

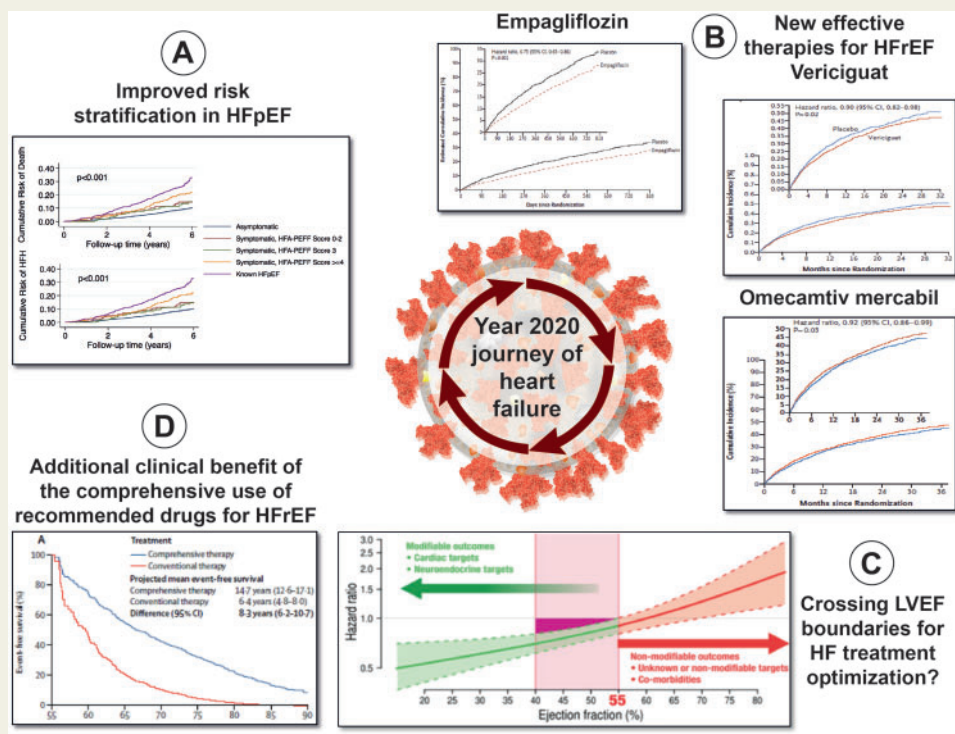
# The year in cardiovascular medicine 2020: heart failure and cardiomyopathies

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## Graphical Abstract



During year 2020, we learned new options to better stratify patients with heart failure and preserved left ventricular ejection fraction (HFpEF) (A), the clinical benefit of three new drugs to improve prognosis of patient with heart failure and reduced left ventricular ejection fraction (HFrEF): empagliflozin, vericiguat and omecantiv mecarbil (B), the potential benefit of a broader utilization of recommended drugs for HFrEF in patients with left ventricular ejection fraction higher than 40% (C), and the potential added clinical benefit of a comprehensive use of recommended drugs for HFrEF (D) in a year marked by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic (central cartoon). Reprinted or adapted from: (A) Selvaraj et al.,<sup>23</sup> (B) Packer et al.,<sup>115</sup> Armstrong et al.,<sup>126</sup> and Teerlink et al.,<sup>132</sup> (C) Böhm et al.,<sup>100</sup> (D) Vaduganathan et al.<sup>139</sup>

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## Keywords

Heart failure • Epidemiology • Clinical practice • Imaging • Biomarkers • Pharmacotherapy • Randomized control trials • SGLT-2 inhibitor • Angiotensin receptor–neprilysin inhibitors • Activators of soluble guanylate cyclase • Cardiac myosin activators and inhibitors • Telemedicine

## Introduction

Heart failure (HF) prevalence remains high worldwide with significant sex-related and regional differences in its presentation, management, and outcomes. In 2020, advances in biomarkers and imaging techniques were reported for the diagnosis and prognosis of diastolic dysfunction, HF with preserved ejection fraction or monitoring cardiotoxicity; a new definition of HF with recovered left ventricular ejection fraction (LVEF) was released. Benefits of renin–angiotensin–aldosterone system inhibitors and  $\beta$ -blockers may extend to patients with an LVEF up to 55%. Sacubitril–valsartan improved LV remodeling, biomarker levels, and rates of sudden cardiac death. Two studies investigating the sodium–glucose cotransporter 2 inhibitors empagliflozin and sotagliflozin in patients with HF were reported: the EMPEROR-Reduced trial in patients with HF with reduced EF with or without type 2 diabetes (T2DM) demonstrated a significant reduction in cardiovascular (CV) death and HF hospitalisations (HFH). In patients with T2DM and HF across the whole EF spectrum after a recent HFH, the SOLOIST trial showed a reduction in the primary endpoint of CV deaths, total HFH, and urgent visits for HF. In addition, in patients with kidney disease with or without diabetes mellitus (DAPA-CKD), dapagliflozin prevented the deterioration of renal function. Two novel drugs, the activator of soluble guanylate cyclase vericiguat and the myosin activator omecamtiv mecarbil, in the large outcome trials VICTORIA and GALACTIC-HF predominantly reduced HFH in high-risk patients with worsening HF. In the AFFIRM-AHF trial, intravenous ferric carboxymaltose reduced HFH in patients with iron deficiency after an HF decompensation.

Year 2020 will be remembered as the year of coronavirus disease of 2019 (COVID-19). The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a massive impact on global health and economy. When this article is published, >80 million people will have been infected and >1.75 million will have died of the disease. Many others will have died or worsened their diseases, many with cardiovascular (CV) disease, as an indirect effect of the fear to seek assistance or the collapse of healthcare systems. Yet, advances in science and medical care continued developing during the year. This article reviews important advances in the field of heart failure (HF) presented in 2020.

## Epidemiology

More than 64 million people are living with HF in the world, with an estimated prevalence of 1–2% among adults in developed countries, most often with several comorbidities (Figure 1).<sup>1</sup> The incidence of HF may be stabilizing globally, with decreases in higher-income countries,<sup>2</sup> but increases in lower-income countries, and a shift towards HF with preserved ejection fraction (HFpEF), and increasing due to population ageing and the increase in obesity.<sup>1</sup> Age, traditional risk factors for HF,

a sedentary lifestyle, and social deprivation are associated with incident HF.<sup>3</sup> Actually, lifestyle and social determinants of health are attracting more attention in the epidemiology and care of patients with HF.<sup>4</sup> In patients with new-onset HF, the most common first events are cardiac events (36%), recurrent HF (28%), and death (29%).<sup>5</sup>

Non-traditional risk factors, such as pacemaker implantation may play a role in the development of HF: within the first 2 years after implantation in patients without known HF, the incidence of fatal and non-fatal HF is 10.6%, six times higher than for age- and gender-matched individuals without HF and pacemaker.<sup>6</sup>

Mortality rates of HF seem to be declining less rapidly than previously in the general population.<sup>1</sup> Among patients with cardiac resynchronization therapy (CRT), a gradual decrease in sudden cardiac death risk has been observed since the early 2000s<sup>7</sup> with implications for the role of implantable defibrillators and the design of comprehensive HF care models.

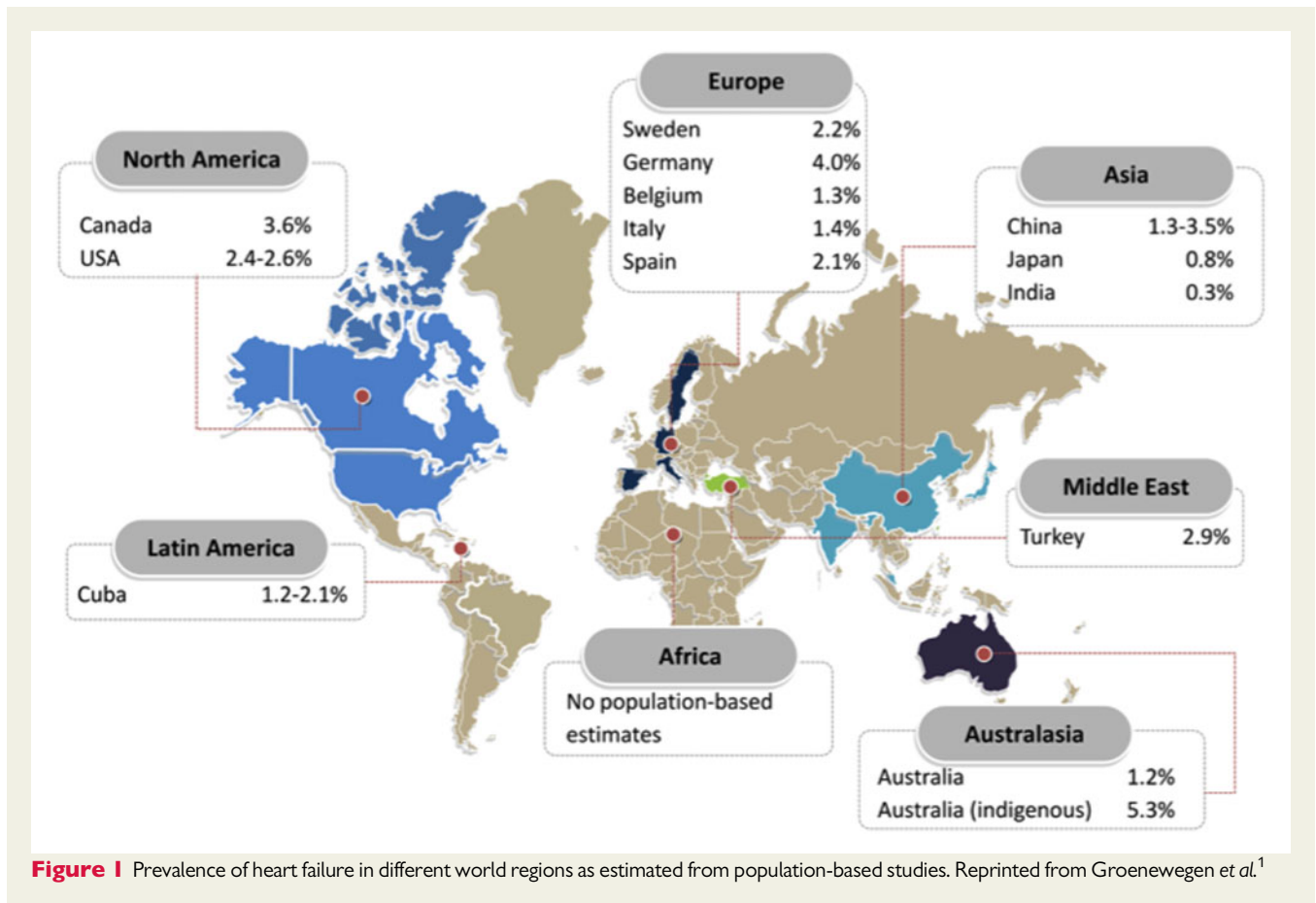
Significant regional differences in the management of acute HF have been identified, including timing and types of treatments used,<sup>8</sup> and rates and time trends of readmission.<sup>2,9,10</sup> However, the importance of distinguishing worsening/chronic HF from new-onset HF in patients with first hospitalization has been highlighted, as patients with worsening/chronic HF have a significantly greater comorbidity burden and higher adjusted risks of mortality and HF readmission.<sup>10,11</sup>

## Clinical aspects

### Diagnostics and risk stratification

#### Imaging

Imaging is pivotal in the diagnosis and risk stratification of patients with HF. The European Society of Cardiology (ESC) Heart Failure Association (HFA) has recently highlighted in a position statement the central role of full echocardiographic examination in patients admitted for acute heart failure (AHF).<sup>12</sup> Once the patient is stabilized, the added value of routine cardiac magnetic resonance (CMR) over echocardiography alone to help diagnose the causes of HF not related to ischaemic heart disease has been questioned.<sup>13</sup> Selective rather than routine CMR for identifying specific HF aetiologies is more cost effective. Noteworthy, CMR could serve to better define HFpEF phenotypes and to select patient specific therapies, such as MRA may be for HFpEF patients with myocardial fibrosis.<sup>14–17</sup> The diagnosis of HFpEF remains challenging especially in patients with coexisting conditions that account for dyspnoea. Diastolic dysfunction, left atrial enlargement, elevated left atrial pressure, and pulmonary hypertension are common in these patients.<sup>18,19</sup> The 2016 diastolic dysfunction grading algorithm proposed by the European Association of Cardiovascular Imaging has shown improved prognostic value compared to the 2009 one.<sup>20</sup> However, the high number of patients with doubtful classification renders clinical decision making



challenging.<sup>21</sup> The analysis of LA mechanics, LA strain, and left ventricular (LV) global longitudinal strain<sup>22</sup> allows to better classify the degree of diastolic dysfunction and improves individual risk stratification. Two algorithms (H<sub>2</sub>FPEF and ESC HFA-PEFF) may facilitate HFpEF diagnosis. These two scores have equivalent predictive power of incident HF hospitalization or death among patients without a clinical diagnosis of HF.<sup>23</sup> Although LV ejection fraction (LVEF) is key for HF classification, it remains a crude estimate of LV function. Intriguingly, 17% of patients with initially preserved LV systolic function show a decrease in LVEF below 40% at 6 months follow-up, which is associated with more cardiac events.<sup>24</sup> Parameters of LV mechanics (LV strain, multilayer strain and myocardial work) provide incremental prognostic information over LVEF.<sup>22,25</sup> The benefit of treatment [i.e. sacubitril/valsartan (SV)] on LV remodelling is also better captured by LV strain.<sup>26</sup> Myocardial mechanics is linked to coronary microvascular dysfunction in patients with hypertensive HF.<sup>27,28</sup> In AHF, cardiac sympathetic nerve dysfunction, as evaluated by <sup>123</sup>I-metaiodobenzylguanidine imaging, is associated with poor outcome irrespective of LVEF.<sup>29</sup>

### Biomarkers

Biomarkers are key for diagnosis and prognostic evaluation in patients with HF. Circulating biomarkers related to extracellular matrix regulation were abnormal in patients with HFpEF, displayed prognostic value, and were influenced favourably by SV in PARAGON-

HF.<sup>30</sup> In HF with reduced LVEF (HFrEF), absolute NT-proBNP, hs-TnT, and sST2 levels predict outcomes independent of age, sex, and LVEF category.<sup>31</sup> Differential circulating levels of biomarkers associated with ageing in patients with HF have been reported, with increasing levels of proteins associated with extracellular matrix organization, inflammatory processes, and tumour cell regulation and lower expression of tumour proliferation functions.<sup>32</sup>

In AHF, a specific challenge is to identify infection as a trigger of AHF. Procalcitonin (PCT) has emerged as an alternative for C-reactive protein in diagnosing bacterial infection. In a recent randomized, multicentre, open study, a strategy of PCT-guided initiation of antibiotic therapy was more effective than standard care in improving clinical outcomes.<sup>33</sup> Omics phenotyping is likely the next frontier to unravel disease mechanisms and heterogeneity.<sup>34</sup> As a recent example, incorporating a panel of three metabolite-based biomarkers into a risk score improved the prognostic utility of NT-proBNP by predicting long-term CV death.<sup>35</sup>

### Heart failure during the COVID-19 pandemic

The role of the angiotensin-converting enzyme (ACE) receptor 2 in the infection of human cells by SARS-CoV-2 and in the pathophysiology of COVID-19,<sup>36</sup> and the poor prognosis of cardiac patients with COVID-19<sup>37</sup> raised the concern of a potential deleterious effect of the treatment with ACE inhibitors and angiotensin receptor

blockers (ARB). These drugs may either decrease acute lung damage, prevent angiotensin-II-mediated pulmonary inflammation or increase the SARS-CoV-2 pulmonary damage by the up-regulation of ACE2 receptors.<sup>38,39</sup> Observational studies refuted the hypothesis of a deleterious effect of ACEI/ARB.<sup>40–43</sup> The BRACE CORONA trial found no worse outcomes in patients with COVID-19 allocated to continuation or interruption of their chronic ACEI/ARB treatment (presented at the ESC Congress, data not published). The incidence of AHF or decompensation of chronic HF among patients with Covid-19 is high and with poor prognosis.<sup>44</sup> Indirect effects of the pandemic included the reduction in HF hospitalizations during local outbreaks<sup>45–47</sup> with increases in their hospital mortality,<sup>45,47</sup> and major challenges for the management and Follow-up of HF patients, and the conduct of clinical trials. Recommendations to overcome these challenges have been released.<sup>48–50</sup>

## Sex and heart failure

Women account for half of patients with HF with a lower incidence rate until the age of 75 years, a higher proportion of HFpEF, probably related to the higher prevalence of obesity and diabetes mellitus.<sup>1</sup> Women with HF present a greater symptom burden and poorer quality of life as compared with men.<sup>51</sup> Significant sex-related differences have been described in Europe in the management of acute and chronic HF<sup>8,52</sup> including a lower use of guideline-directed medical therapies—which seem to be mostly explained by older age and comorbidity rather than by sex itself—with lower crude rates of death and HF hospitalization in women. The lack of sex-related differences in the clinical effect of HF therapies<sup>53,54</sup> does not justify these differences, although the possibility has been suggested that women with HF might benefit from treatment to a higher level of LVEF than previously considered.<sup>54</sup> A different perspective of the gender gap in HF is the lower proportion of female authors in HF practice guidelines and trials, ranging between 11% and 24% only, with modest increases over time in European and US guidelines references but not in HF trials. Importantly, HF trials with a woman first or senior author are associated with a higher proportion of enrolled female participants.<sup>55</sup>

## Comorbidities

Comorbidities are important because they impact the clinical presentation, management, and outcomes of HF patients. The burden of comorbidities is higher in older patients, women and those with HFpEF,<sup>56–58</sup> which are often ignored.<sup>59</sup> Particularly relevant conditions in HF patients include atrial fibrillation,<sup>60</sup> which has complex interrelations with HF needing more research.<sup>61,62</sup> One example is the lack of increase in mortality risk associated with elevated heart rate in patients with HFpEF and atrial fibrillation, as compared to sinus rhythm.<sup>60,63</sup> Renal disease is one other, with renal function often changing during the course of the disease or as a response to HF therapies. Clinical responses, including worsening renal function and pseudo-worsening renal function, and their pathophysiological correlates, i.e. tubular function (diuretic response) beyond estimated glomerular filtration rate (eGFR), need to be understood to be properly managed, adapting therapies to the changing situation.<sup>64,65</sup>

## Specific situations

### Acute heart failure

In patients with acute HFpEF, istaroxime, an inhibitor of the sarcolemmal Na<sup>+</sup>/K<sup>+</sup> pump activating the SERCA2a pump, improved cardiac function without major adverse effects in a small mechanistic trial.<sup>66</sup> Cimlanod, a nitroxyl donor infused over 48 h, was reasonably well tolerated at a lower dose whereas higher doses caused unacceptable hypotension. There was improvement of NT-ProBNP but not on dyspnoea (presented at HFA Discoveries, data not published). A number of position papers have summarized the role of imaging<sup>12</sup> or the management of AHF in specific situations, such as acute coronary syndromes<sup>67</sup> or atrial fibrillation.<sup>68</sup>

### Cardiogenic shock

While its incidence seems to be decreasing, cardiogenic shock still conveys a high mortality risk.<sup>69</sup> A new clinical classification,<sup>70</sup> and two position papers<sup>71,72</sup> on cardiogenic shock have been published this year. The SWEdish evaluation of left Ventricular Assist Device (SweVAD) will examine the impact of mechanical circulatory support vs. guideline-directed medical therapy on survival in a population of AHF patients ineligible for heart transplant.<sup>73</sup>

### Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is the first cause of HF in women during/after pregnancy.<sup>74–76</sup> The ESC EORP registry on PPCM enrolled >700 women with this condition from 49 countries. It showed that PPCM affects women from any region or ethnicity. Within 6 months after diagnosis, the average rates of maternal mortality, readmission, and neonatal mortality were, respectively, 6%, 10%, and 5%, with marked regional variations. Recovery of LVEF occurred in 46% of women.<sup>77</sup> The management of these patients is reviewed in a recent paper.<sup>78</sup>

### HF with recovered left ventricular ejection fraction

This year, a working definition of HF with recovered left ventricular ejection fraction (HFrecEF) has been proposed. This includes: (i) documentation of a decreased LVEF < 40% at baseline; (ii) ≥10% absolute improvement in LVEF; and (iii) a second measurement of LVEF >40%.<sup>79</sup> Reverse LV remodelling is associated with improved myocyte and LV chamber contractility and better clinical outcomes. However, a significant proportion of patients with HFrecEF develop recurrences of LV dysfunction and HF. Despite improvements in structural and functional abnormalities, many of the multilevel molecular changes occurring during LV remodelling remain dysregulated in reverse remodelled hearts. Therefore, guideline-directed medical and device therapy for patients with HFrecEF should be continued indefinitely with close clinical follow-up.<sup>79</sup>

### HF in cancer patients

The role of CV imaging in cancer patients receiving cardiotoxic therapies has been highlighted in a position statement by the HFA<sup>12</sup> and in the European Society for Medical Oncology guidelines.<sup>80</sup> The role of focus echocardiography<sup>81</sup> and CMR<sup>82</sup> has also been recently discussed. In daily practice, caution should, however, be given if using

late gadolinium enhancement or qualitative T2-weighted STIR imaging-only approach for the exclusion of checkpoint inhibitor-associated myocarditis.<sup>83</sup> Imaging is cornerstone for monitoring cardiotoxicity and identifying subtle impairment of myocardial function occurring prior crossing the traditionally defined threshold of LV systolic dysfunction (LVEF < 50%).<sup>84,85</sup>

## Right ventricular dysfunction (RVD)

RV and right atrium dysfunction contribute to HFpEF pathophysiology. Also, RV dysfunction (lower RV systolic velocity and RV fractional area change) and impairment in RV-pulmonary artery coupling are more frequently found in HFpEF patients developing acute lung congestion with exercise.<sup>86</sup> Activation of the endothelin and adrenomedullin neurohormonal pathways is associated with pulmonary haemodynamic derangements, reduced RV functional reserve, reduced cardiac output, and more severe impairment of peak  $\text{VO}_2$  in HFpEF patients.<sup>87</sup> The most common causes of RVD are left-sided heart diseases (46%), pulmonary thromboembolic disease (18%), chronic lung disease/hypoxia (17%), and pulmonary arterial hypertension (11%). Average 1-year mortality in patients with RVD is high (>40%), highest among chronic lung disease patients.<sup>88</sup> The presence of RVD at CRT implantation predicts worsening LV remodelling and survival.<sup>89</sup>

## Pharmacotherapies

### Angiotensin receptor–neprilysin inhibitors (paragon, paradigm, parallax)

Angiotensin receptor–neprilysin inhibitor (ARNI) showed, in a sub-analysis of PARADIGM-HF, a reduction in sudden cardiac death risk regardless of the use of implantable cardiac defibrillators.<sup>90</sup> Reduction in ventricular volumes and increase in LVEF have been observed with standard echocardiography in patients after 6 months on SV, but improvement in global longitudinal strain is apparent after 3 months.<sup>26</sup> In a small cohort of patients with end stage renal disease, SV showed efficacy and safety.<sup>91</sup> The LIFE Trial, comparing SV to valsartan in NYHA Class IV HFREF patients, although prematurely interrupted because of the COVID 19 pandemic, will still provide information about ARNI as a treatment option for advanced HF patients.<sup>92</sup>

The PARALLAX trial tested the efficacy of SV vs. optimal individualised background therapy in HFpEF patients and found a reduction in NT-proBNP from baseline to 12 weeks but no effect on six-minute walk distance from baseline to 24 weeks (presented at ESC 2020—data not published). In the PARAGON Trial in patients with HFpEF, SV did not result in a lower rate of total hospitalizations for HF and death. Of the 12 pre-specified subgroup analyses, sex and LVEF appeared to modify the effect of SV vs. valsartan on the primary composite outcome. Although no benefit was apparent in men, there was a significant reduction in HF hospitalizations in women.<sup>93</sup> Also, patients seemed to derive more benefit from SV when started early after hospitalization.<sup>94</sup> Baseline and mean achieved systolic blood pressure of 120–129 mm Hg identified the lowest risk HFpEF patients, but the blood pressure-lowering effects of SV did not account for its effects on outcomes, regardless of sex.<sup>95</sup> Compared with valsartan, SV reduced the risk of renal events and slowed the decline in estimated glomerular filtration rate.<sup>96</sup> Reduction in serum uric acid was also associated with

improved outcomes.<sup>97</sup> A meta-analysis assessing the efficacy of different renin–angiotensin–aldosterone system (RAAS) antagonists in clinical trials performed in HFpEF patients (PEP-CHF, CHARM-preserved, I-PRESERVE, TOPCAT, PARAGON-HF) showed no statistical difference in all-cause and CV mortality among RAAS antagonists and placebo, but a significantly decreased risk in HF hospitalizations in patients allocated to receive ARNI compared with controls (OR, 0.73, 95% CI, 0.61–0.87) and ARB (OR 0.80, 95% CI, 0.71–0.91).<sup>98</sup>

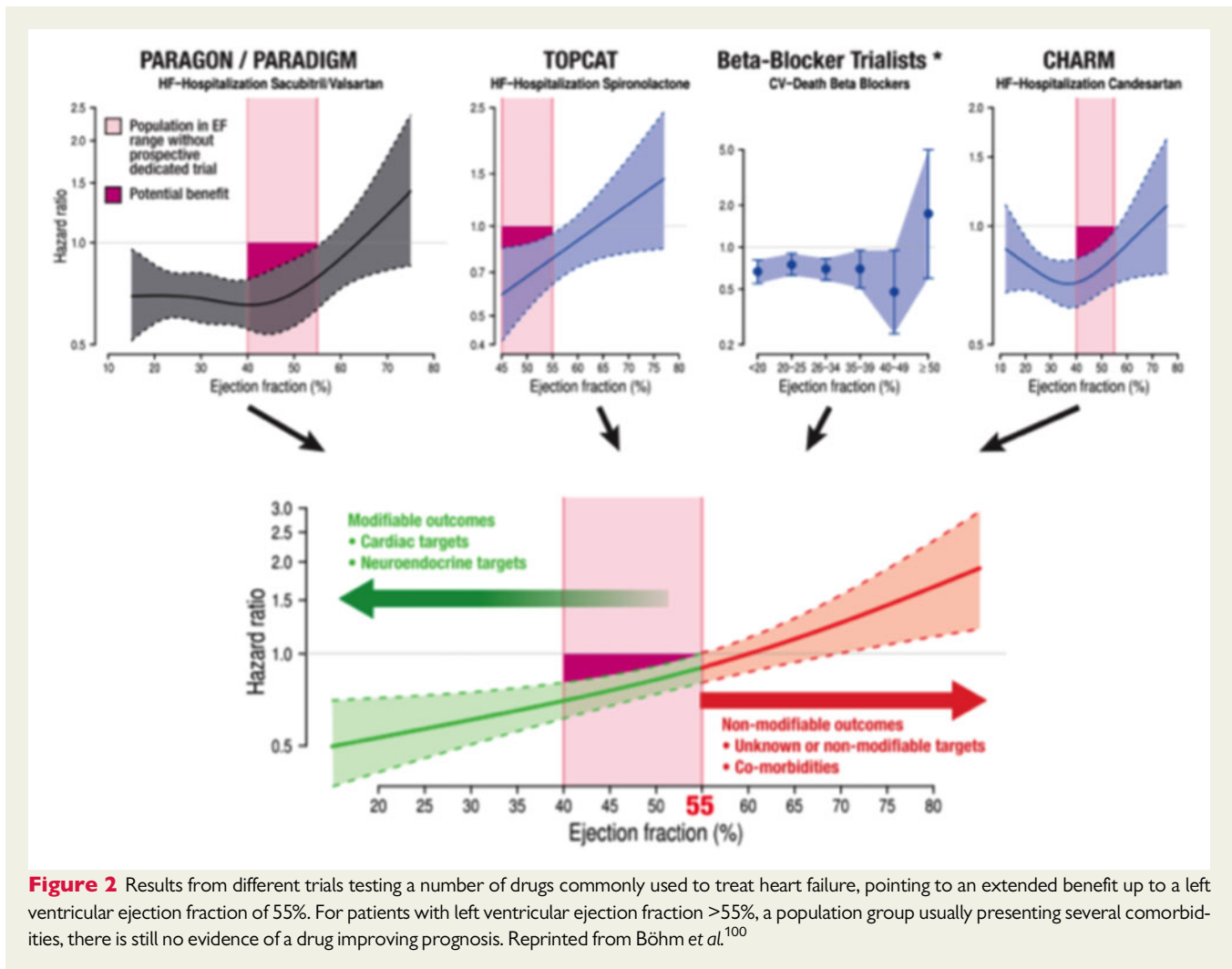
A patient-level data analysis from the PARADIGM-HF and PARAGON-HF trials (SV vs. enalapril in HFREF and SV vs. valsartan in HFpEF, respectively), and the CHARM-Alternative and CHARM-Preserved trials (candesartan vs. placebo) showed that, compared with RAAS inhibitors, SV improved outcomes across the range of LVEF, with a risk reduction (RR) of 0.54 [95% confidence interval (CI) 0.45–0.65] for the recurrent primary endpoint compared with putative placebo ( $P < 0.001$ ). Treatment benefits were robust in patients with LVEF < 60%, but not in those with LVEF > 60%.<sup>99</sup> These results are in line with prior *post hoc* analyses from the TOPCAT study and  $\beta$ -blocker trials suggesting that the cut-off of LVEF for a beneficial treatment effects is ~55%. These analyses show that in the sparsely studied population of patients with an LVEF of 40–55%, several HF treatments might provide benefit (Figure 2).<sup>100</sup>

### Sodium-glucose cotransporter 2 inhibitors (EMPEROR-Reduced, DAPA-HF, SOLOIST, VERTIS, SUGAR-DM-HF, EMPA-TROPISM [ATRU-4])

In patients with type 2 diabetes, the sodium-glucose cotransporter 2 (SGLT-2) inhibitors empagliflozin and dapagliflozin reduce the risk of HF hospitalization regardless of baseline CV risk or history of HF.<sup>101,102</sup> In The VERTIS trial, ertugliflozin did neither significantly reduce CV events, nor the combined endpoint of CV death/HF hospitalization<sup>103</sup> but reduced HF hospitalizations.<sup>104</sup>

In patients with HFREF, DAPA-HF has demonstrated a significant reduction in CV mortality and HF events.<sup>105,106</sup> This robust effect was analysed in more detail in several seminal papers published in 2020. The benefit of dapagliflozin was independent of the diabetes status, occurring across all levels of HbA1C,<sup>107</sup> as well as of baseline renal function or blood pressure, patient age, or background HF therapy.<sup>108–111</sup> Dapagliflozin improved symptoms, physical function, and quality of life<sup>112</sup> and was shown to be a cost-effective treatment for HFREF in the UK, German, and Spanish healthcare systems.<sup>113</sup> Dapagliflozin also reduces the rate of decline in renal function in HFREF patients,<sup>111</sup> as well as in patients with chronic kidney disease, as shown in the DAPA-CKD trial, where treatment with dapagliflozin reduced the risk of worsening renal function, end-stage kidney disease, or death. This protective effect was observed in patients with or without diabetes.<sup>111,114</sup>

Empagliflozin also showed marked beneficial effects in HFREF patients independently from diabetes status (Figure 3), with a significant reduction in the primary composite endpoint of CV death and HF events (hazard ratio (HR), 0.75; 95% CI, 0.65–0.86;  $P < 0.001$ ), the secondary endpoints of total HF hospitalizations (HR, 0.70; 95% CI, 0.58–0.85;  $P < 0.001$ ), the annual rate of decline in the estimated glomerular filtration rate (-0.55 vs. -2.28 mL/min/1.73 m<sup>2</sup> of body-



surface area per year,  $P < 0.001$ ), the risk of serious renal outcomes,<sup>115</sup> and the risk and total number of inpatient and outpatient worsening HF events, which starts early after the initiation of treatment and remains during the duration of treatment.<sup>116</sup> These beneficial effects were also observed to a similar extent in patients pre-treated with ARNI<sup>117</sup> and were independent of baseline diabetes status and across the continuum of HbA1c,<sup>118</sup> and in patients with and without CKD and regardless of the severity of kidney impairment at baseline.<sup>119</sup>

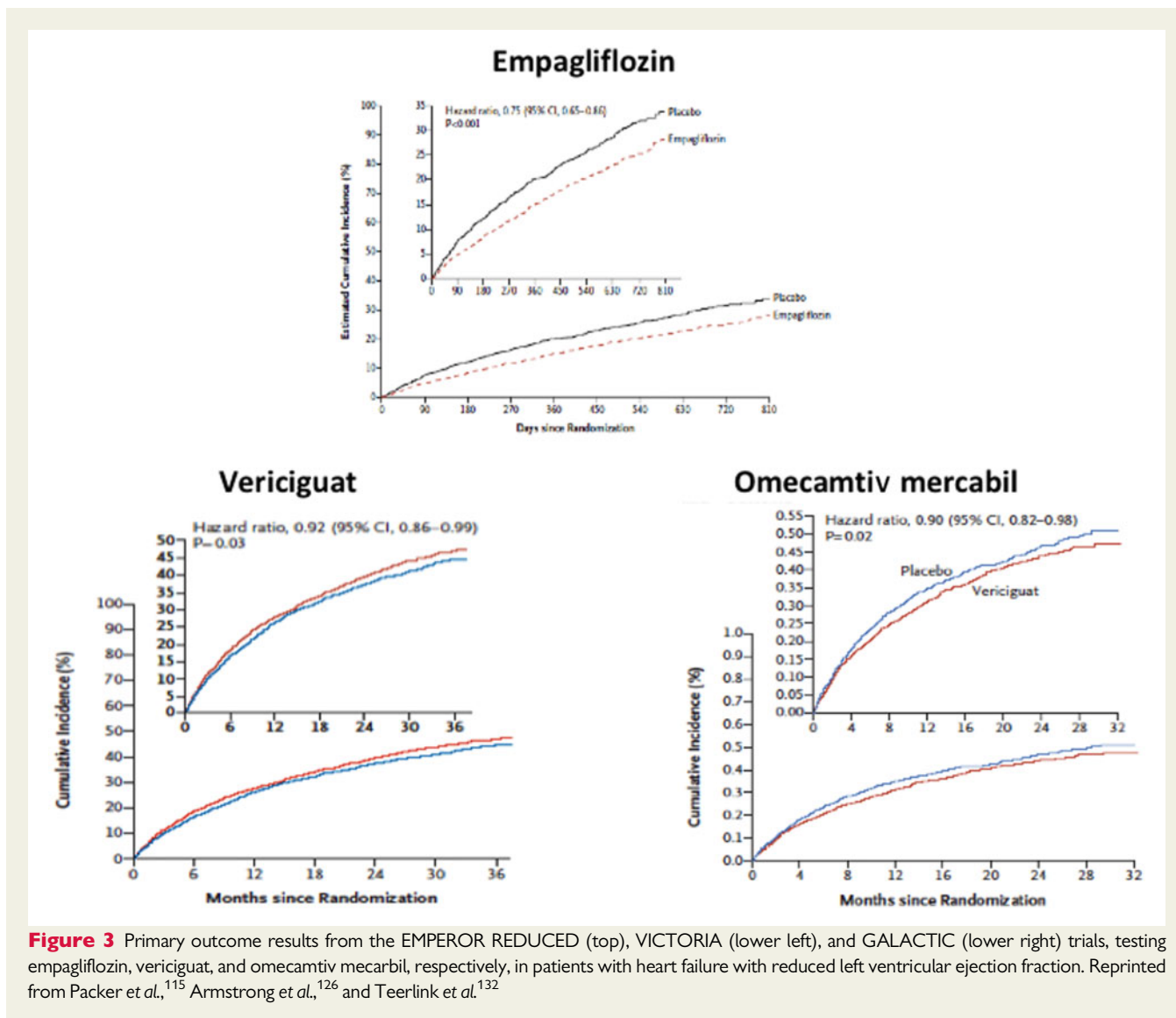
In the SUGAR-DM-HF study, empagliflozin reduced LV volumes measured by CV magnetic resonance in patients with HFrEF and type 2 diabetes or prediabetes.<sup>120</sup> The mechanistic trial EMPA-TROPISM (ATRU-4) showed the beneficial effect of empagliflozin in improving LV volumes, LV mass, LV systolic function, functional capacity, and quality of life in non-diabetic patients with HFrEF<sup>121</sup> (ref). Taken the evidence together, SGLT-2 inhibitors reduce all-cause and CV mortality and improve renal outcomes in patients with HFrEF, supporting the role of dapagliflozin and empagliflozin as a new standard of care for patients with HFrEF.<sup>119,122</sup>

Sotagliflozin, another SGLT-2 inhibitor that displays also gastrointestinal SGLT-1 inhibition and thus reduces intestinal glucose

absorption, was investigated in patients with type 2 diabetes after a recent hospitalization for worsening heart failure (SOLOIST-WHF). Patients were included independent of their ejection fraction, and 78% of patients had an ejection fraction <50%. The primary endpoint of CV death, total hospitalizations, and urgent visits for HF was significantly reduced in patients treated with sotagliflozin (HR, 0.67; 95% CI, 0.52–0.85;  $P < 0.001$ ). The results were consistent among subgroups and especially also in patients with an EF > 50%.<sup>123</sup> Sotagliflozin was also investigated in patients with type 2 diabetes, chronic kidney disease, and elevated CV risk (SCORED);<sup>124</sup> primary endpoint (changed during the study to a composite of CV death, total HF hospitalizations and urgent visits for HF) was significantly reduced in patients treated with sotagliflozin (HR, 0.67; 95% CI, 0.52–0.85;  $P < 0.001$ ). It has to be mentioned that both sotagliflozin trials had to be stopped earlier than planned because of loss of funding from the sponsor.

### Activators of soluble guanylate cyclase (victoria, vitality, capacity)

The activator of soluble guanylate cyclase (sGC) vericiguat was investigated in the VICTORIA study in 5050 patients with recently



**Figure 3** Primary outcome results from the EMPEROR REDUCED (top), VICTORIA (lower left), and GALACTIC (lower right) trials, testing empagliflozin, vericiguat, and omecantiv mecarbil, respectively, in patients with heart failure with reduced left ventricular ejection fraction. Reprinted from Packer *et al.*,<sup>115</sup> Armstrong *et al.*,<sup>126</sup> and Teerlink *et al.*<sup>132</sup>

decompensated chronic HF and LVEF < 45%.<sup>125,126</sup> Vericiguat significantly reduced the primary outcome of CV death or first HF hospitalisation (HR, 0.90; 95% CI, 0.82–0.98;  $P=0.02$ ) (Figure 3). While vericiguat significantly reduced HF hospitalisations (HR, 0.90; 95% CI, 0.81–1.00), CV deaths were not significantly diminished. Adverse events were largely similar among the vericiguat and placebo groups. An analysis comparing HRs and absolute RR in three large recent HFrEF trials demonstrated that while the HR suggests a smaller treatment effect in VICTORIA than in the DAPA-HF and PARADIGM-HF trials, a comparison of 12-month event rates for the primary outcome pointed to a comparable benefit across the three trials.<sup>127,128</sup> Given the significant interaction of vericiguat effects according to baseline NT-proBNP levels, a *post hoc* analysis showed an association of vericiguat benefit on the primary outcome in patients with NTproBNP levels up to 8000 pg/mL, with greatest benefit in patients with NTproBNP < 4000 pg/mL (HR, 0.77, 95% CI, 0.68–0.88).<sup>129</sup>

Vericiguat was evaluated in HFrEF patients in the VITALITY trial,<sup>128</sup> showing no benefit in quality of life and exercise tolerance.<sup>130</sup>

Similarly, in the CAPACITY trial, the sGC stimulator praliquat was well-tolerated but did neither affect the primary efficacy endpoint of pVO<sub>2</sub> nor other predefined outcome parameters.<sup>131</sup>

## Cardiac myosin activators and inhibitors

### Omecantiv mecarbil (GALACTIC-HF, EXPLORER-HCM)

Omecantiv mecarbil, a cardiac myosin activator that enhances cardiomyocyte contraction, given twice daily on the basis of plasma levels of the drug, significantly reduced the primary endpoint of HF hospitalisation and CV death in patients with HFrEF and a recent HF event (HR, 0.92; 95% CI, 0.86–0.99;  $P=0.03$ ) (Figure 3) but had no impact on any of the secondary outcomes (CV death, change in symptom score, first HF hospitalization, and death from any cause).<sup>132</sup>

A similar compound, *danicamiv*, increased stroke volume, improved global longitudinal and circumferential strain, decreased LA minimal volume index, and increased LA function index when compared to placebo in a small phase 2a trial in 40 patients with stable HFrEF.<sup>133</sup>

On the other hand, *mavacamten*, a myosin inhibitor, significantly improved the combined primary endpoint of increase in peak oxygen consumption ( $pVO_2$ ) and reduction in NYHA class in a phase 3 trial in patients with obstructive hypertrophic cardiomyopathy. Also, out-flow tract obstruction and health status were improved.<sup>134</sup>

## Other therapies

### Ferric carboxymaltose (AFFIRM-AHF)

In iron-deficient patients hospitalized for acute HF (AFFIRM-AHF),<sup>135</sup> intravenous ferric carboxymaltose compared to placebo was associated with a trend to reduced total HF hospitalizations and CV death (rate ratio 0.79, 95% CI 0.62–1.01,  $P=0.059$ ). In a pre-specified sensitivity analysis considering the impact of the COVID-19 pandemic, a statistically significant difference in favour of ferric carboxymaltose was reported for the primary endpoint was reported, but not in CV death risk.<sup>136</sup>

### MicroRNA-132 inhibition

In a first clinical trial limited by a small number of HF patients, the anti-sense oligonucleotide drug directed against miR-132, CDR132L,<sup>137</sup> was well tolerated and showed first hints for a cardiac functional improvement.<sup>138</sup>

### Comprehensive disease-modifying pharmacological therapies

Using data from the EMPHASIS-HF, PARADIGM-HF, and DAPA-HF trials lifetime gains in survival have been estimated with comprehensive therapy (SV,  $\beta$ -blocker, MRA, and SGLT-2 inhibitor) vs. RAAS and  $\beta$ -blockers in patients with chronic HFrEF.<sup>11,139</sup> The HR for the composite endpoint of CV death or hospitalisation for HF was 0.38 (95% CI 0.30–0.47). Favourable results were also calculated for CV death alone, hospitalization for HF alone, and all-cause mortality. Comprehensive therapy could prolong overall survival 6.3 years in average in a 55-year-old patient. These results support the combination use of SV,  $\beta$ -blockers, mineralocorticoid receptor antagonists, and SGLT-2 inhibitors as a new therapeutic standard.

## Device/interventional therapies

### Secondary (or functional) mitral regurgitation (COAPT)

Secondary (or functional) mitral regurgitation (SMR) occurs frequently in HFrEF and is associated with progressive symptoms and worse prognosis. If SMR is treated by edge-to-edge repair, patients with optimal result at discharge and 12-month follow-up displayed best outcomes.<sup>140</sup>

### Cardiac resynchronization therapy (STOP-CRT)

Cardiac resynchronization therapy (STOP-CRT) is an integral part of treatment in patients with HFrEF, especially with left bundle branch block and wide QRS. In a selected cohort of patients with LVEF >50% during CRT and neurohormonal blockade, the STOP-CRT

study investigated the feasibility and safety of neurohormonal blocker withdrawal. The incidence of adverse LV remodelling or clinical outcomes was low after discontinuation of betablockade/RAAS inhibition. However, comorbidities prompted the continuation of neurohormonal blockers in many patients.<sup>141</sup>

In patients with HFrEF who are ineligible for CRT, *baroreflex activation therapy* (BAT) may be useful in addition to optimal drug therapy. In the BeAT-HF study, BAT was safe and significantly improved symptoms, quality of life, exercise capacity, and NT-proBNP.<sup>142</sup> On the basis of these data, BAT was approved in the USA, while ongoing follow-up in the BeAT-HF study will assess effects on hard outcomes.

## Specific management issues

### Telemedicine and remote monitoring

The role of telemedicine and remote monitoring in the management of HF patients is still controversial. An observational study in three European countries showed that pulmonary artery pressure-guided HF management is feasible and safe and associated with better outcomes haemodynamic and clinical outcomes.<sup>143</sup> Also, preliminary results testing non-invasive remote physiological monitoring from a wearable sensor showed promising results in the early detection of impending HF rehospitalisation.<sup>144</sup> However, different modes of remote monitoring failed to show a benefit in improving treatment, quality of life,<sup>145</sup> or clinical outcomes.<sup>146</sup> Moreover, remote monitoring with a cardiac implanted electronic device increased clinical activity for patients with HF and AF, with no associated reduction in mortality, and conversely, greater risk of CV hospitalisation amongst patients with persistent/permanent AF.<sup>147</sup> In the COVID-19 era, remote monitoring is a useful tool for managing HF patients.<sup>148</sup>

### Self-care and palliative care

Self-care is essential in the management of chronic HF. Practical advice for key activities and priorities for self-care is given in an HFA manuscript.<sup>149</sup> At the end of the HF pathway, palliative care should be introduced early, focusing on symptom management,<sup>150</sup> regardless of prognosis, but actually only a minority in Europe receive it.<sup>151</sup> Providing palliative care substantially reduces hospitalizations, with no clear adverse effect on survival.<sup>152</sup>

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