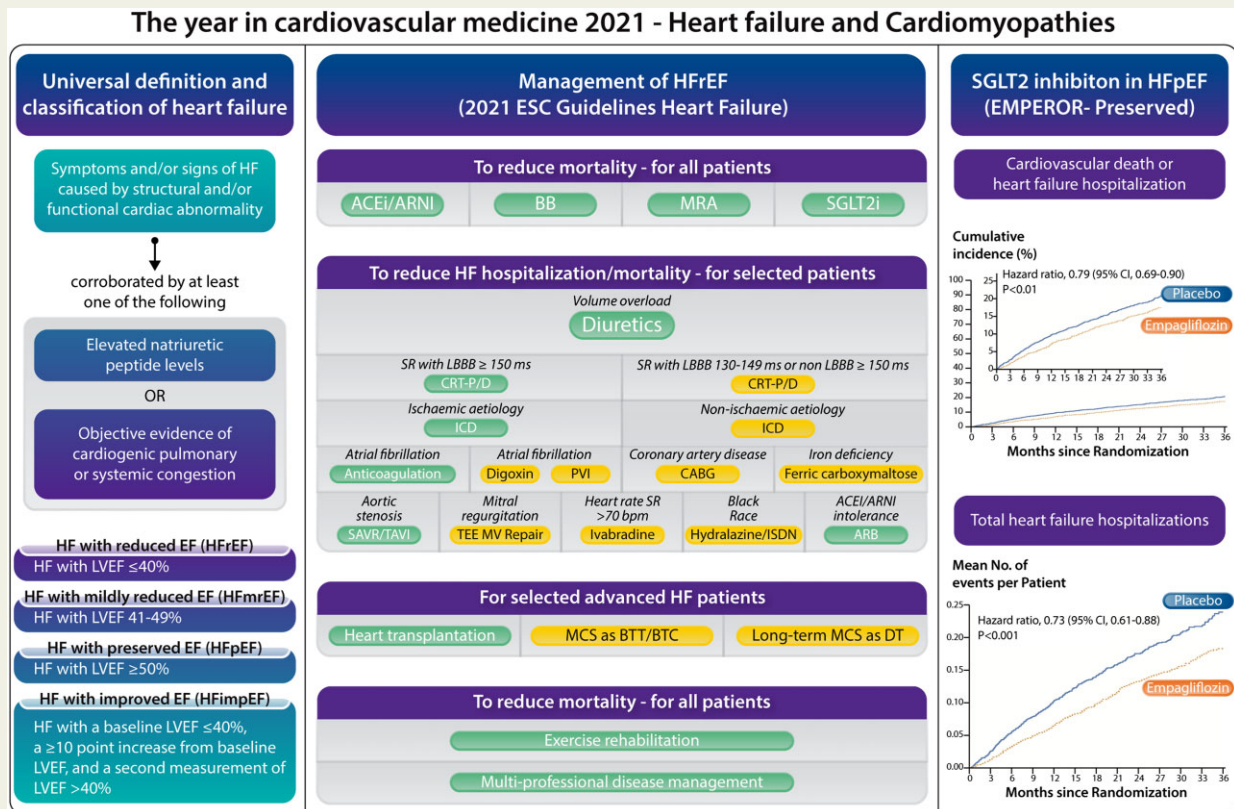


# The year in cardiovascular medicine 2021: heart failure and cardiomyopathies

Johann Bauersachs <sup>1\*</sup>, Rudolf A. de Boer <sup>2</sup>, JoAnn Lindenfeld<sup>3</sup>, and Biykem Bozkurt <sup>4</sup>

<sup>1</sup>Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg-Straße 1, 30625 Hannover, Germany; <sup>2</sup>Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands; <sup>3</sup>Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA; and <sup>4</sup>Winters Center for Heart Failure, Cardiology, Baylor College of Medicine and Michael E. DeBakey VA Medical Center, Houston TX, USA

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**Graphical Abstract** Summary of the universal definition and EF classification of heart failure; management of HFrEF according to 2021 ESC guidelines for heart failure and results of the EMPEROR-preserved trial.

\* Corresponding author. Tel: +49 511 532 3841, Fax: +49 511 532 5412, Email: [bauersachs.johann@mh-hannover.de](mailto:bauersachs.johann@mh-hannover.de)

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In the year 2021, the universal definition and classification of heart failure (HF) was published that defines HF as a clinical syndrome with symptoms and/or signs caused by a cardiac abnormality and corroborated by elevated natriuretic peptide levels or objective evidence of cardiogenic congestion. This definition and the classification of HF with reduced ejection fraction (HFrEF), mildly reduced, and HF with preserved ejection fraction (HFpEF) is consistent with the 2021 ESC Guidelines on HF. Among several other new recommendations, these guidelines give a Class I indication for the use of the sodium–glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin in HFrEF patients. As the first evidence-based treatment for HFpEF, in the EMPEROR-Preserved trial, empagliflozin reduced the composite endpoint of cardiovascular death and HF hospitalizations. Several reports in 2021 have provided novel and detailed analyses of device and medical therapy in HF, especially regarding sacubitril/valsartan, SGLT2 inhibitors, mineralocorticoid receptor antagonists, ferric carboxymaltose, soluble guanylate cyclase activators, and cardiac myosin activators. In patients hospitalized with COVID-19, acute HF and myocardial injury is quite frequent, whereas myocarditis and long-term damage to the heart are rather uncommon.

**Keywords** Heart failure • Epidemiology • Imaging • Biomarkers • Pharmacotherapy • Artificial intelligence • SGLT-2 inhibitor • Angiotensin receptor–neprilysin inhibitors • Activators of soluble guanylate cyclase • Device therapy

## Introduction

Heart failure (HF) remains a major challenge for patients and healthcare systems worldwide. For patients suffering from HF with reduced ejection fraction (HFrEF), several evidence-based treatments are available and have markedly improved prognosis and quality of life; however, a subset of these patients displays a rapid progression of HF despite best care. A recent special article called to action for global approaches to novel drug solutions for these patients,<sup>1</sup> but also for patients with HF with preserved EF (HFpEF), for whom until recently there was not a single evidence-based treatment.

In this article, we summarize important progress that has been made in 2021 regarding the diagnosis and treatment of HF with a special focus on articles published in 2021 in the *European Heart Journal* and the *European Journal of Heart Failure*.

## Definition and classification of heart failure

With the recognition of the need for standardization of an HF definition, the Universal Definition and Classification of Heart Failure was developed, which defined HF as a clinical syndrome with current or prior symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide (NP) levels or objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities (Figure 1).<sup>2</sup> It also provided revised definitions for stages of HF, categorized as 'At-Risk for HF' (former Stage A) for patients at risk for HF but without current or prior symptoms or signs of HF and without structural cardiac changes or elevated biomarkers of heart disease; Pre-HF (former Stage B) for patients without current or prior symptoms or signs of HF but evidence of structural heart disease, abnormal cardiac function, elevated NP levels or elevated cardiac troponin levels; 'Heart Failure' (former Stage C) for symptomatic patients, 'Advanced HF' (former Stage D) for patients with severe symptoms and/or signs of HF (Figure 1). Ejection fraction categories were classified as HFrEF: left ventricular (LV) EF  $\leq 40\%$  (Figure 1); HF with mildly reduced EF (HFmrEF): LVEF 41–49%; HFpEF: LVEF  $>50\%$ ; and HF with improved EF

(HFimpEF): HF with a baseline LVEF  $\leq 40\%$ , a  $\geq 10$  point increase from baseline LVEF, and a second measurement of LVEF  $>40\%$ . The EF categories used in the recent 2021 ESC HF Guidelines were consistent with these classifications.<sup>3</sup> In the Universal Definition of HF, there was also an emphasis on trajectories of HF and to use 'persistent HF' instead of 'stable HF' for patients with ongoing symptoms/signs and 'HF in remission' instead of 'recovered HF' for patients with resolution of symptoms and signs of HF or with the resolution of previous structural/functional heart disease<sup>2</sup> (Figure 1). Though a simple definition of HF predominantly depending on NPs was proposed as an alternative,<sup>4</sup> limitations of such an approach due to variability of NP levels by age, sex, body mass, renal function, and atrial fibrillation; and lack of specificity and lack of evidence in linking treatments to a biomarker-based approach were identified as significant barriers to a simply biomarker-based approach in definition of HF.<sup>4</sup>

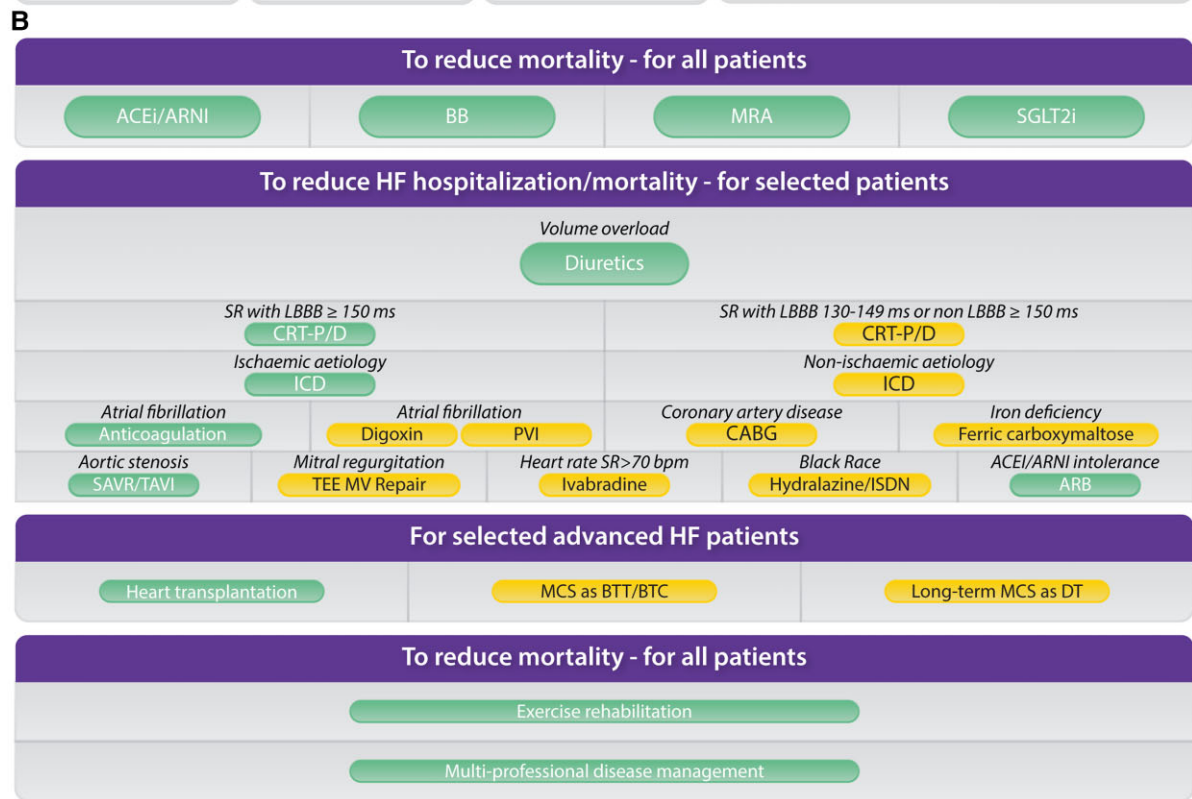
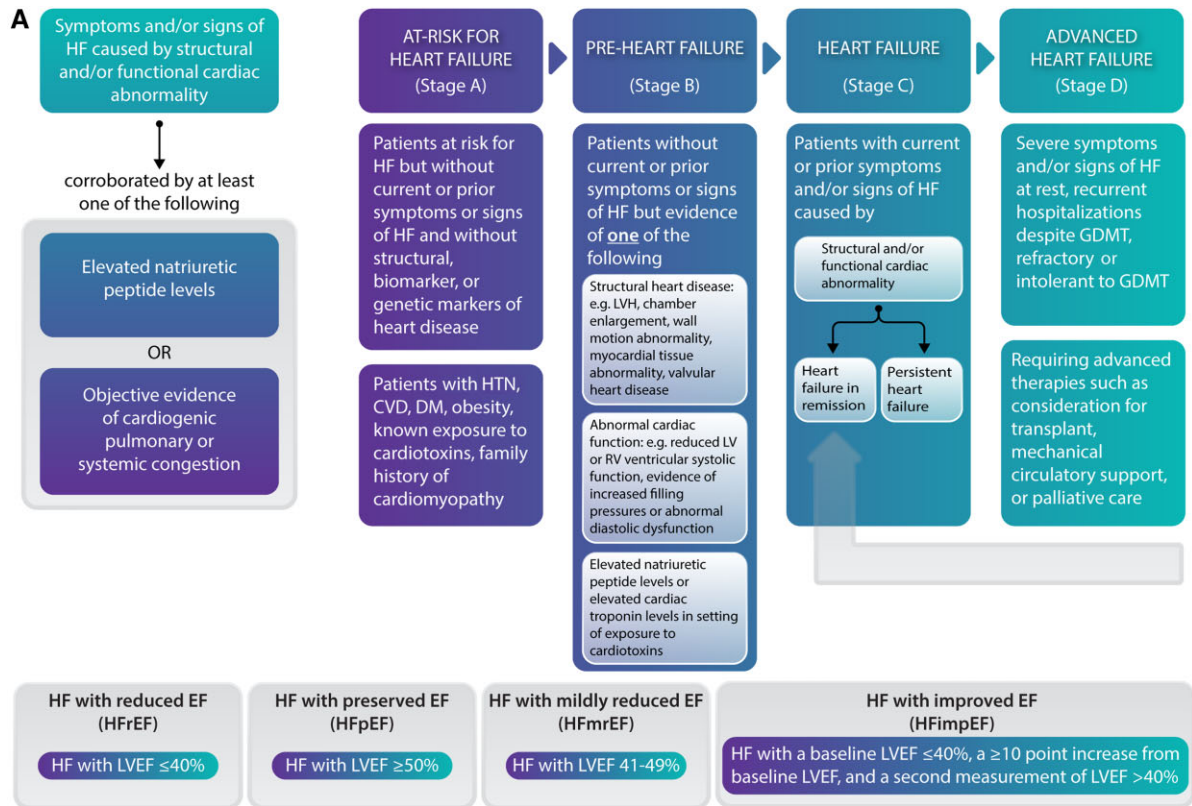
## Epidemiology

The HF Atlas survey reports a wide-ranging incidence of HF and HF hospitalizations across Europe with considerable heterogeneity in the resources for management and the data quality providing data to allow the development of strategies to improve inequalities.<sup>5</sup> Exposure to ambient air pollutants increases the risk of HF in a dose-dependent fashion, and there was a particularly high risk of HF among persons with genetic higher susceptibility to HF (Figure 2).<sup>6</sup> Air pollution probably should be considered in risk scores to predict HF.

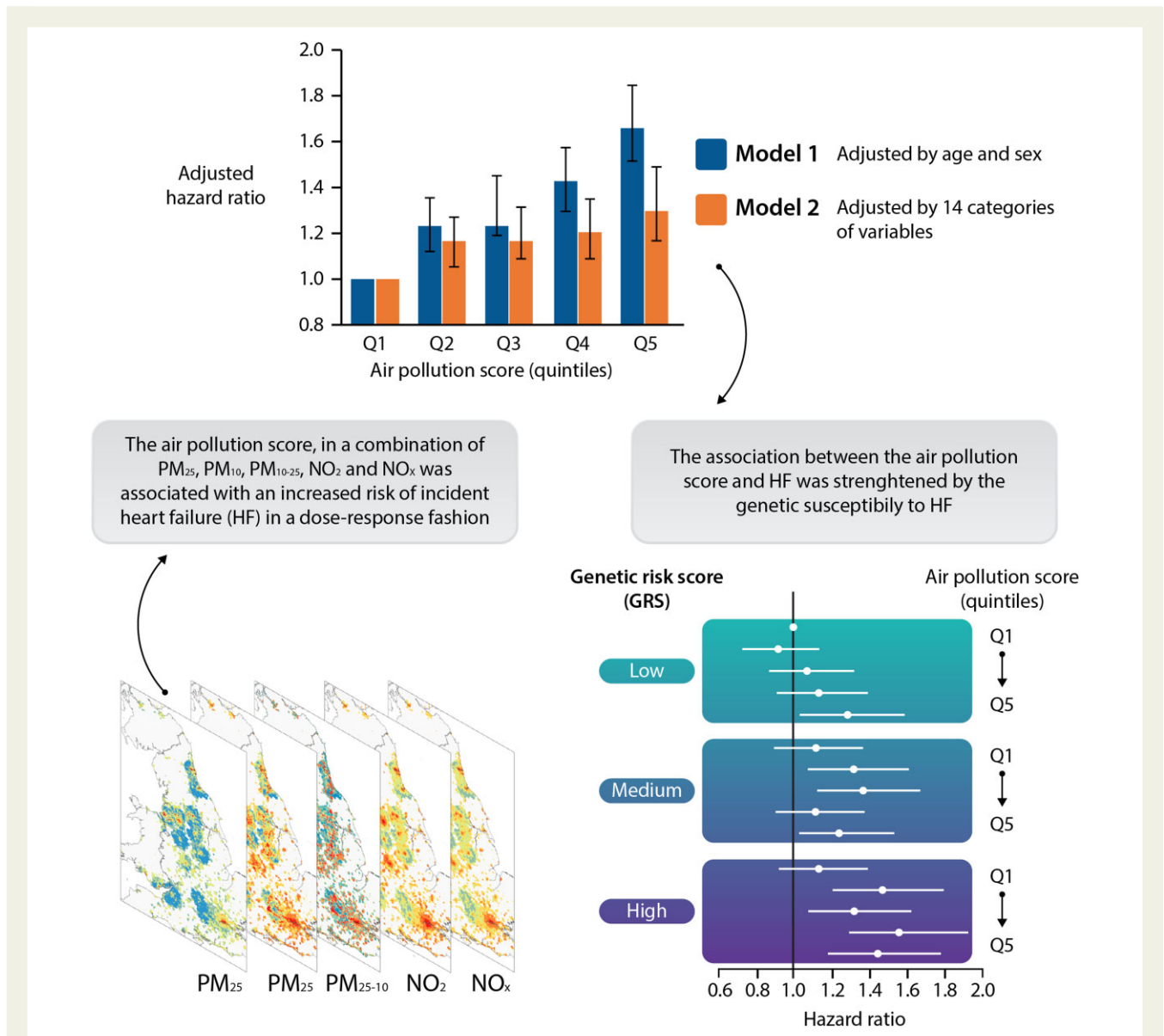
A recent European registry report demonstrated that dilated cardiomyopathy (DCM), not skeletal myopathy, is the major determinant of prognosis in patients with dystrophin gene mutations.<sup>7</sup> Finally, cancer and HF occur more commonly together than predicted by risk models, and a recent study suggests that statins reduce the risk of both and have a greater risk reduction with more prolonged use.<sup>8</sup>

## Diagnostics and risk stratification

For HFrEF, the main diagnostic criterion remains LVEF  $\leq 40\%$ .<sup>3</sup> However, there is more controversy in the other categories,



**Figure 1** (A) Universal definition of heart failure (upper left panel) and new classification of heart failure according to left ventricular ejection fraction (lower panel) and stages of heart failure (upper right panel). Reprinted from Bozkurt *et al.*<sup>2</sup> (B) Overview of the management of pharmacological treatment of heart failure with reduced ejection fraction according to 2021 ESC Guidelines on Heart Failure. Reprinted with permission from McDonagh *et al.*<sup>3</sup>



**Figure 2** Long-term joint exposure to various air pollutants, including PM<sub>2.5</sub>, PM<sub>10</sub>, PM<sub>2.5-10</sub>, NO<sub>2</sub>, and NO<sub>x</sub> is associated with an elevated risk of incident heart failure in an additive manner. Persons with genetic higher susceptibility to heart failure displayed a particularly high risk of heart failure. Reprinted with permission from Wang *et al.*<sup>6</sup>

HFmrEF and HFpEF. Pieske *et al.*<sup>9</sup> formulated, on behalf of the ESC, new diagnostic criteria, including echo parameters, NPs, and if a definitive diagnosis cannot be made, to turn to stress testing and/or invasive haemodynamics.

There is increasing appreciation that classical diagnostics fall short in complex multifactorial diseases with various aetiologies and precipitants, and several studies have addressed whether an agnostic approach, where large data sets are queried by computer algorithms, may be superior in making a specific diagnosis. Such techniques are referred to as machine learning (ML) and artificial intelligence (AI). Peyster *et al.*<sup>10</sup> used an automated image analysis to detect rejection after heart transplantation and described a 'Computer-Assisted Cardiac Histologic Evaluation (CACHE)-Grader' pipeline that was

non-inferior to the rejection grading provided by independent pathologists. Another field of research for which AI provides an attractive tool is the categorization of patients who received a general diagnosis of HF. Verdonschot *et al.*<sup>11</sup> studied 795 consecutive DCM patients with data on aetiology and co-morbidities, imaging studies and endomyocardial biopsies, and identified four distinct phenogroups. Woolley *et al.*<sup>12</sup> using an algorithm based on 363 biomarkers to phenotype, 429 patients with HFpEF identified four clusters with different clinical parameters and important differences in prognosis.

Artificial intelligence/machine learning might be particularly useful for a diagnosis of HF. Kwon *et al.*<sup>13</sup> evaluated data from 34 103 patients who underwent echocardiography and electrocardiogram (ECG) and created an ML algorithm that could detect HFpEF.

Segar *et al.*<sup>14</sup> employed ML models to aid in predicting race-specific risk for incident HF.

In the near future, we will be faced with many more potential utility of AI/ML models, as there is a clear need for individualized approaches and decision-making.<sup>15</sup> It will be essential, however, to provide recommendations as to what input is (minimally) required for models, and the models must be prospectively tested in independent settings. Furthermore, treatment decisions based on the models must be tested in a randomized blinded fashion.<sup>16</sup>

## Imaging and biomarkers

A state-of-the-art diagnosis of HF remains challenging. The ESC guidelines<sup>3</sup> recommend using an array of signs and symptoms, supplemented with imaging and biomarkers studies. The imaging primarily relies on echocardiography and CMR, and NPs and high sensitivity troponins are the preferred biomarkers. However, sophisticated classification of patients in various categories using imaging and biomarkers may enhance adequate phenotyping,<sup>11,17</sup> and imaging of non-cardiac tissues such as fat may have relevance to HF phenotyping, too.<sup>18,19</sup> Furthermore, next-generation genetic analyses has been shown to have a consequence for prognosis<sup>20</sup> and diagnosis<sup>21</sup> of HF. In addition, a recent article highlighted the indications of endomyocardial biopsies.<sup>22</sup>

## Specific situations

### Acute heart failure

The 2021 ESC guidelines did not significantly change recommendations for acute HF, although the use of opioids was downgraded to a Class III recommendation.<sup>3</sup> Evidence continues to accrue supporting the use of urinary sodium in assessing outcomes in acute HF.<sup>23,24</sup>

### Cardiogenic shock

Mortality remains high in cardiogenic shock, and randomized trials assessing therapies remain rare but a single-centre trial randomized patients with cardiogenic shock to either milrinone or dobutamine and showed no differences in any of the primary or secondary outcomes.<sup>25</sup> In the follow-up of the IMPRESS trial in cardiogenic shock, there was no difference in mortality comparing intra-aortic balloon pumps vs. the Impella device at 5 years.<sup>26</sup> A biomarker composite outperformed other risk scores for cardiogenic shock using 4 biomarkers [Cystatin C, Lactate, interleukin-6, and N-terminal pro brain natriuretic peptide (NT-proBNP)].<sup>27</sup> A recent consensus statement outlines important suggestions for optimizing cardiogenic shock trials.<sup>28</sup>

### Ventricular assist devices and heart transplantation

A single entry registry confirms that HeartMate III (HMIII) outcomes are better than historical controls confirming randomized trials.<sup>29</sup> The stroke rate with HMIII is less than with the Heartware ventricular assist device (HVAD)—one of several reasons the HVAD has been withdrawn from use.<sup>30</sup> Disappointingly, left ventricular assist devices (LVAD) use does not reduce

myocardial fibrosis nor does a new risk score improve the prediction of right ventricular failure post-LVAD, but on the bright side, elderly patients have benefits in quality of life and exercise capacity with LVADs.<sup>31–33</sup> There is substantial inter-observer variability in the diagnosis of cellular rejection in myocardial biopsies but automated computation image analysis may allow improved standardization as described in the section on Diagnostics and Imaging. Non-invasive prediction of rejection in cardiac transplant recipients has been elusive, but studies using peripheral blood cell-free DNA show promising early results.<sup>34</sup>

### Pregnancy/patients with peripartum cardiomyopathy

Women with a known cardiomyopathy or at risk for HF planning pregnancy, or presenting with HF during or after pregnancy are in need of individualized pre-, during, and post-pregnancy assessment and counselling.<sup>35</sup>

Patients with peripartum cardiomyopathy are at risk for detrimental outcomes<sup>36,37</sup> but often do recover from HFrEF. Recent publications investigated the value of ECG abnormalities for predicting echocardiographic results and the role of hypertensive disorders during pregnancy.<sup>38,39</sup>

### Hypertrophic cardiomyopathy/ amyloidosis

In the health status analysis of EXPLORER-HCM, mavacamten markedly improved the health status of patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM) compared with placebo.<sup>40</sup> Gaps in evidence for risk stratification for sudden cardiac death in HCM were summarized by Pelliccia *et al.*<sup>41</sup> In a study by Marston *et al.*<sup>42</sup> using Sarcomeric Human Cardiomyopathy Registry, patients with childhood-onset HCM were reported more likely to have sarcomeric disease, carry a higher risk of life-threatening ventricular arrhythmias, and have a greater need for advanced HF therapies. In the German Cardiac Society position statement, Yilmaz *et al.*<sup>43</sup> outline a diagnostic algorithm to detect cardiac amyloidosis, to accurately determine its extent, and to reliably identify the underlying subtype of amyloidosis, thereby enabling subsequent targeted treatment.

### Cancer

Heart failure often complicates the treatment of cancer, and a recent paper proposes definitions of cardiovascular (CV) toxicities.<sup>44</sup> Classically, chemotherapy and radiotherapy have been identified as risk factors, but in the recent decade, immunotherapy with immune checkpoint inhibitors (ICIs) is becoming the mainstay of cancer treatment. However, ICIs also carry a risk for CV side effects. D'Souza *et al.*<sup>45</sup> reported on this risk in a Danish registry and show that ICI is associated with a 1.8% 1-year risk for (peri-)myocarditis, and with an almost 10% risk for any CV complication. Given the increasing use of ICI, this issue will require clinical guidance and further study, as ICIs have an impact on several cells and tissues.<sup>46,47</sup> There are initial reports providing guidance as to treat ICI-induced myocarditis.<sup>48,49</sup>

This field extends the increasing awareness that incident cancer is more common in patients with prevalent HF,<sup>50</sup> and that cancer

and HF may be connected more closely than anticipated before. In support of this, Ren *et al.*<sup>8</sup> demonstrated that the use of statins reduces incident cancer. Finally, a special article by Zannad *et al.*<sup>51</sup> discusses aspects of cancer research that may be applicable to HF research, with the aim of streamlining the clinical trial process and decreasing the time and cost required to bring safe, effective, treatments to HF patients.

## Pharmacotherapies

### New algorithm of the 2021 ESC Guidelines on heart failure for the pharmacological treatment of heart failure with reduced ejection fraction

The 2021 ESC Guidelines on HF provide a Class I recommendation for pharmacological treatment of all HFrEF patients with a combination of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor–neprilysin inhibitor (ARNI), a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium–glucose co-transporter 2 (SGLT2) inhibitor (dapagliflozin or empagliflozin) (Figure 1B).<sup>3</sup> The guideline still recommends the use of ARNI as a replacement for ACE inhibitor; however, an ARNI may also be considered as a first-line therapy instead of an ACE inhibitor. It is recommended that these four disease-modifying drugs are initiated within a short time frame.<sup>3,52</sup> Potential advantages of another algorithm for the sequencing of these drugs have been suggested by McMurray and Packer<sup>53</sup> with beta-blockade and SGLT2 inhibition as first-line therapies. However, albeit appealing from a pathophysiological standpoint such a new sequence is not yet evidence-based.

A recent consensus document of the HFA of the ESC identified nine patient profiles that may be relevant for treatment implementation in patients with HFrEF taking into account heart rate, atrial fibrillation, symptomatic low blood pressure, estimated glomerular filtration rate, or hyperkalaemia. Using such a personalized approach may lead to a better and more comprehensive therapy for each individual patient.<sup>54</sup>

### Angiotensin-converting enzyme inhibition

While ACE inhibitors are a standard for the prevention and treatment of HF for many years, the impact of these drugs as preventive therapy for HF in patients with Duchenne muscular dystrophy was unclear. A large French registry showed that prophylactic treatment of patients without LV dysfunction with an ACE inhibitor was able to prevent the transition to HF and improve survival in Duchenne muscular dystrophy.<sup>55</sup>

### Angiotensin receptor–neprilysin inhibitors (PARAGON, PARADIGM, PARALLAX, PARADISE-MI, LIFE)

In an analysis of the PARADIGM-HF trial, initiation of sacubitril/valsartan, even when titrated to target dose, did not lead to greater discontinuation or down-titration of other guideline-directed medical therapies and was associated with fewer discontinuations

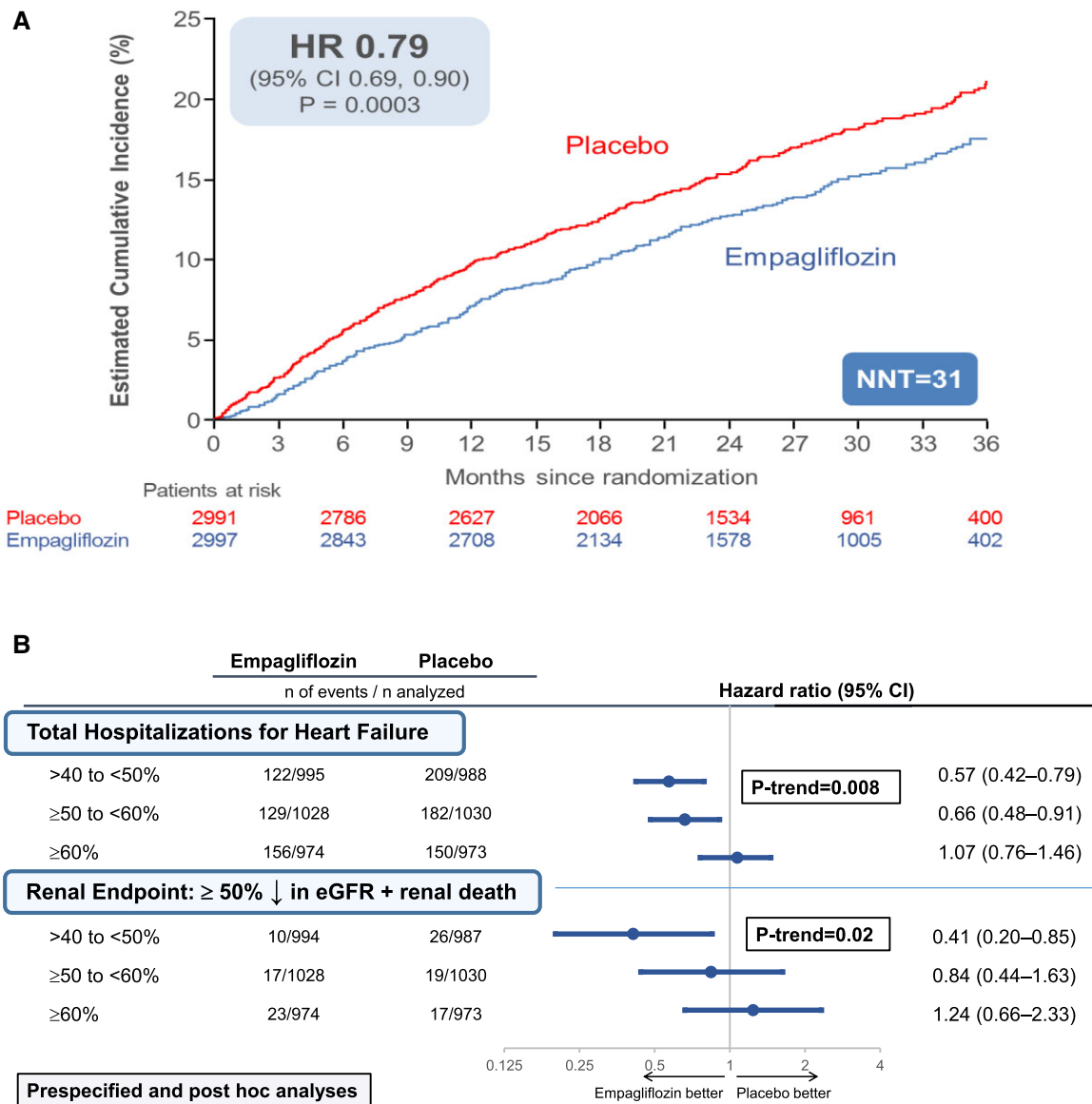
of MRA.<sup>56</sup> In real-world patients with HFrEF, sacubitril/valsartan was effective, safe, and well tolerated.<sup>57–60</sup> Sacubitril–valsartan was found to be useful in treating resistant hypertension in HFrEF in the PARAGON-HF trial when compared with valsartan.<sup>61</sup> In the PROVE-HF trial, in patients with HFrEF, 32% improved their EF to >35% by 6 months and 62% to >35% by 12 months after initiation of sacubitril/valsartan therapy.<sup>62</sup> In patients with asymptomatic LV systolic dysfunction late after myocardial infarction, treatment with sacubitril/valsartan did not have a significant reverse remodelling effect compared with valsartan.<sup>63,64</sup> In the PARADISE-MI trial,<sup>65</sup> sacubitril/valsartan did not significantly reduce the rate of CV death, HF hospitalization, or outpatient HF requiring treatment in patients with LVEF ≤40% and/or pulmonary congestion following acute myocardial infarction, compared with ramipril (results presented at the ACC). In the Sacubitril/Valsartan in Patients with Advanced Heart Failure with Reduced Ejection Fraction in the Advanced Heart Failure (LIFE-HF) trial, which enrolled NYHA Class IV patients and LVEF ≤35%, sacubitril/valsartan did not improve the clinical composite endpoints (presented at ACC 2021). PARALLAX trial will determine if sacubitril/valsartan improves NT-proBNP levels, exercise capacity, quality of life, and symptom burden in HF patients with EF >40%.<sup>66</sup>

In the new 2021 ESC Guidelines on HF,<sup>3</sup> sacubitril/valsartan is recommended as a replacement for an ACE inhibitor in patients with HFrEF as a Class I recommendation. Initiation of sacubitril/valsartan in ACE inhibitor naive patients with HFrEF on the other hand is suggested as a Class IIb recommendation.<sup>3</sup>

### Sodium–glucose co-transporter 2 inhibitors (EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, SOLOIST)

Sodium–glucose co-transporter 2 inhibitors are rapidly becoming the panacea for the entire spectrum of cardiometabolic and renal disease. In trials in type 2 diabetes mellitus (T2DM), a beneficial effect was observed for CV endpoints in general, while the effects on incident HF were overwhelmingly positive. These effects were validated in patients with prevalent HFrEF, first in DAPA-HF and a year later in the EMPEROR-Reduced trial. Numerous subanalyses from these trials were published in 2021.

First, besides the striking effects on hard endpoints, it is more and more recognized that functional status and symptoms are important to patients with HFrEF.<sup>67</sup> Both in DAPA-HF and EMPEROR-Reduced, these were improved,<sup>68,69</sup> although a smaller dedicated trial with empagliflozin did not improve functional status.<sup>70</sup> Further, a series of subanalyses showed no interaction of SGLT2 inhibitors with common HF drugs, such as MRAs, and most importantly, also not with sacubitril/valsartan.<sup>71,72</sup> Furthermore, the equal effects of the drugs were ascertained by analysing the effects across countries and ethnicities.<sup>73</sup> Another striking observation was that dapagliflozin was associated with a lower incidence of new-onset diabetes.<sup>74</sup> Collectively, to date, we have not seen any analysis suggesting a differential or lesser effect of SGLT2 inhibitors in HFrEF. We therefore must start to learn how to employ these drugs practically.<sup>52,75</sup>



**Figure 3** SGLT2 inhibition (EMPEROR-Preserved). (A) EMPEROR-Preserved enrolled 5988 patients with heart failure with preserved ejection fraction and followed them up for a mean of 26 months. The primary endpoint (a composite of cardiovascular death or heart failure hospitalization) was reduced by 21%, translating in a number needed to treat of 31. (B) In a pooled analysis of the EMPEROR-Reduced and -Preserved trials, it was observed that in the higher left ventricular ejection fraction range, the relative benefit of the SGLT2 inhibitor empagliflozin may be attenuated. In the figure, the effects of empagliflozin HF hospitalization and renal outcomes are visualized for the left ventricular ejection fraction 40–50, 50–60, and >60% categories. There is a significant trend towards lesser efficacy in the higher left ventricular ejection fraction categories. Reprinted with permission from <https://www.nejm.org/doi/full/10.1056/NEJMoa2107038>.

Different from HF<sub>r</sub>EF, the efficacy of SGLT2 inhibitors in HF<sub>p</sub>EF remained to be proven. However, the EMPEROR-Preserved study presented during ESC 2021 demonstrated that empagliflozin reduced the primary combined endpoint of CV death and HF hospitalization in almost 6000 patients with HF<sub>p</sub>EF (Figure 3). These data are extremely important and provide hope for millions of HF<sub>p</sub>EF patients for whom there were no evidence-based therapies. Over a median follow-up of 26 months, the primary outcome event occurred in 13.8% of the patients in the empagliflozin group and in 17.1% in the placebo group [hazard ratio (HR): 0.79; 95%

confidence interval (CI): 0.69–0.90;  $P < 0.001$ ]. Empagliflozin was very effective in reducing HF hospitalization, but all-cause mortality was not reduced. The effects of empagliflozin were consistent in patients with or without diabetes.<sup>76,77</sup> Shortly, the result of the second mortality trial in HF<sub>p</sub>EF with the SGLT2 inhibitor dapagliflozin, DELIVER, will be presented.<sup>78</sup>

Sodium–glucose co-transporter 2 inhibitors were also evaluated in patients with acute HF or immediately after acutely decompensated HF. The SOLOIST trial,<sup>79</sup> with the mixed SGLT 1/2 inhibitor sotagliflozin, enrolled 1244 patients with T2DM and recent

worsening HF and showed a beneficial effect of the study drug, initiated before or shortly after discharge, with regard to a significantly lower total number of CV deaths and HF hospitalizations and urgent visits for HF. The ongoing EMPULSE trial will provide more data in the acute HF arena.<sup>80</sup>

Sodium–glucose co-transporter 2 inhibitors do not stop to amaze us in renal disease. After the publication of the hallmark trials CREDENCE and DAPA-CKD,<sup>81</sup> in 2021, the SCORED trial<sup>82</sup> came out, demonstrating in patients with T2DM and chronic kidney disease, allocated to sotagliflozin or placebo, a reduction of 37% in the primary endpoint of CV death and HF events (HR: 0.74; 95% CI: 0.63–0.88;  $P < 0.001$ ). However, sotagliflozin was associated with adverse events such as diarrhoea, genital mycotic infections, volume depletion, and diabetic ketoacidosis.

### Mineralocorticoid receptor antagonists (FIDELIO, FIGARO, HOMAGE)

Mineralocorticoid receptor antagonists are first-line therapies for HFrEF and may also be considered in HFmrEF.<sup>3</sup> Novel non-steroidal MRA such as finerenone differ from steroidal MRA regarding tissue distribution, MR binding, recruitment of cofactors, and downstream gene expression.<sup>83</sup> In FIDELIO-DKD, finerenone improved CV and kidney outcomes in patients with chronic kidney disease and T2D regardless of baseline HF status (G. Filippatos, 2021, submitted for publication). In FIGARO-DKD, finerenone reduced the primary composite endpoint of death from CV causes, non-fatal myocardial infarction, non-fatal stroke, or HF hospitalization with the benefit driven primarily by a lower incidence of HF hospitalization.<sup>84</sup> In HOMAGE, in patients with, or at high risk for, coronary disease and raised NP levels, no interaction between baseline serum galectin-3 and changes in procollagen collagen biomarkers induced by spironolactone treatment was observed. However, blood pressure and NT-proBNP were reduced by spironolactone.<sup>85</sup>

### Activators of soluble guanylate cyclase (VICTORIA)

The novel activator of soluble guanylate cyclase, vericiguat, in a subanalysis of the VICTORIA trial, did not reduce new-onset atrial fibrillation. However, pre-existing atrial fibrillation did not affect the beneficial effect of vericiguat on the primary composite outcome (time to CV death or first HF hospitalization) or its components.<sup>86</sup> Similarly, beneficial effects of vericiguat were consistent across the full range of renal function.<sup>87</sup>

### Cardiac myosin activators

A substudy of the pivotal trial of the myosin activator omecamtiv mecarbil (GALACTIC-HF) in patients with HFrEF found that the drug reduced the primary endpoint of HF hospitalization and CV death more as EF declined with a 17% decrease in the lowest quartile ( $EF \leq 22\%$ ) and no benefit in the highest quartile ( $EF \geq 33\%$ ).<sup>88</sup>

### Ferric carboxymaltose (AFFIRM-AHF; IRON-CRT)

Iron deficiency is related to worse outcomes in HF. The AFFIRM-AHF study demonstrated that in patients with LVEF

$< 50\%$  and iron deficiency after a hospitalization for acute HF, i.v. treatment with ferric carboxymaltose did not only reduce HF hospitalizations but also results in clinically meaningful beneficial effects on quality of life.<sup>89</sup> In HFrEF patients with iron deficiency and a persistently reduced LVEF  $< 45\%$  after cardiac resynchronization therapy (IRON-CRT) study, i.v. ferric carboxymaltose FCM improved cardiac structure and function, as well as quality of life.<sup>90</sup>

Iron deficiency also contributes to resistance to endogenous erythropoietin, an important cause of anaemia in HF.<sup>91</sup>

### Others

In a small clinical trial, CDR132L, an antisense oligonucleotide drug directed against miR-132 was well tolerated and seemed to be associated with cardiac functional improvement in HF patients.<sup>92–94</sup>

In 50 patients with idiopathic chronic DCM and parvovirus B19 persistence, i.v. immunoglobulin therapy did not significantly improve LV systolic function or functional capacity beyond standard medical therapy.<sup>95</sup>

## Device and interventional therapies

### Cardiac resynchronization therapy

In patients with HF, atrial fibrillation and a narrow QRS mortality and HF hospitalizations were reduced by atrioventricular junctional ablation and cardiac resynchronization therapy (CRT) compared with pharmacological treatment alone; this beneficial effect was similar in patients with LVEF  $\leq 35\%$  and  $> 35\%$ .<sup>96</sup> Guidelines for CRT and suggestions for optimized implementation have recently been published.<sup>97,98</sup> The controversy about whether adding an ICD to CRT provide additional mortality benefit, especially in non-ischaeic HF continues.<sup>99</sup>

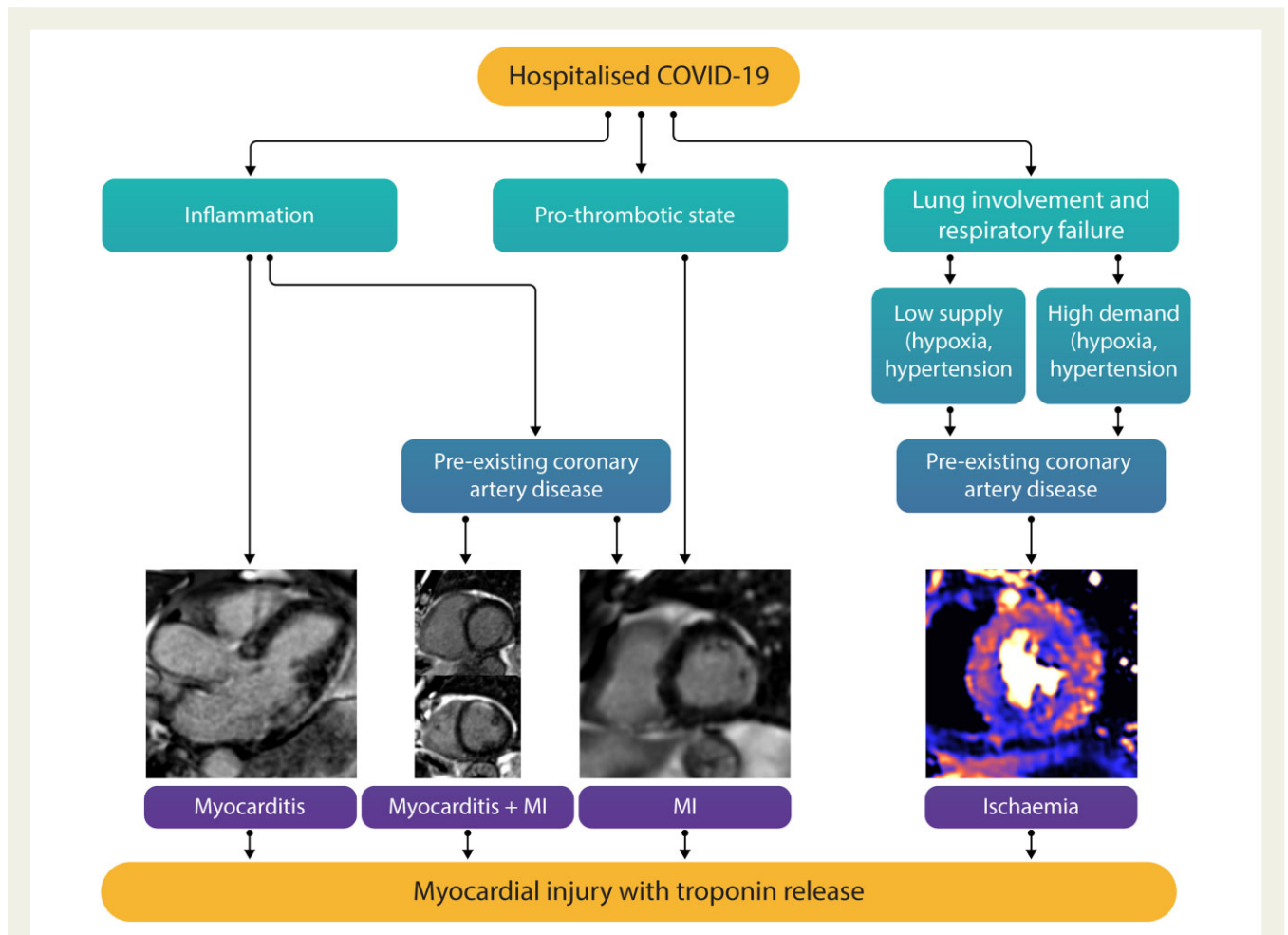
### Percutaneous mitral valve repair

The US Valvular Disease Guidelines as well as the 2021 ESC Guidelines on valvular heart disease recently upgraded the recommendation for transcatheter mitral valve repair (TEER) for secondary (functional) mitral regurgitation (SMR) to a IIA recommendation for patients who meet COAPT criteria.<sup>100,101</sup> A joint position statement from the ESC supports this recommendation.<sup>102</sup> The 3-year results of the COAPT trial demonstrate the ongoing benefit of TEER.<sup>103</sup> An important secondary analysis from COAPT demonstrates that residual 3–4+ SMR is the strongest risk factor for poor outcomes in both the TEER group and in the medical therapy group.<sup>104</sup> In patients with atrial fibrillation, TEER was associated with a lower risk of stroke.<sup>105</sup> Subgroups of MITRA-FR mimicking COAPT patients did not show a benefit of TEER, although a subgroup of COAPT mimicking MITRA-FR patients did show a benefit in HF hospitalizations.<sup>106,107</sup>

### Implantable haemodynamic monitors

The GUIDE-HF trial evaluated haemodynamic guided management to reduce HF hospitalizations and mortality in patients with NYHA II-IV and all ejection fractions. The overall analysis was negative but when COVID-19 was accounted for there was





**Figure 4** Myocardial injury in recovered COVID-19 patients assessed by cardiovascular magnetic resonance. Myocarditis-like injury can be encountered, with limited extent and minimal functional consequence. Reprinted with permission from Kotecha et al.<sup>127</sup>

a significant reduction in HF hospitalization in NYHA II-III patients with either a previous HF hospitalization or elevated NPs.<sup>108</sup>

## Specific management

### Telemedicine and remote monitoring

In a comprehensive review, Bekfani and colleagues discuss unmet needs in the management of patients with HF, how remote monitoring might contribute to future solutions and provide an overview of current and novel remote monitoring technologies.<sup>109</sup> A great variety of innovative remote monitoring technologies and algorithms including patient self-managed testing, wearable devices, technologies integrated into clinically indicated therapeutic devices, such as pacemakers and defibrillators, and landmark clinical trials of remote monitoring were reviewed.

### Rehabilitation

In an Expert Panel consensus document on Cardiac Rehabilitation for Patients with Heart Failure, Bozkurt et al.<sup>110</sup> provide an overview of efficacy and safety evidence of exercise training and cardiac

rehabilitation in HFrEF and HFpEF, recommendations on practical approaches to exercise training and cardiac rehabilitation in patients with HF and examine the reasons and solutions for underutilization of cardiac rehabilitation in HF patients. In the REHAB-HF trial, in a diverse population of older patients who were hospitalized for acute decompensated HF, an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical function domains resulted in greater improvement in physical function than usual care. This is an important study demonstrating the safety and efficacy of initiation of progressive rehabilitation initiated during and early post-hospitalization in HF patients regardless of LVEF.<sup>111</sup>

## Heart failure during the COVID-19 pandemic

Incident acute HF was recognized as a complication in 2%, and myocardial injury in 10% of all patients hospitalized with COVID-19.<sup>112</sup> Elevated admission NT-proBNP levels were associated with higher mortality,<sup>113</sup> and cardiac myocyte-specific

microRNAs were upregulated in critically ill COVID-19 patients indicating cardiac involvement.<sup>114</sup> Declining overall admission rates for HF<sup>115</sup> and higher out-of-hospital mortality rates<sup>116</sup> during lockdown were recognized as alarming issues, reflecting lack of access to care among patients with established HF. Randomized trials demonstrated the safety of continuation of ACE inhibitors or ARB among patients hospitalized with COVID-19.<sup>117–119</sup> Dapagliflozin treatment did not significantly reduce organ dysfunction or death, but was well tolerated in patients hospitalized with COVID-19 (DARE-19 trial).<sup>120</sup> Myocarditis emerged as a rare complication of COVID-19 mRNA vaccinations, especially in young men.<sup>121</sup> Benefit–risk assessment for COVID-19 vaccination was favourable for all age and sex groups; and almost all patients with myocarditis had resolution of symptoms and signs.<sup>121</sup> Long-term complications of SARS-CoV-2 infection include persistent sinus tachycardia, postural orthostatic tachycardia syndrome, atrial arrhythmia, and cardiomyopathy.<sup>122</sup> Among athletes recovering from COVID-19, several CMR studies reported varying rates and degrees of cardiac abnormalities suggestive of myocarditis.<sup>123,124</sup> Screening by troponin, ECG, echocardiography, and additional CMR and/or stress echocardiography if abnormal, resulted in only 0.6% of the athletes being restricted to return to sports, and none had cardiac events.<sup>125</sup> Though myocardial injury is common in COVID-19, and SARS-CoV-2 RNA can be detected in the heart, myocarditis is an uncommon pathologic diagnosis occurring in 4.5% of highly selected cases undergoing autopsy or endomyocardial biopsy.<sup>126</sup> During convalescence after severe COVID-19 infection with troponin elevation, myocarditis-like injury can be detected by CMR, however, with limited extent and minimal functional consequence (Figure 4).<sup>127</sup>

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