

# 2024 update in heart failure

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## Abstract

In the last years, major progress has occurred in heart failure (HF) management. The 2023 ESC focused update of the 2021 HF guidelines introduced new key recommendations based on the results of the last years of science. First, two drugs, sodium–glucose co-transporter-2 (SGLT2) inhibitors and finerenone, a novel nonsteroidal, selective mineralocorticoid receptor antagonist (MRA), are recommended for the prevention of HF in patients with diabetic chronic kidney disease (CKD). Second, SGLT2 inhibitors are now recommended for the treatment of HF across the entire left ventricular ejection fraction spectrum. The benefits of quadruple therapy in patients with HF with reduced ejection fraction (HFrEF) are well established. Its rapid and early up-titration along with a close follow-up with frequent clinical and laboratory re-assessment after an episode of acute HF (the so-called ‘high-intensity care’ strategy) was associated with better outcomes in the STRONG-HF trial. Patients experiencing an episode of worsening HF might require a fifth drug, vericiguat. In the STEP-HFpEF-DM and STEP-HFpEF trials, semaglutide 2.4 mg once weekly administered for 1 year decreased body weight and significantly improved quality of life and the 6 min walk distance in obese patients with HF with preserved ejection fraction (HFpEF) with or without a history of diabetes. Further data on safety and efficacy, including also hard endpoints, are needed to support the addition of acetazolamide or hydrochlorothiazide to a standard diuretic regimen in patients hospitalized due to acute HF. In the meantime, PUSH-AHF supported the use of natriuresis-guided diuretic therapy. Further options and most recent evidence for the treatment of HF, including specific drugs for cardiomyopathies (i.e., mavacamten in hypertrophic cardiomyopathy and tafamidis in transthyretin cardiac amyloidosis), device therapies, cardiac contractility modulation and percutaneous treatment of valvulopathies, with the recent finding from the TRILUMINATE Pivotal trial, are also reviewed in this article.

**Keywords** comorbidities; finerenone; heart failure; prevention; prognosis; SGLT2 inhibitors; treatment

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## Introduction

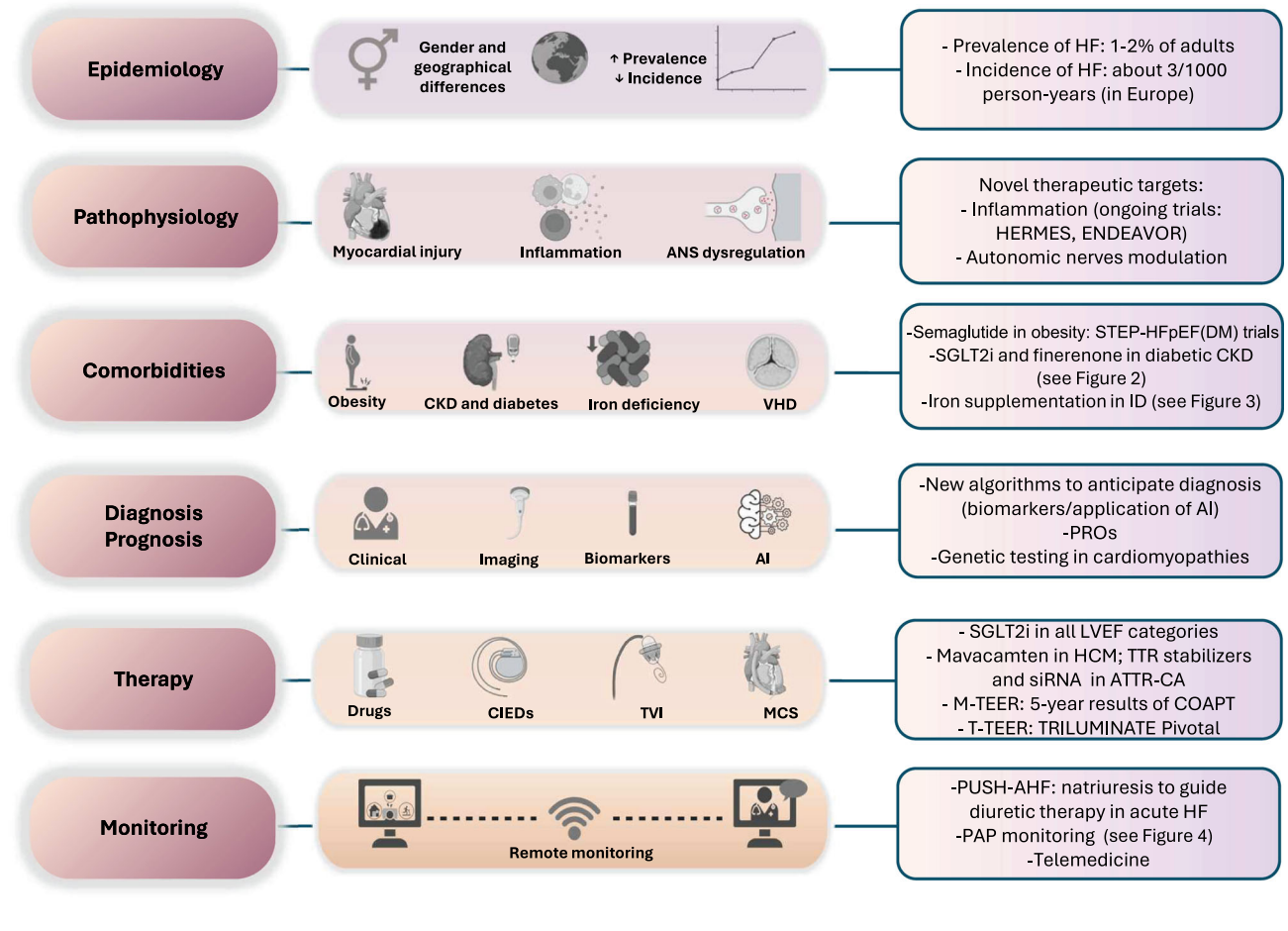
Heart failure (HF) is defined as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality, corroborated by elevated natriuretic peptides and/or objective evidence of pulmonary or systemic congestion.<sup>1</sup> It remains a leading global cause of mortality, morbidity and poor quality of life (QoL) with high use of resources and healthcare costs.<sup>2</sup> Therefore, it is an area of active research.<sup>3</sup> This article aims to highlight the most recent findings of the last years (Figure 1).

## Epidemiology

Although the incidence of HF slightly declined over time, its prevalence is increasing due to improved HF treatments and longer life expectancy in the population.<sup>2</sup> In European countries, the median incidence of HF was 3.20 cases per 1000 person-years, and the median HF prevalence was 17.20 cases per 1000 people.<sup>4,5</sup>

Significant geographical and socio-demographic variations and different temporal trends in HF burden have been described. Among patients with an acute myocardial infarction

**Figure 1** Main topics summarized in this review and key new evidence. AI, artificial intelligence; ANS, autonomic nervous system; ATTR-CA, transthyretin cardiac amyloidosis; CIEDs, cardiac implantable electronic devices; CKD, chronic kidney disease; HCM, hypertrophic cardiomyopathy; HF, heart failure; ID, iron deficiency; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; M-TEER, mitral transcatheter edge-to-edge repair; PAP, pulmonary artery pressure; PROs, patient-reported outcomes; SGLT2i, sodium–glucose co-transporter-2 inhibitor; siRNA, small interference RNA; T-TEER, tricuspid transcatheter edge-to-edge repair; TTR, transthyretin; TVI, transcatheter valve intervention; VHD, valvular heart disease.



(AMI) enrolled in the PARADISE-MI trial, rates of incident HF varied almost six-fold among regions, with the lowest rate in South Asia (1.0/100 person-years) and the highest in Northern Europe (5.9/100 person-years).<sup>6</sup>

Although ischaemic heart disease remains one of the most common causes of HF, the improvements in the management of AMI and secondary prevention have reduced the risk of HF hospitalization (HFH) following the first AMI.<sup>7</sup>

## Gender differences

Gender differences in prevalence, pathophysiological pathways, HF phenotypes, rates of morbidity and mortality, as well as in treatment prescription, have been described.<sup>8–10</sup> Comparing the gene expression of 363 biomarkers, Ravera

*et al.* observed distinct molecular patterns, underlying gender differences in patients with HF: biomarkers associated with lipid metabolic pathways were mainly observed in women, while biomarkers associated with neuro-inflammatory response were more active in men.<sup>11</sup>

In a retrospective study including 155 670 US patients hospitalized for HF from the GWTG-HF Registry, females, when compared with males, had lower adjusted mortality but experienced significantly greater loss of survival time compared with the median US population matched for age and sex and had a higher risk of rehospitalization at 5 years.<sup>12</sup> In a pre-specified secondary analysis of the GALACTIC trial, early intensive and sustained vasodilatation with rapid up-titration of renin–angiotensin–aldosterone system (RAAS) inhibitors during acute HFH was less successful in women versus men.<sup>10</sup> On the other hand, in the STRONG-HF trial, a

similar average percentage of the optimal dose of guideline-directed medical therapies (GDMTs) was reached in both sexes. Also, there was no significant treatment-by-sex interaction in the occurrence of the primary endpoint as well as in QoL improvement or in adverse events.<sup>9</sup>

Gender differences were also described in a large population of patients with transthyretin (TTR) cardiac amyloidosis (ATTR-CA) referred to the UK National Amyloidosis Centre (NAC).<sup>13</sup> Non-indexed wall thickness measurements may have contributed to both under-representation and delays in diagnosis for affected females. Aimo *et al.* confirmed in a different cohort of ATTR-CA patients that interventricular septum thickness and posterior wall thickness were smaller in women than men; therefore, the use of lower cut-off values in women or indexed echocardiographic parameters has been proposed for a more accurate assessment at diagnosis and for disease prognostic stratification.<sup>14</sup>

Women are still under-represented in HF clinical trials.<sup>15</sup>

## Pathophysiology

Cardiac injury can lead to HF.<sup>16</sup> Packer reviewed the intrinsic molecular pathways of cardiac injury, during which the heart recapitulates the foetal signalling programme, which (although advantageous in the short term) is highly deleterious if sustained for long; these changes lead to a marked increase in protein O-GlcNAcylation that is associated with impaired calcium kinetics, contractile derangements, mitochondrial dysfunction, fibrosis and maladaptive hypertrophy.<sup>17</sup> Clonal haematopoiesis of indeterminate potential was associated with biomarkers and risk factors of HF as well as with incident HF in patients aged under 65 years.<sup>18</sup>

## Inflammation

Inflammation plays a central role in HF pathophysiology.<sup>19–23</sup> Twenty-four inflammatory biomarkers were collected in 1231 patients from the CASABLANCA study. These patients were stratified into three levels of inflammation (low, medium and high). The high inflammation group was at increased adjusted risk of HF events across all the stages of HF.<sup>24</sup>

Among unselected patients presenting to the emergency department with acute dyspnoea, those diagnosed with acute HF had higher interleukin-6 (IL-6) concentrations. IL-6 was elevated (>4.45 ng/L) in 83.7% of acute HF patients and was a strong and independent predictor of 1 year mortality.<sup>25</sup> A double-blind, randomized placebo-controlled trial with a human monoclonal antibody directed against the IL-6 ligand (zilvekimab) in patients with HF and left ventricular (LV) ejection fraction (LVEF)  $\geq 40\%$  is ongoing (HERMES trial, NCT05636176).

Seven neutrophil activity-related plasma proteins have been associated with the risk of incident HF and with adverse cardiac remodelling.<sup>26</sup> ENDEAVOR is a combined, seamless phase 2b–3 study investigating the efficacy and safety of mitiperstat, a novel selective myeloperoxidase inhibitor, in patients with HF with mildly reduced ejection fraction (HFmrEF) or with preserved ejection fraction (HFpEF).<sup>27</sup>

Of note, levels of circulating immune checkpoint ligands are increased in HF patients and correlate with disease severity or prognosis. These data underscore the involvement of adaptive immune response in the pathophysiology of HF.<sup>28</sup>

## Autonomic nervous system

A further driver of HF progression is autonomic nervous system dysregulation. Volume recruitment from the splanchnic compartment is a physiological response to stressors such as physical activity and blood loss. Recently, the regulation of sympathetic stimulation through splanchnic nerve modulation has become a target of interventions.<sup>29,30</sup> Analogically, the modulation of pulmonary artery (PA) autonomic nerves may help rebalance the pulmonary pressure in selected patients.<sup>31</sup>

Badrov *et al.* assessed determinants of augmented muscle sympathetic nerve activity (MSNA) in 177 patients with HF versus 658 healthy volunteers. MSNA was higher among HF patients, especially in men with ischaemic heart disease and with sleep apnoea; burst frequency was directly associated with norepinephrine and peripheral vascular resistance and inversely associated with stroke volume, cardiac output and peak oxygen consumption.<sup>32</sup> However, this sympathetic overdrive was detected only in a subgroup of patients with HF (ranging from 32% to 51%); therefore, a selective setup of sympatho-modulatory interventions should be implemented in HF.

## Comorbidities

Patients with HF often suffer from several comorbidities that may affect their health status, management and outcome and are themselves therapeutic targets, particularly in HFpEF.<sup>33–36</sup> Of the 91 463 patients enrolled in the Swedish HF Registry (median age 76 years), 98% had at least one among the 17 explored comorbidities [94% at least one cardiovascular (CV) and 85% at least one non-CV comorbidity]. All comorbidities, except for coronary artery disease (CAD), were more frequent in HFpEF.<sup>36</sup> Among patients with HF with reduced ejection fraction (HFrEF) from the PARADIGM-HF and ATMOSPHERE trials, patients with coexistent peripheral artery disease (PAD) and stroke were at greatest individual risk for

all-cause death, whereas coexistent chronic kidney disease (CKD) and hypertension displayed the highest population attributable fractions and, thus, mattered most from a population perspective.<sup>37</sup>

## Hypertension

Hypertension is a major cause and a common comorbidity of HF. Pugliese *et al.* investigated the haemodynamic and prognostic correlates of hypertensive response to exercise. A steeper systolic blood pressure/workload slope was associated with impaired functional capacity across the HF spectrum and could be a more sensitive predictor of adverse events than absolute systolic blood pressure values, mainly in patients in stages A and B and HFpEF.<sup>38</sup>

Pharmacological or surgical modulation of dysfunctional chemoreceptors is emerging as a potential therapeutic option for patients with hypertension and HF. A recent review summarized the chemoreflex physiology and pathophysiology and its correlation with ventilation and sympathetic

drive, focusing on the importance of careful selection of patients that would benefit the most from chemoreflex modulation strategies.<sup>39</sup>

## Diabetes and kidney dysfunction

Diabetic cardiomyopathy is a form of stage B HF at high risk for progression to overt disease. The ARISE-HF is a phase 3 randomized, placebo-controlled, double-blind clinical study to investigate the efficacy of a novel investigational highly specific aldose reductase inhibitor in patients with diabetic cardiomyopathy at high risk of progression to overt HF.<sup>40</sup>

Diabetic kidney disease is also a crucial risk factor for developing HF.<sup>41–43</sup> Sodium–glucose co-transporter-2 (SGLT2) inhibitors and finerenone, a nonsteroidal and selective mineralocorticoid receptor antagonist (MRA), are now recommended [Class of Recommendation (CoR) I, Level of Evidence (LoE) A] for the prevention of HF in patients with type 2 diabetes mellitus (T2DM) and CKD (Figure 2).<sup>44</sup> SGLT2 inhibitors also reduced CV mortality in these patients. The indication for SGLT2 inhibitors is based on the results of the

**Figure 2** Cardiovascular (CV) and kidney outcomes with sodium–glucose co-transporter-2 inhibitor (SGLT2i) and finerenone in patients with chronic kidney disease (CKD). ACR, albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio; MI, myocardial infarction; RR, rate ratio; T2DM, type 2 diabetes mellitus. \*ESKD, sustained decrease in eGFR to  $<10$  mL/min/1.73 m<sup>2</sup>, sustained decrease in eGFR of  $\geq 40\%$  from baseline or death from renal causes.

	SGLT2i			FINERENONE
	DAPA-CKD	EMPA-KIDNEY	META-ANALYSIS	FIDELITY pooled analysis
POPULATION	CKD (eGFR 25–75 mL/min/m <sup>2</sup> and ACR ratio $\geq 200$ mg/g); with/without T2DM	CKD (eGFR 20–45 or 45–90 mL/min/m <sup>2</sup> and ACR ratio $\geq 200$ mg/g); with/without T2DM	4 trials: T2DM and high CV risk 5 trials: HF 4 trials: CKD	Patients with diabetic CKD (FIDELIO-DKD and FIGARO-DKD trials)
HF hospitalizations	HR for the composite of CV death or HFH: 0.71 (95% CI, 0.55–0.92)	HR for CV death or HFH: 0.84; 95% CI 0.67–1.07	- Overall HR for CV death or HFH: 0.77 (0.74–0.81)  - Considering only CKD trials: HR 0.74 (0.66–0.82) and 0.95 (0.65–1.40) in patients with and without T2DM, respectively	HFH: HR 0.78 (0.66–0.92)  CV composite (CV death, non-fatal MI, non-fatal stroke, or HFH): HR 0.86 (0.78–0.95)
CV death		HR for CV death: 0.84 (0.60–1.19)	Overall HR for CV death: 0.86 (0.81–0.92)	CV death: HR 0.88 (0.76–1.02)
Kidney Outcomes	Sustained decline in eGFR of $\geq 50\%$ , ESKD*, CV or renal death: HR 0.61 (0.51–0.72)	Progression of CKD or CV death: HR 0.72 (0.64–0.82)	RR for the risk of kidney disease progression: 0.63 (0.58–0.69), with similar RRs in patients with and without T2DM	Kidney failure, sustained $\geq 57\%$ decrease in eGFR from baseline over $\geq 4$ weeks, or renal death: HR 0.78 (0.66–0.92)

DAPA-CKD and EMPA-KIDNEY trials and a subsequent meta-analysis of 13 major randomized controlled trials (RCTs), including also CREDESCENCE, SCORED and HF trials.<sup>45,46</sup> FIDELIO-DKD and FIGARO-DKD trials and a pre-specified individual patient-level, pooled analysis of these two trials (FIDELITY pooled analysis) demonstrated the benefits of finerenone on CV and kidney outcomes versus placebo across the entire spectrum of CKD in patients with T2DM (Figure 2).<sup>47–50</sup>

## Coronary artery disease (CAD)

Among patients hospitalized due to acute decompensated HF, obstructive CAD was more prevalent in HF<sub>r</sub>EF than in HF<sub>p</sub>EF.<sup>51</sup> The role of percutaneous or surgical coronary revascularization remains uncertain in patients with HF<sub>r</sub>EF and chronic coronary syndromes.<sup>4,52</sup> Percutaneous coronary intervention (PCI) was not superior in reducing the incidence of death from any cause or HFH compared with GDMT alone in the REVIVED-BCIS2 trial.<sup>52</sup> Iaconelli *et al.* conducted a meta-analysis of five RCTs (some of them not blinded) with a total of 2842 patients to investigate the effects of coronary revascularization on morbidity and mortality in patients with chronic HF due to CAD. Compared with GDMT alone, coronary revascularization was associated with a lower risk of all-cause mortality [hazard ratio (HR) 0.88, 95% confidence interval (CI) 0.79–0.99] and CV mortality (HR 0.80, 95% CI 0.70–0.93) but not the composite of hospitalization for HF or all-cause mortality.<sup>53</sup>

## Aortic valve disease

Of the 15 216 patients from the European Society of Cardiology (ESC) Heart Failure Association (HFA) EURObservational Research Programme (EORP) Heart Failure Long-Term Registry, ~10% had aortic valve disease (AVD), with a higher prevalence in HF<sub>p</sub>EF. Severe aortic stenosis (AS), but not severe aortic regurgitation (AR), was independently associated with an increased risk of CV death and HFH, regardless of LVEF.<sup>54</sup> Both patients with HF<sub>p</sub>EF and severe AS had impaired functional capacity with similarly reduced peak oxygen consumption, peak cardiac output and peak arteriovenous oxygen.<sup>55</sup> Novel data on the 5 year outcomes of patients with severe symptomatic AS at low surgical risk undergoing transcatheter aortic valve replacement (TAVR) as compared with those undergoing surgery have been published.<sup>56</sup>

## Atrial fibrillation

Atrial fibrillation (AF) can coexist, cause or exacerbate HF.<sup>57,58</sup> AF transcatheter ablation in HF is currently reserved for patients with arrhythmia-induced cardiomyopathy and those in whom

the worsening HF symptoms are clearly related to AF.<sup>4,59,60</sup> Several ongoing studies might expand the latter indication.

Real-world data from the Swedish Heart Failure Registry showed that first-time catheter ablation for AF was associated with a lower risk of all-cause mortality or first HFH compared with medical therapy alone, regardless of LVEF; in HF<sub>p</sub>EF patients, catheter ablation also resulted in a reduction of recurrent HFH.<sup>61</sup> The ARC-HF and CAMTAF randomized trials compared early routine catheter ablation and pharmacological rate control in patients with persistent AF and HF; after trial completion, delayed selective catheter ablation was performed when clinically indicated in the rate control group. No differences in long-term outcomes were reported between the early and delayed catheter ablation groups. However, the early catheter ablation group showed greater symptom improvement compared with the rate control group. Furthermore, analyses according to received treatment suggested an association between catheter ablation and improved outcomes as compared with rate control.<sup>62</sup> The single-centre, open-label CASTLE-HTx trial showed that catheter ablation was safe and effective even in patients with symptomatic AF and end-stage HF (patients referred for heart transplantation evaluation) with a significant reduction in the primary endpoint of death from any cause, implantation of an LV assist device (LVAD) or urgent heart transplantation.<sup>63</sup>

## Pulmonary hypertension

Quality indicators for the assessment of care and outcomes of adults with pulmonary hypertension (PH) were developed by ESC.<sup>64</sup> Treatment of PH has improved dramatically in the last years.<sup>65</sup> In a post hoc analysis of the GRIPHON study, the selective prostacyclin receptor agonist selexipag reduced morbidity and mortality versus placebo regardless of concomitant CV comorbidities.<sup>66</sup> Tadalafil did not improve right ventricular (RV) systolic function in adults with congenital heart disease and systemic right ventricles (SERVE trial).<sup>67</sup>

In HF patients, PH is mainly present in isolated post-capillary form because of volume and/or pressure overload; however, chronic isolated post-capillary can lead to vascular remodelling, resulting in the development of combined post-capillary and pre-capillary forms; in addition, pre-capillary forms due to pulmonary arterial hypertension (PAH) can coexist.<sup>4</sup>

The Sildenafil in Heart Failure (SilHF) trial randomly assigned patients with HF<sub>r</sub>EF and PA systolic pressure (PASP)  $\geq 40$  mmHg measured by echocardiography in a 2:1 ratio to receive sildenafil (up to 40 mg three times/day) or placebo. Compared with placebo, sildenafil did not improve symptoms, QoL or exercise capacity.<sup>68</sup> The SPHERE-HF trial investigated the effect of mirabegron (a selective  $\beta_3$  adrenoreceptor agonist) on patients with left heart disease

and combined post-capillary and pre-capillary PH compared with placebo. The primary outcome of reduction of pulmonary vascular resistance (PVR) was not met, even if mirabegron showed a significant improvement in RV ejection fraction (EF) (secondary endpoint).<sup>69</sup>

## Cancer

New guidelines on cardio-oncology and management of cardiotoxicity were published in 2022.<sup>70</sup> Nouhravesh *et al.* examined the 1 year prognosis following new-onset HF stratified by cancer status in patients with breast, gastrointestinal or lung cancer. In total, 193 359 Danish patients with HF were included. Cancer status was categorized as history of cancer (no cancer-related contact within 5 years of HF diagnosis), non-active cancer (curative intended procedure administered) and active cancer. Standardized 1 year all-cause mortality was comparable for patients with a history of cancer and non-active cancer regardless of cancer type but varied comprehensively for active cancers.<sup>71</sup> Tomasoni *et al.* found that a history of cancer (within 5 years) was associated with a higher independent risk of all-cause and non-CV mortality but not with CV mortality.<sup>36</sup> The results were consistent with a previous analysis by Dobbin *et al.*<sup>72</sup> Age- and sex-adjusted incidence of new cancer in the HFrEF and HFpEF trials was 1.09 (95% CI 0.83–1.36) and 1.07 (95% CI 0.81–1.32) per 100 person-years, respectively.<sup>72</sup>

## Anaemia and iron deficiency

The prognostic significance of anaemia and iron deficiency (ID) is well known.<sup>73</sup> Intravenous (IV) iron supplementation has proven to alleviate HF symptoms, improve QoL and exercise capacity, and reduce the risk of HFH in patients with HFrEF/HFmrEF and ID. Secondary analyses of the AFFIRM-AHF trial showed similar benefits with IV ferric carboxymaltose (FCM) compared with placebo regardless of baseline haemoglobin levels<sup>74</sup> and slightly greater effectiveness in patients with ischaemic compared with non-ischaemic aetiology.<sup>75</sup> Furthermore, in a pre-defined analysis of the IRON-CRT trial, treatment with IV FCM was associated with improvement in RV function<sup>76</sup>; an improvement in hypercapnic ventilatory response and sleep-related breathing disorders was also observed.<sup>77</sup> The HEART-FID double-blind, randomized trial enrolled 3065 ambulatory patients with symptomatic HFrEF [New York Heart Association (NYHA) II–IV], ID, and a recent HFH or elevated natriuretic peptide levels. Patients were randomized to FCM or placebo. The unmatched win ratio for the hierarchical composite of death, HFH or change from baseline in the 6 min walk distance was 1.10 (99% CI 0.99–1.23) (Figure 3).<sup>78</sup> In the pre-specified analysis of the IRONMAN trial censoring

follow-up on September 2020 due to coronavirus disease 2019 (COVID-19) pandemic, IV ferric derisomaltose showed a significant reduction of the primary outcome of recurrent HFH and CV death.<sup>79</sup> Meta-analyses of RCTs comparing IV iron supplementation with placebo confirmed a significant reduction of HFH without, however, a benefit on CV or all-cause mortality.<sup>80–83</sup> Based on these data, the 2023 ESC focus update of HF guidelines recommended IV iron supplementation in symptomatic HFrEF or HFmrEF patients with ID to alleviate symptoms and improve QoL (Class I, Level A) or to reduce the risk of HFH (Class IIa, Level A) (Figure 3).<sup>44</sup> The concern regarding IV FCM and its potential association with hypophosphataemia continues to be a topic of ongoing debate and has recently come under scrutiny once more.<sup>84</sup>

Despite the strong recommendation by the guidelines and the cost-effective analysis showing a positive economic impact on healthcare systems,<sup>4,44,85</sup> ID screening and FCM treatment are still underused in clinical practice.<sup>86</sup>

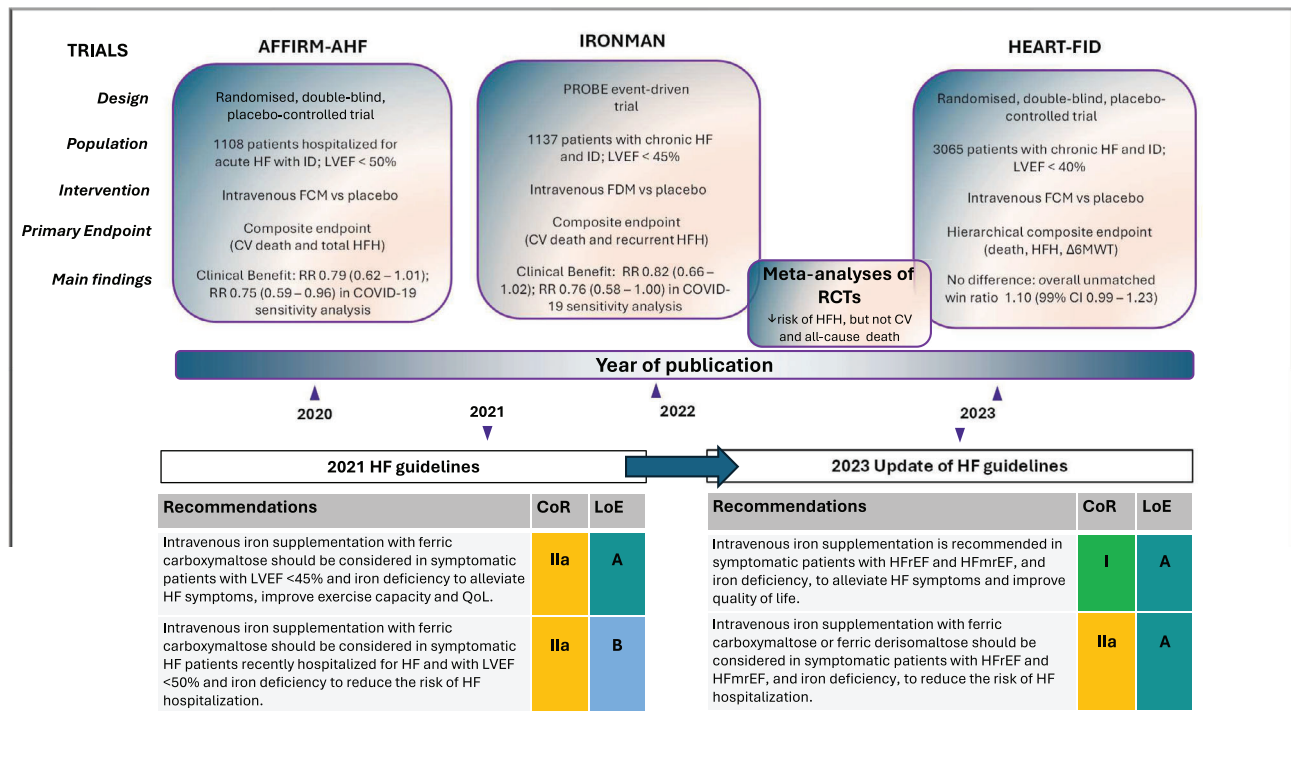
The use of SGLT2 inhibitors has been associated with an increase in haemoglobin and haematocrit levels, even in patients with ID. This benefit might result mainly from an anti-inflammatory effect and a reduction in oxidative stress, which results in a reduction in hepcidin, thus promoting the mobilization of iron from intracellular stores and an increase in erythropoietin.<sup>87,88</sup> A retrospective, single-centre analysis among 160 HFrEF patients showed a greater increase in haemoglobin and haematocrit with IV iron and SGLT2 inhibitors combined treatment compared with IV iron only.<sup>89</sup>

## Infections and COVID-19

The COVID-19 pandemic had enormous consequences on the global healthcare system because of complications of the infection itself, including CV complications, but also because of reduced access to hospitals by patients.<sup>90–96</sup> From January 2019 to December 2021, there were fewer hospitalizations, diagnostic and interventional procedures and outpatient consultations across all CV diseases. The COVID-19 pandemic also had a major impact on clinical trials with reduced enrolment and missed visits at follow-up.<sup>97</sup> The DELIVER trial was one of the most affected, with >75% of follow-up time occurring during the pandemic; nevertheless, treatment benefits of dapagliflozin persisted when censoring at COVID-19 diagnosis and pandemic onset.<sup>98</sup>

COVID-19 vaccination is indicated in all patients with HF, including frail or heart transplant patients.<sup>94,99</sup> Although generally safe, rare post-vaccine myocarditis was observed with mostly mild and transient forms and greater involvement of the female sex.<sup>100</sup> Mid-term follow-up with cardiac magnetic resonance showed that patients who experienced acute myocarditis after the mRNA COVID-19 vaccine had generally preserved biventricular function.<sup>101</sup>

**Figure 3** Novel evidence and indications for the treatment of iron deficiency. 6MWT, 6 min walk test; CI, confidence interval; CoR, Class of Recommendation; CV, cardiovascular; FCM, ferric carboxymaltose; FDM, ferric derisomaltose; HF, heart failure; HFH, heart failure hospitalization; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency; LoE, Level of Evidence; LVEF, left ventricular ejection fraction; PROBE, prospective, randomized, open-label, blinded endpoint; QoL, quality of life; RCTs, randomized controlled trials; RR, rate ratio.



## Diagnosis and prognosis

### Early diagnosis

The HFA of the ESC developed a consensus statement addressed to non-cardiology physicians to facilitate the early diagnosis of HF, including screening through the measurement of natriuretic peptides.<sup>102</sup> By making this simple laboratory test readily available, there is significant potential to improve the early diagnosis of HF, resulting in better patient outcomes and reduced healthcare costs.<sup>103</sup> In addition, because brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) levels are lower in obese patients, adjusting NT-proBNP concentrations in such patients seems to further increase its clinical utility in the rapid detection of HF.<sup>104</sup> Practical algorithms for early diagnosis of HF using NT-proBNP, with different cut-offs depending on patient characteristics and diagnostic likelihood, have been recently published by HFA of ESC.<sup>105</sup> Interestingly, results of standard 12-lead electrocardiograms, when analysed by a deep learning machine learning (ML) process, might also prevent underdiagnosing of HF or cardiomyopathies.<sup>106</sup> Nevertheless, this novel method still requires further verification.<sup>107</sup>

### Clinical assessment

Signs and symptoms of HF include elevated jugular venous pressure, hepatojugular reflux, peripheral oedema, breathlessness, orthopnoea, reduced exercise tolerance and fatigue.<sup>4</sup>

Bendopnoea is related to advanced HF, but its prognostic significance remains uncertain. Including 440 patients with advanced HF, de la Espriella *et al.* showed that a reduction of more than 3% in oxygen saturation when bending forward was associated with the risk of worsening HF compared with those with no change or improvement in oxygen saturation when bending.<sup>108</sup>

QoL and health-related QoL (HRQL) are among the endpoints for clinical trials and are influenced by multiple variables<sup>109–111</sup>; symptom severity was the main determinant of HRQL rather than social factors such as country income level.<sup>112</sup>

Analysing the prognostic implications of longitudinal NYHA class changes (i.e., stable, improving or worsening) in 13 535 patients from the Swedish HF Registry, Lindberg *et al.* showed that a single-point assessment of NYHA class itself predicted morbidity and mortality on top of its trajectory, suggesting that the one-time NYHA class assessment might be the pref-

erable approach for clinical trials' design and in clinical practice.<sup>113</sup>

Patient-reported outcomes (PROs) are relevant outcomes that directly assess the patient's experience, health behaviours, and the impact of the disease and its treatment on the patient's health status. PROs can be assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ) or with other questionnaires. The methodology and use of PROs need to be standardized and implemented in clinical practice.<sup>114,115</sup>

## Biomarkers

Biomarkers remain a milestone for the diagnosis, management and prognosis of HF.<sup>103,116–118</sup> In patients with AF, higher baseline and increasing or persistently elevated values of NT-proBNP, high-sensitivity troponin T (hs-TnT) and growth differentiation factor-15 (GDF-15) over 1 year were associated with higher risk of HF outcomes regardless of HF history or LVEF.<sup>119</sup> Prognostic models in chronic HFpEF, based on NT-proBNP and hs-TnT, along with a few readily available clinical variables, provided effective risk discrimination for both morbidity and mortality.<sup>120</sup> Among 1559 HF patients from the PARADIGM-HF trial, McDowell *et al.* examined whether 11 biomarkers, individually or collectively, improved the performance of the PREDICT-HF prognostic model, which includes clinical, routine laboratory and BNP data. None of the studied biomarkers (including urinary albumin-to-creatinine ratio, hs-TnT and aldosterone) led to a meaningful improvement in the prediction of outcomes.<sup>121</sup>

Biomarkers are also used as inclusion criteria and surrogate or safety endpoints in clinical trials.<sup>122–124</sup>

MicroRNAs (miRNAs), small circulating non-coding RNAs, might have the potential to rule out HF or differentiate HF phenotypes.<sup>125–127</sup> Moreover, proteomic signatures of circulating plasma proteins may also aid our understanding of HF-specific signalling, and thereby, they can support new therapeutic and diagnostic efforts for chronic HF.<sup>128</sup>

## Imaging

Multimodality imaging is a key tool for diagnosis, identification of the cause, proper management and monitoring of therapeutic response in HF.<sup>4,129,130</sup> Global longitudinal strain (GLS) is a reproducible and well-validated echocardiographic parameter that presents a high prognostic value, even higher than LVEF (especially in patients with LVEF > 45%).<sup>131</sup> In a retrospective cohort study including 311 patients with HFpEF, abnormal GLS was a strong predictor for clinical events and future deterioration in LVEF.<sup>132</sup> Left atrial (LA) compliance (ratio of LA reservoir strain to E/e') during exercise versus resting LA compliance or exercise E/e' ratio alone showed superior diagnostic ability in HFpEF patients.<sup>133</sup> Increased LA volume was

associated with PVR, and reduced LA function was associated with a disrupted PVR–compliance relationship.<sup>134</sup> Furthermore, LA remodelling and dysfunction provided important prognostic information.<sup>135</sup> Changes in the LA dimension (positive or adverse remodelling) may be a useful marker of response to GDMT and cardiac resynchronization therapy (CRT).

The DAPA-MODA trial, a multicentre, single-arm, open-label, prospective and interventional study, evaluated the effect of dapagliflozin on cardiac remodelling parameters [LA volume index (LAVI) and LV geometry] over 6 months among a total of 162 patients with HF and LVEF > 40%. Dapagliflozin administration was associated with a significant reduction of LA dimension and improvement of LV geometry (reduced LV mass index, end-diastolic volume and end-systolic volume) in addition to a significant reduction in natriuretic peptide concentrations.<sup>136</sup>

Among 625 patients with de novo HF, approximately one third had RV dysfunction (RVD), defined as tricuspid annular plane systolic excursion (TAPSE) < 17 mm; during up-titration of GDMT, RVD recovery occurred in 49% of the patients and was associated with improved clinical outcomes.<sup>137</sup> In patients with HFpEF and secondary mitral regurgitation (SMR), ~40% of patients improved RV function after percutaneous mitral valve repair and RV function improvement was associated with better long-term survival free from heart transplantation and a lower risk of HFH.<sup>138</sup>

Ultrasound monitoring of congestion during HFH through inferior vena cava (IVC) diameter, jugular vein distensibility ratio or number of B-lines at the lung is widespread in clinical practice.<sup>139,140</sup> Pre-discharge assessment of residual subclinical (echocardiographic) congestion is recommended.<sup>140,141</sup>

## Machine Learning

Artificial intelligence (AI) is used to create mathematical algorithms to better assess and cross-reference large patient data.<sup>142–144</sup> Khan *et al.* summarized the applications of machine learning (ML) techniques in the field of HF.<sup>145</sup> ML-derived risk models have been proposed for takotsubo syndrome<sup>146</sup> and for Asian patients hospitalized for acute HF.<sup>147</sup> A secondary analysis of BLUSHED-AHF showed that there was a good agreement in B-line quantification between an AI/ML automated lung US congestion score and expert-level assessment.<sup>148</sup>

## Specific causes of HF

### Cardiomyopathies

Cardiomyopathies represent an important and heterogeneous cause of HF.<sup>149,150</sup> The 2023 ESC guidelines introduced

non-dilated LV cardiomyopathy as a new phenotype of cardiomyopathies, which includes non-ischæmic LV scarring or fatty replacement in the absence of LV dilatation or isolated global LV hypokinesia without scarring.<sup>151</sup> Two recent documents summarized the optimal management, new advances and future possible therapeutic targets in the treatment of cardiomyopathies.<sup>152,153</sup> Sudden cardiac death (SCD) remains a significant cause of mortality in cardiomyopathies, with an incidence of 0.15%–0.7% per year, highlighting the importance of a thorough risk assessment.<sup>154,155</sup>

## Dilated cardiomyopathy

Genetic testing is crucial for diagnosis, prognosis, arrhythmic risk assessment and therapeutic choice, as well as for providing important information for reproductive counselling in patients with cardiomyopathies.<sup>151,156</sup>

Of 1412 HFrEF patients from the PARADIGM-HF trial with whole-exome sequence data, 4.8% had at least one rare predicted loss-of-function variant. These patients were younger, had lower LVEF and had a less likely ischaemic aetiology.<sup>157</sup> Among individuals with dilated cardiomyopathy (DCM) and CAD, the presence of rare pathogenic variants in DCM genes was associated with an increased risk of death or major adverse cardiac events.<sup>158</sup>

## Hypertrophic cardiomyopathy

Mavacamten (cardiac myosin adenosine triphosphatase inhibitor) is now recommended as the second choice in patients with hypertrophic cardiomyopathy (HCM) and symptomatic LV outflow tract (LVOT) obstruction (LVOTO) after beta-blockers and/or calcium channel blockers (verapamil or diltiazem).<sup>151,159–161</sup> The cross-over VALOR-HCM trial confirmed the efficacy of mavacamten in patients with HCM and symptomatic LVOTO, with sustained improvements in LVOT gradients and symptoms leading to a significant reduction in the need for septal reduction therapy at Week 56.<sup>162</sup> A secondary analysis of the EXPLORER-HCM trial showed improvement in several parameters at the cardiopulmonary exercise testing including peak oxygen uptake with mavacamten compared with placebo.<sup>163</sup> In addition, subgroup analysis of the EXPLORER-HCM and MAVALTE studies showed that mavacamten benefits were reproduced and maintained regardless of beta-blocker use.<sup>164</sup> Future studies might also illuminate how far myosin inhibitors affect intracellular signalling and myocardial remodelling in HCM hearts.<sup>165</sup> The real-world candidacy to mavacamten in a contemporary hypertrophic obstructive cardiomyopathy population has been explored.<sup>166</sup>

In symptomatic non-obstructive HCM, the novel ineranafaxstat, a drug targeting myocardial energetics, was

safe and well tolerated and associated with better exercise performance and health status among those with lower KCCQ at baseline.<sup>167</sup>

## Peripartum cardiomyopathy (PPCM)

PPCM has a major impact on maternal morbidity and mortality during pregnancy.<sup>151,168,169</sup> Novel epidemiological data were published from the large ESC EORP PPCM Registry. Among 535 women with PPCM, 1 year all-cause death, first hospitalization and recurrent rehospitalizations occurred in 8.4%, 14% and 3.5%, respectively.<sup>170</sup> Thrombo-embolism and stroke at the time of PPCM diagnosis were reported in 5.5% and 1.1%, respectively.<sup>171</sup>

## Cardiac amyloidosis

The real prevalence of cardiac amyloidosis (CA) in the general population is still unknown because of underdiagnosis.<sup>172</sup> A higher prevalence of CA was reported among patients with unexplained LV hypertrophy (LVH) or suspected HCM and HFpEF and in the elderly with AS.<sup>173,174</sup> The most common forms of CA are immunoglobulin light chain (AL-) and wild-type (wt) or hereditary (h) TTR (ATTR-) CA, even if more rare forms exist as well.<sup>175</sup>

In a small cohort of 300 patients affected by ATTR-CA, the hereditary form was detected in 12% of the entire population and in 5.3% of patients aged  $\geq 70$  years. Hereditary ATTR-CA (ATTRh-CA) was more frequent in females.<sup>13</sup> Among 2029 patients aged  $\geq 70$  years with ATTR-CA from the UK NAC, up to 20.7% had a pathogenic TTR variant whose presence was associated with increased risk of all-cause mortality, especially when related to the V122I mutation.<sup>176</sup> These data support routine genetic sequencing in all patients with ATTR-CA regardless of age.

Disproportionately elevated levels of natriuretic peptide and troponin are characteristics of patients with CA. Thus, cardiac biomarkers might refine the diagnostic algorithm. Vergaro *et al.*, analysing 1149 patients with suspected CA, found NT-proBNP 180 ng/L and hs-TnT 14 ng/L as optimal cut-off to rule out the diagnosis of CA.<sup>177</sup>

Several independent prognostic factors have been identified in patients with CA.<sup>178,179</sup> RV-PA coupling predicted the risk of mortality or HFH. The TAPSE/PASP ratio was more effective than TAPSE or PASP alone in predicting prognosis.<sup>180</sup> Prevalence, aetiologies and prognostic impact of moderate-to-severe mitral regurgitation (MR) and tricuspid regurgitation (TR) in patients with CA have been reported. The most common aetiologies were atrial functional MR, followed by primary infiltrative MR and secondary TR due to RV overload followed by atrial functional TR.<sup>181</sup> Combined moderate-to-severe MR and TR and isolated

moderate-to-severe TR but not isolated MR have been associated with an increased independent risk of all-cause death or worsening HF events.<sup>181</sup> Also, worsening of MR and TR at 12 and 24 months was independently associated with a worse prognosis.<sup>182</sup> Patients with the V122I mutation showed a more rapid decline in structural and functional echocardiographic parameters compared with both wild-type and T60A ATTR-CA.<sup>182</sup> Atrial amyloidosis is an early manifestation of CA and could be found even in the absence of systemic disease and ventricular involvement, being able to cause AF and thrombo-embolic events.<sup>183,184</sup>

Great progress has been made in the treatment of CA.<sup>185</sup> Tafamidis, a stabilizer of the native TTR tetramer structure, is recommended for the treatment of patients with ATTR-CA and NYHA Class I or II.<sup>4</sup> Also, in patients with severe HF symptoms (NYHA III), it was observed a reduction of all-cause mortality with continuous tafamidis treatment compared with delayed tafamidis treatment (placebo then tafamidis) over a median follow-up of 5 years.<sup>186,187</sup> The ATTRibute-CM trial demonstrated that another stabilizer of TTR tetramer, acoramidis, reduced all-cause mortality and CV hospitalizations in addition to improving functional capacity and QoL, compared with placebo.<sup>188</sup> An analysis of the APOLLO study showed that patisiran (RNA interference therapeutic that inhibits hepatic synthesis of TTR) may delay the progression of LV chamber dysfunction after 9 months of therapy.<sup>189</sup> The APOLLO-B trial enrolled 360 patients with ATTR-CA (variant or wild-type) and a history of HF with the aim to investigate the effect of patisiran versus placebo on functional capacity and QoL at 1 year follow-up. Patisiran reduced the decline in the 6 min walk test distance and improved the KCCQ Overall Summary score (KCCQ-OSS); significant benefits were not observed for the secondary composite endpoint of all-cause death, CV events and change from baseline in the 6 min walk test distance.<sup>190</sup> These new data, as well as data from the HELIOS-B trial, might lead to changes in the indications for small interfering RNA (patisiran and vutrisiran) that are currently approved for hereditary TTR amyloidosis with polyneuropathy only.<sup>185</sup>

## Myocarditis

Acute myocarditis is a possible cause of ventricular dysfunction and a risk condition for malignant arrhythmias; viral infection is the most common aetiology, although viral identification is often not easy without an endomyocardial biopsy.<sup>191</sup> Some rare cases of myocarditis have been associated with COVID-19 vaccination<sup>192</sup>; a clinical consensus document of the HFA summarized incidence, diagnosis, pathophysiology and therapy for COVID-19 vaccination-related myocarditis.<sup>193</sup>

Anakinra (a recombinant non-glycosylated form of human interleukin-1 receptor antagonist) showed a neutral effect on the risk of complications in patients with low-risk acute myocarditis in the ARAMIS trial.<sup>194</sup>

## Treatment of HFrEF

### Pharmacological therapies

Medical therapy has changed the prognosis of patients with HFrEF.<sup>3,4,44</sup> The four pillars for HFrEF treatment include beta-blockers, angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor–neprilysin inhibitor (ARNI) sacubitril/valsartan or angiotensin receptor blockers (ARBs), MRAs and SGLT2 inhibitors.<sup>4</sup> Early benefits of GDMT support its early initiation.<sup>195,196</sup> Despite several strategies proposed to implement GDMT,<sup>197,198</sup> rates of prescription and titration remain suboptimal.<sup>199–204</sup>

Several factors may influence the prescription of GDMT. First, significant differences were found in the management and implementation of therapy for HF between HF specialists and non-specialists, supporting the idea that specific courses may improve physicians knowledge and ultimately benefit patients.<sup>205</sup> Also, pharmaco-disparities must be addressed to improve HFrEF outcomes globally; indeed, despite higher prices in high-income countries, GDMT was more accessible and affordable than in low- and middle-income countries.<sup>206</sup>

Obesity was independently associated with a higher prescription of each treatment and the achievement of the target dose.<sup>207</sup>

CKD and hyperkalaemia are often advocated as reasons for under-prescription of RAAS inhibitors.<sup>204,208–211</sup> Among the 31 668 patients with HFrEF, comorbid CKD was associated with lower rates of evidence-based therapy prescription. However, low rates of prescription were observed even in categories of estimated glomerular filtration rate (eGFR) where these therapies are recommended and have demonstrated benefit.<sup>212</sup> Guidetti *et al.* showed the safety of MRAs in patients with severe CKD.<sup>213</sup> In a pre-specified pooled analysis of PARADIGM-HF and PARAGON-HF trials, sacubitril/valsartan reduced the risk of serious adverse renal outcomes regardless of baseline renal function compared with valsartan or enalapril.<sup>214</sup> Post hoc analysis of EMPHASIS-HF and TOPCAT Americas region trials showed an acute slight decline in eGFR (−2.4 and −2.0 mL/min/1.73 m<sup>2</sup>, respectively) after MRA initiation, and then stable eGFR values during follow-up were described.<sup>215</sup> Moreover, a retrospective study using data from the Taiwan National Health Insurance Research Database (NHIRD) found a reduction of CV and all-cause mortality with an MRA also in patients with HF and end-stage renal disease starting maintenance dialysis.<sup>216</sup>

Potassium binders represent a novel opportunity for enabling GDMT up-titration.<sup>217,218</sup>

## SGLT2 inhibitors

SGLT2 inhibitors are now established as safe and effective drugs for the treatment of HF across the entire spectrum of LVEF.<sup>4,44,219,220</sup> A comprehensive meta-analysis of five main trials with SGLT2 inhibitors in HF (DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved and SOLOIST-WHF) proved statistically significant reductions in HFH by 28%, CV death by 13% and all-cause mortality by 8%.<sup>220</sup> Secondary analysis of SGLT2 inhibitors trials in HF showed a clinical benefit regardless of age,<sup>221</sup> aetiology of HF, body mass index (BMI), liver and renal function,<sup>222,223</sup> AF,<sup>224</sup> background therapy<sup>225</sup> and severity of HFH.<sup>226</sup> The DAPA-VO<sub>2</sub> trial enrolled 90 stable patients with HFrEF and showed a significant increase of peak VO<sub>2</sub> at 3 months with dapagliflozin compared with placebo.<sup>227</sup>

The use of SGLT2 inhibitors was not associated with a clinically relevant risk of hypotension, volume depletion or renal adverse events.<sup>228,229</sup> A mild decrease in eGFR rate may be expected in the first period after the initiation of SGLT2 inhibitors, without increasing the risk of short- or long-term HF, mortality or kidney injury events.<sup>223,230</sup>

Recent evidence in patients with acute HF or with a recent hospitalization due to worsening HF,<sup>223,231–233</sup> as well as the safety profile and tolerability, supports the early initiation of SGLT2 inhibitors in both ambulatory and in-hospital settings as first-line therapy.<sup>196</sup> However, a survey involving 615 cardiologists worldwide showed that the ‘historical sequential’ approach (ACEi, beta-blockers, MRA and, lastly, SGLT2 inhibitors) remains more popular than the initiation of SGLT2 inhibitors as first-line therapy.<sup>234</sup>

An analysis of patients registered in the Swedish HF Registry with eligibility characteristics for SGLT2 inhibitors demonstrated a three-fold increase in their use between 1 November 2020 and 5 August 2022. However, more than 4 in 10 eligible patients remained without therapy. Discontinuation rates at 6 and 12 months were 13.1% and 20.0%, respectively.<sup>235</sup>

## HF therapies after acute myocardial infarction

The superiority of sacubitril/valsartan compared with ramipril among high-risk survivors of AMI is still debated.<sup>236</sup>

One of the mechanisms of action for the benefits of MRA in HF patients is the positive remodelling through the antifibrotic effect. A reduction in serum procollagen type I C-terminal propeptide (PICP, a biomarker of cardiac fibrosis) concentration was found following the administration of spironolactone in a population at risk of HF in the HOMAGE

(Heart ‘Omics’ in AGEing) trial<sup>237</sup>; furthermore, a decrease in PICP with spironolactone was correlated with improved diastolic dysfunction as assessed by E/e’.<sup>238</sup> In the REMI study that enrolled 119 patients with a first acute ST-elevation myocardial infarction (STEMI), Monzo *et al.* showed higher post-STEMI aldosterone concentration correlating with more adverse LV remodelling even in the subgroup of patients with LVEF > 40%.<sup>239</sup>

The impact of SGLT2 inhibitors on patients after AMI is still debated. In the DAPA-MI trial, among 4017 patients with AMI (67% with LVEF between 30% and 49%) and without a history of T2DM or chronic HF, dapagliflozin showed better cardiometabolic outcomes (reduced onset of T2DM and weight loss) compared with placebo but did not impact major outcomes (CV death or HFH).<sup>240</sup>

Similarly, among 6522 patients after AMI (78.3% with LVEF < 45% and 56.9% with acute signs or symptoms of congestion) at increased risk of HF enrolled in the EMPACT-MI trial, treatment with empagliflozin did not lead to a significantly lower risk of a first HFH or death from any cause than placebo (HR 0.90, 95% CI 0.76–1.06, *P* = 0.21). Nevertheless, empagliflozin significantly reduced the risk of HFH.<sup>241</sup>

## Soluble guanylate cyclase stimulators

Vericiguat reduced the composite outcome of CV death or first HFH in HFrEF patients with a recent episode of worsening HF.<sup>140,242</sup> In a pre-specified echocardiographic sub-study of patients enrolled in the VICTORIA trial, significant improvements in LV structure and function occurred over 8 months in the vericiguat group but similarly in the placebo group.<sup>243</sup>

Prior HFH within 6 months was the most common criterion limiting eligibility to vericiguat in a real-world HF population.<sup>244</sup> Butler *et al.* summarized evidence supporting the rationale for investigating the use of soluble guanylate cyclase stimulators in stable low-risk HF: first, the treatment effect of HFrEF medications is not always consistent across the risk spectrum; second, if soluble guanylate cyclase stimulators have cardioprotective effects, these effects may be highlighted when the medication is initiated earlier in the disease process; and third, a novel trial with a longer follow-up may provide data on its effect on CV mortality.<sup>245</sup>

The ongoing VICTOR trial (A Study of Vericiguat in Participants with Chronic Heart Failure With Reduced Ejection Fraction) will evaluate the effect of vericiguat in stable chronic HFrEF patients (NCT05093933).

## Myosin activators

The selective cardiac myosin activator omecamtiv mecarbil might be more effective in patients with more severe HFrEF.<sup>246–248</sup> These data are also confirmed by a

pre-specified analysis of the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in HF) trial that showed a greater effect of omecamtiv mecarbil on the primary composite outcome of a first HF event or CV death in patients with a higher baseline NT-proBNP.<sup>249</sup>

## Non-pharmacological options

### Exercise training

In a Cochrane systematic review and meta-analysis of 60 trials (8728 participants with HF), exercise-based cardiac rehabilitation reduced all-cause hospitalization and improved HRQL.<sup>250</sup> In patients with advanced HF implanted with an LVAD, the Ex-VAD trial demonstrated that 12 weeks of supervised exercise training versus usual care had positive effects on submaximal exercise capacity and physical QoL, although it did not improve peakVO<sub>2</sub>.<sup>251</sup>

### Implantable defibrillator therapy

A post hoc analysis of the PARADIGM-HF trial showed a reduction of the risk of ventricular arrhythmia with ARNI versus enalapril; the effect was independent of baseline implantable cardiac defibrillator (ICD)/CRT—defibrillator (CRT-D) use and greater in patients with a non-ischaeamic aetiology.<sup>252</sup> As medical therapy improves, it may be necessary to reconsider the indications and timing of ICD implantation for primary prevention of sudden death.<sup>253</sup> A careful analysis of predictors of recurrent major arrhythmic events could improve the selection of patients who could benefit from ICD implantation.<sup>254,255</sup> In an observational retrospective cohort study including 698 patients with non-ischaeamic cardiomyopathy, late gadolinium enhancement (LGE) on magnetic resonance imaging (MRI) was the only independent predictor of appropriate ICD therapies, sustained ventricular arrhythmias, resuscitated cardiac arrest and SCD.<sup>256</sup> Genetic testing is also useful in stratifying the risk of arrhythmic events.<sup>151,255</sup>

### CRT

Cleland *et al.* conducted a meta-analysis of COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) and CARE-HF (Cardiac Resynchronization—Heart Failure) trials to identify patient characteristics that predicted the effect of CRT—pacemaker (CRT-P) on clinical outcomes. Patients assigned to CRT-P had lower rates for all-cause mortality and the composite outcome of all-cause mortality or HFH. No pre-specified characteristic, including sex, aetiology of ventricular dysfunction, QRS duration (within the studied range) or morphology or PR interval, significantly influenced the effect of CRT-P on all-cause mortality or the composite outcome. However, CRT-P had a greater effect on the composite outcome for patients with lower body surface area and those receiving beta-blockers.<sup>257</sup> A CRT re-

sponse among lamin A/C (LMNA) cardiomyopathy patients was associated with lower baseline LVEF or a high percentage of RV pacing prior to CRT in patients with pre-existing cardiac implantable electronic device. In patients with ESC Class I guideline indication for CRT, response rates were 61%. Post-CRT improvements in LVEF were associated with survival benefits.<sup>258</sup> The survival benefits of CRT were consistent also in patients with several comorbidities.<sup>259</sup>

The BUDAPEST-CRT Upgrade RCT randomly assigned in a 3:2 ratio 360 patients with symptomatic HF, LVEF ≤ 35% and intermittent or permanent RV pacing (≥20% of RV pacing burden) with wide-paced QRS (>150 ms) to receive the CRT-D upgrade or ICD.<sup>260</sup> The primary outcome was the composite of all-cause mortality, HFH or <15% reduction of LV end-systolic volume assessed at 12 months. The upgrade procedure was safe and showed an 11% reduction in the primary composite endpoint with consistent results in all patient subgroups (including patients with AF).<sup>261</sup>

Excessive prolongation of the PR interval impairs the coupling of atrioventricular (AV) contraction. The HOPE-HF (His Optimized Pacing Evaluated for Heart Failure) randomized, double-blind, cross-over trial evaluated whether AV-optimized His pacing was preferable to no pacing. His bundle pacing did not improve peak oxygen uptake but improved QoL and symptoms without adverse effects.<sup>262</sup>

### Percutaneous treatment of mitral regurgitation

Moderate-to-severe secondary mitral regurgitation (SMR) has been associated with a poor prognosis in chronic HFrfE patients.<sup>263–265</sup>

Prescription and up-titration of GDMT are crucial before the correction of severe SMR.<sup>4</sup> Indeed, up to 40% of severe SMR improved after optimization of medical therapy in different cohorts.<sup>266,267</sup> Furthermore, triple GDMT prescription (beta-blockers, renin–angiotensin system inhibitors and MRAs) at the time of transcatheter edge-to-edge mitral valve repair (M-TEER) was associated with a better long-term prognosis in large registries.<sup>268</sup> Using data from the EuroSMR registry, Adamo *et al.* showed that M-TEER further allowed up-titration of GDMT in 38% of patients. The degree of MR reduction between baseline and 6 month follow-up was an independent predictor of GDMT up-titration after M-TEER.<sup>269</sup> Better tolerability of GDMT might be mediated by higher systolic blood pressure and improvement in renal function through improvement in haemodynamics and RV function.<sup>138</sup> Patients experiencing GDMT up-titration after M-TEER had a lower risk of all-cause death or HFH compared with those without.<sup>269</sup>

A 5 year follow-up of the COAPT trial is now available. SMR correction with MitraClip device confirmed a significant reduction in HFH and all-cause mortality compared with GDMT alone.<sup>270</sup> In the prospective, multicentre, international, single-arm EXPAND study, third-generation MitraClip system devices reduced MR to ≤1+ and MR ≤ 2+ in 93.0% and 98.5% of patients, respectively; this result was sustained at

1 year follow-up.<sup>271</sup> The fourth-generation MitraClip G4 System has further increased procedural success rates at 30 days in the EXPAND G4 study.<sup>272</sup>

Several elements can influence the outcome of patients with severe MR undergoing M-TEER, including LA and RV function.<sup>138,273–278</sup> Cardio-hepatic syndrome was associated with a significant increase in 2 year mortality,<sup>279</sup> and low serum albumin levels were independently associated with reduced 4 year survival.<sup>280</sup> A risk score predicting all-cause death or HFH using the COAPT trial data was developed.<sup>281</sup> However, the COAPT risk score showed a poor performance in the prognostic stratification of real-world patients undergoing M-TEER but a better performance in COAPT-like patients.<sup>282</sup>

Other options for transcatheter treatment of MR are emerging. Transcatheter mitral valve replacement (TMVR) is an alternative to M-TEER.<sup>283,284</sup> Ludwig *et al.* analysed a propensity score-matched comparison between the CHOICE-MI registry (262 patients treated with TMVR) and the EuroSMR registry (1065 patients treated with M-TEER) with 12 demographic, clinical and echocardiographic parameters; TMVR was associated with a greater reduction in MR severity and symptom improvement with no significant differences in mortality beyond 30 days (although post-procedural mortality tended to be higher after TMVR).<sup>285</sup> Potential haemodynamic complications after TMVR, including LVOTO and afterload mismatch, and the peri-procedural management of patients undergoing TMVR have been reviewed.<sup>286</sup>

### Percutaneous treatment of tricuspid regurgitation

TR is common in patients with HF and is associated with higher mortality rates.<sup>181,287–290</sup> Of the 11 298 patients included in the ESC-HFA EORP Heart Failure Long-Term Registry, 5.5% had isolated TR, and 11% had combined MR/TR; HFpEF was associated with an increased risk of isolated TR. TR, isolated or combined with MR, was associated with a worse prognosis.<sup>291</sup> In a different cohort of patients with severe combined MR/TR, an improvement in the degree of TR was observed after M-TEER in about one third of cases.<sup>274</sup>

Although tricuspid valve surgery should be the first therapeutic choice, mortality rates after isolated tricuspid surgery remain high, with up to 12% in-hospital mortality. The TRI-SCORE was proposed to predict in-hospital mortality risk.<sup>292</sup>

Transcatheter tricuspid valve repair might become a valuable alternative to surgery for severe TR.<sup>287,293,294</sup> The TRILUMINATE Pivotal, a prospective randomized trial of percutaneous tricuspid transcatheter edge-to-edge repair (T-TEER) versus medical therapy for severe TR (93% with secondary TR), enrolled 350 symptomatic patients (NYHA II–IV) with LVEF > 20% and at least intermediate surgical risk. T-TEER demonstrated a significant reduction in the severity of TR and an improvement in QoL (assessed by the KCCQ

score). Supporting the absence of effective medical therapy for TR (as opposed to SMR), no improvement in the severity of TR was observed in the control group.<sup>295</sup>

## HFpEF

### Epidemiology, clinical phenotypes and pathophysiology

HFpEF represents a heterogeneous clinical syndrome and accounts for more than half of HFH.<sup>4,296</sup> Cai *et al.* reported clinical characteristics and outcomes of 41 708 patients hospitalized with HFpEF between January 2017 and June 2021 in secondary and tertiary hospitals across 31 provinces of mainland China. The 1 year rate of clinical outcomes was 16.4%, the 1 year rate of HFH was 13.6% and CV death was 3.1%.<sup>297</sup>

A scientific statement of the HFA outlined the most common HFpEF phenotypes and suggested an evidence-based treatment strategy for each.<sup>35</sup>

Obesity and T2DM are common comorbidities in HFpEF and might play a role in the pathogenesis of HFpEF.<sup>36,298</sup> Adverse myocardial remodelling might result from adipokine-mediated inflammatory mechanisms and epicardial adipose tissue.<sup>299</sup> In the PROMIS-HFpEF cohort, increased epicardial adipose tissue was associated with smaller indexed LV end-diastolic and LA volumes, proteomic markers of adipose biology and inflammation, insulin resistance, endothelial dysfunction and dyslipidaemia but not with coronary flow reserve.<sup>300</sup> Other mechanisms potentially involved in the pathogenesis of HFpEF are endothelium-independent microvascular dysfunction, subclinical inflammation, venous dysfunction and impaired myocardial energy homeostasis.<sup>301–304</sup>

A post hoc analysis of the ATHENA trial showed that dronedarone was associated with reduced CV events in patients with paroxysmal or persistent AF or atrial flutter and HFmrEF or HFpEF.<sup>305</sup>

### Diagnosis and prognosis

The H<sub>2</sub>FPEF and HFA-PEFF scores were proposed and validated to aid in the diagnosis of HFpEF, but their diagnostic performance varied in different populations. Tomasoni *et al.* showed that the HFA-PEFF score had a higher diagnostic utility compared with the H<sub>2</sub>FPEF score and held an independent prognostic value for all-cause mortality in patients with HFpEF caused by CA.<sup>306</sup>

Exercise testing has a crucial role in the diagnosis and prognostic assessment of HFpEF.<sup>307–309</sup> Omote *et al.* performed invasive exercise testing in patients with exertional dyspnoea

and LVEF  $\geq 50\%$  ( $n = 764$ ). Among these patients, haemodynamic abnormalities currently used to confirm HFpEF diagnosis were also associated with an increased risk for adverse events. The greatest risk was observed in patients with elevated pulmonary arterial wedge pressure (PAWP) at rest, followed by patients with elevated exercise PAWP and normal resting PAWP.<sup>310</sup> In contrast to patients with HFREF, between 10% and 25% of patients with HFpEF and without lung disease displayed arterial desaturation during exercise. Exertional hypoxaemia was associated with more severe haemodynamic abnormalities and increased mortality.<sup>311</sup> Among patients with HFpEF undergoing comprehensive echocardiography and invasive cardiopulmonary exercise testing, low compared with preserved biventricular cardiac power output reserve ( $< vs. \geq$  median of 1.57 W) was associated with more advanced HFpEF, increased systemic vascular resistance and PVR, reduced exercise capacity and increased adverse events.<sup>312</sup>

## Treatment

### SGLT2 inhibitors

Based on the results of the EMPEROR-Preserved and DELIVER trials, the 2023 Focus Update of 2021 HF guidelines introduced a CoR I, LoE A, for the use of SGLT2 inhibitors in patients with HFmrEF and HFpEF.<sup>44</sup> Global implementation of SGLT2 inhibitor use is warranted to prevent or postpone HFH and reduce HF-related costs.<sup>313</sup>

Among the 12 251 participants from DELIVER and EMPEROR-Preserved, SGLT2 inhibitors reduced the composite endpoint of CV death or first HFH (HR 0.80, 95% CI 0.73–0.87) with a consistent reduction in both the components of CV death (HR 0.88, 95% CI 0.77–1.00) and first HFH (HR 0.74, 95% CI 0.67–0.83).<sup>220</sup>

In a pre-specified analysis of the DELIVER trial, dapagliflozin consistently reduced the risk of the primary endpoint compared with placebo, irrespective of baseline NYHA class, with an improvement in QoL more evident among NYHA III–IV patients.<sup>314</sup> A secondary analysis of EMPEROR-Preserved assessed the effects of empagliflozin across the spectrum of kidney function.<sup>315</sup> Overall, 5988 patients were included and categorized according to concomitant CKD at baseline ( $n = 3198$ , 53.5% with CKD). The efficacy of empagliflozin on the primary outcome of HFH or CV death was consistent across a wide range of renal functions. Empagliflozin also reduced the progression to macroalbuminuria and the risk of acute kidney disease. In a further analysis of EMPEROR-Preserved, empagliflozin, compared with placebo, led to a significant increase in albumin levels and was beneficial irrespective of baseline liver function.<sup>316</sup> The benefits of SGLT2 inhibitors were not influenced by background therapy or by the baseline history of AF.<sup>317,318</sup>

Pooling data from the DAPA-HF and DELIVER trials, Bhatt *et al.* analysed the benefits of dapagliflozin on health status, measured by the KCCQ, across the full spectrum of LVEF. A total of 11 007 participants were included. KCCQ was evaluated at 4 and 8 months. Dapagliflozin improved all key domains of health status irrespective of LVEF.<sup>110</sup> In a larger meta-analysis, including 14 RCTs (21 737 participants), SGLT2 inhibitors demonstrated a significant improvement in QoL across the entire spectrum of LVEF as early as a 3 month follow-up. Results were confirmed at 6 month follow-up, and a wider effect was observed among patients with a recent episode of worsening HF.<sup>319</sup>

### ARNI

In a post hoc analysis of the PARAGON-HF trial, a prior HFH (occurring pre-randomization) was associated with an increased risk for renal events. HFpEF patients experiencing HFH could represent a distinct cohort at elevated risk for accelerated kidney disease progression.<sup>320</sup> Initiation of sacubitril/valsartan was associated with a modestly lower new loop diuretic requirement in follow-up.<sup>321</sup>

In the PARAGLIDE-HF trial, enrolling 466 patients with LVEF  $> 40\%$  and a recent stabilized episode of worsening HF (defined as HFH, emergency department visit or out-of-hospital urgent HF visit, all of them requiring IV diuretic agents within 30 days from randomization), sacubitril/valsartan reduced NT-proBNP concentrations (benefit occurred early with biomarker values diverging at 1 week) and the risk of worsening renal function at the expense of more symptomatic hypotension compared with valsartan alone; however, secondary, the hierarchical outcome of CV death, HFH, urgent HF visits and change in NT-proBNP was not significantly different.<sup>322</sup>

In a pre-specified participant-level pooled analysis of PARAGLIDE-HF and PARAGON-HF, ARNI, compared with valsartan, significantly reduced total worsening HF events and CV death [rate ratio (RR) 0.86, 95% CI 0.75–0.98,  $P = 0.027$ ] with statistical significance already reached by Day 9 after randomization; treatment benefits were larger in those with LVEF  $\leq 60\%$  (RR 0.78, 95% CI 0.66–0.91).<sup>323</sup>

### MRA

The TOPCAT trial was found to be neutral; however, the differences in patients and outcomes between the American and non-American cohorts could explain the lack of benefit in the trial.<sup>324,325</sup>

The STRUCTURE trial, including a subset of HFpEF patients with normal LV filling pressure at rest and increased LV filling pressure with exercise, showed an improvement in both exercise capacity and E/e' with spironolactone, with a significant interaction between treatment with spironolactone and E/e' on peak  $VO_2$ .<sup>326</sup>

An individual patient data meta-analysis including 984 patients with HFpEF from three large trials (HOMAGE, Aldo-DHF

and TOPCAT) compared echocardiographic changes in patients on spironolactone versus placebo. The prescription of spironolactone was associated with a reduction in LA volume, LV mass and thickness and improved systolic and diastolic function.<sup>327</sup>

### Semaglutide

In the STEP-HFpEF trial, the glucagon-like peptide 1 (GLP-1) agonist semaglutide administered once weekly at a dose of 2.4 mg for 1 year significantly decreased body weight (13.3% loss vs. 2.6% in the placebo group) and improved the KCCQ clinical summary score and 6 min walk distance among obese HFpEF patients. The main inclusion criteria were BMI above 30 kg/m<sup>2</sup>, NYHA Class II–IV, elevated natriuretic peptide levels (with thresholds stratified according to the BMI at baseline), LVEF > 45% and evidence of echocardiographic abnormalities. Most of the 529 participants (84%) had LVEF ≥ 50%. The decrease in NT-proBNP levels was ~15% greater with semaglutide than with placebo.<sup>328</sup>

The results of the STEP-HFpEF DM trial are now published. Among patients with obesity-related HFpEF and T2DM, semaglutide led to larger reductions in HF-related symptoms and physical limitations and greater weight loss than placebo at 1 year.<sup>329,330</sup>

### Cardiac contractility modulation (CCM)

CCM may improve functional capacity and reduce HFHs. CCM-HFpEF was a single-arm, multicentre pilot study with the aim of assessing the potential benefits of CCM in 47 HFpEF patients. An increase in KCCQ (primary endpoint) by 18.0 (± 16.6) points ( $P < 0.001$ ) was reported. The event-free rate was 93.6%, and the safety profile was good.<sup>331</sup>

### Device-based percutaneous treatments

Interatrial shunt devices might represent a new therapeutic strategy to decompress and reduce LA pressure.<sup>332</sup> Although initial results to reduce LA pressure seemed promising, the consecutive randomized, multicentre, blinded, sham-controlled REDUCE-LAP II trial reported no prognostic benefit,<sup>333</sup> and this might be attributed to latent pulmonary vascular disease (PVD). Schuster *et al.* hypothesized that non-invasive characterization of cardiac and pulmonary physiology, through rest and exercise stress right heart catheterization, echocardiography and CV magnetic resonance, can more accurately select patients who would benefit most from an interatrial shunt device. Among the 75 patients with HFpEF enrolled, 24 had latent PVD, defined as increased PVR ≥ 1.74 Wood units during exercise stress. Patients with PVD had worse RV functional reserve.<sup>334</sup> In the RELIEVE-HF open-label roll-in cohort, including symptomatic HF despite optimal GDMT with ≥1 HF hospitalization in the prior year or elevated natriuretic peptides, interatrial shunting with the Ventura device was safe and resulted in favourable clinical effects, namely, improvement in KCCQ-OSS by 12–16

points at all follow-up time points (all  $P < 0.004$ ), with similar outcomes in patients with reduced and preserved LVEF. Also, improvements in LV and RV structure and function were consistent with reverse myocardial remodelling.<sup>335</sup>

## HF with supranormal EF

Some studies suggested that LVEF might have a U-shaped relationship with outcomes, but results were inconsistent in different cohorts.<sup>336–339</sup>

In RELAX-AHF-2, supranormal (sn) EF (HFsnEF), defined as LVEF ≥ 65%, was associated with a higher risk of non-CV mortality but not all-cause mortality.<sup>340</sup>

Among the 11 573 patients hospitalized for HF and enrolled in the nationwide Japanese registry, 16.8% were classified as HFsnEF. Compared with HF with normal EF (50% ≤ LVEF ≤ 65%), HFsnEF patients were older, more likely to be women, and had lower natriuretic peptide values and smaller left ventricles. They had a similar risk of CV death or HFH and a lower adjusted HR for HFH.<sup>341</sup> In a merged dataset of 33 699 participants who had been enrolled in six randomized controlled HF trials, the incidence of most clinical outcomes (except non-CV death) decreased as LVEF increased, with an LVEF inflection point of around 50% for all-cause death and CV death, around 40% for pump failure death and around 35% for HFH. Higher than those thresholds, there was little further decline in the incidence rate.<sup>339</sup>

Popovic *et al.* showed that HFsnEF patients had a smaller heart size, increased LV diastolic stiffness and leftward shift in the end-diastolic pressure–volume relationship compared with HFpEF.<sup>342</sup>

A reclassification of HF based on different LVEF categories was proposed (LVEF ≤ 35%, LVEF > 35% to <60%–65% and LVEF ≥ 60%–65%).<sup>343</sup>

## Advanced HF

### Definition and prognosis

The 2018 HFA-ESC definition of advanced HF required the presence of all the following criteria despite GDMT: persistence of severe symptoms (NYHA III–IV), severe cardiac dysfunction, episodes of congestion/arrhythmias/low output causing more than one unplanned hospitalization and severe impairment of exercise capacity.<sup>4</sup> The prognostic impact of this definition was shown in a contemporary, real-world, multicentre high-risk cohort of patients with HF and at least one 'I NEED HELP' criterion.<sup>344</sup> A further assessment of the 'I NEED HELP' criteria in this cohort was published.<sup>345,346</sup>

Patients with advanced HF are burdened with very high mortality and present a challenging management.<sup>248,344,347,348</sup>

A systematic review of observational studies including 862 046 patients reported a 1 year mortality rate that ranged from 8.47% for chronic HF to 29.74% for advanced HF patients.<sup>349</sup>

## Pharmacological therapies

Prescription and up-titration of GDMT remained limited also in this high-risk population of 699 patients with HFrEF and at least one 'I NEED HELP' marker for advanced HF enrolled in the HELP-HF registry. Namely, beta-blockers were administered to 574 (82%) patients, ACEi/ARB/ARNI was administered to 381 (55%) patients and 416 (60%) received MRA. Overall,  $\geq 50\%$  of target doses were reached in 41%, 22% and 56% of the patients on beta-blockers, ACEi/ARB/ARNI and MRA, respectively. Reasons for under-prescription were unknown in a significant proportion of patients, suggesting a potential role of clinical inertia.<sup>204</sup>

Inotropes may represent a potentially useful strategy not only in the short term but also in the chronic treatment of advanced HF.<sup>248,348</sup> A recent clinical consensus statement of HFA-ESC reviewed traditional and novel drugs with inotropic effects.<sup>350</sup>

The LeoDOR multicentre, double-blind, randomized trial evaluated the efficacy and safety of intermittent levosimendan therapy (infusion every 3 weeks for 12 weeks) in advanced HF following HFH. The infusion did not improve post-hospitalization clinical stability, even if, due to the COVID-19 pandemic, the statistical power of the study was reduced due to the impossibility of enrolling the planned number of patients.<sup>351</sup>

## Long-term mechanical circulatory support (MCS)

In view of the shortage of heart donors and the difficulty in accessing transplantation due to possible contraindications, long-term MCS devices represent a valid alternative for patients with advanced HF.<sup>352</sup> In an analysis depicting the evolving landscape of LVAD carriers in Europe over 13 years, improved 1 year survival was observed in patients implanted more recently with continuous-flow LVAD, despite older recipients with more comorbidities. This was likely due to increased centre expertise and improved patient selection (less acutely ill) and pump technology.<sup>353</sup>

Nevertheless, severe complications, including bleeding or thrombosis, might occur and require a careful selection of recipients. The ARIES HM3 trial demonstrated that a strategy with a vitamin K antagonist (VKA) alone was non-inferior to combination treatment with VKA and aspirin in patients who underwent implantation with a HeartMate 3 (HM3) LVAD; in addition, survival free from bleeding and stroke seemed to favour the arm without aspirin.<sup>354</sup> Uriel *et al.*

showed a reduction in the incidence of moderate-to-severe de novo AR with the fully magnetically levitated HM3 LVAD compared with the axial-flow HeartMate II LVAD.<sup>355</sup>

## Palliative care

A comparison of 2021 ESC and 2022 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) HF guidelines regarding the provision of palliative care showed nuanced differences.<sup>356</sup> A clinical consensus statement from the HFA of ESC provided practical guidance promoting cultural competence in the management of patients with advanced HF needing palliative care.<sup>357</sup>

## Worsening HF

Worsening HF can be defined as worsening symptoms and signs of HF in patients with pre-existing HF, requiring intensification of treatment, most often diuretic therapy. It requires a prior diagnosis of HF, excluding episodes of new-onset HF.<sup>140</sup> Episodes of worsening HF characterize the clinical course of patients with chronic HF. Worsening HF must be kept distinct from acute HF, which is a much broader entity including also new-onset HF as well as different clinical presentations such as acute pulmonary oedema, RV failure and cardiogenic shock (CS). Sites of care for worsening HF include hospitalization, emergency department visit with IV therapy, generally loop diuretics and ambulatory treatment, either as outpatients receiving IV therapy in an outpatient setting or as outpatients treated with an escalation of their oral diuretic therapy.<sup>140</sup> Episodes of worsening HF are associated with poorer QoL, increased risks of hospitalization and death and are a major burden on healthcare resources.

The results of the VICTORIA and PARAGLIDE-HF trials have been discussed above.

The optimization of GDMT with a fifth drug (vericiguat) in patients who are symptomatic and with LVEF < 45% should be advised after a worsening HF event.

## Acute HF

Hospitalization due to acute HF has a dramatic burden in terms of symptoms, morbidity and mortality.<sup>140,358–361</sup> In a study including 283 048 patients hospitalized for HF from 2008 to 2017 in Australia and New Zealand, HFH was associated with a loss of 7.3 years in life expectancy, compared with the general population. Survival rates were 48%, 34% and 17% at 3, 5 and 10 years, respectively.<sup>360</sup>

## Precipitating factors and prognostic markers

Several precipitating factors have been recognized. Gualandro *et al.* assessed the rate of acute HF after non-cardiac surgery in a large series of 9164 consecutive high-risk patients. The incidence of acute HF after non-cardiac surgery was 2.5% in the general population and 10% in patients with a history of HF. Post-operative acute HF was an independent predictor of all-cause mortality and HF readmissions.<sup>362</sup>

Valvular heart disease is frequently associated with acute HF. On one hand, a new significant valvular lesion can be the cause of acute decompensation; on the other hand, acute HF may worsen an already compromised haemodynamic status caused by a chronic valve disease. A scientific statement of the HFA, the Association for Acute Cardiovascular Care and the European Association of Percutaneous Cardiovascular Interventions provided insights into the epidemiology and treatment options in patients with valvular heart disease (VHD) and acute HF.<sup>363</sup>

Lee *et al.* investigated the relationship between patient-reported symptoms, evaluated by the KCCQ total symptom score (KCCQ-TSS), and pulmonary congestion, assessed by lung ultrasound, physical examination and chest X-ray, in patients with acute HF. A lower KCCQ-TSS was associated with worse NYHA class and peripheral oedema but not with pulmonary congestion.<sup>364</sup> Kapłon-Cieślicka *et al.* assessed prevalence, hospital course and post-discharge outcomes in patients with hyponatraemia in acute HF. Among 8298 patients enrolled in the ESC Heart Failure Long-Term Registry, hyponatraemia at admission (possibly dilutional) was associated with worse in-hospital and post-discharge outcomes, especially if it did not resolve at discharge; conversely, hyponatraemia developing during hospitalization (possibly depletional) was associated with a lower risk.<sup>365</sup>

## Treatment

### Diuretics and decongestion strategy

IV diuretics are the first option for the treatment of congestion in patients hospitalized due to acute HF. Evidence regarding the optimal strategy of diuretic administration is limited. Among the 15 078 patients included in the REPORT-HF registry, the median time-to-diuretics was 67 min (range from 17 to 190 min). Time-to-diuretic administration did not have an impact on in-hospital mortality but was associated with an increase in mortality risk at 30 days, especially in patients at higher risk.<sup>366</sup>

The ADVOR trial examined the effect of acetazolamide on decongestion in patients with acute HF on top of standard loop diuretic therapy. Overall, 519 patients were enrolled (mean age 78 years, 63% male, mean LVEF 43% and median NT-proBNP 6173 pg/mL). The addition of acetazolamide resulted in a greater incidence of the primary endpoint (i.e.,

successful decongestion within 3 days after randomization) with more decongestion also at discharge and a shorter length of hospital stay versus placebo.<sup>367,368</sup> In a pre-specified sub-analysis of the ADVOR trial, acetazolamide on top of standardized loop diuretic therapy did not lead to clinically important hypokalaemia or hyponatraemia and improved decongestion over the entire range of baseline serum potassium and sodium levels.<sup>369</sup> A greater efficacy was hypothesized in patients with baseline or loop diuretic-induced elevated bicarbonate levels (a marker of proximal nephron  $\text{NaHCO}_3$  retention).<sup>370</sup>

The CLOROTIC trial showed a greater decrease in body weight at 72 h and a greater diuretic response with the addition of hydrochlorothiazide (HCTZ), compared with placebo, on top of furosemide in patients hospitalized for acute HF.<sup>371</sup> Patients with  $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$  had greater weight loss compared with those with  $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ , but no significant differences were observed with the addition of HCTZ in terms of diuretic response, mortality or rehospitalizations, or safety endpoints across different eGFR values at baseline.<sup>372</sup>

Torsemide compared with furosemide did not result in a significant difference in all-cause mortality over 12 months among patients discharged after HFH.<sup>373</sup>

Early assessment of urinary sodium (UNa) concentration is useful to assess intrinsic renal sodium avidity.<sup>374</sup> In the PUSH-AHF trial, natriuresis-guided diuretic therapy in patients with acute HF significantly improved natriuresis and diuresis up to 48 h without impacting all-cause mortality and/or HF hospitalization at 180 days.<sup>375</sup>

In patients hospitalized for acute HF, in-hospital initiation of MRAs was associated with improved post-discharge outcomes, independent of LVEF and other potential confounders.<sup>376</sup>

### SGLT2 inhibitors

The EMPULSE trial randomized 530 patients hospitalized for acute HF, when clinically stable, to receive empagliflozin 10 mg once daily or placebo for up to 90 days. Empagliflozin provided a clinical benefit, defined as a hierarchical composite of death from any cause, number of HF events and time-to-first HF event, or a 5-point or greater difference in change from baseline in KCCQ-TSS at 90 days, as assessed using a win ratio (stratified win ratio 1.36, 95% CI 1.09–1.68,  $P = 0.0054$ ).<sup>377</sup> The initiation of empagliflozin resulted also in the improvement of all analysed indexes of congestion in the trial.<sup>233</sup>

In the EMPAG-HF trial, enrolling 60 patients within 12 h of hospitalization for acute HF, early addition of empagliflozin to standard diuretic therapy increased urine output without affecting markers of renal function.<sup>378</sup> Packer and Butler analysed similarities and distinctions in the diuretic effects of acetazolamide and SGLT2 inhibitors.<sup>379</sup>

### Other drugs

The phase 2a SEISMic trial randomized 60 patients with acute HF with pre-CS, defined as systolic blood pressure <90 mmHg without hypoperfusion, venous lactate  $\geq 2$  mmol/L and/or mechanical or inotropic support, to istaroxime 1.0–1.5  $\mu\text{g}/\text{kg}/\text{min}$  or placebo for 24 h. Istaroxime improved systolic blood pressure without significant differences in serious adverse events. The most frequent adverse events were nausea, vomiting and infusion site pain in the istaroxime-treated patients.<sup>380</sup>

Morphine has been used for decades in patients developing acute cardiogenic pulmonary oedema because it reduces anxiety and dyspnoea and improves the vasoconstriction accompanying hypertensive crises but without evidence from RCTs. The MIMO (Midazolam versus MORphine) is a multicentre, open-label RCT comparing midazolam with morphine in patients with pulmonary oedema. The trial was stopped early after a planned interim analysis by the safety monitoring committee. Overall, 111 patients were randomized at that time (55 to midazolam and 56 to morphine). No differences were found in the primary endpoint (in-hospital mortality), but serious adverse events were less common with midazolam versus morphine.<sup>381</sup>

### Cardiogenic shock

The mortality rate in patients with CS remains extremely high.<sup>382</sup>

The Society for Cardiovascular Angiography and Interventions (SCAI) shock stage classification, released in 2019, has been revised.<sup>383</sup> Medical therapy of CS has been recently reviewed.<sup>384</sup>

### Mechanical circulatory support

MCS devices represent an option for the treatment of CS. Schrage *et al.* assessed the association between MCS use and the primary endpoint of 30 day mortality in a 1:1 propensity-matched cohort of patients with non-ischaeamic CS. In the matched cohort, MCS use was associated with a lower 30 day mortality. This finding was consistent through all tested subgroups except when CS severity was considered, indicating risk reduction especially in patients with deteriorating CS. However, complications occurred more frequently in patients with MCS (e.g., severe bleeding and access site-related ischaemia).<sup>385</sup> The large European nationwide observational cohort study (InEK GmbH) included patients with AMI-related CS treated with Impella (ABIOMED, Danvers, MA, USA) and/or veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in 2020–2021. Impella patients were older and less frequently presented after an out-of-hospital cardiac arrest. In-hospital mortality was lower in the Impella

versus VA-ECMO cohort. Adverse events including acute haemorrhagic anaemia (36% vs. 68%,  $P < 0.001$ ), cerebrovascular accidents (4% vs. 11%,  $P < 0.001$ ), thrombo-embolisms of the extremities (5% vs. 8%,  $P < 0.001$ ), systemic inflammatory response syndrome (21% vs. 25%,  $P = 0.004$ ), acute kidney injury (44% vs. 53%,  $P < 0.001$ ) and acute liver failure (7% vs. 12%,  $P < 0.001$ ) occurred less frequently in Impella-supported patients. Impella patients had shorter hospital stays and lower hospital costs. Notably, possible unmeasured and unadjusted confounders might have influenced the results.<sup>386</sup>

The ECLS-SHOCK trial tested whether routine early implementation of extracorporeal life support (ECLS) compared with usual medical treatment alone improved survival in patients with myocardial infarction and CS with planned early revascularization. Enrolled patients were at high risk for adverse outcomes (median lactate level was 6.9 mmol/L; median LVEF was 30%; and 77.7% received cardiopulmonary resuscitation before randomization). Early ECLS therapy did not reduce the risk of death from any cause at the 30 day follow-up versus medical therapy alone, whereas the risk of major bleedings and vascular complications was increased.<sup>387</sup> The results were in line with an individual patient data meta-analysis by Zeymer *et al.*<sup>388</sup> Park *et al.* evaluated the feasibility of an early LV unloading strategy compared with a conventional strategy in VA-ECMO. A total of 60 patients were randomized in a 1:1 ratio to receive early (LV unloading performed at the time of VA-ECMO insertion) or conventional LV unloading strategies. The early LV unloading strategy was performed using a percutaneous transeptal LA cannulation via the femoral vein incorporated into the extracorporeal membrane oxygenation (ECMO) venous circuit. Compared with the conventional approach, early LV unloading did not improve the VA-ECMO weaning rate, despite a rapid improvement in pulmonary congestion. Also, there were no significant differences in survival at discharge.<sup>389</sup>

Varshney *et al.* evaluated outcomes associated with bridging strategies to durable LVAD or heart transplantation in patients with acute decompensated CS from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Patients bridged with VA-ECMO had the highest mortality (22%), followed by catheter-based temporary MCS (10%), intra-aortic balloon pump (9%) and medical therapy (7%).<sup>390</sup>

Further trials testing the use of MCS in patients with severe CS are ongoing.

### Before discharge, early discharge and after discharge

A scientific statement by the HFA summarized recent findings that have implications for clinical management in both the pre-discharge and early post-discharge phases after a hospitalization for acute HF.<sup>141</sup> First, the early detection and

effective treatment of residual or recurrent congestion may reduce the risk of rehospitalization. Second, the initiation and up-titration of GDMT are crucial to improve both the short- and long-term clinical course.<sup>141</sup>

Schrage *et al.* investigated the association of HFH with the initiation or discontinuation of GDMT and consequent outcomes. Among 6893 patients with LVEF < 50% who experienced an HFH from the Swedish HF Registry, hospitalization usually led to the implementation of GDMT, although it remained suboptimal. Early initiation of GDMT was associated with better survival.<sup>391</sup>

In the STRONG-HF trial, an intensive treatment strategy of rapid up-titration of GDMT and close follow-up after an acute HF admission reduced symptoms, improved QoL and reduced the risk of 180 day all-cause death or HFH compared with usual care.<sup>392</sup> Achieving higher doses of GDMT 2 weeks after discharge was feasible and safe in most patients.<sup>393</sup> The high-intensity care (HIC) strategy was safe and significantly reduced all-cause mortality and HFH at 180 days compared with usual care, irrespective of age, sex, baseline systolic blood pressure, LVEF, NT-proBNP, baseline self-assessed health status and non-cardiac comorbidities.<sup>9,34,394–398</sup>

Importantly, early up-titration of GDMT also significantly improved all dimensions of QoL.<sup>398</sup>

In the HIC arm, the following pre-specified safety indicators were used to guide up-titration: eGFR < 30 mL/min/1.73 m<sup>2</sup>, serum potassium >5.0 mmol/L, systolic blood pressure

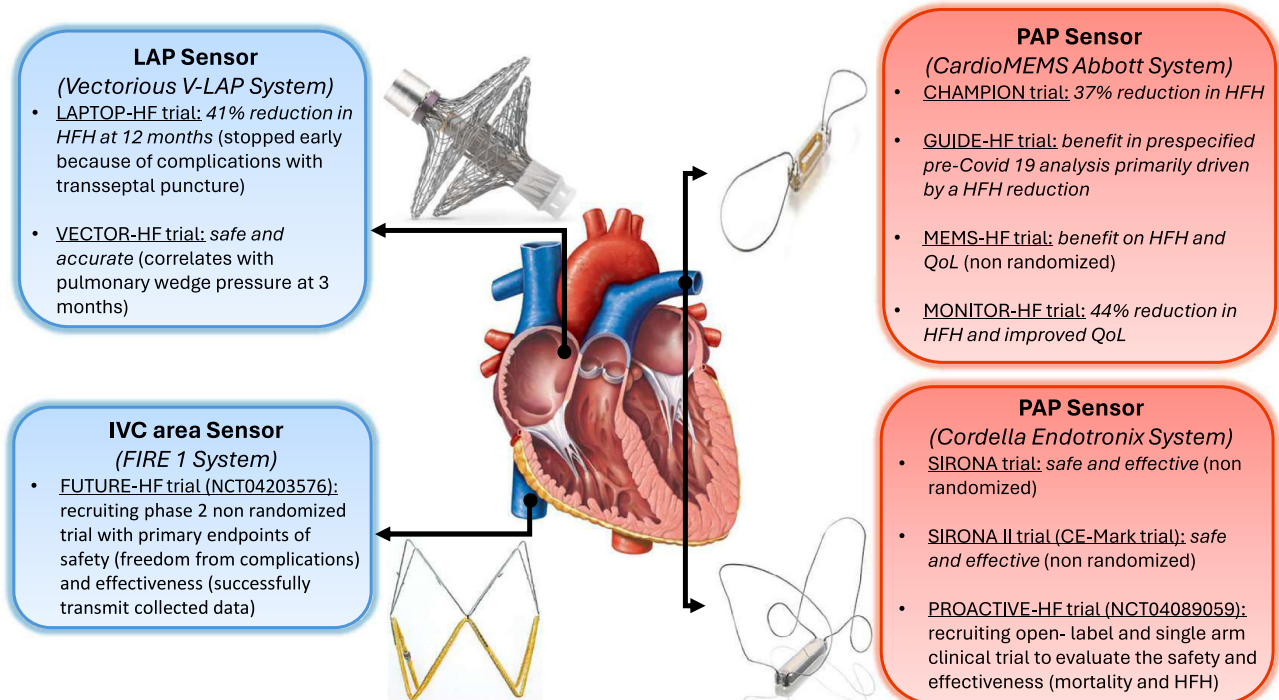
<95 mmHg, heart rate <55 b.p.m. and NT-proBNP > 10% higher than pre-discharge values.<sup>211</sup> Three hundred thirteen of the 542 patients in the HIC arm (57.7%) met ≥1 safety indicator at any follow-up visit 1–6 weeks after discharge. An increase in NT-proBNP was the most frequent safety indicator. These patients achieved slightly lower GDMT doses, but higher than in the usual care group. Importantly, no significant increase in the primary outcome of 180 day HFH or death was reported when safety indicators were appropriately addressed according to the study protocol, highlighting the relevance of close follow-up during rapid and early up-titration of GDMT.<sup>211</sup> An early decrease in eGFR during rapid up-titration of GDMT was associated with more evidence of congestion, yet lower doses of GDMT during follow-up.<sup>399</sup>

Based on the results of the STRONG-HF, recommendations for an intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and frequent and careful follow-up visits in the first 6 weeks following an HFH were introduced.<sup>44</sup>

## Telemedicine and congestion remote monitoring

Remote monitoring in patients with HF includes telemedicine and implantable or wearable devices that can monitor imped-

**Figure 4** Invasive device for haemodynamic pressure monitoring and main findings from trials. HFH, heart failure hospitalization; IVC, inferior vena cava; LAP, left atrial pressure; PAP, pulmonary artery pressure; QoL, quality of life.



ance, pulmonary arterial pressure or arrhythmias. The benefits of non-invasive remote patient management were confirmed across the entire spectrum of LVEF in a pre-specified analysis of the TIM-HF2 trial.<sup>400</sup>

A systematic meta-analysis, including 8 RCTs and 4347 HF patients, compared device-based remote monitoring of congestion to standard therapy; a haemodynamic-guided strategy with invasive devices was associated with a significant reduction in the composite endpoint of all-cause death or HFH mainly driven by the reduction of HFH, while an impedance-guided strategy did not show a significant reduction.<sup>401</sup> The CardioMEMS system is one of the most studied invasive pulmonary arterial pressure monitoring devices. A pre-specified subgroup analysis of the MEMS-HF study showed that the benefits of remote monitoring are confirmed regardless of the presence and subtypes of PH at baseline.<sup>402</sup> In the open-label, randomized MONITOR-HF trial, which enrolled 348 patients with symptomatic HF (NYHA III) and a recent episode of worsening HF, haemodynamic monitoring with CardioMEMS significantly improved QoL and reduced HFH irrespective of the LVEF.<sup>403</sup> Indications for implan-

tation of haemodynamic PA pressure monitoring devices are likely to be strengthened in upcoming guidelines.

Novel devices for congestion monitoring of patients with HF, as an interatrial sensor able to transmit LA pressure or an IVC sensor able to measure IVC cross-sectional area, are being studied (Figure 4).<sup>404–406</sup>

## Conclusions

In recent years, there has been great progress in the management of HF. The 2021 ESC guidelines for the management of HF established the four pillars of HFrEF treatment with ACEI/ARNI, beta-blockers, MRA and SGLT2 inhibitors. A fifth drug, vericiguat, is becoming available across several countries for patients experiencing an episode of worsening HF. SGLT2 inhibitors are the first class of drugs recommended for the treatment of HFmrEF and HFpEF in the 2023 focused update of HF guidelines.

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