A year in heart failure: an update of recent findings

Lorenzo Stretti1, Dauphine Zippo1, Andrew J.S. Coats2, Markus S. Anker3,4,5, Stephan von Haehling6,7, Marco Metra1 and Daniela Tomasoni1*

1Cardiology, Cardio-Thoracic Department, Civil Hospitals; Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; 2University of Warwick, Coventry, UK; 3Department of Cardiology (CBF), Charité - Universitätsmedizin Berlin, Berlin, Germany; 4Berlin Institute of Health Center for Regenerative Therapies (BCRT), Berlin, Germany; 5German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany; 6Department of Cardiology and Pneumology, University of Göttingen Medical Center, Göttingen, Germany; and 7German Center for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany

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 outcomeTrial 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

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

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. 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). Of note, women are consistently under-represented in HF clinical trials, contributing to remarkable research bias. 

**Comorbidities**

Comorbidities have a substantial impact on clinical presentation and outcomes in HF patients. Screening for and treatment of cardiovascular (CV) comorbidities and non-CV comorbidities is recommended. CV comorbidities include hypertension, coronary artery disease, atrial fibrillation (AF), ventricular arrhythmias, valvular heart disease, cerebrovascular disease, and pulmonary hypertension. Non-CV comorbidities include chronic kidney disease and electrolyte disorders, DM, obesity, cachexia, sarcopenia, chronic obstructive pulmonary disease, iron deficiency, and anaemia, thyroid disorders, cancer, infections, arthritis, frailty, and depression. The clinical burden of comorbidities differs between patients with HFrEF and those with HFpEF. 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. It is the result of impaired homeostatic mechanisms and reduced resistance to stressors that might be the consequence of bone 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.).
(sarcopenia) or cachexia, both of which have been shown to be independently associated with increased mortality. Muscle wasting has been described across a vast spectrum of HF aetiologies including ischaemic cardiomyopathy and Chagas disease, and the importance of more clinical and therapeutic action has been highlighted in recent years.

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. HFA of the ESC has recently proposed a new Frailty Score, based on four main domains—clinical, functional, psycho-cognitive, and social.

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. Because signs and symptoms are often non-specific, investigation through biomarkers and imaging is essential for the diagnosis and management.

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. 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.

Laboratory exams

Assessment of biomarkers is a cornerstone of HF management. 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. 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.

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. 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 HfP EF patients. Pulmonary hypertension and right ventricular dysfunction are further markers of poor outcome.

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. In a cohort of subjects with LVEF ≥ 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 ≤33% predicted invasively verified HfP EF diagnosis with 88% sensitivity and 77% specificity, providing diagnostic utility in patients with exertional dyspnoea.

Risk predicting models

Prognostic scores can be important to guide therapeutic strategies in HF and machine learning techniques may provide additional accuracy. 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). 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 HfP EF), with c-statistics between 0.83 and 0.89.
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 HFP EF cases95 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). Moreover, cancer therapies are often cardiotoxic. Main cardiotoxic drugs include anthracyclines, fluoropyrimidines, tyrosine kinase inhibitors, HER2-targeted therapies such as trastuzumab, and immune checkpoint inhibitors. In a cohort of 569 women who underwent breast cancer treatment, Jacobs 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. Radiotherapy without anthracyclines was not associated with increased risk of HF. Troponins and NP should be measured during treatment being important markers of early cardiac injury. 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. 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. 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. 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.

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). 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 (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). Despite the widespread knowledge about the importance of initiating and titrating GDMT, only a minority of eligible patients receive all the medications proven to be effective in preventing death and hospitalizations. Moreover, a significant proportion of patients never receives target doses used in the landmark trials. The underuse and underdosing is particularly evident in elderly subjects. 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.

European real-world evidence about sacubitril/valsartan treatment in HFrEF has been recently reviewed. Sacubitril/valsartan may be safely initiated in hospital or early after discharge in patients hospitalized for acute HF. Sacubitril inhibits nepriysin, 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.

In a recent subgroup analysis of the TRANSITION study (Comparison of Pre- and Post-discharge Initiation of LCZ696...
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. 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. 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. Randomized trials in patients with DM at risk of CV events showed a reduction in HF hospitalizations and renal endpoints with multiple SGLT2 inhibitors. 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. 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. 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; \( P < 0.001 \)). 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 m² of body surface area per year, \( P < 0.001 \)). 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. SGLT2 inhibitors have therefore shown beneficial effects on the clinical course of HF and kidney dysfunction, independent from neurohormonal mechanisms. 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. Dapagliflozin and empagliflozin are now recommended in all patients with HFrEF to reduce mortality and HF events.
This class of drugs is a cost-effective treatment in the European health care systems.\textsuperscript{134}

**Diuretic therapy**

Most patients with chronic HF are on loop diuretic therapy to relieve congestion and improve symptoms.\textsuperscript{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.\textsuperscript{1,2,136} 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.\textsuperscript{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.\textsuperscript{137,138} Treatment of iron deficiency with ferric carboxymaltose (FCM) infusion improved symptoms, functional capacity, and QOL in chronic HFrEF.\textsuperscript{139} Efficiency with intravenous FCM is therefore indicated in Patients With Acute Heart Failure and Iron Deficiency (AF-FIRM-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, \(P = 0.013\)).\textsuperscript{143} This effect was consistent with previous meta-analyses,\textsuperscript{144} and independent from many baseline variables, including LVEF and kidney function.\textsuperscript{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%.\textsuperscript{1,145}

**Soluble guanylate cyclase stimulators**

Vericiguat is an oral soluble guanylate cyclase (sGC) stimulator.\textsuperscript{146} It may improve endothelial function and reduce oxidative stress and inflammation.\textsuperscript{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.\textsuperscript{148} According to this trial, it may be considered in patients with a recent HF event to improve outcomes.\textsuperscript{1,149}

**Myosin activators**

Omecamtiv mecarbil (OM) is a selective cardiac myosin activator that targets only the sarcomere with no influence on Ca\textsuperscript{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%.\textsuperscript{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. Danicaptiv is another selective myosin activator capable of improving LV and atra contractility in experimental models and in a phase 2a trial in patients with HFrEF.\textsuperscript{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.\textsuperscript{154}

**Further options**

Mesenchymal autologous stem-cell therapy has had promising results in ischaemic heart disease and HF.\textsuperscript{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.\textsuperscript{155} N6-adenosine methylation (m6A) of RNA transcripts is the most frequent form of RNA modification in eukaryotes.\textsuperscript{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.\textsuperscript{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.\textsuperscript{158} Treatments based on miRNA-induced changes are currently under investigation.\textsuperscript{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.\textsuperscript{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. 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. Docherty et al. developed a risk model for sudden cardiac death (SCD) in ischaemic cardiomyopathy using data from the Effect of Carvediol on Outcome After Myocardial Infarction in Patients With Left Ventricular Dysfunction trial (CAPRICORN) and the Valsartan in Acute Myocardial Infarction Trial (VALIANT). Independent predictors of SCD included age > 70 years; heart rate ≥ 70 b. p.m.; smoking; Killip class III/IV; LVEF ≤ 30%; AF; history of prior MI, HF, or DM; eGFR < 60 mL/min/1.73 m²; 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 ≤35%, by itself, was a poor predictor of the risk of SCD (C-statistic = 0.54).

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). 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. These data support current indications to CRT in HFrEF.

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%.

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. Percutaneous edge-to-edge mitral valve repair has become a safe, widespread option for patients with HF and SMR. 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.

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. On the other hand, the COAPT trial demonstrated a significant reduction in 2 year HF hospitalization and all-cause mortality. 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.

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. Even a small mitral effective regurgitant orifice area contributes to LA remodelling on top of traditional systolic and diastolic parameters. Percutaneous mitral valve annuloplasty may also effectively reduce mitral valve annulus and have favourable effects on LV remodelling and patients’ symptoms. 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. 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. 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 HFrEF.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 III–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 HFrEF deserving specific treatments. Using a machine learning-based unsupervised cluster analysis, Segar et al.32 identified three phenotypes of patients with
HFrEF, 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). A distinct obese HFrEF phenotype seems identified. These obese HFrEF 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 HFrEF patients, coronary microvascular dysfunction and rarefaction, and myocardial fibrosis.

**Echocardiography and natriuretic peptides** are useful tools for the detection of epicardial or intramyocardial fat, myocardial fibrosis, as well as for the study of microvascular dysfunction.

**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. 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 ≥ 5 is considered diagnostic for HFpEF. This score was then validated in two independent prospective cohorts.

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 accelerometer, 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.

Left ventricular hypertrophy and enlargement and their variation over time have a prognostic impact. 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. Atrial myopathy, either silent or clinically overt, is common in HFpEF and contributes to symptoms, disease progression, and adverse outcomes.

**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 ≥ 40% whereas treatment of HFpEF remained based on the management of congestion and comorbidities.

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). The results were consistent across all prespecified subgroups, including that of the patients with or without diabetes. 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.

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). 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. 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 infarction, 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. aThe 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. bCombination 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{245} Initial concerns that ACE2/ARb use might increase the risk of infection or adverse outcomes due to increased myocardial ACE2 mRNA expression were not confirmed in several studies.\textsuperscript{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.\textsuperscript{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.\textsuperscript{244,249}

Thirdly, COVID-19 often caused CV damage. The large spectrum of CV manifestations included subclinical myocardial injury,\textsuperscript{250} defined as an increase in troponin levels, acute myocarditis, and unusual thromboembolic events.\textsuperscript{53,251,252} Myocardial injury was associated with worse outcome.\textsuperscript{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 HFP EF.\textsuperscript{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.\textsuperscript{53,256} Long-term consequences of COVID-19, including development of subclinical diastolic dysfunction or overt HFP EF, are yet to be discovered.\textsuperscript{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,\textsuperscript{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.

References

1. McDonagh T, Metra M, Adamo M, Gardner R, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland J, Coats A, Crespo-Leiro M, Farmakis D, Gilard M, Heymans S, Hoes A, Jaarsma T, Jankowska E, Lainscak M, Lam C, Lyon A, McMurray J, Mebazee A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano G, Ruschitzka F, Kathrine SA. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. \textit{Eur Heart J} 2021; 42: 3599–3726.

2. Groenewegen A, Rutten F, Mosterd A, Hoes A. Epidemiology of heart failure. \textit{Eur J Heart Fail} 2020; 22: 1342–1356.

3. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. \textit{Eur J Heart Fail} 2019; 21: 1306–1326.

4. Tomasoni D, Adamo M, Anker M, von Haebring S, Coats A, Metra M. Heart failure in the last year: progress and perspective. \textit{ESC Heart Failure} 2020; 7: 3505–3530.

5. Seferovic PM, Vardas P, Jankowska EA, Magoni AP, Timmis A, Milinkovic I, Polovina M, Gale CP, Lund LH, Lopatin Y, Lainscak M, Savarese G, Huculeci R, Kazakiewicz D, Coats AJS. The Heart Failure Association Atlas: heart failure epidemiology and management statistics 2019. \textit{Eur J Heart Fail} 2021; 23: 906–914.

6. Conrad N, Judge A, Tran J, Mhersen H, Hedegcott D, Crespillo AP, Allison M,
Hemwingay H, Cleland JG, McMurray J, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet 2018; 391: 572–580.

7. Lainišćak M, Milinković I, Polovina M, Crespo-Leiro M, Lund L, Anker S, Laroche C, Ferrari R, Coats A, McDonagh T, Filippatos G, Maggioni A, Piepoli M, Rosano G, Ruschitzka F, Simić D, Alain M, Eicher J, Yilmaz M, Seferović P. Sex- and age-related differences in the management and outcomes of chronic heart failure: an analysis of patients from the ESC HFA EORP Heart Failure Long-Term Registry. Eur J Heart Fail 2020; 22: 92–102.

8. Hao G, Wang X, Chen Z, Zhang L, Zhan Y, Wei B, Zheng C, Kang Y, Jiang L, Zhu Z. Prevalence of heart failure and left ventricular dysfunction in China: the China Hypertension Survey, 2012–2015. Eur J Heart Fail 2019; 21: 1329–1337.

9. Li L, Liu R, Jiang C, Du X, Huffman MD, Lam CSP, Patel A, Hillis GS, Anderson CS, Ma C, Zhao X, Wang X, Li L, Chew J. Assessing the evidence–practice gap for heart failure in China: the Heart Failure Registry of Patient Outcomes (HERO) study design and baseline characteristics. Eur J Heart Fail 2020; 22: 646–660.

10. Seferovic PM, Jankowska EA, Coats AJS, Maggioni AP, Lopatin Y, Milinković I, Polovina M, Lainišćak M, Timmis A, Huculeci R, Vardas P. Task Force of the HFA Atlas of Heart Failure, developed in collaboration with the National Heart Failure Societies of the ESC member and ESC affiliated member countries. The Heart Failure Association Atlas: rationale, objectives, and methods. Eur J Heart Fail 2020; 22: 638–645.

11. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D’Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002; 106: 3068–3072.

12. Gutman SJ, Costello BT, Papapostolou S, Iles L, Ja J, Hare JI, Ellims A, Marwick TH, Taylor AJ. Impact of sex, socio-economic status, and remoteness on therapy and survival in heart failure. ESC Heart Fail 2019; 6: 944–952.

13. Chandramouli C, Teng TK, Tay WT, Yap J, MacDonald MR, Tromp J, Yan L, Siwanto B, Reyes EB, Ngarmukos T, Yu CM, Hung CL, Anand I, Richards AM, Ling LH, Regensteiner JG, Lam CSP, Investigators A-H. Impact of diabetes and sex in heart failure with reduced ejection fraction patients from the ASIAN-HF registry. Eur J Heart Fail 2019; 21: 297–307.

14. Lam CS, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Sanmata BT, Sliva K, Voors AA. Sex differences in heart failure. Eur Heart J 2019; 40: 3859–3868.
blockers and beta-blockers in patients hospitalized for acute heart failure. *ESC Heart Fail* 2021; 8: 1944–1953.

114. Greene S, Butler J, Albert N, DeVore A, Sharma P, Duffy C, Hill C, McGague K, Mi X, Patterson J, Speratus J, Thomas L, Williams F, Hernandez A, Fonfrere M, G. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol* 2018; 72: 351–366.

115. Packer M, Metra M. Guideline-directed medical therapy for heart failure does not exist: a non-judgmental framework for describing the level of adherence to evidence-based drug treatments for patients with a reduced ejection fraction. *ESC Heart Fail* 2020; 22: 1759–1767.

116. Marié G, Fonarow G, Anker S, Yancy C, Vaduganathan M, Greene S, Ahmed A, Januzzi J, Gheorghiade M, Filippatos G, Butler J. Medication dosing for heart failure with reduced ejection fraction—opportunities and challenges. *ESC Heart Fail* 2019; 21: 286–296.

117. Stolfo D, Ujił A, Benson L, Scharge B, Fudites S, Van Dam W, Stadtsaal S, Sinagra G, Dahlström U, Rosano G, Savarese G. Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction. A propensity score–matched analysis from the Swedish Heart Failure Registry. *ESC Heart Fail* 2020; 22: 103–112.

118. Giovinazzo S, Carmisciano L, Tomà M, Benenati S, Tomasoni D, Sormani M, Porto I, Canepa M, Senni M, Metra M, Ameri P. Sacubitril/valsartan in real-life European patients with heart failure and reduced ejection fraction. A systematic review and meta-analysis. *ESC Heart Fail* 2021; 8: 3547–3556.

119. Wachter R, Senni M, Belohlavek J, Strabuzynska-Migai E, Witte K, Kobalza V, Fonseca G, Gonzaleseva E, Cavuoto J, Strabuzynska A, Chabaran S, Böhmer E, Pouleur A, Mueller C, Tribouilloy C, Lonn E, Buraiki J, Gniot J, Mozheiko M, Lelonek M, Noè A, Piepoli MF, Chioncel O, Bao W, Polovina M, Suradzinska-Migaj E, Belohlavek J, P. Incidence of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *ESC Heart Fail* 2021; 2: 909–1007.

120. Nogué H, Pezel T, Picard F, Sadoune M, Arrigo M, Beauvais F, Launay J, Cohen-Solal A, Vodovan A, Logeart D. Effects of sacubitril/valsartan on natriuretic peptides in chronic heart failure: a mechanistic clinical study. *ESC Heart Fail* 2019; 21: 598–605.

121. Senni M, Wachter R, Witte K, Strabuzynska-Migai E, Belohlavek J, Fonseca G, Mueller C, Lonn E, Chakrabarti A, Bao W, Noe A, Schwende H, Butylin D, Pascual-Figal D. Initiation of sacubitril/valsartan shortly after hospitalisation for acutely decompensated heart failure in patients with newly diagnosed (de novo) heart failure: a subgroup analysis of the TRANSITION study. *ESC Heart Fail* 2020; 22: 303–312.

122. Piepoli M, Hussain R, Comin-Colet J, Dos Santos R, Ferber P, Jaarsma T, Edelmann F. OUTSTEP-HF: randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction. *ESC Heart Fail* 2021; 23: 127–135.

123. Butler J, Handelsman Y, Bakris G, Verma S. Use of sodium-glucose co-transporter-2 inhibitors in patients with and without type 2 diabetes: implications for incident and prevalent heart failure. *ESC Heart Fail* 2020; 22: 604–617.

124. Herrington WQ, Savarese G, Haynes R, Marx N, Mellbin L, Lund LH, Dendale P, Seferovic P, Rappold N, Baigent C, Cosentino F. Cardiac, renal, and metabolic effects of sodium-glucose co-transporter 2 inhibitors: a position paper from the European Society of Cardiology ad-hoc task force on sodium-glucose co-transporter 2 inhibitors. *ESC Heart Fail* 2021; 22: 1260–1275.

125. Seferović P, Fragasso G, Petrie M, Mullens W, Ferrari R, Thum T, Bauersachs J, Anker S, Ray R, Čavušoğlu Y, Polovina M, Metra M, Ambrosio G, Prasad K, Seferović J, Jhund P, Dattilo G, Čelutkienė J, Piepoli M, Moura B, Chioncel O, Ben Gal T, Heymans S, De Boer R, Jaarsma T, Hill L, Lopatin Y, Lyon A, Polonkis P, Lainščik M, Jankowska E, M, Cosentino F, Lund L, Filippatos G, Ruschitzka F, Coats A, Rosano G. Sodium-glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology. *ESC Heart Fail* 2020; 22: 1495–1503.

126. Seferović P, Fragasso G, Petrie M, Mullens W, Ferrari R, Thum T, Bauersachs J, Anker S, Ray R, Čavušoğlu Y, Polovina M, Metra M, Ambrosio G, Prasad K, Seferović J, Jhund P, Dattilo G, Čelutkienė J, Piepoli M, Moura B, Chioncel O, Ben Gal T, Heymans S, De Boer R, Jaarsma T, Hill L, Lopatin Y, Lyon A, Polonkis P, Lainščik M, Jankowska E, M, Cosentino F, Lund L, Filippatos G, Ruschitzka F, Coats A, Rosano G. Heart Failure Association of the European Society of Cardiology. *ESC Heart Fail* 2020; 22: 1495–1503.

127. McMurray J, Solomon SD, Inzucchi SE, Kober L, Kvisbordor MN, Martinez FA, Polonkis P, Sabatine MS, Anand
IS, Belohlavek J, Bohm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukat A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Niccolai JC, O’Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Doherty KF, Jhund PS, Bengtsson O, Sjostrand M, Langkilde AM, Committees D-HT, Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381: 1995–2008.

128. McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjostrand M, Solomon SD, Committees D-H, Investigators. The Dapaagliozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. Eur J Heart Fail 2019; 21: 862–873.

134. MeEwan P, Darlington O, McMurray J, Jhund P, Doherty K, Böhm M, Petrie M, Bergersen K, Qin L. Cost-effective-ness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. Eur J Heart Fail 2020; 22: 2147–2156.

135. Kapelos C, Laroche C, Crespo-Leiro M, Anker S, Coats A, Díaz-Molina B, Filipatos G, Lainscak M, Maggioni P, McDonagh T, Mebazaa A, Metra M, Moura B, Mullens W, Piepoli M, Rosano G, Rutschitzka F, Seferovic P, Lund L. Association between loop diuretic dose changes and outcomes in chronic heart failure: observations from the ESC-EORP Heart Failure Long-Term Registry. Eur J Heart Fail 2020; 22: 1424–1437.

136. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Marra Gozzi M, Tani WW, Orse F, Rossignol P. The influence of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019; 21: 137–155.

137. von Haehling S, Ebner N, Eferer Z, Ponikowski P, Anker SD. Iron deficiency in heart failure: an overview. JACC Heart Fail 2019; 7: 36–46.

138. Chopra VK, Anker SD. Anaemia, iron deficiency and heart failure in 2020: facts and numbers. ESC Heart Fail 2020; 7: 2007–2011.

139. Anker S, Comin Colet J, Filipatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher T, Bart B, Banaświa P, Niegowska J, Kirwan B, Mori C, Von Eisenhart RB, Pocock S, Poole-Wilson P, Ponikowski P. Ferric carboxymaltose for iron-deficiency anemia in patients with heart failure and iron deficiency. N Engl J Med 2009; 361: 2436–2448.

140. Ponikowski P, Van Veldhuisen D, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filipatos G, Rutschitzka F, Anker S. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur J Heart Fail 2015; 17: 657–668.

141. Van Veldhuisen D, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, Voors A, Macdougall I, Anker S, Roubert B, Zakin L, Cohen-Solal A. Effect of ferric carboxymaltose or exercise capacity in patients with chronic heart failure and iron deficiency. Circulation 2017; 136: 1374–1383.

142. Barandinara Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, Henkens MTHM, Weerts J, Spanjers MHA, Knackstedt C, van Empel VPM. Iron deficiency impacts prognosis but less ex- ercise capacity in heart failure with preserved ejection fraction. ESC Heart Failure 2021; 8: 1304–1313.

143. Chaudhari P, Kirwan B, Anker S, McDonagh T, Dorobantu M, Drozdz J, Fabien V, Filipatos G, Göhring U, Keren A, Khintibidze I, Krugten H, Martinez F, Metra M, Milicic D, Nicolau J, Ohlsosn M, Parkhomenko A, Pascual-Figal D, Rutschitzka F, Sim D, Skouri H, Van der Meer P, Lewis B, Comin-Colet J, Von Haehling S, Cohen-Solal A, Danchin N, Doehner W, Dargie H, Motro M, Butler J, Friede T, Jensen K, Pocard S, Jankowski E. Ferric carboxymaltose for iron defi-cit at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet (London, England) 2020; 396: 1895–1904.

144. Khan MS, Usman MS, von Haehling S, Doehner W, Stewart Coats AJ. Ferric carboxymaltose for ferric-deficiency anemia in treatment of iron-deficient heart failure patients: a systematic review and meta-analysis. ESC Heart Fail 2020; 7: 3392–3400.

145. Doehner W, von Haehling S. Intravenous iron supplementation is state of the art therapy in patients with heart failure and iron deficiency. Eur J Heart Fail 2019; 21: 1165–1165.

146. Lombardi CM, Cimino G, Pagnesi M, Dell’Aquila A, Tomasoni D, Ravera A, Inciardi R, Carubelli V, Vizzardi E, Nodari S, Emdin M, Almo A. Vericiguat for heart failure with reduced ejection fraction. Circulation 2021; 1437: 2344–2355.

147. Kramer F, Voss S, Roessig L, IgI B, But ler J, Lam C, Maggioni A, Shah S, Pieske B. Evaluation of high-sensitivity C-reactive protein and uric acid in vericiguat-treated patients with heart failure with reduced ejection fraction. Eur J Heart Fail 2020; 22: 1675–1683.

148. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O’Connor CM. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med 2020; 382: 1883–1893.

149. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, Heckman GA, Howlett JG, Koshman SL, Lepage S, Mielniczuk L, Moe GW, O’Meara E, Swiggum E, Toma M, Zieroth S, Anderson K, Bray SA, Clarke B, Cohen-Solal A, D’Aousts M, Davis M, De S, Grant ADM, Grzeszlo A, Heshka J, Keen S, Kous S, Lee D, Masoudi FA, McKeown R, Parent MC, Poon S, Rajda M, Sharma A, Siatetski K, Storm K, Susan B, Van Spall H, Yip AMC. CCS/CHFS heart failure guidelines update: defining a new pharmacologic standard of care for heart failure with reduced
ejection fraction. Can J Cardiol 2021; 37: 531–546.

150. Teerlink J, Diaz R, Felker G, McMurray J, Metra M, Solomon S, Adams K, Anand I, Arias-Mendoza A, Biering-Sørensen T, Böhm M, Bonderman D, Cleland J, Corbalan R, Crespo-Leiro M, Dahlström U, Echeverria Correa L, Fang J, Filippatos G, Fonseca C, Gonalvescova E, Goudev A, Howlett J, Lanfer D, Lund M, Macdonald P, Mareev V, Momomura S, O’Meara E, Parkhomenko A, Ponikowski P, Ramires F, Serpytis P, Sliwa K, Spinar J, Suter T, Tomcsanyi J, Vanderckehove H, Vinereanu D, Voors A, Yilmaz M, Zannad F, Sharpstén I, Legg J, Abbasi S, Varin C, Malik F, Kurtz C. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: GALACTIC-HF baseline characteristics and comparison with contemporary clinical trials. Eur J Heart Fail 2020; 22: 2160–2171.

151. Teerlink J, Diaz R, Felker G, McMurray J, Metra M, Solomon S, Adams K, Anand I, Arias-Mendoza A, Biering-Sørensen T, Böhm M, Bonderman D, Cleland J, Corbalan R, Crespo-Leiro M, Dahlström U, Echeverria L, Fang J, Filippatos G, Fonseca C, Gonalvescova E, Goudev A, Howlett J, Lanfer D, Li J, Lund M, Macdonald P, Mareev V, Momomura S, O’Meara E, Parkhomenko A, Ponikowski P, Ramires F, Serpytis P, Sliwa K, Spinar J, Suter T, Tomcsanyi J, Vanderckehove H, Vinereanu D, Voors A, Yilmaz M, Zannad F, Sharpstén I, Legg J, Abbasi S, Varin C, Malik F, Kurtz C. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med 2021; 384: 105–116.

152. Teerlink JR, Diaz R, Felker GM, McMurray Jv, Metra M, Solomon SD, Legg JC, Buchele G, Varin C, Kurtz CE, Malinak M, Honarpour N. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: rationale and design of GALACTIC-HF. JACC Heart Fail 2020; 8: 329–340.

153. Voors A, Tamby J, Cleland J, Koren M, Forgosh L, Gupta D, Lund L, Camacho A, Karra R, Swart H, Pellicori P, Wagner F, Hershberger R, Prasad N, Andersson R, Anderson R, Anto A, Bell K, Edelberg J, Fang L, Henze M, Kelly C, Kurio G, Li W, Wells K, Yang C, Teichman S, Del Río C, Solomon S. Effects of daniactiv, a novel cardiac myosin activator, in heart failure with reduced ejection fraction: experimental data and clinical results from a phase 2a trial. Eur J Heart Fail 2020; 22: 1649–1658.

154. Buvendiek U, Berliner D, Davila L, Schwab J, Maier L, Philipp S, Rieth A, Westenfeld R, Piorokowski C, Weber K, Hänselmann A, Oldhafer M, Schallhorn S, von der Leyen H, Schröder C, Veltmann C, Störk S, Böhm M, Koch A, Bauersachs J. Rationale and design of the DIGIT-HF trial (DIGI-toxin to Improve ouToMe in patients with advanced chronic Heart Failure): a randomized, double-blind, placebo-controlled study. Eur J Heart Fail 2019; 21: 676–684.

155. Mathiasen A, Qayyum A, Jørgensen E, Helqvist S, Kofoed K, Haack-Sørensen M, Eklund A, Kastrup J. Bone marrow-derived mesenchymal stromal cell treatment in patients with ischaemic heart failure: final 4-year follow-up of the MSC-HF trial. Eur J Heart Fail 2020; 22: 894–892.

156. Bartunek J, Terzic A, Davison B, Behfar A, Sanz-Ruiz R, Wojakowski W, Sherman W, Heyendrickx G, Metra M, Filippatos G, Waldman S, Teerlink J, Henry T, Gersh B, Hajjar R, Tendera M, Senger S, Cotter G, Povsic T, Wijs N. Cardioprotective stem cell therapy in ischaemic heart failure: long-term clinical outcomes. ESC Heart Fail 2020; 7: 3345–3354.

157. Berulava T, Buchholz E, Elerdashvili V, Pena T, Islam M, Birk D, Mohamed B, Renner S, Levenson L, Sacherer M, Bohnsack K, Bohnsack M, Jain G, Capece V, Cleve N, Burkhardt S, Hasenfuss G, Fischer A, Toischker K. Changes in m6A RNA methylation contribute to heart failure progression by modulating translation. Eur J Heart Fail 2020; 22: 54–66.

158. Garg A, Foinquinos A, Jung M, Janssen-Peters H, Biss S, Bauersachs J, SK G, T T. MiRNA-181a is a novel regulator of aldosteronemineralocorticoid receptor-mediated cardiac remodeling. Eur J Heart Fail 2020; 22: 1366–1377.

159. Batkai S, Genschel C, Viercek J, Rump S, Bär C, Borchert T, Traxler D, Riesenhuber M, Spannbauer A, Lukovic M, Honarpour N, Abbasi S, Malik F, Kurtz C. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med 2021; 384: 105–116.

160. Cao T, Jones D, Voors A, Quinn P, Sandhu J, Chan D, Parry H, Mohan M, Mordi I, Sama I, Anker S, Cleland J, Dickstein K, Filippatos G, Hillege H, Metra M, Ponikowski P, Samani N, Van Veldhuisen D, Zannad F, Lang C, Ng L. Plasma proteomic approach in heart failure with mildly reduced systolic function. Eur J Heart Fail 2021; 23: 1168–1178.

161. Kristensen S, Castagno D, Shen L, Jhund P, Docherty K, Rørth R, Abraham W, Desai A, Dickstein K, Rouleau J, Zile M, Swedberg K, Packer M, Solomon S, Köber L, McMurray J. Prevalence and incidence of intra-ventricular conduction delays and outcomes in patients with heart failure and reduced ejection fraction: insights from PARADIGM-HF and AT-MOSPHERE. Eur J Heart Fail 2020; 22: 2370–2379.

162. Hallerua F, Cuzzo G, Parlatio A, Raval NY, Kucharz J, Stewart Coats AJ. A comprehensive individual patient data meta-analysis of the effects of cardiac contractility modulation on functional capacity and heart failure-related quality of life. ESC Heart Fail 2020; 7: 2922–2932.

163. Tschope C, Butler J, Farmakis D, Morley D, Rao I, Filippatos G. Clinical effects of cardiac contractility modulation in heart failure with mildly reduced systolic function. ESC Heart Fail 2020.

164. Anker SD, Borggrefe M, Neuser H, Ohlow MA, Roger S, Goette A, Remppis BA, Kuck KH, Najarian KB, Gutterman DD, Roussos B, Burkhoff D, Hasenfuss G. Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction. Eur J Heart Fail 2019; 21: 1103–1113.

165. Tschop C, Kherad B, Klein O, Lipp A, Blaschke F, Gutermann D, Burkhoff D, Hamdani N, Spellmann F, Van Linthout S. Cardiac contractility modulation:
mechanisms of action in heart failure with reduced ejection fraction and beyond. *Eur J Heart Fail* 2019; 21: 14–22.

170. Packer M. Disproportionate functional mitral regurgitation: a new therapeutic target in patients with heart failure and a reduced ejection fraction. *Eur J Heart Fail* 2020; 22: 23–25.

171. Pagnesi M, Adamo M, Sama IE, Anker SD, Cleland JG, Dickstein K, Filippatos GS, Lang CC, Ng LI, Tonikowski P, Ravaer A, Samani NJ, Zannad F, van Veldhuisen DJ, Voors AA, Metra M. Impact of mitral regurgitation in patients with worsening heart failure: insights from BIOSTAT-CHF. *Eur J Heart Fail* 2021; 23: 1750–1758.

172. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, de Boer RA, Drexel H, Ben Gal T, Hill I, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure in chronic heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; 21: 1169–1186.

173. Reichart D, Kalbacher D, Rüsämen N, Tigges E, Thomas C, Schirmer J, Reichenspurner H, Blankenberg S, Tigges E, Thomas C, Schirmer J, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure in chronic heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; 21: 1169–1186.

174. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieco A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; 379: 2318–2307.

175. Adamo M, Fiorelli F, Melica B, D’Ortona R, Lupi L, Giannini C, Silva G, Fiorina C, Branca L, Chiari E, Chizzola G, Spontoni P, Espada Guerriero C, Curello S, Petronio AS, Metra M. COAPT-like profile predicts long-term outcomes in patients with secondary mitral regurgitation undergoing MitraClip implantation. *JACC Cardiovasc Interv* 2021; 14: 15–25.

176. Ilidiis C, Baldus S, Kalbacher D, Boekstegers P, Schillinger W, Quarrrak T, Zahn R, Butter C, Zuer C, von Bardeleben R, Senges J, Bekercedjian R, Eggebrecht H, Pfister R. Impact of left atrial diameter on outcome in patients undergoing edge-to-edge mitral valve repair: results from the German TRANscatheter Mitral valve Interventions (TRAMI) registry. *Eur J Heart Fail* 2020; 22: 1202–1210.

177. Tamargo M, Obokata M, Reddy YNV, Pilsar UV, Lin G, Egbe AC, Nishimura RA, Biorlu BA. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020; 22: 489–498.

178. Inciardi R, Rossi A, Bergamini C, Chiari E, Guerriero C, Curello S, Petronio AS, Beiras-Fernandez A, Witte KK, Munzel T, Metra M. COAPT-like pro-long-term outcomes in patients with heart failure. *Eur J Heart Fail* 2020; 22: 1311–1321.

179. Tamargo M, Obokata M, Reddy YNV, Pilsar UV, Lin G, Egbe AC, Nishimura RA, Biorlu BA. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020; 22: 489–498.

180. Ruf TF, Kreidel F, Tamm AR, Geyer M, Hahad O, Zirbs JC, Schwidtal BL, Beiras-Fernandez A, Witte KK, Munzel T, von Bardeleben RS. Transcatheter indirect mitral annuloplasty induces annular and left atrial remodelling in secondary mitral regurgitation. *ESC Heart Fail* 2020; 7: 1400–1408.

181. Giallauria F, Di Lorenzo A, Parlato A, Testa C, Bobbio E, Vigorito C, Coats AJS. Individual patient data meta-analysis of the effects of the CARILLON(R) mitral contour system. *ESC Heart Fail* 2020; 7: 3383–3391.

182. Messika-Zeitoun D, Verta P, Gregson J, Pocock S, Boero I, Feldman T, Abraham W, Lindenfeld J, Bax J, Leon M, Enriquez-Sarano M. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail* 2020; 22: 1803–1813.

183. Betzler C, Unterhuber M, Rommel KP, Unger E, Hartung P, Roeder M, Noack T, Zachäus M, Halm U, Borger M, Desch S, Thiele H, Lurz P. Nutritional status in tricuspid regurgitation: implications of transcatheter repair. *Eur J Heart Fail* 2020; 22: 1826–1836.

184. Zhao C, Di Pasqua M, Fiorina C, Curello S, Metra M, Adamo M. Transcatheter therapies for tricuspid valve regurgitation. *J Cardiovasc Med (Hagerstown)* 2020; 21: 964–974.
A year in heart failure

chanciously Assisted Circulatory Support (IMACS) Registry analysis. *Eur J Heart Fail* 2020; 22: 1878–1887.

194. Hill L, Prager Geller T, Baruah R, Beat-
tie J, Boyne J, de Stoutz N, Di Stolfi G, Lambrinou E, Skib budel A, Uchmanowicz J, Rutten F, Celutkiene J, Piepoli M, Jankowska E, Chioncel O, Ben Mal T, Seferovic P, Ruschitzka F, Coats A, Strömberg A, Jaarsma T. In-
tegration of a palliative approach into heart failure care: a European Society of Cardiology Heart Failure Association position paper. *Eur J Heart Fail* 2020; 22: 2327–2339.

195. Sahlblöy N, Lee C, Shirin A, Joseph P. The impact of palliative care on clinical and patient-centred outcomes in patients with advanced heart failure: a systematic review of randomized con-
trolled trials. *Eur J Heart Fail* 2020; 22: 2340–2346.

196. Galinier M, Roubille F, Berdague P, Brierre G, Cante P, Dary P, Ferradou J-M, Fondard O, Labarre JP, Mansourati J, Picard F, Ricci J-E, Salvat M, Tartet L, Vidaudets J-B, Bongard V, Delval C, Lanceram G, Pasche H, Ramirez-Gil JF, Pathak A, Investigators oboO. Telemonitoring versus standard care in heart failure: a randomised multicentre trial. *Eur J Heart Fail* 2020; 22: 985–994.

197. Koehler J, Stengel A, Hofmann T, Wegscheider K, Koehler K, Sehner S, Rose M, Deckwart O, Anker SD, Koehler F, Laufs U. Telemonitoring in patients with chronic heart failure and moderate depressed symptoms: results of the Telemeical Interventional Monitoring in Heart Failure (TIM-HF) study. *Eur J Heart Fail* 2021; 23: 186–194.

198. Mullens W, Sharif F, Dupont M, Rothman AMK, Wijns W. Digital health care solution for proactive heart failure management with the Cordella Heart Failure System: results of the SRONA first-in-human study. *Eur J Heart Fail* 2020; 22: 1912–1919.

199. Angermann CE, Assmus B, Anker SD, Assellergs FW, Brachmann J, Brett M-E, Brugs JI, Ertl G, Ginn G, Hilker L, Koehler F, Rosenkranz S, Zhou Q, Adamson PB, Böhm M, Investigators ftM-H. Pulmonary artery pressure-guided therapy in ambulatory patients with symptomatic heart fail-
ure: the CardioMEMS European Moni-
toring Study for Heart Failure (MEMS-
HF). *Eur J Heart Fail* 2020; 22: 1891–1901.

200. Zakeri R, Morgan JM, Phillips P, Kitt S, Ng GA, McComb JM, Williams S, Wright DJ, Gill JS, Seed A, Witte KK, Cowie MR, Investigators R-H. Impact of remote monitoring on clinical outcomes for patients with heart failure and atrial fibrillation: results from the REM-HF trial. *Eur J Heart Fail* 2020; 22: 543–550.

201. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelaguru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS, Group CTS. Wire-
less pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011; 377: 659–666.

202. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmannshof D, Krim SR, Maisel A, Mehra MR, Paul S, Sears SF, Sauer AJ, Smart F, Zughib M, Castaneda P, Kelly J, Johnson N, Sood F, Ginn G, Henderson J, Adamson PB, Costanzo MR. Haemodynamic-guided management of heart failure (GUIDE-
HF): a randomised controlled trial. *Lancet* 2021; 398: 991–1001.

203. Lieske B, Tschöpe C, de Boer R, Fraser A, Anker S, Donal E, Edelmann F, Fu M, Guazzi M, Lam C, Lancellotti P, Melenovsky V, Morris D, Nagel E, Pieske-Kraigher E, Ponikowski P, Solo-
mon S, Vasan R, Rutten F, Voors A, Ruschitzka F, Paulus W, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algo-
rithm: a recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020; 22: 391–412.

204. Packer M. Do most patients with obe-
sity or type 2 diabetes, and atrial fibril-
lation, also have undiagnosed heart failure? A critical conceptual frame-
work for understanding mechanisms and improving diagnosis and treat-
ment. *Eur J Heart Fail* 2020; 22: 214–227.

205. Pugliese N, Mazzola M, Fabiani I, Gar
gani L, De Biase N, Pedrinelli R, Melenovsky V, Morris D, Nagel E, Natali A, Dini F. Haemodynamic and metabolic phenotyping of hypertensive patients with and without heart failure by combining carciopulmonary and echocardiographic stress test. *Eur J Heart Fail* 2020; 22: 458–468.

206. Tromp J, Teng TH, Tay WT, Hung CL, Narasimhan C, Shimizu W, Park SW, Liew HB, Ngarmukos T, Reyes EB, Siswanto BB, Yu CM, Zhang S, Yap J, MacDonald M, Ling LH, Leineweber K, Richards AM, Zile MR, Anand IS, Lam CSP, Investigators A-H. Heart fail-
ure with preserved ejection fraction in Asia. *Eur J Heart Fail* 2019; 21: 23–36.

207. Paulus WJ, Tschöpe C. A novel para-
digm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodel-
ing through coronary microvascular en-
dothelial inflammation. *J Am Coll Cardiol* 2013; 62: 263–271.

208. Packer M, Lam C, Lund L, Maurer M, Borlaug B. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influ-
ence of sex on the evolution and poten-
tial treatment of the disease. *Eur J Heart Fail* 2020; 22: 1551–1567.

209. Packer M. Derangements in adrenergic-adipokine signalling estab-
lish a neurohormonal basis for obesity-related heart failure with a pre-
served ejection fraction. *Eur J Heart Fail* 2018; 20: 873–878.

210. Wu C, Lee J, Hsu J, Su M, Wu Y, Lin T, Lan C, Hwang J, Lin L. Myocardial adi-
pose deposition and the development of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020; 22: 445–454.

211. Yang J, Obokata M, Reddy Y, Redfield M, Lerman A, Borlaug B. Endothe-
lium-dependent and independent coro-
nary microvascular dysfunction in patients with heart failure with pre-
served ejection fraction. *Eur J Heart Fail* 2020; 22: 432–441.

212. Quarta G, Gori M, Iorio A, Deiia E, Moon J, Iacovoni A, Burocchi S, Schelbert E, Brambilla P, Sironi S, Caravita S, Parati G, Gavazzi A, Maisel A, Butler J, Lam C, Senni M. Cardiac magnetic resonance in heart failure with preserved ejection fraction: myocyte, interstitium, microvascular, and metabolic abnormalities. *Eur J Heart Fail* 2020; 22: 1065–1075.

213. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca H, Henkens M, Heymans S, Beussink-Nelson L, Shah SJ, van Empel VP. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020; 22: 413–421.

214. Ouwerkerk W, Tromp J, Jin X, Jaufeerally F, Yeo P, Leong K, Ong H, Ling L, Loh S, Sim D, Lee S, Soon D, Chin C, Richards A, Lam C. Heart fail-
ure with preserved ejection fraction di-
agnostic scores in an Asian population. *Eur J Heart Fail* 2020; 22: 1737–1739.

215. Reddy YNV, Rikhi A, Obokata M, Shah SJ, Lewis GD, AbouEzzedine OF, Dunlay S, McVulty S, Chakraborty H, Stevenson LW, Redfield BA. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail* 2020; 22: 1009–1018.

216. Yamanaka S, Sakata Y, Nochioka K, Miura M, Kasahara S, Sato M, Aoyanagi H, Fujihashi T, Hayashi H, Shirotu T, Sugimura K, Takahashi J, Miyata S, Shimokawa H. Prognostic impacts of dynamic cardiac structural changes in heart failure patients with preserved left ventricular ejection fraction. *Eur J Heart Fail* 2020; 22: 2258–2268.

217. Khan M, Memon M, Murad M, Vaduganathan M, Greene S, Hall M, Triposkiadis F, Lam C, Shah A, Butler J, Shah S. Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Heart Fail* 2020; 22: 472–485.

218. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, Brunner-La Rocca HP, Choi DJ, Chopra
V. Chuquiere-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juantey JR, Merkely B, Nicholls SJ, Perrone SV, Pina IL, Ponikowski P, Senni M, Sim D, Spinhar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M, Investigators EM-PT. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; 385: 1451–1461.

219. Anker S, Butler J, Filippatos G, Shahzeb Khan M, Ferreira J, Bocchi E, Bohm M, Brunner-La Rocca H, Golino A, Kimmoun A, Takagi K, Gall E, Ishihara S, Hammon P, El Béze N, Bourgois A, Chassard G, Pegorier-Şfes H, Gayat E, Solal AC, Hollinger A, Merkling T, Mebazaa A, Team M. Temporal trends in mortality and readmission after acute heart failure: a systematic review and meta-regression in the past four decades. *Eur J Heart Fail* 2021; 23: 420–431.

220. Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Boursac FH, Harjola V-P, Antohi E-L, Arrigo M, Gal TB, Celutkienė J, Collins SP, DeBacker D, Iliescu VA, Jankowska E, Jaarsma T, Keramida K, Lainscak M, Lund LH, Lyon AR, Masip J, Metra M, Miro O, Mortara A, Mueller C, Mullens W, Nikolau M, Piepoli M, Price S, Rosano G, Vellasild-Baron A, Weinstein JM, Anker SD, Filippatos G, Ruszticha F, Coats AJ, Seferovic P. Epidemiology, pathophysiology and contemporary management of cardiacogenic shock—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020; 22: 1315–1341.

221. Harjola V-P, Parissis J, Boursac FH, Brunner-La Rocca H, Nero J, Maccio E, Chioncel O, Coats AJ, Collins SP, de Boer RA, Filippatos G, Gayat E, Hill L, Laine M, Lassus J, Lommi J, Masip J, Mebazaa A, Metra M, Miró O, Mortara A, Mueller C, Mullens W, Peacock WF, Pentikainen M, Piepoli MF, Polyzogopoulos E, Rudiger A, Ruszticha F, Sefirovic P, Sionis A, Teerlink JR, Thum T, Varpula M, Weinstein JM, Yilmaz MB. Acute coronary syndromes and acute heart failure: a diagnostic dilemma and high-risk combination. A statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020; 22: 1298–1314.

222. Aissaoui N, Puymirat E, Delmas C, Orunto E, Durand E, Bataille V, Drouet E, Bonnet Y, Courad E, Lesmeles G. Trends in cardiogenic shock complicating acute myocardial infarction. *Eur J Heart Fail* 2020; 22: 664–672.

223. Helgestad OK, Josiassen J, Hassager C, Jensen LO, Holmvang L, Sorensen A, Frydland M, Lassen AT, Udesen NL, Schmidt H. Temporal trends in incidence and patient characteristics in cardiogenic shock following acute myocardial infarction from 2010 to 2017: a Danish cohort study. *Eur J Heart Fail* 2021; 23: 1370–1378.

224. Ter Maaten JM, Kremer D, Demissei A, Struck J, Bergmann A, Anker SD, Ng LL, Dickstein K, Metra M, Samani NJ. Bio-naïve patients with heart failure: pathophysiology and therapeutic application. *Eur J Heart Fail* 2019; 21: 163–171.

225. Voors AA, Kremer D, Geven C, Ter Maaten JM, Struck J, Bergmann A, Pickkers P, Metra M, Mebazaa A. ADRENAL study: outcomes in heart failure with reduced ejection fraction. *Eur J Heart Fail* 2020; 22: 713–722.

226. Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Boursac FH, Harjola V-P, Antohi E-L, Arrigo M, Gal TB, Celutkienė J, Collins SP, DeBacker D, Iliescu VA, Jankowska E, Jaarsma T, Keramida K, Lainscak M, Lund LH, Lyon AR, Masip J, Metra M, Miro O, Mortara A, Mueller C, Mullens W, Nikolau M, Piepoli M, Price S, Rosano G, Vellasild-Baron A, Weinstein JM, Anker SD, Filippatos G, Ruszticha F, Coats AJ, Seferovic P. Epidemiology, pathophysiology and contemporary management of cardiacogenic shock—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020; 22: 1315–1341.

227. Harjola V-P, Parissis J, Boursac FH, Brunner-La Rocca H, Nero J, Maccio E, Chioncel O, Coats AJ, Collins SP, de Boer RA, Filippatos G, Gayat E, Hill L, Laine M, Lassus J, Lommi J, Masip J, Mebazaa A, Metra M, Miró O, Mortara A, Mueller C, Mullens W, Peacock WF, Pentikainen M, Piepoli MF, Polyzogopoulos E, Rudiger A, Ruszticha F, Sefirovic P, Sionis A, Teerlink JR, Thum T, Varpula M, Weinstein JM, Yilmaz MB. Acute coronary syndromes and acute heart failure: a diagnostic dilemma and high-risk combination. A statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020; 22: 1298–1314.

228. Aissaoui N, Puymirat E, Delmas C, Orunto E, Durand E, Bataille V, Drouet E, Bonnet Y, Courad E, Lesmeles G. Trends in cardiogenic shock complicating acute myocardial infarction. *Eur J Heart Fail* 2020; 22: 664–672.

229. Helgestad OK, Josiassen J, Hassager C, Jensen LO, Holmvang L, Sorensen A, Frydland M, Lassen AT, Udesen NL, Schmidt H. Temporal trends in incidence and patient characteristics in cardiogenic shock following acute myocardial infarction from 2010 to 2017: a Danish cohort study. *Eur J Heart Fail* 2021; 23: 1370–1378.

230. Ter Maaten JM, Kremer D, Demissei A, Struck J, Bergmann A, Anker SD, Ng LL, Dickstein K, Metra M, Samani NJ. Bio-naïve patients with heart failure: pathophysiology and therapeutic application. *Eur J Heart Fail* 2019; 21: 163–171.

231. Voors AA, Kremer D, Geven C, Ter Maaten JM, Struck J, Bergmann A, Pickkers P, Metra M, Mebazaa A. ADRENAL study: outcomes in heart failure with reduced ejection fraction. *Eur J Heart Fail* 2020; 22: 713–722.

232. Pandhi P, ter Maaten JM, Emmens JE, Struck J, Bergmann A, Cleland JG, Givertz MM, Metra M, O’Connor CM, Teerlink JR, Ponikowski P, Cotter G, Davison B, van Veldhuisen DJ, Voors AA. Clinical value of pre-discharge bio-adrenomedullin as a marker of residual congestion and high risk of heart failure hospital readmission. *Eur J Heart Fail* 2020; 22: 683–691.

233. Kuan WS, Ibrahim I, Chan SP, Li Z, Liew OW, Frampton C, Troughton R, Pemberton CJ, Chong JPC, Tan LL, Lin W, Ooi SBS, Richards AM. Mid-regional pro-adrenomedullin outperforms N-terminal pro-B-type natriuretic peptide for the diagnosis of acute heart failure in the presence of atrial fibrillation. *Eur J Heart Fail* 2020; 22: 692–700.

234. Chioncel O, Mebazaa A, Maggioni AP, Harjola VP, Rosano G, Laroche C, Piepoli MF, Crespo-Leiro MG, Lainscak M, Ponikowski P. Clinical value of pre-discharge natriuretic peptide for the diagnosis of acute heart failure in the presence of atrial fibrillation. *Eur J Heart Fail* 2020; 22: 692–700.

235. Biegus J, Zymiliński R, Sokelski M, Todd J, Cotter G, Metra M, Jankowska EA, Banasiak W, Ponikowski P. Serial assessment of spot urine sodium predicts effectiveness of decongestion and outcome in patients with acute heart failure. *Eur J Heart Fail* 2019; 21: 624–633.

236. Damman K, Ter Maaten JM, Coster JE, Krikkent JA, van Deursen VM, Krijnen HK, Hofman M, Nieuwland W, van Veldhuisen DJ, Voors AA, van der Meer P. Clinical importance of urinary sodium excretion in acute heart failure. *Eur J Heart Fail* 2020; 22: 1438–1447.

237. Biegus J, Zymiliński R, Sokelski M, Todd J, Cotter G, Metra M, Jankowska EA, Banasiak W, Ponikowski P. Renal profiling based on estimated glomerular filtration rate and spot urine sodium identifies high-risk acute heart failure patients. *Eur J Heart Fail* 2021; 23: 729–739.

238. Damman K, Busekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, van Eck JWM, Heerspink HJL, Voors AA. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail* 2020; 22: 713–722.

239. Bromage D, Carubá A, Rind I, Gregorio C, Piper S, Shah A, McDonagh T. The impact of COVID-19 on heart failure hospitalization and management: report from a Heart Failure Unit in London during the peak of...
the pandemic. 

240. König S, Hohenstein S, Meier-Hellmann A, Kuhlen R, Hindricks G, Bollmann A. In-hospital care in acute heart failure during the COVID-19 pandemic: insights from the German-wide Helios hospital network. Eur J Heart Fail 2020; 22: 2190–2201.

241. Tomasoni D, Adamo M, Italia L, Branca L, Chizzola G, Fiorina C, Lapi U, Inciardi R, Cani D, Lombardi C, Curello S, Metra M. Impact of COVID-2019 outbreak on prevalence, clinical presentation and outcomes of ST-elevation myocardial infarction. J Cardiovasc Med (Hagerstown) 2020; 21: 874–881.

242. Frattini S, Maccagni G, Italia L, Metra M, Danzi G. Coronavirus disease 2019 and cardiovascular implications. J Cardiovasc Med (Hagerstown) 2020; 21: 725–732.

243. Cannatá A, Bromage D, Rind I, Gregorio C, Bannister C, Albarjas M, Piper S, AM S, TA M. Temporal trends in decompensated heart failure and outcomes during COVID-19: a multicentre report from heart failure referral centres in London. Eur J Heart Fail 2020; 22: 2219–2224.

244. Task Force for the management of C-otESoC. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1—epidemiology, pathophysiology, and diagnosis. Eur Heart J 2021.

245. Tomasoni D, Italia L, Adamo M, Inciardi R, Lombardi C, Solomon S, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. Eur J Heart Fail 2020; 22: 957–966.

246. Savarese G, Benson L, Sundström J, Lund L. Association between renin-angiotensin-aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis. Eur J Heart Fail 2021; 23: 476–485.

247. Tomasoni D, Inciardi R, Lombardi C, Tedino C, Agostoni P, Ameri P, Barbieri L, Bellasi A, Camporotondo R, Canale C, Carubelli V, Carugo S, Catagnano F, Dalla Vecchia L, Danzi G, Di Pasquale M, Gaudenzi M, Giovannazzo S, Gneecchi M, Iorio A, La Rovere M, Leonardi S, Maccagni G, Mapelli M, Margonato D, Merlo M, Monzo L, Mortara A, Nuzzi V, Piepoli M, Porto I, Pozzi A, Sarullo F, Sinagra G, Volterrani M, Zaccone G, Guazzi M, Senni M, Metra M. Impact of heart failure on the clinical course and outcomes of patients hospitalized for COVID-19. Results of the CardioCOVID-ITALY multicentre study. Eur J Heart Fail 2020; 22: 2238–2247.

248. Inciardi R, Adamo M, Lapi U, Cani D, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabricatore D, Curnis A, Faggiano P, Gorga E, Lombardi C, Milesi G, Vizzardi E, Volpinì M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. Eur Heart J 2020; 41: 1821–1829.

249. Task Force for the management of C-otESoC. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2—care pathways, treatment, and follow-up. Eur J Heart Fail 2021.

250. Lombardi C, Carubelli V, Iorio A, Inciardi R, Bellasi A, Canale C, Camporotondo R, Catagnano F, Dalla Vecchia L, Giovannazzo S, Maccagni G, Mapelli M, Margonato D, Monzo L, Nuzzi V, Oriecia C, Peveri G, Pozzi A, Provenzale G, Sarullo F, Tomasoni D, Ameri P, Gneecchi M, Leonardi S, Merlo M, Agostoni P, Carugo S, Danzi G, Guazzi M, La Rovere M, Mortara A, Piepoli M, Porto I, Sinagra G, Volterrani M, Specchia C, Metra M, Senni M. Association of troponin levels with mortality in Italian patients hospitalized with coronavirus disease 2019: results of a multicenter study. JAMA Cardiology 2020; 5: 1274–1280.

251. De Roquetaillade C, Chousterman B, Tomasoni D, Zeitouni M, Houdart E, Guedon A, Reiner P, Borderie B, Gayat E, Montalescot G, Metra M, Mebazaa A. Unusual arterial thrombotic events in Covid-19 patients. Int J Cardiol 2021; 323: 281–284.

252. Ameri P, Inciardi R, Di Pasquale M, Agostoni P, Bellasi A, Camporotondo R, Canale C, Carubelli V, Carugo S, Catagnano F, Danzi G, Dalla Vecchia L, Giovannazzo S, Gneecchi M, Guazzi M, Iorio A, La Rovere M, Leonardi S, Maccagni G, Mapelli M, Margonato D, Merlo M, Monzo L, Mortara A, Nuzzi V, Piepoli M, Porto I, Pozzi A, Provenzale G, Sarullo F, Sinagra G, Tedino C, Tomasoni D, Volterrani M, Zaccone G, Lombardi C, Senni M, Metra M. Pulmonary embolism in patients with COVID-19: characteristics and outcomes in the Cardio-COVID Italy multicenter study. Clin Res Cardiol 2021; 110: 1020–1028.

253. Nuzzi V, Merlo M, Specchia C, Lombardi C, Carubelli V, Iorio A, Inciardi R, Bellasi A, Canale C, Camporotondo R, Catagnano F, Dalla Vecchia L, Giovannazzo S, Maccagni G, Mapelli M, Margonato D, Monzo L, Oriecia C, Peveri G, Pozzi A, Provenzale G, Sarullo F, Tomasoni D, Ameri P, Gneecchi M, Leonardi S, Agostoni P, Carugo S, Danzi G, Guazzi M, La Rovere M, Mortara A, Piepoli M, Porto I, Volterrani M, Senni M, Metra M, Sinagra G. The prognostic value of serial troponin measurements in patients admitted for COVID-19. ESC Heart Fail 2021; 8: 3504–3511.

254. Hadžibegović S, Lena A, Churchill T, Ho J, Potthoff S, Denecke C, Rössnick L, Heim K, Kleinschmidt M, Sander L, Witzenrath M, Suttrop N, Krannich A, Porthun J, Friede T, Butler J, Wilkenshoff U, Pieske B, Landmesser U, Anker S, Lewis G, Tischöpe C, Anker M. Heart failure with preserved ejection fraction according to the HFA-PEFF score in COVID-19 patients: clinical correlates and echocardiographic findings. Eur J Heart Fail 2021.

255. Lassen M, Skarup K, Lind J, Alhakak A, Sengeløv M, Nielsen A, Espersen C, Ravnikilde K, Hauser R, Schöps L, Holt E, Johansen N, Modin D, Djernæs K, Graff C, Bundgaard H, Hassager C, Jabbri R, Carlsten J, Lebech A, Kirk O, Bodtgør U, Lindholm M, Joseph G, Wiese L, Schüdt F, Kristiansen O, Walsted E, Nielsen O, Madsen B, Tønder N, Benfeldt T, Jeschke K, Ulrik C, Knop F, Lamberts M, Sivapalan P, Gislason G, Marott J, Magelvang R, Jensen G, Schnörh P, Søgaard P, Solomons V, Iversen K, Jensen S, Schau M, Biering-Sørensen T. Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. ESC Heart Fail 2020; 7: 4189–4197.

256. Anker MS, Landmesser U, von Haeling S, Butler J, Coats AJ, Anker SD. Weight loss, malnutrition, and cachexia in COVID-19: facts and numbers. J Cachexia Sarcompenia Muscle 2021; 12: 9–13.

257. Zaccone G, Tomasoni D, Italia L, Lombardi C, Metra M. Myocardial involvement in COVID-19: an interaction between comorbidities and heart failure with preserved ejection fraction. A further indication of the role of inflammation.Curr Heart Fail Rep 2021; 18: 99–106.

258. Italia L, Tomasoni D, Bisegna S, Pancaldi E, Stretti L, Adamo M, Metra M. COVID-19 and heart failure: from epidemiology during the pandemic to myocardial injury, myocarditis, and heart failure sequelae. Front Cardiovasc Med 2021; 8: 713560.