 84% of outpatients were eligible for sacubitril/valsartan based on European Medicines Agency/Food and Drug Administration label, but only 12–28% met the criteria used in guidelines. Data from Germany showed a still insufficient rate of initiation and dose up-titration of this agent. Reasons behind this under-prescription must be explored to ensure guideline-directed medical therapy (GDMT). Indeed, physicians and patients’ adherence to GDMT is associated with improved outcomes over both the short term and longer term. Many factors, including older age, hypotension, and impaired renal function, may contribute to underuse of GDMT. A slow titration of ARNI is associated with better treatment success also in patients with slow systolic blood pressure. In EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), renal function did not influence beneficial effects of eplerenone, even if patients with impaired renal function were more susceptible to adverse events (hyperkalaemia and renal failure events) and drug discontinuation. Hyperkalaemia represents another limiting factor in the prescription of renin-angiotensin–aldosterone system inhibitors. Novel potassium-lowering agents, such as patiromer and sodium zirconium cyclosilicate, may be helpful in achieving optimization of therapy, but further studies are needed.

Medical treatment of heart failure with reduced ejection fraction

**Neurohormonal antagonists**

Neurohormonal antagonists, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists, play a pivotal role in the treatment of HFrEF, improving the clinical course of the disease. In the more recent PARADIGM-HF trial, sacubitril/valsartan was superior to enalapril in reducing the risks of death and of hospitalization for HF. A similar efficacy was shown in the reduction of recurrent events (Wei, Lin, and Weissfeld HR in the sacubitril/valsartan group 0.79; 95% CI 0.71–0.89). Moreover, treatment with sacubitril/valsartan allows a greater reduction in loop diuretic doses compared with enalapril. Results from the Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event (TRANSITION) study suggest that initiation of ARNI in HFrEF patients stabilized after an acute HF event, either in hospital or shortly after discharge, is feasible. De novo HFrEF patients had also major benefits compared with those with prior diagnosis, showing faster and greater decreases in NT-proBNP and high-sensitivity troponin T and lower rates of HF and all-cause rehospitalization.

Sodium–glucose co-transporter 2 inhibitors

In the last years, major advances occurred concerning antidiabetic drugs and CV risk, and a new pathway of HF treatment—different from the neurohormonal one—has been opened (Figure 3). Sodium–glucose co-transporter 2 (SGLT-2) inhibitors—empagliflozin, canagliflozin, and dapagliflozin—have consistently shown a reduced risk of HF hospitalization or CV death in diabetic patients regardless of baseline CV disease and previous history of HF. Dalogliflozin And Prevention of Adverse outcome in Heart Failure (DAPA-HF) is the first trial proving a significant benefit of an SGLT-2 inhibitor—dapagliflozin—with a reduction in the risk of the composite endpoint of CV death or worsening HF (hospitalization or an urgent visit requiring intravenous therapy for HF) in HFrEF patients with or without diabetes (HR 0.74; 95% CI 0.65–0.85). Each of the three components of the composite outcome was less frequent in the dapagliflozin group. The baseline characteristics of DAPA-HF patients were similar to those
in contemporary HFrEF registries and trials.\textsuperscript{174} The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) included patients with a more severe LV systolic dysfunction, higher levels of NPs, and lower estimated glomerular filtration rate, as compared with the patients in the DAPA-HF trial. Empagliflozin reduced the combined risk for CV death or hospitalization for HF compared with placebo (HR 0.75; 95\% CI 0.66–0.86; \(P < 0.001\)), a difference that was primarily related to a reduction in hospitalization for HF. Indeed, CV death was not significantly reduced probably because EMPEROR-Reduced trial had less statistical power than DAPA-HF (less number of events in a smaller size of the trial and shorter follow-up). The beneficial effects of empagliflozin were consistent in subgroup analyses (diabetes vs. non-diabetes; ARNI treatment vs. no ARNI treatment). Furthermore, empagliflozin was associated with a slower rate of decline in the estimated glomerular filtration rate and with a lower risk of serious renal outcomes. Thus, the EMPEROR-Reduced trial extends the benefits of SGLT-2 inhibitors in stable, more advanced HF population.\textsuperscript{175,176} In the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial, sotagliflozin showed beneficial effects in patients with diabetes and recent worsening HF.\textsuperscript{177} Further studies will assess the efficacy of SGLT-2 inhibitors in other settings (i.e. HFpEF or acute HF).\textsuperscript{178,179}

The mechanisms behind the beneficial effects of SGLT-2 inhibitors are largely unknown. Besides glycosuric and natriuretic effects, empagliflozin seems to have a direct pleiotropic effect on cardiomyocytes. It improves adenosine triphosphate production and myocardium metabolism, diastolic function, and cardiac remodelling and has favourable effects.\textsuperscript{180–183}

### Treatment of iron deficiency

Iron deficiency is common in HF patients and is associated with poor exercise capacity, directly affecting mitochondrial respiration and the function of skeletal muscle and cardiomyocytes.\textsuperscript{184–188} Indeed, cellular oxidative metabolism relies largely on iron availability in skeletal muscle.\textsuperscript{189–192} Iron depletion is also associated with reduced quality of life and survival. Treatment with intravenous ferric carboxymaltose (FCM) has been shown to lead to improvements of functional capacity, symptoms, and quality of life in chronic HF patients.\textsuperscript{193} A recent meta-analysis including four major randomized trials showed a reduction of HF hospitalizations and CV mortality in iron deficiency patients treated with FCM.\textsuperscript{194} AFFIRM-AHF (Study to Compare Ferric Carboxymaltose with Placebo in Patients with Acute Heart Failure and Iron Deficiency) evaluated the effects of intravenous FCM in patients hospitalized for acute heart failure.\textsuperscript{195} It showed that treatment with FCM was safe and reduced the risk of HF hospitalisations.\textsuperscript{196}

### Other options

Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) was a randomized, placebo-controlled trial evaluating safety and efficacy of vericiguat in HFrEF patients with recent worsening HF.
Vericiguat was superior to placebo in the reduction of composite endpoint of CV death or HF hospitalization (HR 0.90; 95% CI 0.82–0.98; P = 0.02). Baseline characteristics of VICTORIA-enrolled subjects showed a high-risk population when compared with PARADIGM-HF. The median MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk score was 23 (interquartile range 18–27) in VICTORIA vs. 20 (interquartile range 16–24) in PARADIGM-HF trial. In the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) trial, the selective cardiac myosin activator omecamtiv mecarbil showed a reduction in the primary composite endpoint of a first HF event or death from CV causes.

Neladenoson bialanate, a partial adenosine A1 receptor agonist, failed to demonstrate favourable changes in NT-proBNP, LVEF, high-sensitivity troponin T, or CV mortality and HF hospitalization in PANTHEON trial. On the other hand, a decrease in renal function was observed. Standard treatment of advanced HF remains unsatisfactory. Positive inotropes may be used as bridge strategy and palliative care, while no positive inotrope is currently approved for long-term treatment in chronic HF. However, intermittent administration of levosimendan in ambulatory patients has been associated with reduction in NT-proBNP levels and HF hospitalization. The DIGIT-HF (DIGitoxin to Improve outcomes in patients with advanced chronic Heart Failure) trial has been designed to demonstrate a role of digitoxin on the top of standard care in improving mortality and morbidity in advanced HFrEF.

### Devices

#### Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) is less frequently used than expected, even when indicated by guidelines.

In an individual patient data meta-analysis of five randomized controlled trials, QRS duration was the only independent predictor of CRT benefit on mortality. Along with QRS duration, lower height but not sex played a role in the composite endpoint of all-cause mortality or first hospitalization for HF. In another study, body mass index was associated with outcome: overweight or obese patients receiving CRT with defibrillator were at a lower risk of death compared with underweight subjects.

According to an analysis from the ESC CRT Survey II, the benefit and complication rates from CRT upgrading, in implantable cardioverter defibrillator (ICD) or pacemaker carriers, are the same as for de novo CRT patients. Therefore, patients with a pacing-induced cardiomyopathy must be closely monitored, and an upgrade to CRT or His bundle pacing device might be considered.

Cardiac resynchronization therapy may be less effective in patients with AF because both atrioventricular (AV) and biventricular resynchronization are required. However, AV junction ablation might represent a safe option: in a small trial, CRT with defibrillator patients with permanent AF, who underwent AV junction ablation, experienced less ICD shocks and a lower incidence of HF hospitalization, compared with patients with AF medical therapy alone.

A study on neonatal rat ventricular cardiomyocytes showed that irregular pacing induces pro-fibrotic signalling with paracrine effects and oxidative stress, eventually leading to a remodelling process. A similar mechanism might be involved in AF-related HF with arrhythmic ventricular contractions and increased morbidity and mortality.

#### Implantable cardioverter defibrillator

The selection of patients who might benefit from ICD implantation is often challenging. Myocardial infarction survivors with LVEF > 35% burdened by diabetes and/or kidney dysfunction have a high risk of sudden cardiac death (SCD), but the risk of a non-SCD event is even higher, suggesting that the extension of ICD implantation in such patients might not be worthwhile. A combined analysis of four major primary prevention trials in HFrEF patients assessed the effects of ICD implantation in diabetic vs. non-diabetic patients. The use of ICD was associated with a reduced risk of mortality in non-diabetic patients (HR 0.56; 95% CI 0.46–0.67) but not among those with diabetes.

#### Percutaneous treatment of mitral and tricuspid regurgitation

Transcatheter mitral valve interventions are spreading as treatment options in patients with HF and severe secondary mitral regurgitation. Two randomized controlled trials investigated the prognostic impact of percutaneous edge-to-edge mitral valve repair by MitraClip in HF patients. Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MitraFR) showed no reduction in HF hospitalizations or mortality in patients undergoing MitraClip compared with those receiving conservative management up to 2 year follow-up. On the other hand, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) demonstrated an impressive reduction in both 2 year HF hospitalizations, which was the primary endpoint, and 2 year all-cause death. Such a discrepancy might be due to the different characteristics of the patients included, suggesting that only carefully selected patients may derive a prognostic benefit from secondary mitral regurgitation.
Further data, coming from observational studies, showed safety and efficacy of MitraClip in improving symptoms and clinical status also in patients with advanced HF, such as those with low ejection fraction (EF) and pulmonary hypertension. Orban et al. showed a significant improvement in New York Heart Association class 6, min walk test distance, and quality of life in 50 patients undergoing percutaneous edge-to-edge repair on the tricuspid valve. Schlotter et al. reported outcomes of 159 patients with severe functional tricuspid regurgitation, who underwent transcatheter tricuspid valve repair. Patients were stratified into four aetiology-based clinical scenarios: patients receiving chronic haemodialysis, patients with significant mitral regurgitation, patients with severe pulmonary hypertension, and patients with a history of AF/flutter. Patients with pulmonary hypertension had the highest rates of the primary composite endpoint (death, HF hospitalization, or reintervention), while the highest mortality rate was observed in haemodialysis patients (33.3%).

### Mechanical circulatory support

Left ventricular assist device is a promising option for patients with advanced HF, either as a bridge to transplant or as a lifelong treatment. In a Spanish retrospective study, 291 patients waiting for cardiac transplant received LVAD. They had a better outcome, compared with those undergoing temporary biventricular assist devices or extracorporeal membrane oxygenation as bridge to heart transplantation. LVAD implantation may also favour a recovery of LV function especially when associated with administration of neurohormonal antagonists. Data from the Postgraduate Course in Heart Failure (PCHF)-VAD registry showed a better survival in LVAD patients who also received a cardiac implantable electronic device with a defibrillator component (HR 0.64; 95% CI 0.46–0.91; \( P = 0.012 \)) compared with those who only had LVAD support. Also, exercise training may provide incremental benefits in LVAD carriers. The rationale behind the Exercise training in patients with a LVAD (Ex-VAD) trial is to assess if a 12 week supervised exercise training could improve the quality of life and the functional capacity in LVAD patients. However, among patients with a reduced EF and New York Heart Association Classes III–IV eligible for heart transplantation or LVAD, more than half declines the indication. Infections, as well as bleeding and thrombo-embolic events, are the most common and severe complications of LVAD. The platelet activity state may predict the risk of thrombo-embolic complications after LVAD. LVAD design continues to improve and will be subject to ongoing evaluation.

### Telemedicine and disease management

Home telemonitoring is a useful tool for the management of HF patients. TIM-HF2 (Telemedical Interventional Management in Heart Failure II study) trial showed a positive impact of telemedicine on unplanned CV hospitalization and mortality. The HOME-HF study was designed to assess the feasibility and efficacy of BNP home measurement in reduction of HF-related events. It was early interrupted because of slow enrolment, low event rate, and the need of standardize BNP spontaneous fluctuation. The HFA has developed a well-visited tool to assist in patient communication and education, a crucial part of ongoing disease management, which the development of e-health strategies will likely accelerate, as will better mechanisms to enhance dosing choices in guideline-directed HF medication.

### Novel perspectives

New therapeutic strategies are emerging for patients with HF of ischaemic aetiology.

BioVentrix Revivent TC System is a transcatheter technique that aims at limiting myocardial scar on the beating heart of HF patients. At 12 month follow-up, symptomatic patients with previous anterior myocardial infarction who received this treatment had an improvement of LV function, symptoms, and quality of life.

The Autologous Mesenchymal Stromal Cell Therapy in Heart Failure (MSC-HF) trial randomized patients with ischaemic HF to receive either intramyocardial injections of bone marrow-derived mesenchymal stromal cells or placebo. At 4 year follow-up, patients experienced improved myocardial function and myocardial mass. The Stem Cell therapy in Ischaemic Non-treatable Cardiac disease (SCIENCE) trial will assess the efficacy and safety of intramyocardial cell therapy of adipose-derived stromal cells from healthy donors (allogeneic donation) in patients with ischaemic HF. Contrast contractility modulation has been shown to have the potential to improve functional capacity, especially in those with HF and mildly reduced LVEF (25–45%).

Central sleep apnoea (CSA) is a predictor of CV morbidity and mortality in HF patients. The Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients with Heart Failure (SERVE-HF) trial compared adaptive servo-ventilation and medical therapy in patients with HF and CSA. The primary endpoint, changes in LVEF at 1 year, was similar between the two groups. However, CV mortality was higher in the adaptive servo-ventilation vs. control arm. Furthermore, other endpoints, such as changes in LV dimensions and cardiac biomarkers, were not affected by the adaptive servo-ventilation.
Heart failure with preserved ejection fraction

Clinical phenotypes and pathophysiology

Heart failure with preserved ejection fraction is a heterogeneous syndrome with several clinical manifestations.\(^{251-253}\)

Using a machine learning-based cluster analysis, Segar et al. identified three phenogroups of patients with HFrEF enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) trial. Patients in the first phenogroup had a higher burden of co-morbidities, increased levels of NPs, and LV impairment; the second phenogroup had less co-morbidities but a worst diastolic dysfunction; the third phenogroup had lower levels of NPs, intermediate co-morbidities, and the most favourable diastolic profile. Phenogroup 1 had higher rates of HF rehospitalizations and mortality, when compared with Phenogroup 3. Phenogroups 2 and 3 shared the same risk of mortality. A greater risk of rehospitalization was observed in Phenogroup 2 vs. 3,\(^{254}\) a feature also seen with the increased risk associated with co-morbid pulmonary disease in this syndrome.\(^{255}\)

The pathophysiology of HFrEF remains largely unknown. Coronary microvascular dysfunction might play a central role in the development of HFrEF. It can be equally caused by both endothelium-based and endothelium-independent mechanisms. When the microvascular dysfunction is not endothelium related, patients show a worse diastolic function and prognosis.\(^{256}\)

Another possible mechanism is the systemic and intramyocardial inflammation.\(^{119}\) Obesity and type 2 diabetes mellitus are common in HFrEF patients and often coexist. They both cause inflammation and expansion of epicardial adipose tissue, leading to atrial damage and LV fibrosis/stiffness.\(^{257,258}\) AF often represents the first manifestation of HFrEF and can be a consequence of atrial myopathy.\(^{258}\)

A study by Wu et al. investigated the role of myocardial steatosis in diastolic dysfunction. Intramyocardial fat deposition was measured using CMR in 305 subjects (34 patients with HFrEF, 163 with HFrEF, and 108 non-HF controls). HFrEF patients display a more pronounced intramyocardial fat deposition, when compared with HFrEF patients or controls, leading to diastolic impairment.\(^{119}\) Such phenomenon is—once again—more clear in patients burdened by obesity and metabolic syndrome, in whom adiposity is greater and is associated with myocardial injury and AF.\(^{240}\) Differences between Asia and western countries are also seen in the presentation of HFrEF.\(^{259}\)

Diagnosis and prognosis: a challenge for the medical community

The diagnosis of HFrEF remains challenging. Recently, two independently derived algorithms for the HFrEF diagnosis have been published: the H\(_2\)FPEF score from the Mayo Clinic (Rochester, MN, USA) and the European HFA-PPEF 4-step algorithm.\(^{260,261}\) The American H\(_2\)FPEF score was based on clinical and echocardiographic characteristics and validated with invasive haemodynamic testing as gold standard. It identified six variables as HFrEF predictors: obesity (body mass index > 30 kg/m\(^2\)), AF, age > 60 years, treatment with two or more antihypertensive drugs, E/e' > 9, and pulmonary artery systolic pressure > 35 mmHg. The resultant total H\(_2\)FPEF score ranged from 0 to 9, with the scores ≥2 suggesting a low likelihood and scores ≥6 reflecting a high likelihood of HFrEF. The European HFA-PPEF 4-step algorithm is a new stepwise diagnostic tool. It starts from pretest assessment (based on signs, symptoms, electrocardiographic alterations, and laboratory tests), going through risk stratification with rest imaging, analysing specific functional and morphological echocardiographic parameters. The HFA-PPEF score is the sum of points from functional, morphological, and biomarker domains (2 points for each major criteria and 1 for each minor criteria). A total score ≥5 is considered diagnostic for HFrEF, while a total score <1 determines a very low probability of HFrEF. The intermediate values will need further investigation, with stress echocardiography and invasive haemodynamics. The diagnostic pathway could be finally completed with aetiological workup. Baranadiarán Aizpurua et al. tried to validate the second step of the HFA-PPEF algorithm, based on echocardiographic findings and NPs.\(^{262}\) However, these results might be overestimated due to the high HFrEF case-control ratio and to the low diagnostic support with invasive measurements.
Diagnostic tools aiming to assess tolerance to exercise are mandatory in HFrEF patients. However, co-morbidities could limit exercise capacity. Elderly patients with elevated left atrial pressure and impaired reservoir present an abnormal exercise haemodynamics. The evaluation of left atrial reservoir strain could be helpful to discriminate HFrEF from non-cardiac dyspnoea. In patients who are capable of performing exercise, oxygen consumption trajectory has been suggested as a predictor of disease severity. Estimated plasma volume status has been also proposed as a tool for the prediction of long-term outcome in HFrEF patients.

Treatment: lack of favourable results

Despite the growing impact of HFrEF, there is still no established pharmacological therapy. In the Prospective comparison of ARNI with angiotensin receptor blockers Global Outcomes in HFrEF (PARAGON-HF) trial, sacubitril/valsartan did not reduce the incidence of HF hospitalizations or CV death. However, the subgroup analysis showed that women and patients with lower EF should have a benefit from the treatment.

In obesity-related HFrEF, underlying pathophysiological abnormalities may be related to derangements in beta-adrenergic drive and to increased aldosterone and nephrilin activity. Thus, drugs acting against these pathways could be beneficial.

In patients with HFrEF and diabetes, insulin treatment is associated with poor outcome. Moreover, neither furosemide nor torasemide was associated with effect on myocardial fibrosis in these patients. Given their anti-inflammatory and anti-fibrotic actions, SGLT-2 inhibitors might ameliorate cardiac remodelling also in HFrEF patients. Ongoing trials will assess whether such drugs will be extended to HFrEF.

Novel specific Na+/Ca2+ exchange inhibitor ORM-11035 is able to reduce cardiac remodelling and diastolic dysfunction with no effects on systemic blood pressure in rats. Considering the promising results, future trials are needed to evaluate the feasibility of such treatment also in humans.

Acute heart failure

Epidemiology

Several precipitating factors may lead to acute HF, namely, arrhythmia, respiratory infections, and other non-CV factors. Worsening HF may develop in an outpatient or an inpatient setting, with a similar drastic increase in event rates. The Heart Failure Registry of Patient Outcomes (HERO) study is a prospective, longitudinal multicentre registry including patients hospitalized with acute HF in China. In hospital or 3 day post-discharge mortality was 3.2%. Death or readmission rate from the 4th day post-discharge to first follow-up was 22.4%. In the first 30 days after admission for acute HF, 2% of patients experience SCD or resuscitated SCD or ventricular tachycardia/fibrillation. In an Italian series, the 1 year mortality rate was 20%, with the highest risk of death during the index hospitalization. The admission department seems to play a role in the natural history of HF, with the general medicine department associated with a poor prognosis, probably due to different characteristics of patients (older age and several co-morbidities).

Management

Clinical signs, biomarkers, and imaging are essential in the diagnostic process, in-hospital monitoring, and pre-discharge evaluation of acute HF. The clinical classification of acute HF into four different profiles, defined by the presence of congestion and/or peripheral hypoperfusion, provides information on both early and long-term outcomes. Signs and symptoms of congestion represent the major cause of HF hospitalization both in HFrEF and in HFrEF patients. Clinical residual congestion at discharge was detected in 30.9% of patients in the ESC-EORP-HFA Heart Failure Long-Term Registry, and it was associated with increased 1 year mortality. The Reprieve System, a device that continuously measures urine output and supplies intravenous fluid to maintain fluid balance, may represent a useful tool to control decongestion.

The serial assessment of spot urine sodium predicts effectiveness of decongestion and outcome, as well as decrease in NT-proBNP levels. Higher levels of mid-regional pro-adrenomedullin and its active form, bio-adrenomedullin, were observed in the presence of volume overload and have been proposed as markers of congestion. Mid-regional pro-adrenomedullin and bio-adrenomedullin provide a great accuracy in diagnosis of acute HF and detection of residual congestion. Elevated levels of blood lactate, associated with hypoperfusion, and markers of multi-organ injury/dysfunction are predictors of poorer outcomes. Worsening renal function is only associated with adverse events in patients without decreased BNP. We are seeing the importance of assessing adequacy of the decongestive therapies in acute HF.

Echocardiography estimates LV and RV filling pressure. Higher inferior vena cava diameter and lower jugular venous ratio are independently associated with poorer outcome also in outpatients. Lung ultrasound, through the assessment of B-lines, ensures an accurate tool for differential diagnosis of acute dyspnoea, has a prognostic value, and has been proposed to guide diuretic treatment in outpatients with benefits. A recent expert consensus aims at...
standardizing approach in image acquisition methods and B-line quantification.

**Medical therapy**

Treatment of acute HF may be divided into three phases—initial stabilization, after initial stabilization, and pre-discharge and post-discharge period. Decongestion is the main goal of acute HF therapy. Loop diuretics are the first choice in order to achieve euvoelma, and diuretic resistance is associated with poorer outcomes. In patients at high risk for diuretic resistance, addition of acetazolamide may be useful.

Treatment of the acute phase failed to improve outcomes so far. Vasodilators seem to be neutral, although an excessive pressure drop is associated with kidney impairment and worse outcome. Inotropes and/or vasopressors are associated with an increased risk of all-cause death. Despite the neutral results of the second RELAX in Acute Heart Failure (RELAX-AHF-2) trial, a recent meta-analysis including serelaxin trials has shown that serelaxin reduces the risk of 5 day worsening HF and has beneficial effects on markers of renal function and cardiac damage. Furthermore, in the RELAX-AHF-EU study, serelaxin showed a reduction of worsening HF and all-cause death through Day 5 when added to standard of care therapy. Ongoing studies will assess tolerability and efficacy of BMS-986231, a novel nitroxyl donor with potential benefits on haemodynamics.
Meanwhile, the optimization of oral treatment in the pre-discharge and post-discharge period plays a pivotal role in improving survival. Early initiation of sacubitril/valsartan before or shortly after discharge is safe and beneficial. The STRONG-HF (Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of Heart Failure therapies) trial will assess whether fast up-titration of GDMT can be a safe and feasible option in patients discharged after acute HF.

Conclusions

We have summarized the most recent findings in HF discussing many aspects such as epidemiology, diagnosis, co-morbidities, and treatment. Despite improvements in treatment of HFrEF, HF is still a major cause of poor quality of life, morbidity, and mortality worldwide. However, major advances have been achieved recently in the management of HFrEF with the discovery of new therapeutic pathways, namely, SGLT-2 inhibitors, and with better treatment of co-morbidities. New devices are emerging for specific conditions such as sleep apnoea, and percutaneous treatment of mitral and tricuspid regurgitation may have a major impact on symptoms and clinical outcomes. HFrEF remains an unsolved issue, particularly in terms of diagnosis and treatment. Better patient phenotyping seems the next promising step. However, this hypothesis needs testing in properly designed clinical studies.

Conflict of interest

D.T. and M.A. declare that they have no conflict of interest. M.S.A. has received personal fees from Servier, outside the submitted work. SvH has been a paid consultant for and/or received honoraria payments from Bayer, Boehringer Ingelheim, BRAHMS, Chugai, Grünenthal, Helsinn, Hexal, Novartis, Pharmacosmos, Respicardia, Roche, Sorin, and Vifor. SvH owns shares in Actimed. SvH reports research support from IMI and the German Center for Cardiovascular Research (DZHK). M.M. has received in the last 3 years personal honoraria from Abbott Vascular, Actelion, Amgen, AstraZeneca, Bayer, LivaNova, Servier, Vifor Pharma, and Windtree Therapeutics for participation to trials’ committees or advisory boards and speaker honoraria from Abbott Vascular, Edwards Therapeutics, and Servier.

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