

# Reflecting on the advancements of HFrEF therapies over the last two decades and predicting what is yet to come

Ileana L. Piña<sup>1</sup>, Gregory T. Gibson<sup>1</sup>, Shelley Zieroth<sup>2</sup>, and Rachna Kataria<sup>3\*</sup>

<sup>1</sup>Division of Cardiology, Thomas Jefferson University, 4201 Henry Ave, Philadelphia, PA 19144, USA; <sup>2</sup>Section of Cardiology, Max Rady College of Medicine, University of Manitoba, 750 Bannatyne Ave, Winnipeg, MB R3E 0W2, Canada; and <sup>3</sup>Division of Cardiology, Warren Alpert Medical School of Brown University, Lifespan Cardiovascular Institute, Rhode Island Hospital, 2 Dudley Street, Providence, RI 02905, USA

## KEYWORDS

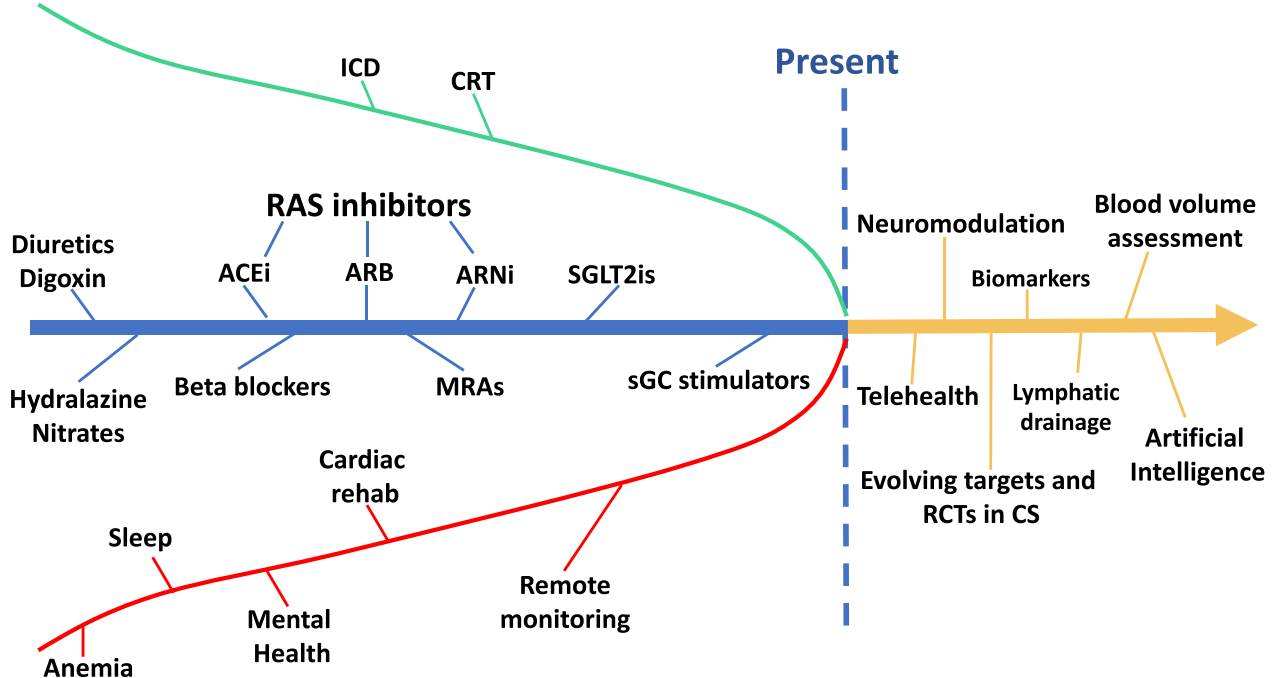
Heart failure with reduced ejection fraction;  
Guideline-directed medical therapy;  
Cardiogenic shock;  
Mechanical circulatory support;  
Remote monitoring;  
Artificial intelligence

What was once considered a topic best avoided, managing heart failure with reduced ejection fraction (HFrEF) has become the focus of many drug and device therapies. While the four pillars of guideline-directed medical therapies have successfully reduced heart failure hospitalizations, and some have even impacted cardiovascular mortality in randomized controlled trials (RCTs), patient-reported outcomes have emerged as important endpoints that merit greater emphasis in future studies. The prospect of an oral inotrope seems more probable now as targets for drug therapies have moved from neurohormonal modulation to intracellular mechanisms and direct cardiac myosin stimulation. While we have come a long way in safely providing durable mechanical circulatory support to patients with advanced HFrEF, several percutaneous device therapies have emerged, and many are under investigation. Biomarkers have shown promise in not only improving our ability to diagnose incident heart failure but also our potential to implicate specific pathophysiological pathways. The once-forgotten concept of discordance between pressure and volume, the forgotten splanchnic venous and lymphatic compartments, have all emerged as promising targets for diagnosing and treating heart failure in the not-so-distant future. The increase in heart failure-related cardiogenic shock (CS) has revived interest in defining optimal perfusion targets and designing RCTs in CS. Rapid developments in remote monitoring, telemedicine, and artificial intelligence promise to change the face of heart failure care. In this state-of-the-art review, we reminisce about the past, highlight the present, and predict what might be the future of HFrEF therapies.

\*Corresponding author. Tel: +1 (401)4445803, Fax: +1 (401)7937200,  
Email: rachkataria@gmail.com

## Graphical Abstract

## The past, present and future of therapies for HFrEF



HFrEF: heart failure with reduced ejection fraction; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; RAS: renin-angiotensin system; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNi: angiotensin receptor neprilysin inhibitor; SGLT2is: sodium-glucose cotransporter-2 inhibitors; MRAs: mineralocorticoid receptor antagonists; sGC: soluble guanylate cyclase; RCTs: randomized controlled trials; CS: cardiogenic shock.

## The awakening

The truth: In the 1970s and 1980s, the syndrome of heart failure (HF), as a diagnosis, was not popular among cardiologists at large, and the topic was avoided, mainly due to the paucity of successful therapies, the high mortality, and the frustration of only having digoxin and diuretics to treat the patients. Causes of mortality included pump failure, and sudden death, among others. There were false hopes in drugs, such as prazosin, that after early encouraging data, was shown to be no better than a placebo.<sup>1-4</sup> The vasodilator theory was prominent with an emphasis on reducing preload and afterload, such as with the hydralazine-nitrate combination tested vs. placebo and prazosin in the Vasodilator in Heart Failure (V-HeFT) I trial.<sup>1</sup> With the 1987 publication of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) in Class IV patients, the neurohormonal hypothesis arrived with blazing guns to the field.<sup>5</sup> The European CONSENSUS trial was followed by the National Heart, Lung, and Blood Institute (NHLBI) 1991-92 Studies of Left Ventricular Dysfunction (SOLVD) trials in the less sick and in asymptomatic patients.<sup>6,7</sup> Comparing the vasodilator combination with the angiotensin-converting enzyme inhibitor (ACEi) was the subject of the second vasodilator V-HeFT II trial and the ACEi beating the vasodilator but with remaining questions about benefit by race.<sup>8</sup> With the pursuit of testing and advancing the neurohormonal theory for HF with reduced ejection fraction (HFrEF), patients have benefitted tremendously from the medical/device therapy that has consumed Guidelines for over 15 years. The discovery of

the benefits in blocking the renin-angiotensin-aldosterone system (RAAS) was followed by leading studies that challenged the old fear of beta-blocker avoidance in low EF and changed the practice by showing strong similar mortality benefits from at least three beta-blocking agents.<sup>9-11</sup> For those patients who were unable to tolerate an ACEi due to cough or angioedema, angiotensin receptor blockers came into focus as an alternative to ACEi, in trials, such as Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM) and Valsartan Heart Failure Trial (Val-HeFT).<sup>12,13</sup> Close to that time, aldosterone and mineralocorticoid antagonists (MRAs) took centre stage in very sick patients studied in the Randomized Aldactone Evaluation Study (RALES) trial and less sick in the Eplerenone in Mild Patients Hospitalization and Survival Study (EMPHASIS), taking its place in the Guidelines.<sup>14,15</sup> Therefore, the three basic therapies became designated as 'Guideline Directed Medical Therapy' (GDMT) consisting of ACEi/Angiotensin II receptor blockers (ARB) if intolerant to ACEi, beta-blocker, and MRA. A return to the question of vasodilators by race was the subject of the 2004 African-American Heart Failure Trial (A-HeFT) leading to the approval of a vasodilator combination specifically for self-described Black patients.<sup>16</sup>

Simultaneous to the pharmacologic trials bringing us consecutive successful results, the electrophysiology (EP) field acknowledged that despite reducing pump failure deaths, patients were dying of arrhythmic events, including sudden death and that the drugs were inconsistent in their benefits

on sudden death. The NHLBI funded the historic Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) in the 1990s which compared the popular antiarrhythmic, amiodarone, to a placebo and to a simple 'shock box'-implantable cardioverter-defibrillator (ICD).<sup>17</sup> The ICD won over the drug and the placebo regardless of the aetiology of HF with 72% of patients already on beta-blockers and recommended MRAs. This study led the way for others and ICDs were added to the Guidelines for HFrEF. By 2003, another EP intervention recognized that patients with left bundle branch block and ventricular dyssynchrony would benefit from resynchronization therapy and hence cardiac resynchronization therapy, particularly with an ICD was added to the recommended therapies in HFrEF.<sup>18</sup> This was the status of medical/device therapy by the end of 2005.

But how short-lived is memory... Today, we are trying to better understand why in spite of powerful data and benefits, providers are not recommending and/or prescribing these life-saving therapies, such as RAAS inhibitors, MRAs, and beta-blockers and on the device side, underuse of ICD therapy, especially in women.<sup>19,20</sup> Sometimes, history is forgotten. And for at least 10 years, the field wondered if any other therapies would be discovered, given that some patients remained symptomatic, and others were truly intolerant.

## A hiatus

All this 'waiting' for new treatments was embedded in the recognition that the prevalence and incidence of HF were rapidly growing for both men and women and although we impacted mortality with our drugs, hospitalizations became a dominant issue in the healthcare economics prompting the intrusion of payers, such as Medicare, to reduce hospital admissions.

During years of a stalling of novel therapies, the Centers for Disease Control and Prevention published a critical study of the high rate of 30-day readmissions for HF and the fact that less than 50% of the patients were followed up early post-discharge.<sup>21</sup> This publication caused a frenzy of attempts at a reduction in 30-day readmissions, particularly when Medicare announced financial penalties for those hospitals that exceeded the national average. In a defensive response, hospitals rushed to form post-discharge groups, and the word 'quality' emerged as a goal in HF care. HF programmes were created and strengthened in their resolve to reduce readmissions and deliver quality care. All these efforts needed to be in a cost-effective environment.<sup>22,23</sup> Specialty clinics for HF care were charged with constructing structures, and processes of care to achieve favourable outcomes. Most of the oral therapies were generic and thus controlled at the pharmacy with plans abounding to reduce costs.<sup>24</sup>

## Hope anew

Nonetheless, armed with faith in science, Investigators and Industry partners continued to pursue further work in the field looking at the syndrome from different perspectives, such as combining proteins to form one compound, newer pathways in the actin-myosin relationship, moving diabetic drugs toward HF, a sinus node channel agent, and returning to vasodilation with cyclic GMP. A sobering thought, however, is that newer therapies will be

more expensive but may be cost-effective when comparing them to better outcomes overall.

Not surprisingly, the advent of LCZ696 (sacubitril plus valsartan) as a new agent for HFrEF was received with great fanfare in 2014, given how silent the field had been.<sup>25</sup> PARADIGM-HF was novel in that it combined two drugs (an Angiotensin receptor blocker and a neprilysin inhibitor) into one (sacubitril/valsartan) and challenged the standard of care, enalapril, in a head-to-head comparison using the doses of the SOLVD trial. A flurry of publications followed in a similar fashion to the ACE inhibitor and ARB stories of past years, e.g. SOLVD, CHARM, VAL-HeFT.<sup>12,13,26</sup> Shortly after the PARADIGM-HF trial, European Investigators tested another novel mechanism, that of inhibiting the funny current channel in the sinoatrial node cells to lower heart rate, in addition to a beta-blocker. Ivabradine was approved in the United States for use in patients whose heart rates were over 70 in spite of adequate beta-blocker dosing. Its use in the US has been at best, modest.<sup>27</sup>

## Becoming the fourth (pillar), and other novel drug therapies

A remarkable new chapter in the medical therapy for HFrEF started with an unexpected and dramatic decrease in HF hospitalizations in a trial of diabetics.<sup>28</sup> Industry rapidly tested the hypothesis prospectively in several trials hoping that sodium-glucose cotransporter-2 (SGLT2) inhibitors would replicate the findings of the initial trial. The trials confirmed the benefits of these drugs, not only in diabetics, but also in non-diabetics, and not only in the prevention of incident HF hospitalizations, but also in patients with known HF. Even more surprising is the renal protection that appears to be a Class effect with SGLT2 inhibitors. More rapidly than in any other era, these drugs have become the fourth pillar of GDMT for HFrEF. Interestingly today, a firm mechanism of action is the topic of much speculation including diuretic effects, changes in metabolism, reverse remodelling, among others.<sup>29,30</sup>

The focus of the HF community was once again returned to the importance of vasodilation with the emergence of vericiguat, a direct stimulator of soluble cyclic GMP (sGC) that bypasses the need for nitric oxide-mediated activation and increases cGMP concentration with resultant vasodilation. Vericiguat is now approved as an adjunct to Guideline Directed Medical Therapy (GDMT) following the positive randomized controlled Study of Vericiguat in Participants with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial, which had one of the highest event rates out of recent trials, but with no significant change in mortality.<sup>31</sup> The population enrolled was sicker than PARADIGM-HF and affirmed concerns about the impact of hospitalization and high NT-pro-BNP on outcomes.

During these same years, inotropes had become the inevitable course of therapy for patients with advanced HF who were being listed and waiting for heart transplantation or receiving mechanical assistance, or palliative care alone when other options were not available. Inotropes have always been used with the caveat that mortality may be negatively impacted.<sup>32</sup> The HF field has long hoped for an oral inotrope agent that would not increase mortality but would augment cardiac output and could be easily administered in the ambulatory setting.

Omecamtiv mecarbil was being quietly developed and studied in progressively sicker populations leading to a large, randomized placebo-controlled trial of HFREF patients—Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC) trial. The mechanism of this drug is truly novel in that systole is delayed, although minimally so, but without an increase in myocardial O<sub>2</sub> demands and without calcium toxicity. The GALACTIC trial met its endpoint, primarily driven by hospitalizations with no change in mortality. It is not yet approved for clinical use.<sup>33</sup> Both trials, GALACTIC and VICTORIA, have also raised questions about subgroups of patients within the spectrum of HF, lending to new hypotheses and proposing that perhaps the choice of the next drug for HFREF should be from a menu of options depending on the patient characteristics. How to sequence drugs to achieve the optimal type and dose is quickly becoming the subject of much speculation and planning.

### Beyond drugs and devices

The HF clinical field has come to understand that regardless of the GDMT and device therapy, patients with HF are complex and increasingly sicker when referred to specialty centres or providers. We have also understood that we cannot transplant every HF patient or implant them with LVADs.<sup>34</sup> However, the emphasis on health status is rising to its proper place in care: do we not want to improve patient symptoms, deal with comorbidities and improve their quality of life? Clinical trials in more recent years have embedded health status and functional capacity into the goals of endpoints.<sup>35</sup> In fact, instruments to test health status are becoming a common-piece language, although one size may not fit all the trials. These instruments are seldom used in clinical care when they could help clinicians identify the impact of HF syndrome on the daily life of our patients.<sup>36</sup>

This concern for the patient's well-being beyond the GDMT agents now includes workup for iron deficiency, with or without anaemia, sleep disorders, depression/mental health, and hyperkalaemia with or without renal dysfunction.<sup>37</sup> Very importantly cardiac rehabilitation which truly belongs in the company of our drug/devices, but is seldom ordered or followed through must be encouraged and followed as a quality measure. As a reinforcer of health status, cardiac rehab in HFREF has been studied and found to be safe and improve health status including quality of life and if adherent, reduced CV events. Furthermore, CMS covers 36 sessions of cardiac rehabilitation.<sup>37</sup>

Sometimes even GDMT diligence alone does not accomplish these other goals. Given the disappointing reporting of registries which showed that the GDMT recommended was not being applied to the patient population adequately, with only a small percentage that was optimally treated, an important aid to care arose: binders of potassium to facilitate up-titration of RAAS inhibitors and MRAs. Using one of two approved agents is now mentioned in the Guidelines to facilitate GDMT.<sup>37</sup>

Whether the addition of potassium binders will affect outcomes by allowing optimization of therapy is still to be proven.

### Moving targets of the future

#### Biomarkers

Biomarker testing in HF is hardly a new concept and for several years biomarkers have proved to be cost-effective, efficient tools to diagnose or exclude HF. Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP), despite their inherent limitations, are widely used in conjunction with the clinical diagnosis of HF as markers of left ventricular wall stress.<sup>38,39</sup> The ADHF national registry and ad-hoc analyses of the Val-HEFT trial highlighted the importance of serial measurements of these natriuretic peptides.<sup>40</sup> Recognition of the importance of these biomarkers in the management of HF has led to biomarker testing being incorporated into various consensus documents focused on the management of HF and in many ways the natriuretic peptides have become the reference standard against which novel biomarkers are evaluated.<sup>38</sup> The development and progression of HF are the results of a complex interplay between several pathophysiological pathways and novel biomarkers representing these different pathways have been identified. High-sensitivity troponin (hsTn) is one such marker capable of detecting more myocardial necrosis than conventional troponin assays and of allowing reliable risk stratification in HF patients. In addition to well-established markers of renal function, newer markers of acute kidney injury (AKI) have emerged. Among them, elevated levels of neutrophil-gelatinase-associated lipocalin (NGAL) have been seen in acute decompensated HF and have been shown to predict incident AKI with modest accuracy. In a *post hoc* analysis of the Val-HEFT trial, baseline concentrations of growth differentiation factor-15 (GDF-15), a marker of apoptosis, were found to be weakly associated with risk of mortality (HR 1.02, 95% CI 1.014-1.019;  $P < 0.001$ ).<sup>41</sup> Serial measurements of the soluble suppression of tumorigenesis-2 (sST2), a protein member of the interleukin-1 receptor family released under conditions of myocardial and vascular strain, were found to better delineate risk of mortality as well as predict worsening HF, rehospitalization, heart transplantation, and death, better than the natriuretic peptides. These are just a few of the many novel biomarkers that have emerged. An ideal biomarker panel would include multiple biomarkers representing different pathophysiologic pathways and a few multibiomarker HF risk scores do already exist. However, the low interpretability of existing multibiomarker panels has resulted in a dismal uptake in clinical practice and future studies examining the application of multibiomarker panels will be quintessential to improving HF care.<sup>38</sup>

#### Pressure overload is not the same as volume overload

It is a common perception that most HF exacerbations are caused by volume overload resulting in cardiopulmonary congestion. Yet, fluid removal strategies such as diuresis and ultrafiltration, do not always prove to be the right approach. Ambulatory weight-based monitoring lacks sensitivity and often fails to detect imminent decompensation of HF needing hospitalization. Similarly, weight loss is not consistently seen during hospitalization for ADHF. A recent



increase in the adoption of ambulatory intracardiac pressure-based monitoring, has shown us that right and left-sided pressures often increase in the absence of weight gain or an increase in total body volume.<sup>42</sup> This observation is further supported by elegantly executed total body volume analyses showing that several patients with HF exacerbation are in fact normovolemic or hypovolemic and patients with low/normal volume status seem to be at the highest risk for HF hospitalization.<sup>43</sup> Collectively, these findings reinforce that pressure does not equal volume! There is renewed interest in the regulation of splanchnic blood volume and the mechanisms by which the splanchnic venous compartment, the major blood reservoir, contributes to inappropriate volume handling in patients with HF.<sup>42</sup> The future holds promise for reliable and readily available methods to measure blood volume and its redistribution in HF. Drug and device therapies aimed at increasing and maintaining splanchnic vascular capacitance are an area of an ongoing investigation and may change the therapeutic targets for HF as we know them today.

### Neuromodulation

In healthy individuals, the autonomic nervous system and neurohormonal mediators are cardioprotective. However, the syndrome of HF is associated with increased activation of the sympathetic nervous system and a simultaneous withdrawal of the parasympathetic tone, resulting in an unfavourable imbalance. Well-established guideline-directed medical therapies target neurohormonal mediators of HF. Neuromodulating device therapies and interventions are an area of ongoing research. Cardiac sympathetic denervation is fairly well established for the management of ventricular arrhythmias and in pilot studies of patients with HF, it has shown promising initial evidence of symptomatic benefit and improvement in left ventricular ejection fraction (LVEF). Renal denervation, excessively examined for the treatment of refractory hypertension, has shown mixed results in the management of HF. The prospective, randomized, multicentre SIMPLICITY-HF trial failed to show improvements in cardiac function and HF symptoms at 12 months after renal denervation.<sup>44</sup> Vagus nerve stimulation is aimed at increasing parasympathetic tone and showed promising results in several animal studies. However, these did not translate into benefits when examined in three separate randomized trials of HF patients. However, the three trials used slightly different stimulation protocols making a head-to-head comparison difficult. There is continued interest in targeting afferent fibres of the vagal nervous system as part of future developments in the technique. Cardiac contractility modulation (CCM) and baroreceptor activation therapy (BAT) have each garnered significant attention in recent times. CCM comprises of biphasic impulses to the RV septum for 5-12 h a day and is recommended for patients with New York Heart Association (NYHA) Class II or III patients with LVEF <35%, who do not meet criteria for CRT. Animal studies of CCM showed that increasing septal contractility results in reflex activation of vagal afferent fibres and thereby a reduction in sympathetic activation. CCM has been studied in various randomized trials that collectively show an improvement in functional capacity, exercise tolerance, and quality of life in patients with LVEF 25-40%, NYHA Class III symptoms despite optimal medical therapy, and sinus rhythm

with normal QRS duration. These trials all employed the Optimizer 3-lead systems, which were recently approved by the US Food and Drug Administration (US FDA).<sup>44</sup> Adverse events, however, seem to relate to the number of leads. Future research in this arena will focus on advancements to minimize device-related AEs, on including patients with non-sinus rhythms, on examining its effects on mortality and HF hospitalizations, and on improving patient selection.<sup>45</sup> BAT targets carotid sinus mechanoreceptors resulting in decreased SNS stimulation and augmentation of the parasympathetic nervous system. The Barotism® Hope for Heart Failure (HOPE4HF) Phase II randomized<sup>46</sup> and the Baroreflex Activation Therapy for Heart Failure (Be-AT HF) Phase III randomized,<sup>47</sup> unblinded trials showed improvements in quality of life, functional capacity, and NT-pro-BNP levels resulting in a pre-market FDA approval. While the post-market phase will focus on HF hospitalizations and CV mortality, only time will show us the long-term safety and durability of this treatment modality.<sup>44</sup>

### Lymphatic drainage

Some have argued that the reason we fail at HF is that the definition of HF is too narrow and does not consider the failure of peripheral compensatory mechanisms.<sup>48</sup> The lymphatic system is an important, yet often overlooked, a contributor to maintaining total body volume. HF is characterized by venous congestion, which in turn, results in an increased efflux of fluid out of the vasculature and into the interstitial space at a rate that exceeds the ability of the lymphatic system to remove this fluid. Congestion also impedes the drainage of interstitial fluid via the thoracic duct into the central venous circulation.<sup>49</sup> The systemic pro-inflammatory state in HF results in increased permeability of the lymphatic system and results and further propagates the accumulation of extravascular fluid. Recent advances in imaging techniques have potential to enhance our appreciation of the contributions of lymphatic dysregulation to HF, as well as to guide the future development of therapeutic approaches.<sup>50</sup> Pre-clinical and clinical studies certainly point towards the feasibility of targeting the lymphatic system in HF and some novel device-based therapies are currently under investigation.<sup>49</sup>

### Return of the PA catheter

Pulmonary artery catheters (PACs) were developed and then became commercially available in the 1970s. They were enthusiastically adopted and swiftly transitioned from being placed in the catheterization laboratory only to then be placed at the bedside in intensive care units and in operating rooms, and from being used as a diagnostic tool only to then begin used to tailor therapies.<sup>51</sup> By the 1980s, they were being placed in 20-40% of critically ill hospitalized patients. This was in the absence of randomized controlled trials or any data, for that matter, looking at safety or efficacy. Data were generated in the late 1990s and early 2000s. A prospective cohort study of critically ill patients, analysed using propensity matching to avoid treatment selection bias, was the first to report increased mortality and resource utilization associated with the use of PACs.<sup>52</sup> Enthusiasm around the use of PACs began dwindling. This was followed by three different randomized controlled trials of critically ill or high-risk

patients in whom the use of PAC failed to show marked benefit.<sup>51</sup> Then came the randomized controlled ESCAPE trial of clinical management plus PAC vs. clinical management alone.<sup>53</sup> The trial included patients with severe symptomatic HF despite recommended therapies but excluded those that were felt to be ‘too sick’ to need an urgent crossover to the PAC group. They found no additional benefit of PAC use, an increase in anticipated adverse events and no effect on mortality or hospitalization. With these and other reports of increased harm with PAC use in patients with acute myocardial infarction (AMI), the PAC steadily fell out of favour; the decline in usage was most prominent for patients with AMI followed by patients with HF.<sup>54</sup> Given that patients in cardiogenic shock (CS) were almost always excluded from these analyses and with the recent widespread increase in the utilization of temporary mechanical circulatory support (tMCS) in patients with CS, there has been renewed interest in hemodynamically guided management to improve outcomes in CS.<sup>55</sup> Thus began the era of PAC resuscitation, with studies showing benefits in both AMI and HF-related CS.<sup>56,57</sup> However, a randomized clinical trial is yet to be successfully designed and conducted.

### Despite multiple failed clinical trials, a resurgence of interest in early diagnosis and management of CS

Outcomes of patients who progress to CS have remained dismal despite advances in drug therapy, revascularization, tMCS, and intensive care unit care models, to name a few. The complex pathophysiology of CS, its unique presentation in every single patient, and regional variations in resource availability and utilization, have all limited the feasibility of conducting successful randomized controlled trials or even creating standardized algorithms for care. Various perfusion targets have been proposed but remain ill-defined.<sup>58</sup> Several societies have come together to put forth a standardized classification of CS severity, which has shown impressive prognostic capability.<sup>59</sup> The recent update to the Society for Cardiovascular Angiography and Interventions (SCAI) shock classification also considers some additional risk factors that improve mortality risk stratification such as right atrial pressure, worsening SCAI shock stage, and a delayed deterioration of SCAI stage. The proposed three-axis model emphasizes the assessment of the global clinical picture of each individual patient.<sup>60</sup> The CS working group has proposed a further modification to the SCAI stages such that hypoperfusion alone, as evidenced by biochemical markers in the absence of hypotension, may adequately identify patients in SCAI Stage B before they worsen.<sup>61</sup> The most optimal assessment of incident or underlying renal dysfunction in CS as well as optimal timing for initiation of renal replacement therapy remains elusive. Similarly, goals for mean arterial pressure, lactate clearance, and mechanical ventilation all have insufficient supporting evidence. Randomized clinical trials in CS are a major unmet need and many issues remain unresolved.<sup>62</sup> However, as our understanding of hemodynamical profiles and CS phenotypes improves<sup>63,64</sup> with simultaneous improvement in drug therapies and device technology, we are looking at a promising future in this arena.<sup>58</sup> With advances in our understanding of CS phenotypes, we can expect an era of

precision medicine in CS. Advanced drug therapies might lead us to oral inotropes. Finally, improvements in device technology may result in dischargeable tMCS devices to allow for myocardial recovery without needing heart replacement therapies (such as durable left ventricular-assisted device or heart transplant).

### Remote monitoring

Remote monitoring devices for HF have evolved in the face of the ever-increasing burden of HF hospitalizations and readmissions.<sup>65</sup> Classic methods for ambulatory HF monitoring such as daily weights and symptom monitoring have failed to mitigate HF hospitalizations.<sup>66</sup> Simultaneously, there is an increased appreciation of the fact that changes in intracardiac pressures precede signs of overt congestion and can therefore provide early knowledge about incident decompensation.<sup>42</sup> This has led to increased enthusiasm around the use of remote invasive monitoring tools, namely the CardioMEMS HF system with multiple clinical studies demonstrating safety and clinical efficacy. Initial US FDA approval for the CardioMEMS system was obtained in 2014 for use in patients with NYHA Class III symptoms who had been hospitalized for HF in the previous year.<sup>65</sup> In 2022, based on results of the Haemodynamic-guided management of heart failure (GUIDE-HF) trial, the US FDA approved an expanded indication for the use of the CardioMEMS system in patients with NYHA Class II and III symptoms who were either hospitalized for HF in the previous year and/or have elevated natriuretic peptide levels.<sup>67</sup> While on the one hand, it is important to have these data, increases in pressure do not always equal increases in total body volume.<sup>43</sup> The COVID-19 pandemic has certainly highlighted the importance of remote monitoring and it is undoubtedly the way of this future.<sup>65</sup> An ideal remote monitoring device would be one that can measure both pressure and volume and in other words, help phenotype each individual patient to tailor therapies to their individual needs. Robust yet flexible treatment algorithms and large-scale platforms that allow for real-time monitoring of several hundreds of patients will prove to be game-changing.

### Telehealth and artificial intelligence

Post-discharge follow-up visits have been shown to reduce 30-day readmissions for HF. Yet, missed outpatient visits are common.<sup>68,69</sup> A pilot study found that replacing in-person visits with video visits was feasible and safe, with a reduction in missed appointments, which did not receive statistical significance.<sup>68</sup> Soon thereafter, we found ourselves in the trenches of a pandemic. Telemedicine was at the forefront of HF care during the initial surges of COVID-19. Both telephone and video visits were employed.<sup>70</sup> Few different studies emerged showing contradicting effects of telemedicine on patient outcomes.<sup>71,72</sup> Studies appraising the accessibility of telemedicine found that widespread adoption may be limited by poor internet services and other technological deficiencies as well as lack of patient education.<sup>72</sup> Artificial intelligence (AI) will play a pertinent role in managing the large volumes of data generated by telemedicine. While AI is already transforming cardiovascular care, its future application in HF has immense potential for changing the face of HF care.<sup>73</sup> By synthesizing large data, AI promises to enhance precision medicine in HF, provide equitable care, and improve patient-related outcomes.<sup>73</sup> Multi-stakeholders addressing regulatory challenges, healthcare policy, and

reimbursement models will be crucial to the universal adoption of both telemedicine and AI in HF.<sup>72</sup>

## Concluding remarks

The landscape of HF therapies has undergone a paradigm shift and the targets for therapies in HF with reduced ejection fraction continue to evolve. Never before have drug therapies, temporary and durable devices, as well as other health status interventions received equal recognition and efforts at advancement. Unique think tank forums, aimed at advancing our understanding of the cardiovascular, cardiorenal, and cardiometabolic markers in HFrEF are crucial to advancing the common goal of improving outcomes in HFrEF. The future of HF therapies is incredibly promising. Multi-stakeholder participation, including clinicians, allied health professionals, pharmacists, industry partners, regulatory agencies, research organizations, payers, lawyers, and most importantly, patients; is the only way forward. It does take a village.

## Acknowledgments

None declared.

## Funding

This paper was published as part of a supplement sponsored by Novartis Pharma AG. The content was developed independent of the sponsor and the authors did not receive an honorarium.

**Conflict of interest:** I.L.P.: Vifor Pharma Advisory Board, Modest. Other authors have nothing to declare.

## Data availability

No new data were generated or analysed in support of this research.

## References

- Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a veterans administration cooperative study. *N Engl J Med* 1986;**314**:1547-1552.
- Miller RR, Awan N, Amsterdam EA, Mason DT. Afterload reduction in congestive heart failure. *Adv Cardiol* 1978;**22**:199-204.
- Packer M, Meller J. Oral vasodilator therapy for chronic heart failure: a plea for caution. *Am J Cardiol* 1978;**42**:686-689.
- Straub EJ. Clinical use of prazosin in CHF. *Circulation* 1978;**57**:200.
- The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative north Scandinavian enalapril survival study (CONSENSUS). *N Engl J Med* 1987;**316**:1429-1435.
- The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293-302.
- The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;**327**:685-691.
- Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, *et al.* A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;**325**:303-310.
- Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, *et al.* Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;**106**:2194-2199.
- Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjeksush J, *et al.* Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). MERIT-HF study group. *JAMA* 2000;**283**:1295-1302.
- The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomized trial. *Lancet* 1999;**353**:9-13.
- McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-added trial. *Lancet* 2003;**362**:767-771.
- Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667-1675.
- Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. *N Engl J Med* 1999;**341**:709-717.
- Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, *et al.* Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11-21.
- Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Ferdinand K, *et al.* Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;**351**:2049-2057.
- Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225-237.
- Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, *et al.* Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845-1853.
- Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, *et al.* Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019;**73**:2365-2383.
- Alaeddini J, Wood MA, Amin MS, Ellenbogen KA. Gender disparity in the use of cardiac resynchronization therapy in the United States. *Pacing Clin Electrophysiol* 2008;**31**:468-472.
- Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 2009;**360**:1418-1428.
- Pacho C, Domingo M, Nunez R, Lupon J, Moliner P, de Antonio M, *et al.* Early postdischarge STOP-HF-clinic reduces 30-day readmissions in old and frail patients with heart failure. *Rev Esp Cardiol (Engl Ed)* 2017;**70**:631-638.
- Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. *Arch Intern Med* 2008;**168**:687-694.
- McIlvennan CK, Eapen ZJ, Allen LA. Hospital readmissions reduction program. *Circulation* 2015;**131**:1796-1803.
- McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al.* Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993-1004.
- Bangdiwala SI, Weiner DH, Bourassa MG, Friesinger GC, Ghali JK, Yusuf S. Studies of left ventricular dysfunction (SOLVD) registry: rationale, design, methods and description of baseline characteristics. *Am J Cardiol* 1992;**70**:347-353.
- Komajda M, Bohm M, Borer JS, Ford I, Robertson M, Manolis AJ, *et al.* Efficacy and safety of ivabradine in patients with chronic systolic heart failure according to blood pressure level in SHIFT. *Eur J Heart Fail* 2014;**16**:810-816.
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117-2128.
- Lam CSP, Chandramouli C, Ahojja V, Verma S. SGLT-2 Inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. *J Am Heart Assoc* 2019;**8**:e013389.
- Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. *Heart* 2021;**107**:1032-1038.
- Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, *et al.* Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020;**382**:1883-1893.
- Ahmed T, Miller PE, McCullough M, Desai NR, RIELLO R, Psotka M, *et al.* Why has positive inotropy failed in chronic heart failure? Lessons from prior inotrope trials. *Eur J Heart Fail* 2019;**21**:1064-1078.



33. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, *et al.* Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med* 2021;**384**:105-116.
34. Wordingham SE, McIlvennan CK, Dionne-Odom JN, Swetz KM. Complex care options for patients with advanced heart failure approaching End of life. *Curr Heart Fail Rep* 2016;**13**:20-29.
35. Bekelman DB, Allen LA, McBryde CF, Hattler B, Fairclough DL, Havranek EP, *et al.* Effect of a collaborative care intervention vs usual care on health Status of patients with chronic heart failure: the CASA randomized clinical trial. *JAMA Intern Med* 2018;**178**:511-519.
36. Rumsfeld JS. Health status and clinical practice: when will they meet? *Circulation* 2002;**106**:5-7.
37. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation* 2022;**145**:e895-e1032.
38. Ibrahim NE, Januzzi JL Jr. Established and emerging roles of biomarkers in heart failure. *Circ Res* 2018;**123**:614-629.
39. Castiglione V, Aimo A, Vergaro G, Saccaro L, Passino C, Emdin M. Biomarkers for the diagnosis and management of heart failure. *Heart Fail Rev* 2022;**27**:625-643.
40. Masson S, Latini R, Anand IS, Barlera S, Angelici L, Vago T, *et al.* Prognostic value of changes in N-terminal pro-brain natriuretic peptide in val-HeFT (valsartan heart failure trial). *J Am Coll Cardiol* 2008;**52**:997-1003.
41. Anand IS, Kempf T, Rector TS, Tapken H, Allhoff T, Jantzen F, *et al.* Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. *Circulation* 2010;**122**:1387-1395.
42. Fudim M, Hernandez AF, Felker GM. Role of volume redistribution in the congestion of heart failure. *J Am Heart Assoc* 2017;**6**:e006817.
43. Yaranov DM, Jefferies JL, Silver MA, Burkhoff D, Rao VN, Fudim M. Discordance of pressure and volume: potential implications for pressure-guided remote monitoring in heart failure. *J Card Fail* 2022;**28**:870-872.
44. Sobowale CO, Hori Y, Ajijola OA. Neuromodulation therapy in heart failure: combined use of drugs and devices. *J Innov Card Rhythm Manag* 2020;**11**:4151-4159.
45. Wiegand P, Chan R, Jost C, Saville BR, Parise H, Prutchi D, *et al.* Safety, performance, and efficacy of cardiac contractility modulation delivered by the 2-lead optimizer smart system: the FIX-HF-5C2 study. *Circ Heart Fail* 2020;**13**:e006512.
46. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, *et al.* Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. *JACC Heart Fail* 2015;**3**:487-496.
47. Zile MR, Lindenfeld J, Weaver FA, Zannad F, Galle E, Rogers T, *et al.* Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2020;**76**:1-13.
48. Houck P, Dandapanthula H, Hardegree E, Massey J. Why we fail at heart failure: lymphatic insufficiency is disregarded. *Cureus* 2020;**12**:e8930.
49. Fudim M, Salah HM, Sathananthan J, Bernier M, Pabon-Ramos W, Schwartz RS, *et al.* Lymphatic dysregulation in patients with heart failure: JACC review topic of the week. *J Am Coll Cardiol* 2021;**78**:66-76.
50. Itkin M, Rockson SG, Burkhoff D. Pathophysiology of the lymphatic system in patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:278-290.
51. Marik PE. Obituary: pulmonary artery catheter 1970 to 2013. *Ann Intensive Care* 2013;**3**:38.
52. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, *et al.* The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT investigators. *JAMA* 1996;**276**:889-897.
53. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, *et al.* Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* 2005;**294**:1625-1633.
54. Wiener RS, Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993-2004. *JAMA* 2007;**298**:423-429.
55. Saxena A, Garan AR, Kapur NK, O'Neill WW, Lindenfeld J, Pinney SP, *et al.* Value of hemodynamic monitoring in patients with cardiogenic shock undergoing mechanical circulatory support. *Circulation* 2020;**141**:1184-1197.
56. Basir MB, Kapur NK, Patel K, Salam MA, Schreiber T, Kaki A, *et al.* Improved outcomes associated with the use of shock protocols: updates from the national cardiogenic shock initiative. *Catheter Cardiovasc Interv* 2019;**93**:1173-1183.
57. Garan AR, Kanwar M, Thayer KL, Whitehead E, Zweck E, Hernandez-Montfort J, *et al.* Complete hemodynamic profiling with pulmonary artery catheters in cardiogenic shock is associated with lower in-hospital mortality. *JACC Heart Fail* 2020;**8**:903-913.
58. Mathew R, Fernando SM, Hu K, Parlow S, Di Santo P, Brodie D, *et al.* Optimal perfusion targets in cardiogenic shock. *JACC Adv* 2022;**1**:100034.
59. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, *et al.* SCAI Clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the American college of cardiology (ACC), the American heart association (AHA), the society of critical care medicine (SCCM), and the society of thoracic surgeons (STS) in April 2019. *Catheter Cardiovasc Interv* 2019;**93**:29-37.
60. Naidu SS, Baran DA, Jentzer JC, Hollenberg SM, van Diepen S, Basir MB, *et al.* SCAI SHOCK stage classification expert consensus update: A review and incorporation of validation studies: this statement was endorsed by the American college of cardiology (ACC), American college of emergency physicians (ACEP), American heart association (AHA), European society of cardiology (ESC) association for acute cardiovascular care (ACVC), international society for heart and lung transplantation (ISHLT), society of critical care medicine (SCCM), and society of thoracic surgeons (STS) in December 2021. *J Am Coll Cardiol* 2022;**79**:933-946.
61. Kapur NK, Kanwar M, Sinha SS, Thayer KL, Garan AR, Hernandez-Montfort J, *et al.* Criteria for defining stages of cardiogenic shock severity. *J Am Coll Cardiol* 2022;**80**:185-198.
62. Samsky M, Krucoff M, Althouse AD, Abraham WT, Adamson P, Aguel F, *et al.* Clinical and regulatory landscape for cardiogenic shock: A report from the cardiac safety research consortium ThinkTank on cardiogenic shock. *Am Heart J* 2020;**219**:1-8.
63. Thayer KL, Zweck E, Ayouty M, Garan AR, Hernandez-Montfort J, Mahr C, *et al.* Invasive hemodynamic assessment and classification of in-hospital mortality risk among patients with cardiogenic shock. *Circ Heart Fail* 2020;**13**:e007099.
64. Zweck E, Thayer KL, Helgestad OKL, Kanwar M, Ayouty M, Garan AR, *et al.* Phenotyping cardiogenic shock. *J Am Heart Assoc* 2021;**10**:e020085.
65. Kennel PJ, Rosenblum H, Axsom KM, Alishetti S, Brener M, Horn E, *et al.* Remote cardiac monitoring in patients with heart failure: a review. *JAMA Cardiol* 2022;**7**:556-564.
66. Brugs JJ, Radhoe SP, Aydin D, Theuns DA, Veenis JF. Clinical update of the latest evidence for CardioMEMS pulmonary artery pressure monitoring in patients with chronic heart failure: a promising system for remote heart failure care. *Sensors (Basel)* 2021;**21**:2335.
67. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, *et al.* Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *Lancet* 2021;**398**:991-1001.
68. Gorodeski EZ, Moennich LA, Riaz H, Jehi L, Young JB, Tang WHW. Virtual versus in-person visits and appointment No-show rates in heart failure care transitions. *Circ Heart Fail* 2020;**13**:e007119.
69. Xu H, Granger BB, Drake CD, Peterson ED, Dupre ME. Effectiveness of telemedicine visits in reducing 30-day readmissions among patients with heart failure during the COVID-19 pandemic. *J Am Heart Assoc* 2022;**11**:e023935.
70. Sammour Y, Spertus JA, Austin BA, Magalski A, Gupta SK, Shatla I, *et al.* Outpatient management of heart failure during the COVID-19 pandemic after adoption of a telehealth model. *JACC Heart Fail* 2021;**9**:916-924.
71. Yuan N, Botting PG, Elad Y, Miller SJ, Cheng S, Ebinger JE, *et al.* Practice patterns and patient outcomes after widespread adoption of remote heart failure care. *Circ Heart Fail* 2021;**14**:e008573.
72. Silva-Cardoso J, Juanatey JRG, Comin-Colet J, Sousa JM, Cavalheiro A, Moreira E. The future of telemedicine in the management of heart failure patients. *Card Fail Rev* 2021;**7**:e11.
73. Ski CF, Thompson DR, Brunner-La Rocca HP. Putting AI at the centre of heart failure care. *ESC Heart Fail* 2020;**7**:3257-3258.