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REVIEW

A year in heart failure: an update of recent findings

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Abstract

Major changes have occurred in these last years in heart failure (HF) management. Landmark trials and the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of HF have established four classes of drugs for treatment of HF with reduced ejection fraction: angiotensin-converting enzyme inhibitors or an angiotensin receptor-neprilysin inhibitor, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose co-transporter 2 inhibitors, namely, dapagliflozin or empagliflozin. These drugs consistently showed benefits on mortality, HF hospitalizations, and quality of life. Correction of iron deficiency is indicated to improve symptoms and reduce HF hospitalizations. AFFIRM-AHF showed 26% reduction in total HF hospitalizations with ferric carboxymaltose vs. placebo in patients hospitalized for acute HF (P = 0.013). The guanylate cyclase activator vericiguat and the myosin activator omecamtiv mecarbil improved outcomes in randomized placebo-controlled trials, and vericiguat is now approved for clinical practice. Treatment of HF with preserved ejection fraction (HFpEF) was a major unmet clinical need until this year when the results of EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic HFpEF) were issued. Compared with placebo, empagliflozin reduced by 21% (hazard ratio, 0.79; 95% confidence interval, 0.69 to 0.90; $P < 0.001$), the primary outcome of cardiovascular death or HF hospitalization. Advances in the treatment of specific phenotypes of HF, including atrial fibrillation, valvular heart disease, cardiomyopathies, cardiac amyloidosis, and cancer-related HF, also occurred. Coronavirus disease 2019 (COVID-19) pandemic still plays a major role in HF epidemiology and management. All these aspects are highlighted in this review.

Keywords Heart failure; HFpEF; HFrEF; Acute HF; Advanced HF; Diagnosis; Prognosis; Treatment; COVID-19

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Introduction

Heart failure (HF) remains a major cause of morbidity and mortality worldwide, with a 5 year mortality rate close to 50%.[1–3] Progress has occurred in its management with major randomized controlled trials finally showing positive findings.[4] This article aims to providing an update of the most recent findings.

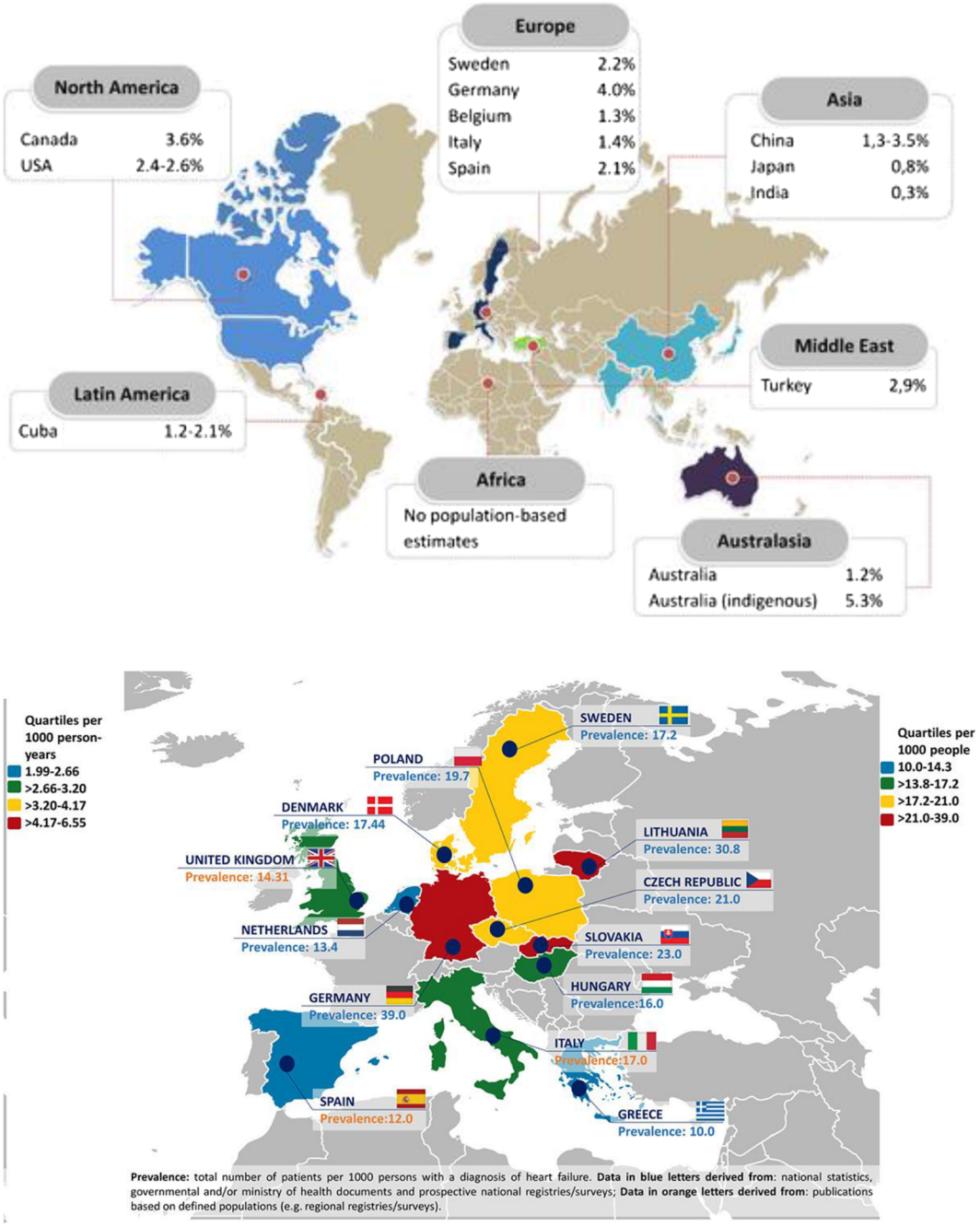
Epidemiology

Data about epidemiology of HF are still limited. The overall prevalence of HF ranges from about 1.5% to 4% in developed countries (*Figure 1*).[2,3,5,6] It has been growing in the last years likely because of ageing of the population and the improvement in HF treatment.[2,7] No major difference can now be found between European and Asian countries, including China.[8,9] The Heart Failure Association (HFA) Atlas aimed to establish a reliable contemporary European dataset on HF epidemiology, resources, and reimbursement policies.[10] In this survey, the median incidence of HF was 3.2 cases [interquartile range (IQR) 2.66–4.17] per 1000 person-years, while the median HF prevalence was 17.20 (IQR 14.30–21) cases per 1000 people (*Figure 1*).[5]

Sex-related differences

Overall, the lifetime risk of HF in men and women is comparable.[11,12] Women more frequently develop HF with

Figure 1 Prevalence of heart failure in population-based studies worldwide, shown as percentage of the total population (upper panel, from Groenewegen *et al.*[2]) and in Europe, shown as number per 1000 people (lower panel, from Seferović *et al.*[5]).



preserved ejection fraction (HFpEF), probably due to the higher prevalence of obesity and diabetes mellitus (DM),[13] whereas men mainly develop HF with reduced ejection fraction (HFrEF), because of their predisposition to ischaemic cardiomyopathy.[14] Sex differences in biomarker profiles have been highlighted.[15]

Differences in outcomes were investigated in 9428 patients with chronic HF from the European Society of Cardiology (ESC) HF Long-Term Registry. Compared with men, women had lower rates of all-cause mortality and HF hospitalization at 1 year.[7] Sex was not an independent predictor of outcome. The use of guideline-directed medical therapy

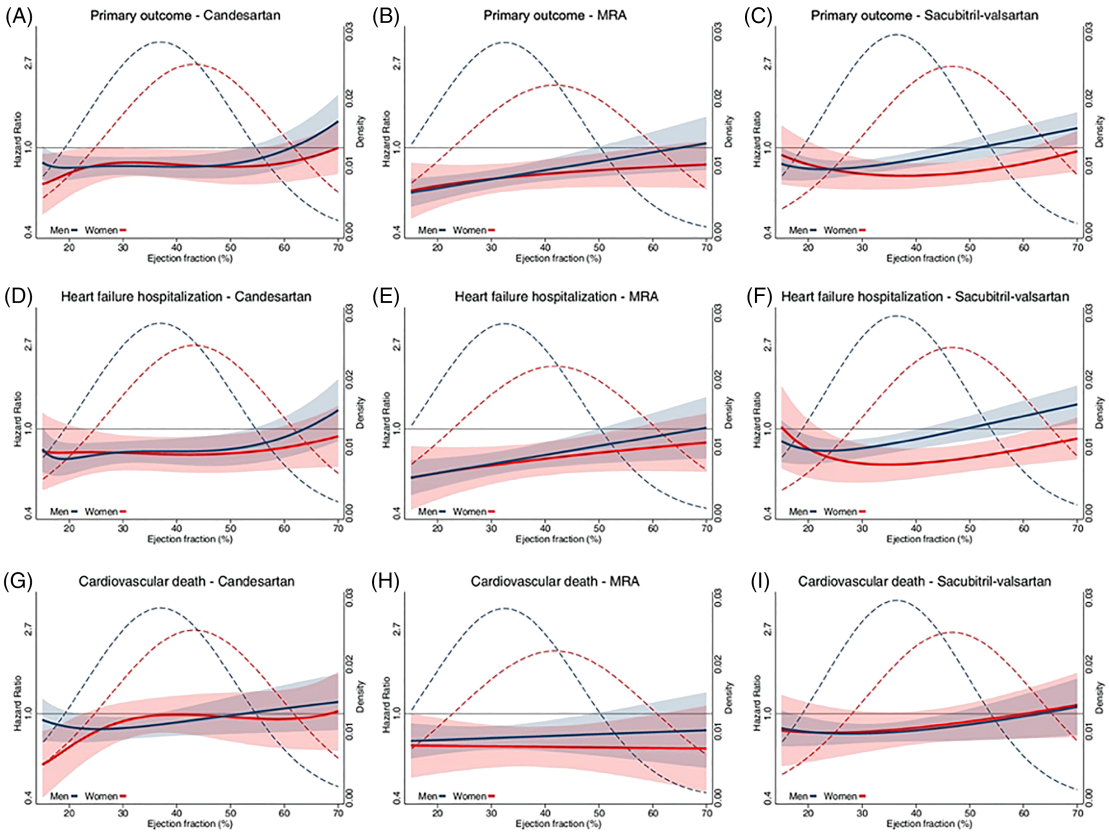
(GDMT) was lower in women than in men, probably due to older age and comorbidity. Even though no sex-related differences have been noted in the effect of therapies, a recent post hoc analysis including eight major randomized clinical trials (RCTs) suggested that women might benefit from treatment also with higher left ventricular ejection fraction (LVEF) values (*Figure 2*).[16] Of note, women are consistently under-represented in HF clinical trials, contributing to remarkable research bias.[17,18]

Comorbidities

Comorbidities have a substantial impact on clinical presentation and outcomes in HF patients.[19] Screening for and treatment of cardiovascular (CV) comorbidities and non-CV comorbidities is recommended.[1] CV comorbidities include hypertension,[20] coronary artery disease,[21] atrial fibrillation (AF),[22] ventricular arrhythmias, valvular heart disease,[23–25] cerebrovascular disease, and pulmonary hypertension. Non-CV comorbidities include chronic kidney disease[26,27] and electrolyte disorders,[28,29] DM,[30] obesity,[31–34] cachexia,[35–38] sarcopenia,[37–42] chronic obstructive pulmonary disease,[19,43] iron deficiency[44,45] and anaemia,[46,47] thyroid disorders,[48] cancer,[49–51] infection,[52,53] arthritis,[54,55] frailty,[56,57] and depression. The clinical burden of comorbidities differs between patients with HFrEF and those with HFpEF.[58–60] Some examples of the role of comorbidities are given below.

Frailty and muscle wasting have been object of active research in these last years. Frailty is defined as a state of vulnerability related to elderly age, which confers a poor prognosis due to increased rates of mortality, institutionalizations, falls, and hospitalizations.[37,57,61–64] It is the result of impaired homeostatic mechanisms and reduced resistance to stressors that might be the consequence of bone[65] and muscle wasting

Figure 2 Variation of treatment effect with left ventricular ejection fraction (LVEF) in heart failure. Dotted curves show normalized distribution of LVEF in men and women. Solid lines show a continuous hazard ratio for the primary composite and its components, according to treatment group in the range of LVEF included. The shaded areas represent the 95% confidence intervals. Primary outcome (heart failure hospitalization/cardiovascular death): (A) candesartan vs. placebo; (B) mineralocorticoid receptor antagonist (MRA) vs. placebo; (C) sacubitril/valsartan vs. renin–angiotensin–aldosterone system inhibitor. Heart failure hospitalization: (D) candesartan vs. placebo; (E) MRA vs. placebo; (F) sacubitril/valsartan vs. renin–angiotensin–aldosterone system inhibitor. Cardiovascular death: (G) candesartan vs. placebo; (H) MRA vs. placebo; (I) sacubitril/valsartan vs. renin–angiotensin–aldosterone system inhibitor (from Dewan *et al.*[16]).



(sarcopenia) or cachexia, both of which have been shown to be independently associated with increased mortality.[31,39,66] Muscle wasting has been described across a vast spectrum of HF aetiologies including ischaemic cardiomyopathy and Chagas disease,[67] and the importance of more clinical and therapeutic action has been highlighted in recent years.[63,64,68] In a retrospective analysis of PARADIGM-HF [Prospective comparison of angiotensin receptor-neprilysin inhibitors with angiotensin-converting enzyme inhibitors to Determine Impact on Global Mortality and morbidity in HF] and ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure), 63% of patients with HF were considered frail, based on a Frailty Index > 0.21.[62] HFA of the ESC has recently proposed a new Frailty Score, based on four main domains—clinical, functional, psycho-cognitive, and social.[57]

Diagnosis and prognosis

The diagnosis of HF requires the presence of symptoms and/or signs of HF (e.g. breathlessness, fatigue, ankle swelling, pulmonary crackles, elevated jugular venous pressure, and peripheral oedema) and objective evidence of cardiac dysfunction.[1,69] Because signs and symptoms are often non-specific, investigation through biomarkers and imaging is essential for the diagnosis and management.[1,69,70]

Clinical signs

Vital signs are predictors of outcome. The role of heart rate in patients with AF and HF may differ in patients in sinus rhythm or AF.[71] Higher heart rate was found to be an independent predictor of CV poor outcome in patients with HFrEF in sinus rhythm but not in those with AF, although an effect of a higher heart rate on mortality was found during the first years of follow-up also in patients with AF in one study from the Swedish HF registry.[71,72]

Laboratory exams

Assessment of biomarkers is a cornerstone of HF management.[73–76] Abnormalities of serum potassium levels are associated with poorer outcomes either when low or high. Studies showed a U-shaped association between serum potassium concentrations and mortality, with a potassium level of 4.2 mmol/L related to the lowest risk of death.[77] In a cohort of patients from the Swedish HF Registry, hypokalaemia was associated with increased mortality both in short term and in long term, whereas hyperkalaemia in short term only. Hyperkalaemia can lead to underuse and premature discontinuation of renin–angiotensin–aldosterone system inhibitors (RAASi) and be associated with increased mortality mainly through this mechanism.[1]

Imaging

Imaging techniques allow the evaluation of left and right ventricular function, valvular disease, congestion, and pulmonary pressure. Clinical presentation and natural history of HFrEF may change depending on left ventricular (LV) geometry remodelling.[78] Initial ventricular dysfunction leads to early shortening of LV systolic ejection time (SET) and lengthening of pre-ejection periods (PEPs). Among 545 ambulatory patients with HF, median SET was shorter and median PEP was longer in those with reduced LVEF compared with those with preserved LVEF. In addition, longer SET was independently associated with improved outcome in HFrEF but not in HFpEF patients.[79] Pulmonary hypertension and right ventricular dysfunction are further markers of poor outcome.[80]

Two-dimensional and three-dimensional echocardiography, myocardial deformation, computed tomography (CT), and cardiac magnetic resonance (CMR) allow the assessment of atrial size and function. 'Atrial disease', also referred as atrial failure or myopathy, represents an intersection of subclinical structural, electrophysiological, and functional changes that primarily affect the atria with the potential to produce clinical consequences.[1] In a cohort of subjects with LVEF $\geq$ 50% referred for assessment of exertional dyspnoea, who underwent simultaneous echocardiography and right heart catheterization, left atrial (LA) reservoir and pump strain correlated with exercise pulmonary capillary wedge pressure. Reservoir strain at cut-off of $\leq$33% predicted invasively verified HFpEF diagnosis with 88% sensitivity and 77% specificity, providing diagnostic utility in patients with exertional dyspnoea.[81]

Risk predicting models

Prognostic scores can be important to guide therapeutic strategies in HF and machine learning techniques may provide additional accuracy.[82] The Machine learning Assessment of RisK and EaRly mortality in Heart Failure (MARKER-HF) score is a new predicting risk score derived from a machine learning algorithm based on eight simple variables (diastolic blood pressure, creatinine, blood urea nitrogen, haemoglobin, white blood cell count, platelets, albumin, and red blood cell distribution width) that showed high power in predicting mortality (area under the curve 0.88).[83] In a hospital-based cohort of 4064 patients, MARKER-HF was substantially more accurate than LVEF in predicting mortality and was highly accurate in all three HF subgroups according to LVEF (HFrEF, HFmrEF, and HFpEF), with *c*-statistics between 0.83 and 0.89.[84]

Specific causes of heart failure

Cardiomyopathies

Cardiomyopathies, including dilated (DCM), hypertrophic (HCM), restrictive (RCM), arrhythmogenic right ventricular (ARVC), and non-classified cardiomyopathies, represent a heterogeneous group of heart muscle diseases causing HF.[85–88] The electrocardiogram (ECG) may be very helpful for the first approach to patients with suspected DCM. Red flags based on ECG or clinical signs can help identifying specific DCM forms.[89,90] Survival of patients with DCM is improved. Over 20% of patients with DCM can show LV reverse remodelling, with a much favourable prognosis compared with other forms of cardiomyopathies.[91]

Hypertrophic cardiomyopathy is a genetic disorder causing LV hypertrophy, hypercontractility, and impaired diastolic function. Novel treatment strategies are being developed, including pharmacotherapy (e.g. mavacamten, a modulator of cardiac β-myosin, causing reversible inhibition of actin–myosin cross bridging), septal reduction techniques (e.g. surgical papillary muscle realignment and radiofrequency ablation), biventricular pacing,[92] mitral valve manipulation (e.g. percutaneous repair in order to reduce systolic anterior motion-septal contact in patients who are unsuitable for septal reduction techniques), and gene-based therapies.[93]

A consensus document summarizing recommendations for the CV management in Fabry disease has been recently published.[94] Fabry disease is a lysosomal storage disorder caused by total or partial deficit of α-galactosidase A enzyme activity. Early diagnosis and treatment with enzyme replacement or small pharmacological chaperones may prevent cardiac involvement.

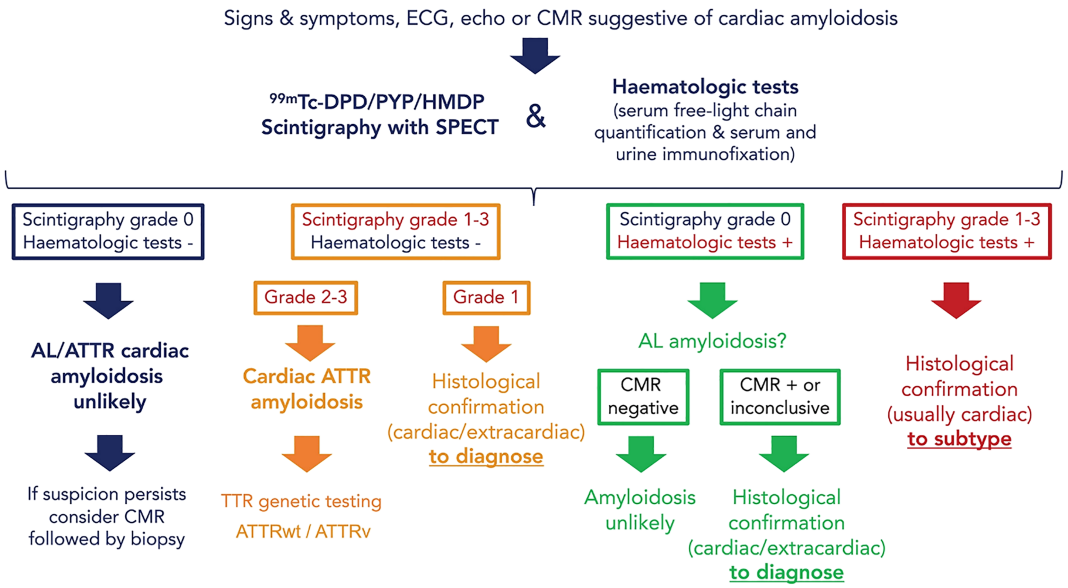
Cardiac amyloidosis

Cardiac amyloidosis (CA) is an underestimated cause of HF. Transthyretin (TTR) CA (ATTR-CA) accounts for 12–13% of HFpEF cases[95] and between 8% and 16% cases of severe aortic stenosis (AS) scheduled for percutaneous aortic valve replacement.[96] Of note, amyloid deposition did not worsen prognosis of patients undergoing transcatheter aortic valve replacement (TAVR).[96] A novel algorithm for the diagnosis of CA has been recently proposed (*Figure 3*).[1,97] In the last years, major advances occurred in the treatment of ATTR-CA. Targeted therapies interfering with TTR deposition include TTR tetramer stabilizers (tafamidis, diflunisal, and epigallocatechin-3-gallate), TTR silencers (inotersen and patisiran), and fibril disruptors (monoclonal antibodies, doxycycline, and tauroursodeoxycholic acid).[98] Tafamidis is now recommended in patients with TTR-CA and New York Heart Association (NYHA) class I or II symptoms to reduce symptoms, CV hospitalization, and mortality.[1]

Cancer

Cancer and HF have a bidirectional relationship.[99–102] First, muscle wasting caused by cancer, that is, sarcopenia, can involve also the heart causing 'cardiac wasting-associated

Figure 3 Diagnostic algorithm for cardiac amyloidosis. AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CMR, cardiac magnetic resonance; ECG, electrocardiogram; SPECT, single photon emission computed tomography; TTR, transthyretin (from Garcia-Pavia *et al.*[97]).



cardiomyopathy' (*Figure 4*).[102] Moreover, cancer therapies are often cardiotoxic.[51,103] Main cardiotoxic drugs include anthracyclines, fluoropyrimidines, tyrosine kinase inhibitors, HER2-targeted therapies such as trastuzumab, and immune checkpoint inhibitors.[51] In a cohort of 569 women who underwent breast cancer treatment, Jacobse *et al*. found that anthracyclines were associated with impaired myocardial function [decrease in LVEF, impaired global longitudinal strain (GLS), and higher N-terminal pro-brain natriuretic peptide (NT-proBNP) levels]. The risk of HF increased with cumulative doses of anthracyclines.[104] Radiotherapy without anthracyclines was not associated with increased risk of HF.[105] Troponins and NP should be measured during treatment being important markers of early cardiac injury.[51,106] In a recent meta-analysis, lower levels of cardiac troponin in patients undergoing cancer therapy showed a negative predictive value for LV dysfunction of 93%. On the other hand, NT-proBNP levels, despite increasing during cancer treatment, apparently did not predict LV dysfunction.[107] In a study on 548 treatment-naïve patients, a higher heart rate at rest was associated with higher levels of cardiac biomarkers and higher rates of all-cause mortality, especially in lung and gastrointestinal cancers.[108] In a prospective study including 120 unselected patients with lung, colon, or pancreatic cancer and 43 healthy controls, the prevalence of non-sustained ventricular tachycardia was higher in cancer patients vs. controls and it was associated with a higher risk of mortality.[109] A CV risk stratification at baseline is useful in order to optimize the primary and secondary prevention. Closer surveillance should be deserved for patients at high CV risk.[110]

Treatment of heart failure with reduced ejection fraction

Pharmacotherapy is the cornerstone of HFrEF treatment in order to reduce mortality, prevent worsening HF, and improve clinical status, functional capacity, and quality of life (QOL).[1,111] GDMT includes neurohormonal antagonists and the novel sodium-glucose co-transporter 2 (SGLT2) inhibitors. New compounds may expand the spectrum of HFrEF pharmacotherapy with the possibility of an individualized approach[112] (*Figure 5*).

Neurohormonal modulators

Neurohormonal modulators include the angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan (possibly as first-line therapy), or an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) if ACEi is not tolerated, a beta-blocker and a mineralocorticoid receptor antagonist (MRA).[1] Despite the widespread knowledge about the importance of initiating and titrating GDMT,[113] only a minority of eligible patients receive all the medications proven to be effective in preventing death and hospitalizations.[114] Moreover, a significant proportion of patients never receives target doses used in the landmark trials.[111,115,116] The underuse and underdosing is particularly evident in elderly subjects.[7,111] In an analysis of the Swedish HF Registry, beta-blockers were associated with a reduced risk of all-cause mortality and CV events also in older patients.[117]

European real-world evidence about sacubitril/valsartan treatment in HFrEF has been recently reviewed.[118] Sacubitril/valsartan may be safely initiated in hospital or early after discharge in patients hospitalized for acute HF.[119] Sacubitril inhibits neprilysin, a protease responsible for BNP cleavage. Effects of sacubitril/valsartan treatment on NPs trajectory have been studied, showing an increase in atrial natriuretic peptide (ANP) and no change in plasma brain natriuretic peptide (BNP) and plasma BNP activity, and a mild decrease in NT-proBNP concentrations.[120]

In a recent subgroup analysis of the TRANSITION study (Comparison of Pre- and Post-discharge Initiation of LCZ696

Figure 4 The heart of cancer patients. CAD, coronary artery disease (from Anker *et al*.[102]).

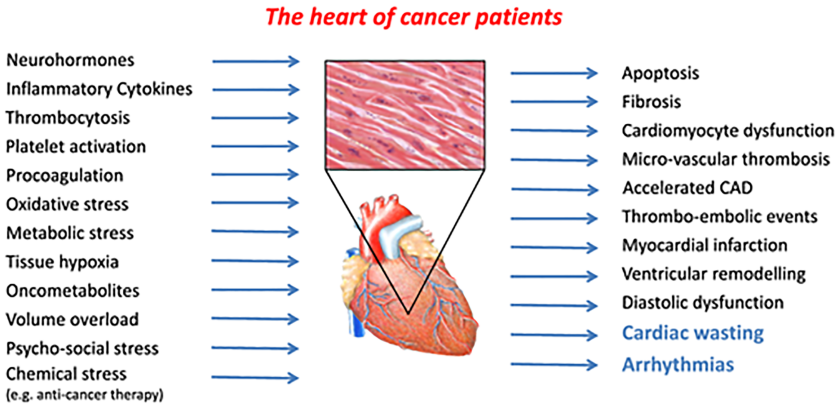
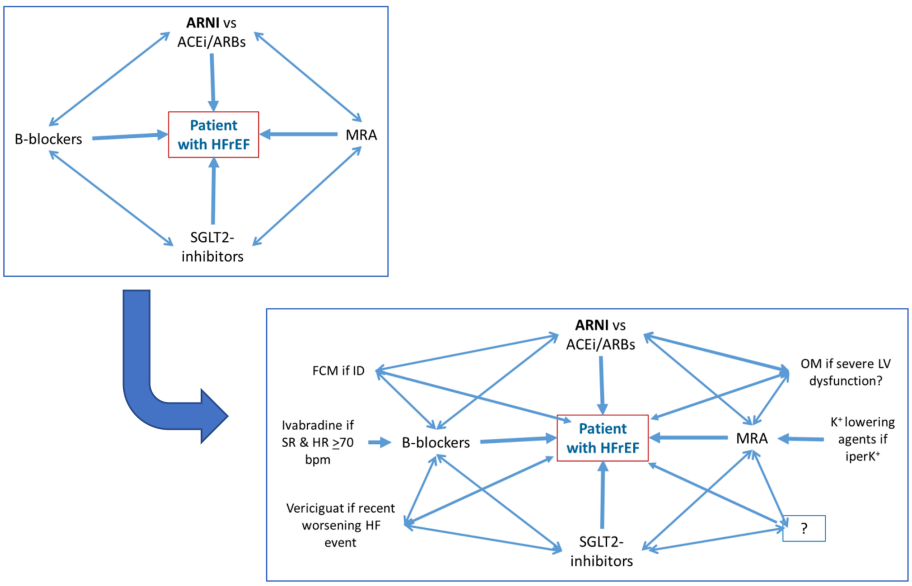


Figure 5 Foundational therapies in HFrEF patients and new compounds that may expand the spectrum of HFrEF pharmacotherapy, with the possibility of an individualized approach. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; FCM, ferric carboxymaltose; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; ID, iron deficiency; MRA, mineralocorticoid receptor antagonist; OM, omecamtiv mecarbil; SGLT2, sodium-glucose co-transporter 2; SR, sinus rhythm.



Therapy in HFrEF Patients After an Acute Decompensation Event), the use of sacubitril/valsartan as a first-line therapy was associated with a better risk–benefit profile in patients with de novo HF than those with known HFrEF, with more subjects reaching the target dose, greater decrease in NT-proBNP and high-sensitivity cardiac troponin T levels, and lower rates of HF or all-cause hospitalization.[121] The OUTSTEP-HF study was a randomized controlled trial comparing short-term effects of sacubitril/valsartan vs. enalapril on daily physical activity in patients with chronic HFrEF. After 12 weeks of treatment, a trend towards longer distance 6 min walking test was observed in patients receiving sacubitril/valsartan, albeit not statistically significant.[122]

Sodium-glucose co-transporter 2 inhibitors

Type 2 DM is a risk factor for incident HF, a common comorbidity in patients with established HF, and it is associated with significant morbidity and mortality.[123] Randomized trials in patients with DM at risk of CV events showed a reduction in HF hospitalizations and renal endpoints with multiple SGLT2 inhibitors.[1,30,124–126] In 2019, DAPA-HF (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure) was the first trial proving benefits of dapagliflozin in patients with HFrEF, regardless of diabetes history, with a 26% reduction of the composite endpoint of CV death or worsening HF [hazard ratio (HR), 0.74; 95% confidence interval (CI), 0.65 to 0.85; $P < 0.001$] as well as its components of CV death and first HF events.[127,128] In 2020, the Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure (EMPEROR-Reduced) trial confirmed these positive results with empagliflozin in HFrEF patients with a slightly increased risk for HF events likely because of the higher NT-proBNP levels required for study entry.[129] Compared with placebo, empagliflozin reduced the primary outcome of CV death or HF hospitalizations by 25% (HR, 0.75; 95% CI, 0.65 to 0.86; $P < 0.001$).[130] The empagliflozin group also showed a slower decline of the estimated glomerular filtration rate (eGFR) compared with the placebo group (−0.55 vs. −2.28 mL/min/1.73 m^2 of body surface area per year, $P < 0.001$).[130] In the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial, patients with a recent episode of worsening HF (irrespective of LVEF) and diabetes were randomized to sotagliflozin (a combined SGLT1/2 inhibitor) or placebo. Sotagliflozin was effective in the reduction of the total number of deaths from CV causes and hospitalizations or urgent visits for HF.[131] SGLT2 inhibitors have therefore shown beneficial effects on the clinical course of HF and kidney dysfunction, independent from neurohormonal mechanisms.[4,30,125,126] Their mechanisms of action are likely multifactorial and include enhanced natriuresis and osmotic diuresis, anti-inflammatory and antioxidant effects, improved myocardial metabolism and function, autophagy stimulation, and intracellular sodium reduction.[123,132,133]

Dapagliflozin and empagliflozin are now recommended in all patients with HFrEF to reduce mortality and HF events.[1]

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This class of drugs is a cost-effective treatment in the European health care systems.[134]

Diuretic therapy

Most patients with chronic HF are on loop diuretic therapy to relieve congestion and improve symptoms.[135] Higher doses of loop diuretics are associated with worse outcomes, and guidelines recommend usage of the lowest effective dose of loop diuretics needed to relieve congestion.[1,28,136] In an analysis from the ESC-EORP Heart Failure Long-Term Registry, Kapelios *et al*. showed that an increase in diuretic dose was associated with HF death, while down-titration with a trend for better outcomes.[135]

Iron deficiency

Clinical or subclinical iron deficiency is a common finding in HF patients, affecting up to 50% of ambulatory patients and leading to poorer prognosis and exercise intolerance.[137,138]

Treatment of iron deficiency with ferric carboxymaltose (FCM) infusion improved symptoms, functional capacity, and QOL in chronic HFrEF.[139–141] Efficacy on symptoms may be slightly larger in patients with HFrEF than with HFpEF.[142] In the Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency (AFFIRM-HF), the use of intravenous FCM in patients hospitalized for acute HF, an LVEF $<$ 50%, and with evidence of iron deficiency reduced HF hospitalization at a 52 week follow-up (risk ratio, 0.74; 95% CI, 0.58 to 0.94, P = 0.013).[143] This effect was consistent with previous meta-analyses,[144] and independent from many baseline variables, including LVEF and kidney function.[143] Treatment of iron deficiency with intravenous FCM is therefore indicated to improve symptoms and reduce HF rehospitalizations in either outpatients with chronic HF or patients hospitalized for acute HF with an LVEF $<$ 45–50%.[1,145]

Soluble guanylate cyclase stimulators

Vericiguat is an oral soluble guanylate cyclase (sGC) stimulator.[146] It may improve endothelial function and reduce oxidative stress and inflammation.[147] In the Study of Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction (VICTORIA) trial, vericiguat, in addition to guideline-based medical therapy, reduced the composite outcome of death from CV causes or first hospitalization for HF (HR, 0.90; 95% CI, 0.82 to 0.98; P = 0.02) in patients with a history of recent hospitalization or who had received intravenous diuretic therapy.[148] According to this trial, it may be considered in patients with a recent HF event to improve outcomes.[1,149]

Myosin activators

Omecamtiv mecarbil (OM) is a selective cardiac myosin activator that targets only the sarcomere with no influence on Ca^{2+} transients. In the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial, oral treatment with OM on top of standard HF therapy decreased the combined outcome of HF events and CV death (HR, 0.92; 95% CI, 0.86 to 0.99; P = 0.03) in HFrEF patients with LVEF $<$ 35%.[150–152] This was driven primarily by a reduction in HF events, with a possible greater effect observed in patients with more severe LV dysfunction. No differences on blood pressure, ischaemic events, or arrhythmias were noted.

Danicamtiv is another selective myosin activator capable of improving LV and atria contractility in experimental models and in a phase 2a trial in patients with HFrEF.[153] Digoxin is still active on other old drugs acting on cardiac function. DIGIT-HF is an ongoing trial designed to better clarify the role of digoxin on top of standard care in advanced HFrEF.[154]

Further options

Mesenchymal autologous stem-cell therapy has had promising results in ischaemic heart disease and HF.[155,156] In the final 4 year follow-up of the Autologous Mesenchymal Stromal Cell Therapy in Heart Failure (MSC-HF) trial, intramyocardial injection of mesenchymal stromal cells (MSC) in patients with ischaemic HF improved cardiac function and mass and reduced the amount of scar tissue compared with controls. Fewer hospitalization for angina were noted, with no differences in other hospitalization or survival.[155]

N6-adenosine methylation (m6A) of RNA transcripts is the most frequent form of RNA modification in eukaryotes.[157] In hypertrophic and failing heart, the m6A methylation pattern is altered, with transcription-dependent and transcription-independent effects on protein expression: modulation of this process might be an interesting target for future therapies.[157]

The miRNA miR-181a is a regulator of the aldosterone–mineralocorticoid receptor pathway with cardioprotective effects, and its overexpression in an animal model limited post-myocardial infarction (MI) cardiac remodelling.[158] Treatments based on miRNA-induced changes are currently under investigation.[159] In a network analysis of the plasma proteome of high-risk HF patients who died or were rehospitalized, Cao *et al*. found that glutathione, arginine and proline, and pyruvate pathways were activated.[160] These pathways might as well become novel targets for HF therapies.

Non-pharmacological therapies

Implantable defibrillator therapy and cardiac resynchronization therapy

The reduction in mortality with implantable cardioverter defibrillator (ICD) depends on HF substrate, arrhythmic risk profile, and concurrent medical therapy, particularly in non-ischaemic cardiomyopathies.[161] In an analysis including 17 901 US veterans with HFrEF receiving a new ICD placement between January 2007 and January 2015, 1 year mortality was around 13%. Age at implant was associated with higher rates of mortality, an effect not only attributable to comorbidities' burden.[162] Docherty *et al*. developed a risk model for sudden cardiac death (SCD) in ischaemic cardiomyopathy using data from the Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left Ventricular Dysfunction trial (CAPRICORN) and the Valsartan in Acute Myocardial Infarction Trial (VALIANT).[163] Independent predictors of SCD included age $>$ 70 years; heart rate $\geq$ 70 b.p.m.; smoking; Killip class III/IV; LVEF $\leq$ 30%; AF; history of prior MI, HF, or DM; eGFR $<$ 60 mL/min/1.73 m^2; and no coronary reperfusion or revascularization therapy for index MI. The risk score performed well (*C*-statistic = 0.72), both early and later after acute MI. By contrast, an LVEF of $\leq$35%, by itself, was a poor predictor of the risk of SCD (*C*-statistic = 0.54).[163]

A recent joint position statement from three ESC Associations, HFA, European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI), focused on optimized implementation of cardiac resynchronization therapy (CRT).[164] CRT improves QOL and symptoms, reduces mortality and HF hospitalization, and favours LV reverse remodelling.

Among patients enrolled in PARADIGM-HF and ATMOSPHERE trials, 15.1% had left bundle branch block (LBBB), 4.4% right bundle branch block (RBBB), 3.8% non-specific intraventricular conduction delay, 21.8% 'mildly abnormal' QRS (110–129 ms), and 54.9% QRS $<$ 110 ms at baseline and the annual incidence of new-onset LBBB was around 2.5%. The risk of the primary composite endpoint was higher among those with a wide QRS, irrespective of morphology.[165] These data support current indications to CRT in HFrEF.[1]

Cardiac contractility modulation

Cardiac contractility modulation (CCM) consists of biphasic high-voltage bipolar signals delivered to the right ventricular septum during the absolute refractory period and has been shown to improve intramyocardial calcium handling. CCM has improved symptoms, exercise tolerance, and QOL and reduced the rate of HF hospitalizations in patients with ejection fractions between 25% and 45%.[166–169]

Percutaneous treatment of mitral or tricuspid regurgitation

Up to one-third of HFrEF patients present severe mitral secondary regurgitation (SMR), which is associated with poor outcomes.[24,170,171] Percutaneous edge-to-edge mitral valve repair has become a safe, widespread option for patients with HF and SMR.[1,23,24,172] Patients with no or low-grade residual mitral regurgitation at discharge and after 12 months from correction of mitral regurgitation with the MitraClip system showed better outcomes compared with patients with higher degree of residual mitral regurgitation.[173]

Since the publication of the MITRA-FR and COAPT trials on MitraClip device, the attention has been focused on identifying the causes of the different results between the two trials and the patients who may benefit from this procedure. MITRA-FR trial failed to demonstrate a reduction in mortality or HF hospitalization in patients with severe FMR undergoing MitraClip compared with those receiving standard conservative therapy.[174,175] On the other hand, the COAPT trial demonstrated a significant reduction in 2 year HF hospitalization and all-cause mortality.[176] Different outcomes might be, at least partially, explained by differences in patients' baseline characteristics. In a European multicentre retrospective study, a COAPT-like profile was associated with better outcomes at both 2 and 5 years, compared with non-COAPT-like profile. COAPT-like profile was defined as absence of (i) severe LV impairment, (ii) moderate to severe right ventricular dysfunction, (iii) severe tricuspid regurgitation, (iv) severe pulmonary hypertension, and (v) haemodynamic instability.[177]

Other factors are important. LA dysfunction is a major cause of impairment of exercise capacity and abnormal haemodynamic response to exercise and an independent predictor of negative outcomes after percutaneous mitral valve repair.[178,179] Even a small mitral effective regurgitant orifice area contributes to LA remodelling on top of traditional systolic and diastolic parameters.[180] Percutaneous mitral valve annuloplasty may also effectively reduce mitral valve annulus and have favourable effects on LV remodelling and patients' symptoms.[181,182] Tricuspid regurgitation is highly prevalent in HF patients. Severe tricuspid regurgitation is associated with signs of right ventricular failure, impairment of hepatic and renal function, malnutrition, and adverse outcomes.[183,184] Despite the availability of different transcatheter device for tricuspid valve repair (TVR), there are still no randomized trials that demonstrate their effect on major outcomes.[185] In a study by Kresoja *et al*., transcatheter TVR improved symptoms irrespective of left-side HF type but a

benefit on mortality and HF hospitalization at 12 months was observed only in HFpEF.[186]

Advanced heart failure

Patients with HF progress to an advanced stage with severe symptoms, poor tolerance of evidence-based medical therapy, frequent episodes of decompensation, and high mortality.[187] Management of these patients remains a major largely unmet medical need.[1]

Inotropes

Positive inotropes failed to improve survival.[188,189] The chronic use of inotropes in outpatients with advanced HF represents a palliative strategy to improve haemodynamics and, thus, symptoms and QOL. LeoDOR, a randomized, double-blind, placebo-controlled, international, multicentre trial, will explore the safety and effectiveness of repetitive levosimendan in advanced HF patients, with a recent acute HF hospitalization.[190]

Mechanical circulatory support

The selected use of mechanical circulatory support (MCS) in patients with advanced HF has favourable effects on survival, functional capacity, and QOL.[191] Indications to short-term and long-term MCS are outlined in current guidelines.[1] The SweVAD trial will investigate the impact of guideline-directed left ventricular assist device (LVAD) destination therapy using the HeartMate 3 vs. GDMT on survival in advanced HF patients (NYHA class IIIB–IV, INTERMACS profile 2–6) who are not eligible for heart transplantation.[192]

Aortic regurgitation (AR) is associated with only partial unloading of the left ventricle, reduced peripheral perfusion, increased myocardial wall stress, higher levels of NPs, higher hospitalization rates, and increased mortality in patients with MCS. In a recent analysis of the ISHLT Mechanically Assisted Circulatory Support (IMACS) registry, patients with preoperative moderate-to-severe AR who underwent LVAD implantation and concomitant aortic procedures had similar survival rates compared with those who did not receive any aortic procedure. Aortic valve replacement was, however, associated with a greater risk of mortality than aortic valve repair and was identified as an independent predictor of mortality.[193]

Palliative care

Palliative care aims to improve symptoms and QOL, namely, in patients at their end of life. A recent position paper of the ESC proposed an integrated approach of palliative and HF cares. It focused on early recognition and assessment of patients' needs, managing distressing symptoms with pharmacological and non-pharmacological therapy, and communication with patients, family, or other caregivers.[194] Palliative care interventions have been associated with fewer hospitalization and improvements in QOL and symptoms burden.[195]

Remote monitoring and telemedicine

It is difficult to question the usefulness of telemonitoring above all in the current era of coronavirus disease 2019 (COVID-19) pandemic.[53] However, as when other disease management modalities are compared, it is often difficult to show a benefit of a new one, mainly because treatment of the control group by skilled cardiologists is often satisfactory. In the OSICAT trial, 937 patients with recent HF hospitalization were randomized to telemonitoring or standard care. Telemonitoring showed no reduction in all-cause death or hospitalization for HF compared with standard care, except in patients with severe HF or socially isolated.[196] Consistently, the role of careful patients' selection has been shown in the successful Telemedical Interventional Monitoring in HF (TIM-HF) study.[197] Implantable pulmonary artery pressure monitoring systems are safe and were successful in reducing rates of hospitalization in symptomatic patients with HF.[198–202]

Heart failure with preserved ejection fraction

Epidemiology, clinical phenotypes, and pathophysiology

Heart failure with preserved ejection fraction accounts for more than half of HF hospitalizations.[1,2,203] Its prevalence is growing due to the ageing of the population and the increasing prevalence of obesity, DM, chronic kidney disease, and hypertension.[2,203–206] It is a highly heterogeneous condition although some common mechanisms may exist. As outlined in a seminal paper, an extracardiac cause, such as obesity, DM, hypertension, or chronic kidney disease, may lead to inflammatory activation, production of reactive oxygen species (ROS), formation of peroxynitrite ($ONOO^-$), and reduced nitric oxide (NO) bioavailability with reduced sGC activity and myocardial hypertrophy and stiffening.[207]

Major attempts are performed to try to identify phenotypes of patients with HFpEF deserving specific treatments. Using a machine learning-based unsupervised cluster analysis, Segar *et al*.[82] identified three phenotypes of patients with

HFpEF, with different clinical characteristics, comorbidities, and outcomes, among those enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT).[82] A distinct obese HFpEF phenotype seems identified.[208,209] These obese HFpEF patients showed greater myocardial and epicardial fat deposition compared with HFrEF or non-HF patients. Release of cytokines and adipokines from the epicardial fat may induce myocardial inflammation both in the left atrium, with increased susceptibility to AF, and in the LV with increased stiffness and intraventricular filling pressure. These patients also have a larger blood volume and reduced vascular compliance with increased right atrial and pulmonary capillary wedge pressure, compared with non-obese HFpEF patients, coronary microvascular dysfunction and rarefaction, and myocardial fibrosis.[32,204,208–211] Echocardiography and, with better accuracy, CMR are useful tools for the detection of epicardial or intramyocardial fat, myocardial fibrosis, as well as for the study of microvascular dysfunction.[212]

Diagnosis and prognosis

Diagnosis of HFpEF requires objective evidence of cardiac abnormalities and elevated levels of natriuretic peptides. A diagnostic stress test is recommended when these markers are inconclusive. A position statement by HFA has proposed a stepwise diagnostic algorithm.[203] Step 1 (P = pre-test) includes a complete assessment of HF symptoms and signs, clinical and demographical history, and diagnostic tests to exclude other causes of dyspnoea. The second step (Step E = echocardiographic and natriuretic peptide score) requires the integration of a comprehensive echocardiographic examination and measurement of natriuretic peptides in the HFA-PEFF score. A low HFA-PEFF score is associated with a very low likelihood of HFpEF, whereas a score $\geq$ 5 is considered diagnostic for HFpEF. This score was then validated in two independent prospective cohorts.[213,214] Step 3 (F_1 = functional testing, with echocardiographic or invasive haemodynamic exercise stress tests) is reserved to patients with intermediate values of the HFA-PEFF score. The final step (F_2 = final aetiology) aims to identify specific aetiologies that may benefit from targeted treatments.[203]

In a secondary analysis of the National Heart, Lung, and Blood Institute-sponsored RELAX, NEAT-HFpEF, and INDIE-HFpEF trials, Reddy *et al*. found that QOL was correlated with functional capacity, measured by peak aerobic capacity, levels of activity by accelerometry, and submaximal exercise capacity with 6 min walking test, while no association was found between QOL and NT-proBNP levels, echocardiographic resting parameters, and HF hospitalizations. Patients with worst QOL were young, obese, and diabetic.[215]

Left ventricular hypertrophy and enlargement and their variation over time have a prognostic impact.[216] In a study including 280 patients with HFpEF, those with mild-to-moderate mitral regurgitation presented greater LA volume, reduced LA strain and compliance, and greater mitral annular dilatation compared with those without mitral regurgitation. Annular dilatation was strongly correlated with LA dilatation (r = 0.63, $P < 0.0001$) and weakly related to LV remodelling (r = 0.37), suggesting that mitral regurgitation may reflect atrial myopathy.[179] Atrial myopathy, either silent or clinically overt, is common in HFpEF and contributes to symptoms, disease progression, and adverse outcomes.[179,217]

Treatment

At the time of the 2021 ESC HF guidelines, treatment with neurohormonal modulators could be considered based on mostly retrospective analyses of trials in patients with an LVEF $\geq$ 40% whereas treatment of HFpEF remained based on the management of congestion and comorbidities.[1]

In the recent EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction) trial, empagliflozin reduced the composite endpoint of CV death or HF hospitalization in patients with LVEF > 40% and NYHA class II–IV, irrespective of DM history (HR, 0.79; 95% CI, 0.69 to 0.90; $P < 0.001$).[218] The results were consistent across all prespecified subgroups, including that of the patients with or without diabetes.[218] This is the first trial proving benefits on major clinical endpoints in HFpEF. Of note, EMPEROR-Preserved enrolled patients with a higher burden of comorbidities, more severe cardiac dysfunction, higher median NT-proBNP, and greater use of MRAs compared with previous HFpEF trials.[219]

Sodium-glucose co-transporter 2 inhibitors also improved symptoms, QOL, and functional capacity in smaller trials. In a multicentre, randomized trial, enrolling 324 patients with HFpEF, those receiving dapagliflozin had a significant increase in the primary endpoint of Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS) at 12 weeks after treatment initiation (effect size, 5.8 points; 95% CI, 2.3 to 9.2; P = 0.001) and in 6 min walking test distance (mean effect size of 20.1 m; 95% CI, 5.6 to 34.7; P = 0.007).[220] A new era of medical treatment of patients with HFpEF is now open.

Acute heart failure

Epidemiology

Acute HF is a major public health burden worldwide.[221–224] In a systematic review of acute HF studies from 1980 to 2017, Kimmoun *et al*. showed, during time, a decline in 30 day all-cause death (odds ratio for a 10 year increment, 0.74; 95% CI, 0.61 to 0.91; P = 0.004) and 1 year all-cause death (odds ratio, 0.86; 95% CI, 0.77 to 0.96; P = 0.007). On the

other hand, 30 day and 1 year all-cause readmission rate remained unchanged.[225]

Cardiogenic shock (CS) is the most severe presentation of acute HF, with in-hospital mortality rates up to 60%. HFA of ESC has recently published a position statement focusing on pathophysiology and management of CS.[226] Acute coronary syndrome is a major cause of acute HF and CS.[227] In a French registry enrolling 10 000 patients with acute myocardial infraction, the prevalence of CS decreased between 2005 and 2015 from 5.9% to 2.8%.[228] However, population-based annual incidence of acute MI complicated by CS increased from 65.3 per million person-years in 2013 to 80.0 per million person-years in 2017 in a Danish study (*P*-value for trend < 0.001).[229]

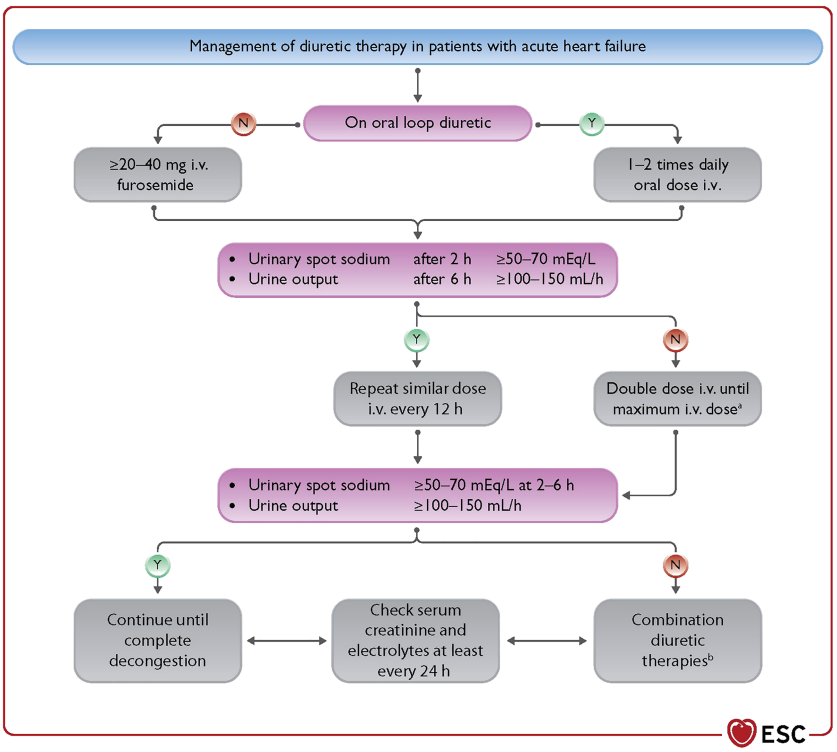
Management and treatment

Biomarkers are widely used for the management of acute HF. Mid-regional pro-adrenomedullin (MR-proADM) and bio-adrenomedullin (bio-ADM) have been proposed as alternative markers of congestion in acute HF.[230–232] In a study including 1107 breathless patients, MR-proADM exhibited higher accuracy for the diagnosis of acute HF, compared with NT-proBNP, in patients with concomitant AF (73% vs. 62%, respectively).[233]

Because congestion represents the first cause of hospitalization for decompensated HF,[234] diuretics are the mainstay of acute HF treatment.[222] *Figure 6* illustrates the flowchart for the management of diuretic therapy in patients with acute HF.[1] Urine sodium is an early predictor of effective decongestion after diuretic initiation.[136,235–237] Damman *et al*. demonstrated a strong association between urinary sodium (uNa) excretion, measured 6 h after loop diuretic initiation, and urine volume at 24 h (standardized beta = 0.702, $P < 0.001$). Lower 6 h uNa excretion was a strong predictor of all-cause mortality (HR, 3.81; 95% CI, 1.92 to 7.57; $P < 0.001$ for the lowest vs. the highest tertile).[236]

The role of empagliflozin in acute HF has been studied in EMPA-RESPONSE-AHF (Effects of Empagliflozin on Clinical Outcomes in Patients with Acute Decompensated Heart Failure).[238] Treatment with empagliflozin reduced the risk of death or worsening/hospitalization for HF at 60 days, but the trial was not powered to study these strong endpoints. Ongoing studies will clarify the clinical benefit and safety of SGLT2 inhibitors in the acute setting.[136]

Figure 6 Management of diuretic therapy in patients with acute heart failure. i.v., intravenous. [a]The maximal daily dose for i.v. loop diuretics is generally considered furosemide 400–600 mg though up to 1000 mg may be considered in patients with severely impaired kidney function. [b]Combination therapy is the addition to the loop diuretic of a diuretic with a different site of action, for example, thiazides or metolazone or acetazolamide (from McDonagh *et al*.[1]).



COVID-19 and heart failure

In the last year, COVID-19 pandemic had a catastrophic impact on health systems worldwide. Because of the fear of acquiring infection and the congestion of the health services, hospitalizations for acute CV syndromes (including acute HF) collapsed and patients who finally sought medical attention presented sicker, had more complications, and had worse outcomes.[53,239–243] In the ambulatory setting, outpatients' visits have been postponed due to safety reasons, and this has led to the urge of remote monitoring services.[53,244]

Beyond epidemiology, a close and intriguing relationship has been described between COVID-19 and HF. First, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, binds angiotensin-converting enzyme 2 (ACE2) to infect human cells. ACE2 is part of the renin–angiotensin system (RAS). It is an enzyme responsible for the cleavage of angiotensin II into angiotensin 1–7, which has vasodilating and anti-inflammatory effects. SARS-CoV-2 down-regulates ACE2 expression, reducing angiotensin 1–7 levels and increasing angiotensin II stimulation, which contributes to the hyper-inflammatory reaction of COVID-19 and potentially leads to HF.[245] Initial concerns that ACEi/ARB use might increase the risk of infection or adverse outcomes due to increased myocardial ACE2 mRNA expression were not confirmed in several studies.[53,246]

Secondly, patients with pre-existent CV disease, namely, HF, have a higher risk of complications and death. A history of HF was an independent predictor of increased in-hospital mortality.[239,240,243,247,248] A summary of current knowledge and a practical guidance for the management of patients with CV disease and COVID-19 has been recently published.[244,249]

Thirdly, COVID-19 often caused CV damage. The large spectrum of CV manifestations included subclinical myocardial injury,[250] defined as an increase in troponin levels, acute myocarditis, and unusual thromboembolic events.[53,251,252] Myocardial injury was associated with worse outcome.[53,245,253] Echocardiographic abnormalities were also frequent. Although LV systolic function was not usually impaired, many patients presented right ventricular dysfunction and diastolic impairment, suggesting a possible association between COVID-19 and HFpEF.[254,255] COVID-19 patients may also develop acute HF, either as a de novo manifestation or as an acute decompensation of a pre-existing chronic HF, and often developed weight loss.[53,256] Long-term consequences of COVID-19, including development of subclinical diastolic dysfunction or overt HFpEF, are yet to be discovered.[257,258]

Conclusions and future directions

The last 2 years have shown major changes in our current treatment of the patients with HF. A completely new class of drugs, acting through mechanisms at least mostly independent from neurohormonal modulation, has been shown to significantly improve outcomes of the patients not only with HFrEF but also with a preserved LVEF. Based on the results of EMPEROR-Preserved,[129,218] just HF symptoms and increased plasma levels of natriuretic peptides will be necessary for an indication to treatment with empagliflozin and, likely, in the next future, other SGLT2 inhibitors. New drugs, such as vericiguat and OM, acting also in their case, not through neurohormonal mechanisms, have been also shown to have beneficial effects. Treatment of CV and non-CV comorbidities, namely, iron deficiency, diabetes, AF, and valvular heart disease, gives further option. Future research will also hopefully show benefits also in other aspects of the HF syndrome such as, namely, QOL and frailty, still deserving better assessment and further improvement.

Conflict of interest

M.S.A. reports personal fees from Servier, outside the submitted work.

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