

Highlights in heart failure

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Abstract

Heart failure (HF) remains a major cause of mortality, morbidity, and poor quality of life. It is an area of active research. This article is aimed to give an update on recent advances in all aspects of this syndrome. Major changes occurred in drug treatment of HF with reduced ejection fraction (HFrEF). Sacubitril/valsartan is indicated as a substitute to ACEi/ARBs after PARADIGM-HF (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.73 to 0.87 for sacubitril/valsartan vs. enalapril for the primary endpoint and Wei, Lin and Weissfeld HR 0.79, 95% CI 0.71–0.89 for recurrent events). Its initiation was then shown as safe and potentially useful in studies in patients hospitalized for acute HF. More recently, DAPA-HF trial showed the beneficial effects of the sodium–glucose transporter type 2 (SGLT2) inhibitor dapagliflozin vs. placebo, added to optimal standard therapy [HR, 0.74; 95% CI, 0.65 to 0.85; 0.74; 95% CI, 0.65 to 0.85 for the primary endpoint]. Trials with other SGLT2 inhibitors and in other patients, such as those with HF with preserved ejection fraction (HFpEF) or with recent decompensation, are ongoing. Multiple studies showed the unfavourable prognostic significance of abnormalities in serum potassium levels. Potassium lowering agents may allow initiation and titration of mineralocorticoid antagonists in a larger proportion of patients. Meta-analyses suggest better outcomes with ferric carboxymaltose in patients with iron deficiency. Drugs effective in HFrEF may be useful also in HF with mid-range ejection fraction. Better diagnosis and phenotype characterization seem warranted in HF with preserved ejection fraction. These and other burning aspects of HFpEF research are summarized and reviewed in this article.

Keywords heart failure; HFrEF; HFpEF; HFmrEF; acute heart failure; treatment

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Introduction

Heart failure (HF) remains a major cause of mortality, morbidity, namely hospitalizations, and poor quality of life. Landmark trials, able to cause major changes in evidence based clinical practice, continue to be too few. However, new data are continuously produced, and a summary of recent new findings is provided herewith.

Epidemiology

Heart failure has a worldwide diffusion. Several studies assessed its characteristics in different regions of the world.

Asian patients with HF are younger and have different risk factors, compared with Western patients.¹ In an analysis of the ASIAN-HF registry, the prevalence of diabetes ranged between 34.1% in Japanese/Koreans and 51.9% in Malaysian patients. The increase in the risk of death and HF hospitalizations associated with diabetes remained significant and independent from ethnicity at multivariable analysis (hazard ratio [HR] 1.37, 95% confidence intervals [CI] 1.19–1.57 for death or HF hospitalizations).² Outcomes differ in Asian patients, compared with the European ones. Nagai et al. assessed the accuracy of published prediction models to predict mortality in British vs. Japanese patients. Whereas these models were moderately accurate in British patients, they consistently overestimated mortality in Japanese, consistently with their better prognosis.³

Classification and specific causes

Classification of HF remains based on left ventricular (LV) ejection fraction (EF). The main reason is that trials enrolling patients with a reduced EF (HFrEF) were successful in the identification of drugs and devices improving their outcomes.⁴ Thus, a reduced LVEF defines a phenotype of patients in whom neurohormonal activation and other mechanisms, such as tachycardia or LV dyssynchrony, contribute to the progression of LV dysfunction and patients' outcomes. Accordingly, a network meta-analysis showed that the combination of three neurohormonal antagonists, possibly with the addition of ivabradine, when indicated, is associated with the largest reduction in the risk of death or HF hospitalizations or of deaths alone in HFrEF patients.⁵

A still often overlooked cause of HF is cardiac amyloidosis. This is even more critical nowadays as a specific treatment for transthyretin amyloidosis has been identified in a randomized clinical trial. As stated in a recent consensus document by the HF Association, older patients with HF, particularly those with preserved ejection fraction (HFpEF) who are not hypertensive or who have features of hypertrophic or restrictive cardiomyopathy, degenerative aortic stenosis, and progressive HF, should be considered for screening for cardiac transthyretin amyloidosis. Hereditary transthyretin amyloidosis may have some peculiar features, such as younger age of onset and higher likelihood of a mild neurological involvement, compared with wild type transthyretin amyloidosis.⁶

Genetic analysis may allow personalized treatment. Specific mutations in the gene for lamin A and lamin C may be associated with different outcomes of their carriers. The amount of mutated protein in the nuclear envelope is associated with poorer outcomes of the patients with lamin A and lamin C missense mutations carriers.⁷ Titin mutations may also directly cause a dilated cardiomyopathy phenotype or increase heart's susceptibility to injury.⁸

Diagnosis and prognosis

A diagnostic algorithm for acute and chronic HF is provided by the 2016 European Society of Cardiology (ESC) guidelines.⁴ The use of natriuretic peptides (NPs) is recommended to rule-out HF, but is not diagnostic, since its positive predictive value is low. The diagnostic accuracy of NPs is particularly reduced in elderly subjects with acute dyspnoea as they do not discriminate cardiac vs. respiratory origin.⁹ Beyond age, multiple variables influence NPs values, such as sex, obesity,¹⁰ and heart rhythm with higher levels in atrial fibrillation.¹¹

Heart failure remains associated with poor outcomes, comparable, if not worse, to that of the most common cancers.¹² Unplanned hospitalizations for HF and, in general, episodes of worsening HF are landmark events in patients' clinical course

and are followed by a marked increase in mortality and rehospitalizations, compared with when the patients remain ambulatory.^{13–16}

Clinical signs

Simple clinical signs retain a main prognostic value as summarized in guidelines and position statements.^{4,17} Poorer outcome are associated with a lower systolic blood pressure and higher heart rate and their decrease or lack of decrease, respectively, during follow-up.^{18–20} The role of comorbidities is outlined in the next chapters.

Biomarkers

Biomarkers maintain a major role for the prognostic assessment of HF patients. Multimarker strategies are emerging. More data compare novel biomarkers with established ones, such as serum creatinine and BNP. N-terminal pro BNP (NT-proBNP) and troponin outperformed other emerging biomarkers in prediction of adverse outcome in some recent studies.^{21–23} Multimarker models and serial measurements during the hospitalization may improve risk prediction.^{24,25}

Plasma renin activity has prognostic value with poorer outcomes in those patients with its greater activation. However, it did not allow to identify the patients with a better response to treatment with aliskiren in the Aliskiren Trial on Acute HF Outcomes (ASTRONAUT).²⁶ Elevated levels of growth differentiation factor-15, were associated with diabetes, age, creatinine, high-sensitive troponin T, NT-proBNP, and New York Heart Association (NYHA) Class III/IV in patients with ambulatory HFrEF from the Prospective comparison of Angiotensin Receptor neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor (ACEi) to Determine Impact on Global Mortality and morbidity in HF trial (PARADIGM-HF). Growth differentiation factor-15 was strongly related with mortality and cardiovascular (CV) outcomes but this relation was not modified by sacubitril/valsartan.²⁷

MicroRNAs are another major area of research. Circulating levels of different microRNAs may be differentially expressed in patients with HF of different aetiologies (ischaemic and nonischaemic).²⁸ Plasma levels may have prognostic value in acute or chronic HF and may change after treatment, although final evidence is still lacking.^{29–31}

Risk stratification models

A multiparametric approach is often proposed for risk stratification of HF patients. The prognostic accuracy of the metabolic exercise test data combined with cardiac and kidney indexes risk score was found as superior to the HF Survival Score and Seattle HF model risk scores in a cohort of 6112

ambulatory stable HF patients.³² Predictors of mortality differ from predictors of HF hospitalization. In an analysis of the systems BIOlogy Study to Tailored Treatment in Chronic HF (BIOSTAT-CHF) cohort, the five strongest independent predictors of mortality were more advanced age, higher blood urea nitrogen and NT-proBNP, lower haemoglobin, and failure to prescribe a beta blocker. The five strongest predictors of HF hospitalization were more advanced age, previous HF hospitalization, presence of oedema, lower systolic blood pressure, and lower estimated glomerular filtration rate.³³

Imaging techniques and invasive haemodynamics

Algorithms to estimate LV filling pressure based on echocardiography have been developed and validated.^{34,35} Assessment of right ventricular (RV) function also requires a multiparametric approach. RV function has an independent value compared with pulmonary pressure both in patients with HFrEF and, interestingly, also in patients with preserved EF (HFpEF).^{36,37}

Right heart catheterization allows discrimination between those patients with LV dysfunction who have isolated post capillary pulmonary hypertension and those with combined postcapillary and precapillary pulmonary hypertension. These last patients are those with the worst outcomes.³⁸ The value of the finding of a negative diastolic pulmonary pressure gradient is now challenged by its high dependency from mitral regurgitation and other variables.³⁹

Medical treatment of HFrEF

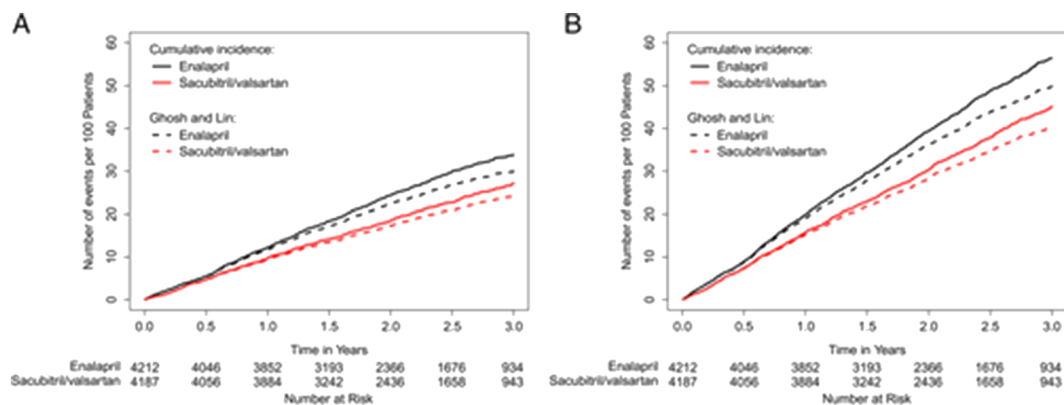
Neurohormonal antagonists

Medical treatment of ambulatory patients with HFrEF is based on diuretics to relieve congestion and neurohormonal

antagonists to improve the clinical course, to reduce HF hospitalizations, and to improve mortality. ACEi or angiotensin receptor blockers (ARB), beta blockers, and mineralocorticoid antagonists (MRA) are the pillars of current management of HFrEF.⁴ Ivabradine is indicated in patients in sinus rhythm whose heart rate remains >70 bpm.⁴ PARADIGM-HF trial showed a reduction in the combined endpoint of CV death or HF hospitalizations, (HR, 0.80; 95% CI, 0.73 to 0.87) as well as all-cause death, CV death and HF hospitalizations alone, and an improvement in symptoms with sacubitril/valsartan vs. enalapril.⁴⁰ Further, 34% of the patients who had a primary event experienced at least one other HF hospitalization and sacubitril/valsartan had a similar efficacy to reduce recurrent events (Figure 1).⁴¹ Quality of life improved and diuretic doses were slightly but significantly reduced in the patients on sacubitril/valsartan, consistent with favourable effects also on symptoms.^{42,43} Based on these results,^{40,44} sacubitril/valsartan is currently recommended as a replacement for ACEi/ARBs in ambulatory patients with HFrEF who remain symptomatic despite optimal medical treatment.^{4,45} Based on more recent trials,^{44,46} it may be considered also in patients hospitalized for acute HF, including also those with new onset HF.⁴⁵

Combined treatment with the drugs above is associated with the largest reduction in mortality and hospitalizations.⁵ Adherence to evidence based therapy and guidelines is an independent determinant of patients' outcomes.^{47,48} Further research is therefore focused on the optimization of medical treatment in HFrEF patients.⁴⁹ When the inclusion criteria of PARADIGM-HF were applied in a large cohort of ambulatory patients with HFrEF, only 12% at baseline and 21% during follow-up met the criteria for treatment. However, this proportion rose to 60% if background treatment was not considered.⁵⁰ A slow titration of sacubitril/valsartan was associated with better tolerance and persistence on maximal doses in the patients with lower systolic blood pressure in the Safety and Tolerability of Initiating LCZ696 in HF Patients (TITRATION) study.⁵¹

Figure 1 Effect of sacubitril/valsartan vs. ACE inhibitors on recurrent events. Cumulative rate of heart failure hospitalizations (A) and the primary composite endpoint (B). From reference 41.



Potassium lowering agents

Data from large observational studies have consistently shown a U-shaped relationship between serum potassium levels and mortality in patients with HF as well as hypertension and myocardial infarction. Ideal serum potassium levels range between 3.5 and 4.5 mmol/L and an increase in mortality can be shown with serum potassium levels >5 mmol/L.⁵² Hyperkalaemia has a major role limiting the use and titration to target doses of ACEi/ARBs and, to an even larger extent, MRAs, in patients with HF_{rEF}, especially when associated with chronic kidney disease (CKD).^{53–57} Novel potassium binders may be considered in patients with HF, with or without CKD, and may allow the initiation and titration of neurohormonal antagonists in more patients with HF_{rEF}. Their efficacy in lowering serum potassium levels is proven. However, we lack of data showing the impact of these drugs on patients' outcomes.⁴⁵

Treatment of iron deficiency

In addition to its role in anaemia, iron has direct effects on mitochondrial function in skeletal muscle and the heart itself. Its deficiency may be also a cause of impaired contractility.^{58–60} Ferric carboxymaltose improves functional capacity, symptoms, and quality of life of HF patients with iron deficiency.^{61,62} A meta-analysis of data from the four major randomized controlled trials conducted, to date, demonstrated also a reduction in recurrent CV hospitalizations

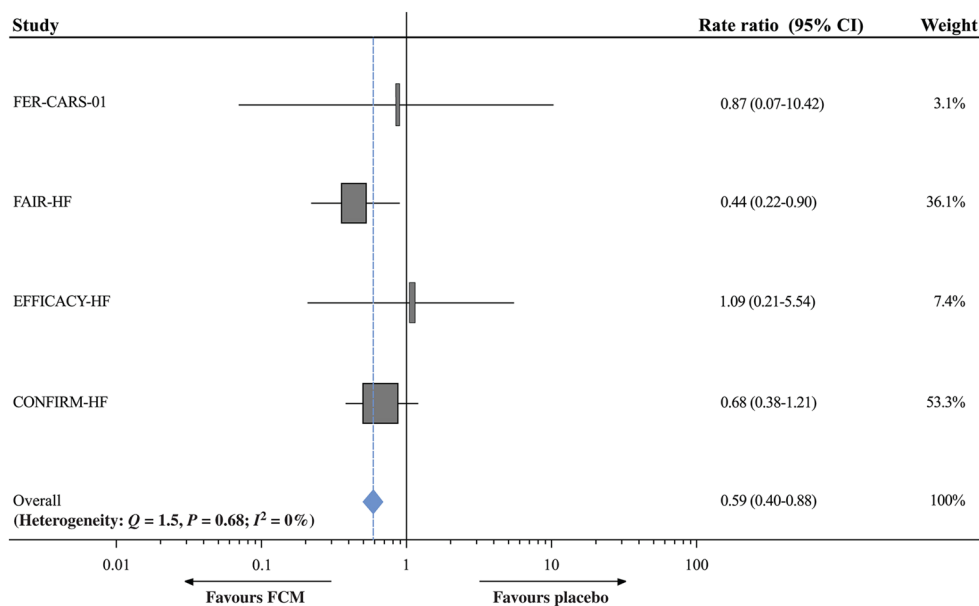
(Figure 2).⁶³ Ongoing trials are aimed at showing the impact of iron therapy on outcomes, including mortality.^{45,62}

Antidiabetic drugs

The choice of antidiabetic drugs has a pivotal role in the development and progression of HF and other CV outcomes.^{64,65} Since the discovery that rosiglitazone is associated with an increased risk of myocardial infarction and CV death,⁶⁶ the assessment of CV events has gained a central role in the evaluation of antidiabetic treatment. These studies has allowed the identification of antidiabetic drugs that may improve CV outcomes of diabetic patients and has then opened the pathway for a new treatment of HF, independently from the presence of diabetes.

An analysis of 24 012 patients with HF from four large randomized trials and of an administrative database of 4 million individuals, 103 857 of whom with HF, showed that insulin treatment is independently associated with increased all-cause mortality and HF hospitalizations.⁶⁷ Incretin-based therapies, glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, do not seem to have major effects on HF events, although an increase in HF admissions was observed with the dipeptidyl peptidase-4 inhibitor saxagliptin.⁶⁸ The glucagon-like peptide-1 agonist liraglutide reduced CV deaths and all-cause deaths but had no significant effect on HF hospitalizations in a major trial.⁶⁹ No effects on LV function were found in another trial.⁷⁰

Figure 2 Effects of ferric carboxymaltose on clinical outcomes in iron-deficient heart failure patients. Rate ratios for cardiovascular hospitalisations and cardiovascular mortality for the individual data from randomised controlled trials included in this meta-analysis. CI, confidence interval; FCM, ferric carboxymaltose. From reference 63



The Empagliflozin CV Outcome Event Trial in type 2 diabetes mellitus patients at high risk of CV events (EMPA-REG Outcome) was the first trial showing a favourable effect of sodium–glucose transporter type 2 (SGLT2) inhibitors on HF events. Compared with placebo, empagliflozin reduced CV mortality, all-cause mortality and HF hospitalizations by 38%, 30%, and 35%, respectively.^{64,71,72} Further trials showed a reduction in HF hospitalizations in diabetic patients at risk of CV events also with the two other SGLT2 inhibitors canagliflozin and dapagliflozin.^{73,74} Rates of major CV events, namely stroke and myocardial infarction, were not changed whereas renal events and CKD progression were reduced in these trials.^{72–74}

The mechanisms of action of SGLT2 inhibitors are still unsettled and likely go beyond their glycosuric and natriuretic effects and involve direct effects on myocardial metabolism and function,^{71,75–77} (Figure 3). The results of these studies led to the start of randomized controlled trials in patients with HF, both with and without diabetes. The first trial has been recently accomplished. The Dapagliflozin And Prevention of Adverse-outcomes in HF (DAPA-HF) trial was an international, multicentre, parallel group, randomized, double-blind, study in 4744 patients with chronic HFrEF. It assessed the effect of dapagliflozin 10 mg, compared with placebo, administered once daily, in addition to standard therapy, on the primary composite outcome of a worsening HF event (hospitalization or equivalent event, i.e. an urgent HF visit) or CV death.⁷⁸ Median follow-up was of 18.2 months. The primary outcome occurred in 16.3% of the patients in the dapagliflozin group vs. 21.2% of the patients on placebo (HR, 0.74; 95% CI, 0.65 to 0.85). Reductions in

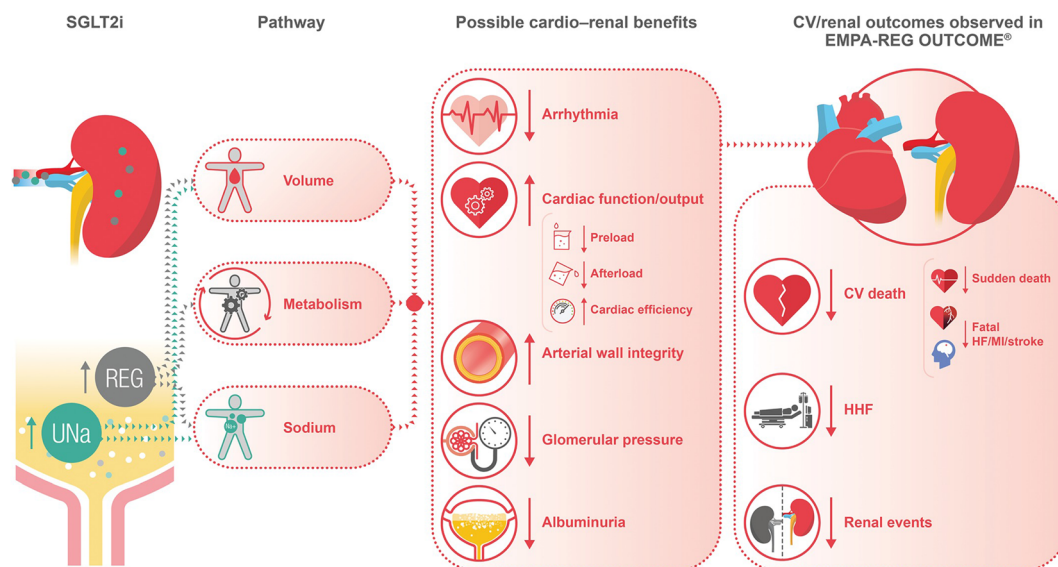
the worsening HF event (HR, 0.70; 95% CI, 0.59 to 0.83), CV death (HR, 0.82; 95% CI, 0.69 to 0.98), and all-cause death (HR, 0.83; 95% CI, 0.71 to 0.97) were also significant with dapagliflozin vs. placebo. Importantly, results were similar in patients with diabetes vs. those without diabetes with no interaction with drug efficacy.⁷⁹ The frequency of adverse events did not differ between treatment groups.⁷⁹ Trials with other SGLT2 inhibitors are ongoing. These results open a new pathway for HFrEF, if not HF overall, treatment with drugs having different mechanisms of action, independent from the neurohormonal pathways exploited, to date.

Other options

Treatment of advanced chronic HF remains a major unmet need.¹⁷ A meta-analysis has recently suggested that ambulatory infusions of inotropic agents may have favourable effects on symptoms with neutral effects on mortality.⁸⁰ Intermittent inotropes infusions improve quality of life in these patients and do not seem to affect long-term survival.^{81,82} In recent trial, intermittent administration of intravenous levosimendan lowered NT-proBNP levels, primary endpoint of the trial, reduced HF hospitalization and improved the quality of life in 69 outpatients with advanced chronic HF.⁸³

Currently, routine use of ultrafiltration is not recommended and should be limited to patients who fail to respond to diuretics.⁴ Differently from the original intention-to-treat analysis a per-protocol analysis of CARdiorenal REScue Study in acute decompensated HF (CARRESS-HF) showed a larger fluid removal with ultrafiltration vs. diuretic therapy.^{84,85}

Figure 3 Potential pathways linking empagliflozin with heart failure outcomes improvement. CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; MI, myocardial infarction; REG, removal of excess glucose; SGLT2i, sodium–glucose co-transporter 2 inhibitors. UNa, urinary sodium. From reference 71



Palliative care is still largely underused in patients with advanced HF, and its implementation should be a target of next efforts.^{17,86,87}

Devices

Cardiac resynchronization therapy

Currently, the use of cardiac resynchronization therapy (CRT) is lower than what could be expected based on guidelines indications.^{88–90} Multiple predictors of the response to CRT have been identified. An individual patient meta-analysis of three double-blind, randomized trials showed that longer QRS duration and lower LVEF independently predict early clinical response to CRT.⁹¹ Both QRS duration and morphology, with a greater response in patients with left bundle branch block, were significant in other studies.^{92,93} Contractile reserve after dobutamine infusion predicted the response to CRT in a meta-analysis of nine observational studies including 767 patients.

An individual-patient data meta-analysis of five randomized controlled trials assessed the impact of sex, QRS duration, HF aetiology, LV end-diastolic diameter, and height on the effects of CRT, vs. control, on deaths and the composite endpoint of deaths and HF hospitalizations.⁹⁴ QRS duration was the only independent predictor of CRT benefit on mortality. For the composite outcome, height and QRS duration, but not sex, were independent predictors of CRT benefit with a continuous and independent relationship with the risk reduction with CRT vs. control. The effect of height may explain the greater benefit of CRT in women. The authors of this analysis concluded that QRS threshold for CRT indication, now fixed at 130 ms,⁴ may need adjustment based on patient's height.⁹⁴

An analysis from the ESC CRT Survey II showed that the upgrade to CRT in carriers of permanent pacemaker or of an implantable cardioverter defibrillator (ICD) has the same success and complications rates as for patients undergoing de novo CRT implantation.⁹⁵ In patients with atrial fibrillation treated with CRT, atrioventricular junction ablation was associated with reduced ICD shocks and hospitalizations compared with the use of medical therapy to slow heart.⁹⁶

New pacing modalities are under study. LV-only pacing timed with native RV activation when the AV interval is normal showed better results, compared with traditional CRT, on LVEF and strain through better apical and septal function.⁹⁷ The effects of this new pacing modality is currently tested in large multicentre trial.⁹⁸

Implantable cardioverter defibrillator

Current indications to ICD implantation may need some revisions after publication of Danish ICD Study in Patients With

Dilated Cardiomyopathy (DANISH), a randomized, controlled, multicentre study to assess the efficacy of ICD in patients with non-ischaemic systolic HF on mortality.⁹⁹ In his study, implantation of an ICD reduced SCD by 50% but not all-cause mortality, (HR, 0.87; 95% CI, 0.68 to 1.12) in patients with nonischaemic cardiomyopathy. A significant treatment-by-subgroup interaction was found for age with a 49% reduction in mortality in the patients aged <58 years, $P = 0.02$, a non-significant 25% reduction in mortality in the patients aged 58 to 67 years and a nonsignificant 19% increase in mortality in the patients aged >68 years ($P = 0.009$ for interaction).⁹⁹ These results were likely caused by the larger contribution of non-HF-related causes of deaths in older patients. Based on these data, it has been hypothesized that one may consider not to implant an ICD in patients with nonischaemic HFrEF who are aged >70 years or have advanced symptoms of HF or have life-shortening co-morbidity (e.g. severe lung disease or Stage IV CKD) as they are likely to die for non-SCD related reasons.⁴⁵

Consistent results regarding the limitations of ICDs in the prevention of all-cause deaths were found in a patient-level combined-analysis of four major primary prevention trials in HFrEF patients. The effects of ICD on all-cause deaths were assessed in diabetic vs. nondiabetic patients. ICDs were associated with a reduced risk of all-cause mortality among patients without diabetes (HR, 0.56; 95% CI, 0.46–0.67) but not among patients with diabetes (HR, 0.88; 95% CI, 0.7–1.12; interaction $P = 0.015$).¹⁰⁰ More generally, an increase in the comorbidity burden is associated with a reduced efficacy of ICDs for mortality reduction.¹⁰¹

Telemedicine

Telemedicine has often yielded disappointing results in randomized controlled trials. For instance, in a recent randomized controlled trial, remote monitoring through the CRT-defibrillator, compared with standard therapy, did not reduce mortality or hospitalizations, primary endpoint of the study, with, however, a reduction in in-office visits.¹⁰² Neutral results may be caused by both the type of the intervention and patients selection. A network meta-analysis including 53 randomized controlled trials (12,356 patients) showed that, among services that decreased all-cause mortality and all-cause readmissions after HF hospitalizations, nurse home visits were the most effective in both cases, compared with usual care.¹⁰³ Nurse home visits had also the greatest pooled cost savings. Telephone, telemonitoring, pharmacist, and education interventions did not improve clinical outcomes.¹⁰³ The HF Outpatient Monitoring Evaluation (HOME-HF) was a randomized controlled trial testing the feasibility of home BNP measurement to prevent events in HF patients. Although the trial showed the feasibility of this approach, it was terminated early because of slow enrolment, low event rates, and

the need of an algorithm taking care of spontaneous BNP fluctuations.¹⁰⁴ Telemedical Interventional Management in HF II (TIM-HF2) was a randomized, controlled trial investigating the impact of telemedicine on unplanned cardiovascular hospitalizations and mortality in HF patients. Study patients were selected based on the analysis of the previous TIM-HF trial, which was neutral. In this trial, the patients that seemed to fair better were those who had a recent hospitalization for HF and who did not present with major depression and who were from rural, rather than urban areas.¹⁰⁵ TIM-HF2 showed a reduction in the percentage of days lost due to unplanned CV hospitalizations and all-cause death with telemonitoring, compared with usual care with also a reduction in all-cause death alone. These data show the efficacy of telemonitoring when used in a well-defined HF population.¹⁰⁵

Percutaneous treatment of mitral regurgitation

Functional mitral regurgitation may be both an effect or a cause of HF. It results from left-chambers remodelling and may lead to volume overload, pulmonary hypertension, and worsening of HF signs and symptoms.

Recently, two randomized controlled clinical trials have investigated the impact of percutaneous treatment of mitral regurgitation with the MitraClip device on the outcomes of HF patients: Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) and Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT). Both trials randomized patients to MitraClip plus guideline-directed medical therapy or guideline-directed medical therapy alone. No reduction in the primary endpoint of all-cause mortality or HF hospitalizations was shown in MITRA-FR, whereas a

significant reduction in HF hospitalizations (primary endpoint) as well as in mortality alone was observed in COAPT (*Figure 4*).^{106,107} These different results may be, at least partially, explained by differences in the patients enrolled. Compared with MITRA-FR patients, those in COAPT had more severe mitral regurgitation, less dilated left ventricles, and no signs of right ventricular failure.¹⁰⁸ Optimistic data come from the German Transcatheter Mitral Valve Interventions (TRAMI) registry, suggesting the safety, feasibility, and benefit of MitraClip therapy even in advanced stages of disease such as in patients with pulmonary hypertension and severe reduced LV function.^{109,110}

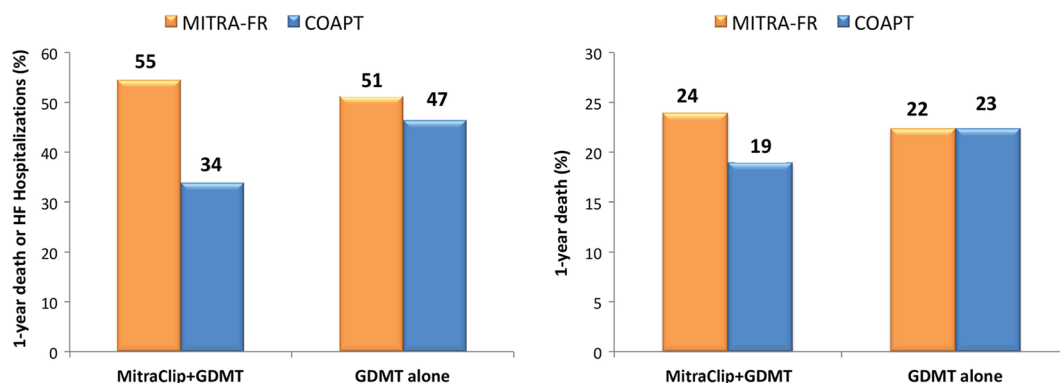
Functional tricuspid regurgitation may contribute to right heart failure and HF severity and poor prognosis. Orban et al. described the 6-months outcomes of 50 patients undergoing transcatheter edge-to-edge tricuspid valve repair for severe tricuspid regurgitation. These patients had an improvement in NYHA class, 6-min walk test distance, and quality of life after this procedure.¹¹¹

Mechanical circulatory support

The role of proper physicians' and patients' education was shown by a multicentre prospective study conducted in Sweden. Patients with HFrEF, NYHA Class II–IV and on CRT and/or ICD were screened for an indication to LV assist device (LVAD) implantation. Up to 26% of the patients with low LVEF and NYHA Class II–IV had a potential indication to LVAD and only half of them accepted the procedure once offered.¹¹²

In patients with HFrEF who cannot be stabilized with medical therapy, mechanical circulatory support (MCS) can be used as a bridge to heart transplantation or as destination therapy.^{4,113} In a retrospective study conducted in Spain on 291 patients listed for urgent heart transplantation, bridging with temporary LVAD was associated with more favourable outcomes than bridging with temporary biventricular assist

Figure 4 Comparison of hard endpoints from MITRA-FR and COAPT. The composite endpoint of all-cause death or hospitalization for heart failure (HF) and the single endpoint of mortality at 1 year have been reported comparing MITRA-FR and COAPT populations through their randomization arms. GDMT, guideline-directed medical therapy. From reference 108



devices or venoarterial extracorporeal membrane oxygenation.¹¹⁴ LVAD implantation may be associated with some degree of recovery of LV function. Treatment with neurohormonal antagonists may help with this regard. Eighty-one patients on LVAD support underwent paired myocardial tissue samples prior to LVAD implantation and at transplantation for histopathology. Patients had a significant improvements in cardiac structure and function over the 6 months following LVAD implantation. The degree of improvement was greater in the patients on neurohormonal antagonists and this difference persisted after adjustment for baseline differences. Treatment with neurohormonal antagonists was associated with a reduction in fibrosis.¹¹⁵

Infections and thromboembolic and haemorrhagic complications remain major causes of morbidity and mortality.¹¹³ Predictors of such adverse events, such as abnormalities in platelet activity,¹¹⁶ are sought. Major advances have been obtained with the most recent devices. In the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3), the HeartMate 3 centrifugal-flow LVAD was compared with the HeartMate II axial-flow device, either as a bridge to transplantation or as destination therapy, in 1028 patients with advanced HF. Heartmate 3 was associated with less frequent need for pump replacement, mainly caused by pump thrombosis and was superior with respect to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device.¹¹⁷

Experimental treatments

Increased adrenergic activity and reduced vagal tone play a major role in the progression of HF. Autonomic nervous system is therefore a potential target for HF treatment. Four major trials of vagal nerve stimulation did not show favourable effects in patients with HF. The ideal stimulation protocol and therapeutic dose are, however, still unsettled and may have had a major role for the results of these trials.¹¹⁸ Further trials, including trials on baroreceptor activation therapy, are ongoing.¹¹⁸ Carotid body resection was associated with a reduction in muscle sympathetic activity, reduced chemosensitivity, and better exercise tolerance in a pilot study in patients with HFrEF.¹¹⁹

Central sleep apnoea (CSA) is associated with increased CV morbidity and mortality in patients with HF. The treatment of sleep-disordered breathing with predominant central sleep apnoea by adaptive SERVO VENTilation in patients with HF (SERVE-HF) trial randomized 1325 patients with HFrEF and predominant CSA to adaptive servo ventilation or optimal medical treatment alone. The incidence of the composite primary endpoint was similar between the two treatment groups. However, all-cause and CV mortality were significantly increased in the adaptive servo-ventilation group.¹²⁰

No effects on the LV remodeling and function, cardiac biomarkers, renal function, and systemic inflammation was shown by this device.¹²¹ Another trial, the effect of Adaptive servo VENTilation on survival and hospital admissions in HF (ADVENT-HF), including patients with HFrEF and CSA, is ongoing.¹²² Phrenic nerve stimulation is another tool to treat CSA. It has improved sleep metrics and quality of life and reduced HF hospitalizations in a first study in patients with HF.¹²³

Regenerative therapy is still an area of active research for HFrEF treatment. Tools to increase its efficacy, such as the injection of muscle-derived stem/progenitor cells modified with connexin-43 gene¹²⁴ or the administration of granulocyte colony stimulating factor combined with autologous bone-marrow derived cells¹²⁵ showed promising results. The Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART) study evaluated the effects of intramyocardial administration of cardiopoietic stem cells in patients with HFrEF. Although results on the primary endpoint were neutral, cardiopoietic cells administration was associated with a decrease in LV volumes, and the effect was larger in the patients who received a moderate number of injections (<20).¹²⁶

HF with preserved EF

Diagnosis and prognosis: Role of exercise testing and cardiac imaging

Ezekowitz *et al.* prospectively tested the ESC 2007 and ESC 2016 criteria for the diagnosis of HFpEF in a community-based cohort of 565 patients.¹²⁷ Both criteria lacked sensitivity to detect HFpEF, 44.1% and 51.8%, respectively but were highly specific, 93.9% and 89%, respectively. Thus, the likelihood ratios of the existing criteria did not meet the level necessary of diagnostic accuracy and further progress is needed.¹²⁷

Diastolic stress testing with echocardiography and/or invasive haemodynamic monitoring are now considered the best methods to establish a diagnosis of HFpEF in patients with breathlessness.¹²⁸ It is still controversial to which extent echocardiography can substitute invasive hemodynamic monitoring, above all during exercise, for the diagnosis of HFpEF.³⁵

The mechanisms of reduced exercise tolerance are multiple in patients with HFpEF. They include an impairment of the cardiac output and of the skeletal muscle diffusion of oxygen during exercise with a different contribution in each patient with HFpEF.¹²⁹ Chronotropic incompetence has a major role in the limitation of the cardiac output response, in addition to the impairment of the stroke volume increase.¹³⁰ Pulmonary mechanisms leading to an increase in the lung dead space have also been shown.¹³¹

Cardiac and extracardiac comorbidities have a major role in patients with HFpEF.^{132–134} They may influence exercise capacity and limit the value of cardiopulmonary exercise testing or the 6-min walk test distance for the assessment of the patients with HFpEF.^{135–138} A flattening oxygen consumption trajectory during exercise has been recently introduced as a new measurement of disease severity and a prognostic determinant and its value was independent from LVEF in a first study.¹³⁹

Two-dimensional speckle tracking echocardiography can evaluate LV global longitudinal strain, which can detect LV systolic dysfunction at an earlier stage than EF and whose impairment is associated with a worse outcome.^{140–142} Global longitudinal strain may be abnormal also in patients with HFpEF, showing that LV systolic dysfunction is present also in these patients, despite a normal LVEF.^{141,142}

Different phenotypes

Heart failure with preserved ejection fraction is a heterogeneous syndrome with different clinical presentations. Identification of specific phenotypes may be helpful. Among them, that of the patients with obesity-related HFpEF represents a large subgroup. These patients have specific characteristics, such as an increase in epicardial fat, total heart volume, and right ventricular filling pressure.^{143,144} Increased epicardial fat volume is positively correlated with markers of myocardial injury.¹⁴⁵ Neurohormonal activation with heightened beta-adrenergic drive and increased aldosterone and neprilysin activity leading to myocardial fibrosis and diastolic dysfunction are possible specific mechanisms in these patients.^{146–148} Drugs blocking these pathways might therefore be beneficial also in this HFpEF phenotype.^{147–150}

Treatment: Lack of favourable results

Heart failure with preserved ejection fraction is associated with severe profibrotic changes, among which excessive cross-linking and deposition of collagen type I plays a major role. A phenotype of high collagen cross-linking identifies patients resistant to the effects of spironolactone.¹⁴⁹ Unfortunately, no drug has been identified as able to inhibit fibrosis and be effective in these patients and biomarkers to better estimate myocardial fibrosis are under investigation.^{151,152}

No treatment has been shown to reduce mortality and morbidity, so far. Geographical differences and enrolment of patients from Russia and Georgia may have played a major role for the neutral results on the primary outcome in the Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) trial.^{153–155} Analysis of TOPCAT based on the patients' LVEF has, however, fostered the hypothesis that the beneficial effects of spironolactone may

be LVEF dependent.¹⁵⁶ On the other hand, the anti-hypertensive effects of spironolactone have no role since there was no correlation between baseline systolic blood pressure and outcomes.¹⁵⁷

The Prospective comparison of ARNI with angiotensin-receptor blockers Global Outcomes in HFpEF (PARAGON-HF) is another major randomized trial in patients with HFpEF is the last major randomized trial concluded in patients with HFpEF.¹⁵⁸ The effects of sacubitril/valsartan were compared with those of valsartan alone in 4822 patients with HF, a LVEF >45%, elevated NPs and structural heart disease. Sacubitril-valsartan failed to reduce significantly the incidence of the primary endpoint of study, a combination CV death and HF hospitalizations (HR, 0.87; 95% CI, 0.75 to 1.01; $P = 0.06$) as well as the incidence of CV deaths alone (HR, 0.95; 95% CI, 0.79 to 1.16). HF hospitalizations were reduced and NYHA class and quality of life were improved by the active treatment. Subgroup analysis suggested heterogeneity of the results with possible benefits with sacubitril-valsartan in patients with lower EF and in women.¹⁵⁸

Heart rate reduction with ivabradine had no effect on diastolic function and exercise tolerance in patients with HFpEF.¹⁵⁹ Similar sildenafil, a powerful phosphodiesterase type 5 (PDE-5) inhibitor, useful for the treatment of primary pulmonary hypertension, has failed to improve hemodynamic measurements, exercise capacity and quality of life in patients with HFpEF in a randomized controlled trial.^{160,161} The SOLuble guanylate Cyclase stimulator in heArT failure patientS with PRESERVED EF (SOCRATES-PRESERVED) study investigated the role of the soluble guanylate cyclase stimulator vericiguat on health status, finding an improvement in patient-reported outcomes, although further research is needed.^{162,163} A major Phase 3 clinical trial is ongoing.¹⁶⁴

Physical training improved exercise capacity and quality of life in HFpEF patients, above all when used in specific phenotypes, such as the obese HFpEF patients.^{165–168} Caloric restriction and exercise training had a synergic effect in a randomized controlled trial in obese patients with chronic stable HFpEF.¹⁶⁹

Heart failure with mid-range ejection fraction

The 2016 guidelines for HF of ESC created the new category of patients with a mid-range LVEF, e.g. a LVEF between 40% and 49% (HFmrEF).⁴ This started a number of analyses aimed at showing the characteristics of these patients as well as their response to treatment. Compared with the patients with HFpEF, those with HFmrEF show a higher prevalence of coronary artery disease and, generally, have characteristics more similar to those of the patients with HFrEF so that they may be considered as having a milder form of HFrEF.^{170–176} With

respect of outcomes, prognosis of the patients with HFmrEF is slightly better than that of the patients with HFrEF in most, but not all,¹⁷⁷ of the studies. Progression from HFmrEF to HFrEF is an ominous prognostic sign as well as having neurohormonal activation and/or multiple echocardiographic signs of LV systolic and diastolic dysfunction.^{171,172,175,178,179}

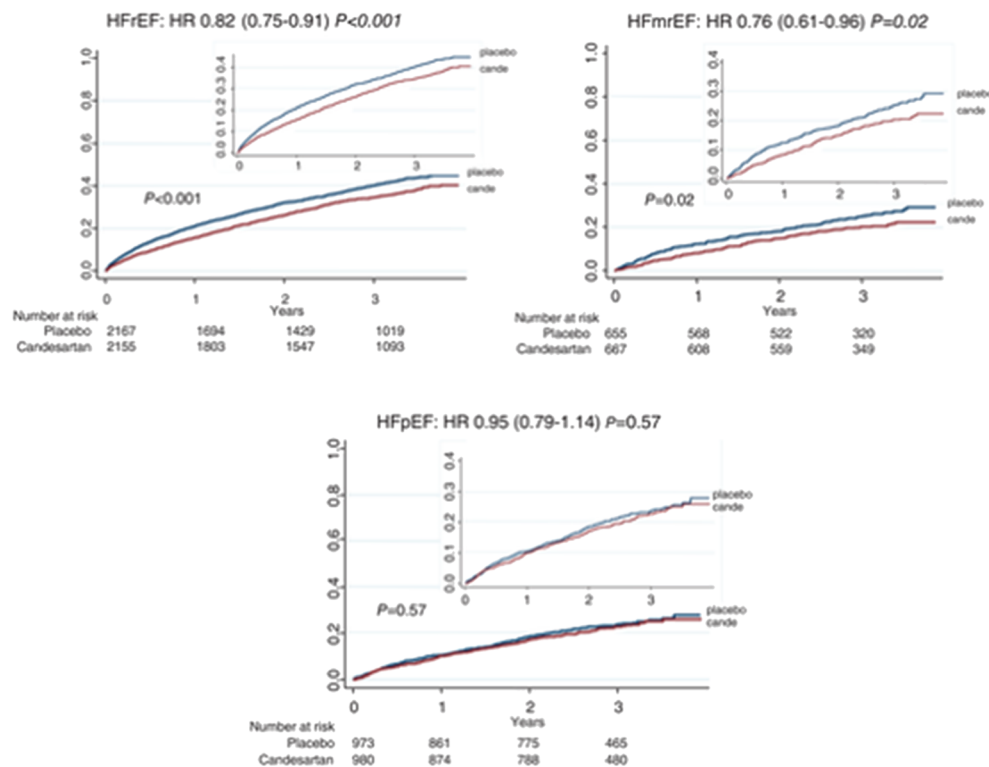
Retrospective analyses of clinical trials suggest that the response to treatment of the patients with HFmrEF is similar to that of those with HFrEF with favourable effects on outcomes of beta blockers, ARB, such as candesartan (Figure 5), mineralocorticoid receptor antagonists, such as spironolactone, and even digoxin.^{45,156,180–182} More recently, these results were confirmed by the Prospective comparison of ARNI with angiotensin-receptor blockers Global Outcomes in HFpEF (PARADIGM-HF) with the patients' subgroup with a LVEF $\leq 57\%$, median value, having a decrease in major events with sacubitril/valsartan.¹⁵⁸

Amyloidosis

Cardiac amyloidosis (CA) is a cause of HF. It impairs exercise capacity and causes breathlessness through diastolic

dysfunction and a reduction in the stroke volume response to exercise.¹⁸³ Immunoglobulin light-chain amyloidosis is the most frequent form of CA. It has a poor prognosis further worsened when myocardial inflammation is present.¹⁸⁴ Transthyretin amyloidosis (ATTR) represents about 20% of CA and commonly occurs in elderly patients, including those with severe aortic stenosis.¹⁸⁵ Different phenotypes of ATTR, including hereditary forms associated with specific mutations, have been identified.⁶ Bone scintigraphy is a reliable tool for its diagnosis.¹⁸⁶ Tafamidis, preventing transthyretin tetramer dissociation, may improve clinical outcomes of ATTR patients. In the Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy (ATTR-ACT) trial, 441 patients with ATTR and HF received, in a 2:1:2 ratio, 80 mg of Tafamidis, 20 mg of Tafamidis, or placebo for 30 months. Compared with placebo, Tafamidis increased survival free from of all-cause death and cardiovascular hospitalization and improved functional capacity and quality of life.¹⁸⁷ In a recent consensus document, it was stated that tafamidis should be considered in patients with symptomatic HF due to confirmed ATTR to improve exercise capacity and quality of life and reduce CV hospitalizations and mortality though also considering its high costs.⁴⁵

Figure 5 Effect of candesartan on the primary outcome by ejection fraction category. Kaplan–Meier time to event rates for candesartan vs. placebo for the primary composite outcome: time to cardiovascular death or first heart failure hospitalization in the three ejection fraction categories. Large graphs show y-axis up to 1.0; inserted graphs show y-axis up to 0.4. HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio. From reference 181



Comorbidities

Comorbidities now have a major role for the clinical presentation and outcomes of the HF patients.^{101,102,188,189} The contribution of comorbidities to patients' outcomes may be similar in patients with HFrEF, compared with those with HFpEF,¹⁸⁹ or be larger in those with HFpEF according to other analyses.¹³²

The most frequent noncardiac comorbidities include chronic kidney disease,^{21,32,134,190–193} chronic obstructive pulmonary disease,¹⁹⁴ central nervous system abnormalities,¹⁹⁵ sleep disordered breathing,^{196,197} diabetes mellitus,^{65,198,199} cancer,^{188,200} and iron deficiency.^{60,61,63,201} They were all shown to have a major impact on clinical presentation, response to treatment and outcomes. It is, however, unproven that their specific treatment may be associated with better outcomes. The only exception are SGLT2 inhibitors whose administration to diabetic patients at high risk of CV events was associated with a lower rate of the primary outcomes and HF hospitalizations.^{45,65}

The prevalence of sarcopenia, cachexia, and anorexia is increased in patients suffering from chronic HF. Losing muscle with or without weight loss impairs functional capacity, quality of life, and outcome to a larger extent than weight loss alone.^{202–205} It is well-established that frailty has a key role in HF. It is most commonly defined as meeting three out of five phenotypic criteria: low physical activity, unintentional weight loss, slow walking speed, weak grip strength, and/or exhaustion. Similar to the results in the patients with HFrEF, frailty was very common also among patients with HFpEF, and it was associated with higher risk of cardiovascular outcomes and mortality in TOPCAT.²⁰⁶

Adiposity is associated with increased ventricular-arterial stiffness among the elderly and suggest a potential role in the development of HF.²⁰⁷ Further to a mere assessment of body mass index, abdominal fat, measured via waist-to-hip ratio has a tighter relationship with outcomes, especially in female patients.²⁰⁸

Cancer therapies are associated with side effects including up to nine categories of cardiovascular complications.^{200,209} Cardiotoxicity involves direct effects of the cancer treatment on heart function and structure as well as accelerated development of CV disease, especially in the presence of traditional cardiovascular risk factors. Anthracycline-based chemotherapy for the treatment of breast cancer is associated with an increased risk of HF.²¹⁰ The incidence of cardiotoxicity for anthracyclines, anti-human epidermal growth factor receptor (HER2) agents and tyrosine kinase inhibitors were 75.8%, 69.8%, and 61.1%, respectively in a large cardio-oncology service.²¹¹ Development of cardiac dysfunction after anthracycline therapy is associated with similar outcomes as other nonischaemic cardiomyopathies.²¹² High rates of cardiac therapy optimization and cancer treatment continuation were shown after the establishment of a cardio-oncology service.²¹¹ Prospective registries are established.²¹³

Acute heart failure

Worsening of symptoms and/or signs of HF, generally caused by congestion, are the main cause of unplanned emergency visits and hospitalizations of the patients with HF, independently of their LVEF and of whether worsening HF developed in an outpatient vs. an inpatient setting.^{214,215} Precipitating factors may be found in most of the cases of acute HF, and they may also have a prognostic role. Poorer outcomes were described in the patients with a cardiovascular, compared with a noncardiovascular, precipitating factor, in one analysis, and in the patients with an infection, in another study.^{15,216–218}

Multiple factors may contribute to the poor outcomes of the patients after the hospitalization for acute HF, including socioeconomic factors, poor patient support, and poor adherence to prescribed medications.^{47,57,90,150,219–221} This is consistent with the relatively high proportion of patients who have an early rehospitalization for non-cardiac causes.²²² Other mechanisms are more directly related with congestion and possibly with myocardial, renal, and hepatic injury with persistent organ dysfunction. Such acute injury, shown by laboratory markers, has independent prognostic value and may be a cause of poor post-discharge outcomes.^{24,223–227} Unfortunately, strategies aimed at a better medical treatment of the acute phase, have failed to improve outcomes in major multicentre trials.^{228,229} The role of sudden cardiac death (SCD) in postdischarge outcomes was investigated in an analysis from Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial. In this trial, about 2% of patients had SCD, resuscitated SCD, or ventricular tachycardia/ventricular fibrillation within 30 days of admission with SCD alone to account for 17% of all deaths within 30 days.²³⁰

Clinical signs have a major role for the prognostic assessment and treatment selection in the patients with acute HF. Among them, the most important is by far systolic blood pressure. A low blood pressure identifies the patient with low cardiac output and peripheral hypoperfusion, and these patients have the highest mortality during follow-up.^{15,231,232} A decrease in blood pressure after treatment is also an ominous prognostic sign and a possible reason of the lack of efficacy of drugs with vasodilating activity when administered to patients who are not hypertensive.²³³ Heart rate has prognostic value also in acute HF with tachycardia and a lack of decrease in heart rate before discharge associated with poorer outcomes.¹⁸

In addition to clinical signs, imaging techniques are used to detect the severity of the haemodynamic impairment and relief from congestion.²²⁵ Echocardiography allows an estimate of LV filling pressure and pulmonary artery pressure.^{34,234} The assessment of lung B-lines by lung ultrasound allows an accurate estimate of lung congestion and has prognostic value.^{235,236} Inferior vena cava diameter and jugular venous

distension are indexes of venous congestion and right ventricular filling pressure.²³⁶

Among laboratory exams, the role for the diagnosis and prognostic stratification of acute HF patients is well-established.^{4,237} Hypochloreaemia has emerged as a main prognostic variable with also a potential role as a cause of HF decompensation as it may cause activation of the renin-angiotensin system.²³⁸ Its value outperforms that of hyponatremia itself.^{239–241} Another simple laboratory parameter, such as haemoconcentration, may be used to estimate decongestion in clinical practice.^{242,243} Hypoalbuminemia as well as high blood urea nitrogen are repeatedly shown as a major independent prognostic factors likely because of their relation with the nutritional status.^{213,244}

Whereas treatment of acute HF has failed to have a favourable impact on outcomes, to date, a major role remains for optimization of oral treatment before discharge. This remains associated with subsequent outcomes and remains the most powerful tool in our hands to change patients' outcomes.²⁴⁵ Consistently, early administration of sacubitril/valsartan before discharge was shown to be safe and associated with favourable changes in biomarkers and outcomes in recent studies.^{44,46}

Medical therapy

The European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry investigated the long-term safety of intravenous cardiovascular agents in acute HF; vasodilators did not present any association with long-term outcome, while inotropes and/or vasopressors were associated with an increased all-cause mortality.²⁴⁶

BMS-986231, a novel second-generation nitroxy donor with potential inotropic, lusitropic and vasodilatory effects in patients hospitalized with decompensated heart failure and reduced ejection fraction (HFrEF), was safe and had beneficial haemodynamic effects.²⁴⁷ A major trial is ongoing.²⁴⁸ Loop diuretics represent the first option for the treatment of congestion in acute HF and diuretic resistance is associated

with poorer outcomes. The cause of such diuretic resistance is mostly due to some defects at the level of renal tubules, rather than reduced diuretic delivery.²⁴⁹ The Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial is designed to investigate if acetazolamide combined to loop diuretic therapy can improve decongestion in acute HF with volume overload.²⁵⁰

The use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) support is becoming more frequent in refractory cardiogenic shock but is associated with a rise in LV afterload. Different techniques of LV unloading may be used to overcome this limitation.²⁵¹ The concomitant implantation of Impella on top of VA-ECMO reduced in-hospital mortality (47% vs. 80%, $P < 0.001$) and increased successful bridging to either recovery or further therapy (68% vs. 28%, $P < 0.001$), compared with VA-ECMO alone.²⁵²

Conclusions

We summarized the most recent data regarding the epidemiology, diagnosis, and prognosis of HF as well as its main clinical phenotypes. Major changes are occurring for the treatment of the patients with HFrEF with respect of the implementation and, possibly, somehow larger indications to sacubitril/valsartan, and the revolutionary recent data with SGLT2 inhibitors. Mitral regurgitation has a role in HF progression, but results from recent major randomized trials differed and we need further assessment after ongoing trials have ended. Treatment of comorbidities, such as hyperkalaemia and iron deficiency, might further improve prognosis through the implementation of neurohormonal antagonists with potassium lowering agents and direct effects with iron replacement therapy. Whereas treatment of HFrEF is undergoing continuous improvement, treatment of HFpEF remains elusive with the only progress regarding the patients with HFmrEF whose pathogenic mechanisms and response to treatment seem similar to those of the patients with HFrEF.

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