Heart Failure Drug Treatment

Patrick Rossignol, MD;^{1,2} Adrian F. Hernandez, MD;³ Scott D. Solomon, MD;⁴ Faiez Zannad, MD,^{1,2}

¹Université de Lorraine, Inserm, Centre d'Investigations Cliniques- 1433, and Inserm U1116; CHRU Nancy; Nancy, France; ²F-CRIN INI-CRCT, Nancy, France ; ³Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, North Carolina, United States; ⁴Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts, United States

Corresponding Author: Professor Patrick Rossignol, Centre d'Investigations Cliniques-INSERM CHRU de Nancy, Institut lorrain du Cœur et des Vaisseaux Louis Mathieu, 4 rue du Morvan, 54500 Vandoeuvre Lès Nancy, France. Tel : +33 3 83 15 73 20/Fax : +33 3 83 15 73 24; email: p.rossignol@chru-nancy.fr

Word Count: 4,999 words

Abstract

Heart failure (HF) is the most common cardiovascular reason for hospital admission over the age of 60. There are few areas in medicine where progress has been as remarkable as that observed with HF therapy over the last three decades. However, progress has been consistent only for chronic HF with reduced ejection fraction (HFrEF). In acutely decompensated HF and HF with preserved ejection fraction (HFpEF), none of the therapies tested to date have been definitively proven to improve survival. Delaying or preventing HF has become increasingly important in HF-prone patients. It is also of paramount importance to prevent worsening chronic HF and hospitalisations for acute decompensation. The objective of this review article is to provide concise and practical summary of the current state of HF drug therapy. We support the implementation of the international guidelines. Where gaps in evidence are present, we offer views based on personal experience. The best possible evidence based drug therapy is useful only when optimally implemented. However, implementation may be challenging. We believe that disease management programmes may be helpful in providing a multidisciplinary, holistic approach to the delivery of optimal medical care.

Abstract Word Count: 199

Key Words:

Heart failure – medical therapeutics- disease management programmes- reduced ejection fraction- preserved ejection fraction - narrative review

Introduction

Heart failure (HF) is the most common cardiovascular reason for hospital admission among individuals over the age of 60.¹ The prevalence of HF is increasing worldwide because of an increasing incidence related to population aging, rising prevalence of poorly controlled risk factors (i.e., hypertension, diabetes mellitus, and obesity), and prolonged survival of patients with HF due to implementation of evidence-based therapies.² It is a clinical syndrome characterised by fatigue and dyspnoea, induced by left (or global) ventricular dysfunction, often with signs of congestion. The New York Heart Association (NYHA) classification is used to describe symptom severity (Figure 1 and Short panel). Heart failure carries a poor prognosis. Thirty day all-cause readmission rates of 19% have been reported in the United States.³ One-year all-cause mortality rates for acute HF and stable/ambulatory HF patients were 17% and 7%, respectively, and the 12-month hospitalisation rates were 44% for hospitalised patients and 32% for ambulatory patients, respectively, in recent observational data from Europe.⁴ Similar data have been reported in the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry; 19.2% of patients died or were hospitalized for HF within 1 year.⁵ The THESUS-HF (Sub-Saharan Africa Survey of Heart Failure) reported an estimated 6-month mortality of 17.8%.⁶ The International Congestive Heart Failure (INTER-CHF) study, representing Africa, China, India, the Middle East, southeast Asia, and South America, reported an overall 1-year mortality of 16.5%, with substantial variation by region (Africa 34%, India 23%, southeast Asia 15%, South America 9%, Middle East 9%, and China 7%).⁷

In most patients, abnormalities of systolic and diastolic function coexist, irrespective of the ejection fraction (EF), which in clinical trials was the most used classifier to define either heart failure with reduced EF (HFrEF) if EF<40%, or heart failure with preserved EF (HFpEF).

In a recent European survey, mortality at 1 year was 8.8% and 6.3% in HFrEF and HFpEF, respectively.⁸ The HFrEF subtype has been the most well studied, yielding a robust body of evidence to support clinical practice guidelines.^{9,10}

The objective of this review article is to provide concise and practical summary of the current state of HF drug therapy. We support the implementation of the available international guidelines. These may differ in some occasional respects, and there are persistent gaps in evidence, in which cases we offer views based on our personal expertise.

Priorities for future research in terms of unmet needs and evidence gaps are also identified.

Search strategy and selection criteria

Data for this narrative review were identified by searches of MEDLINE and PubMed, and references from relevant articles, in addition to the most recent European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines.⁹⁻¹¹

Diuretic and sodium management

Regardless of EF, heart failure symptoms are mostly related to congestion,¹² and congestion is one of the main predictors of poor patient outcome.¹³ Despite the lack of large randomised outcome trials, loop diuretics are strongly (Grade 1^{9,10}) recommended for decongestion, albeit with a lower level of evidence (B⁹ or C¹⁰) by the ESC and ACC/AHA guidelines to improve symptoms in chronic and acutely decompensated HF. Diuretic dosing is largely empiric. Diuretic doses should be titrated according to the decongestion target. The use of inappropriately low

91 doses of diuretics may result in persistent congestion. Conversely, the use of inappropriately high
92 doses of loop diuretics may trigger hypokalaemia and hypovolaemia with a related risk of
93 hypotension and worsening renal function,¹⁰ which may lead to down titration of life- saving
94 drugs (ACEI, MRA). Furthermore, this may further stimulate the RAAS, which may worsen HF.
95 Once optimal decongestion has been achieved, the lowest dose that maintains euvolaemia should
96 be prescribed, and some heart failure centers educate appropriately selected patients to manage
97 symptoms with “as needed” diuretics. Candidate patients might be those not requiring daily
98 diuretic who can be educated to follow the strategy and will contact clinical staff quickly if
99 symptoms worsen, although it is acknowledged that this strategy has not been well studied.
100 However, determination of optimal decongestion and early detection of a re-congestion is
101 challenging. Indeed, although numerous clinical scores, imaging and hemodynamic tools, and
102 biological tests are available to assist physicians in ascertaining and quantifying congestion, not
103 all are appropriate for use along the course of the disease and across all settings of patient
104 presentations (pre-admission, admission to the emergency department, in-hospital management,
105 and lastly, discharge and continued monitoring in the community).¹³ For instance, weight loss
106 lacks sensitivity. Imaging (i.e., chest x-ray, B-mode lung ultrasound, inferior vena cava and other
107 echocardiography measures) may be helpful.¹⁴ Clinical trials of chronic optimisation of therapy
108 guided by natriuretic peptide levels, have led to conflicting results.^{15,16}
109 Diuretic resistance may occur in the most severe patients. In this setting, specific
110 pharmacological algorithms encompassing loop diuretic dose adjustments, inotropes, and the
111 addition of thiazide-like diuretics may be proposed as an alternative to extracorporeal
112 ultrafiltration in hospitalized patients, while the efficacy of either approaches in outcome trials
113 are lacking.¹⁷ Neurohormonal imbalances created by HF lead to an inability to excrete sodium

and water. Therefore, conventional wisdom has advised limiting sodium and fluid intake.¹⁸ Major HF guidelines lack consensus on recommendations for dietary sodium (and fluid) restriction. Currently, 4 trials are ongoing (NCT02467296, NCT02148679, NCT01733017, NCT02012179) targeting sodium restriction in HF, including one large trial evaluating clinical outcome endpoints.¹⁹ Altogether, we believe it is possible that detection, dynamic monitoring, and management of congestion/decongestion could help improve HF management. However, we acknowledge that evidence from robust randomized outcome trials are lacking. One possible exception is a single trial using a remote monitoring of pulmonary artery diastolic pressures with an implanted device.²⁰ In a randomised clinical trial that enrolled over 500 patients with HFrEF and HFpEF, monitoring and managing patients demonstrated improved clinical outcomes including hospitalisation for HF. Of note, one limitation of the trial is that the control group did not have a systematic form of disease management practiced, so that one might question whether the trial truly showed benefit of the invasive technology over and above non-invasive disease management. In addition, the reduction in HF hospitalization with the implanted device appeared to be associated with increased use of diuretics and vasodilators; to what extent this increase in doses may have contributed to the better outcomes remains an open question.

Chronic heart failure with reduced ejection fraction medical treatment

The primary pathophysiological cardiac abnormalities in HFrEF are cardiac chamber enlargement due to cardiac remodelling, weak contraction (deficient inotropism), elevated filling pressures (preload), and increased peripheral resistance (afterload), leading to an inability to provide adequate cardiac output at rest or with exercise. These elevated intracardiac pressures

may also cause lung and peripheral congestion. Myocyte number and function decline and are replaced by myocardial interstitial fibrosis, which stiffens the heart and creates the anatomical substrate basis for lethal arrhythmias. The disease is increasingly viewed as a syndrome with multiple systemic mechanisms potentially involving inflammation and disorders of neurohormonal systems, involving the renin angiotensin aldosterone (RAAS), the autonomic nervous, the endothelium, the natriuretic peptide (NP), and the vasopressin systems. Other potential pathophysiologic mechanisms include elevated heart rate, atrial fibrillation, and abnormalities of ventricular-vascular coupling, and complex cardiorenal interactions (i.e. “cardiorenal syndrome”).²¹

Better management of acute coronary syndromes has resulted in less frequent progression to post-MI HFrEF.²² Non-ischaemic aetiologies account for up to 30% of HFrEF and include valvular heart disease,²³⁻²⁵ familial cardiomyopathy, and secondary cardiomyopathies (e.g., inflammatory, cardiotoxic [alcohol, chemotherapy induced], infectious).

Current treatment guidelines are based on robust evidence stemming from well-designed randomised outcome trials.^{9,10} Inhibitors of the RAAS (i.e. ACE-inhibitors or angiotensin receptor blockers), mineralocorticoid receptor antagonists (MRA), and beta-blockers are strongly recommended (Class IA) for improving survival, decreasing sudden death, and preventing HF hospitalisations.⁹ Based on the results of the PARADIGM HF trial (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure), sacubutril-valsartan is recommended to replace ACE-inhibitors to further reduce the risk of HF hospitalisation and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment. Unless contraindicated, all symptomatic HFrEF patients should receive the

above-mentioned medications in combination, preferably at target maximally tolerated doses.^{9,11}

The combined optimal use of these class IA therapies in clinical trials has led to a decline in mortality among patients with severe as well as mild-moderate HFrEF (Figure 2).²⁶ Furthermore, a recent network meta-analysis of 58 trials dominated by 15 large-scale trials with 1984 to 18898 patient-years of follow-up showed that combining evidence-based drugs – may produce cumulative reduction in all-cause mortality up to 60% and in all-cause hospitalizations with reductions up to 40%, on average. Concomitantly, in patients enrolled in clinical trials, the annual rate of sudden cardiac death has declined below 5%.²⁷

International registry data showed that physician’s adherence to guideline recommended medications in HFrEF was associated with better outcomes.²⁸ Unfortunately, current guidelines are not being optimally implemented, both in terms of overall use as well as under-dosing,²⁹ most often because of excessive concern about adverse events.⁴ Hypotension, hyperkalemia and worsening renal function are the most frequently cited reasons for under-dosing, underuse, and discontinuation of RAAS inhibitors and MRAs⁴. In a large US database including more than 20,000 HF patients, nearly 60% who discontinued RAASi after an hyperkalaemic episode experienced an adverse outcome or mortality compared with 52% of patients on RAASi submaximal doses and 44% of patients on maximum doses (all comparisons $P < .05$). Patients on submaximal dose or who discontinued RAASi died twice as frequently as patients on maximum dose.³⁰ Beta blocker use may be hampered by concerns about hypotension, fatigue, and bradycardia. However, most of these adverse events are predictable, reversible, and manageable. Most importantly, occurrence of these events does not diminish survival benefits.³¹ Thus, in our opinion, concerns about adverse events may be excessive in some cases, and it should be recognized that this has the potential to deprive patients of life-saving therapies. Hypotension if

symptomatic can often be managed by discontinuing unnecessary vasodilators (e.g., calcium channel antagonists, alpha-blockers, nitrates), or by reducing diuretic doses to the lowest dose that maintains euvolaemia, and ultimately by staggering doses of RAAS inhibitors and beta-blockers. Frequent monitoring (within 3 days of initiation or dose adjustments and every 4 months once stable) of eGFR, serum potassium and blood pressure, slow up-titration, and avoidance of other concomitant, non-essential, interacting drugs (e.g., non-steroidal anti-inflammatory drugs, potassium supplements, dietary potassium, other blood pressure-lowering drugs, excessive diuretic doses) are strategies to achieve optimal use of these therapies. Down-titration of doses or discontinuation of RAAS inhibitors may be warranted temporarily for persistent or severe hyperkalemia, hypotension, or worsening renal function. However, this should not prevent attempts at re-initiation or up-titration of therapy as soon as safely possible. The use of potassium binders may facilitate up-titration in patients prone to hyperkalemia,³² although whether this may prevent cardiovascular outcome occurrence needs to be demonstrated in a dedicated outcome trial. It should be acknowledged that patients with HFrEF are increasingly older and have multiple comorbidities. Clinical trials have generally excluded these types of patients, and as a result, their response to HF therapy and the best approaches for managing comorbid conditions and concomitant drug therapies that may have pharmacodynamic or pharmacokinetic interactions with the HF regimen is less certain. However, there is no evidence that such patients would not benefit from standard HF therapy,³³ and guidelines should also be followed in these patients, with individual adjustments in dose or monitoring as clinically indicated according to comorbidity or interacting medications.

Ivabradine or digoxin may prevent HF hospitalisation in patients with sinus rhythm, after attempts to optimise beta-blocker therapy if heart rate remains above 75 beats per minute.⁹ Beta-

blockers and digoxin may help control ventricular response in patients with atrial fibrillation (AF), although with no demonstrated outcome benefit. There is no consensus about an optimal target heart rate in patients with AF and HF, with recommended targets varying between 60 bpm to 110 bpm.^{9,34} Because of safety concerns, amiodarone is not preferred as first line for rate control. Rhythm control using electrical or pharmacological conversion may be considered to improve symptoms in patients with persisting symptoms and/or signs of HF, despite optimal medical therapy and adequate control of ventricular rate. Anticoagulation, preferably with direct oral anticoagulants, should be offered to patients with HF and AF, recognizing that bleeding rates may be higher than in non-HF patients, since HF is a component of the CHADS2VASC2 score.³⁵

Furthermore, even in the absence of AF, based on the underlying pathophysiologic hypothesis that thrombin could play a key role in worsening chronic HF, the ongoing COMMANDER HF trial is exploring the efficacy and safety of rivaroxaban 2.5 mg bid compared with placebo (with standard care) after an exacerbation of HF in patients HFrEF and documented coronary artery disease and sinus rhythm.³⁶

Intravenous iron may be used for improving functional capacity and quality of life in patients with iron deficiency (serum ferritin <100 mg/L or ferritin between 100 and 299 mg/L and transferrin saturation <20%).^{9,37,38} However long-term data on the cardiovascular efficacy and on safety are lacking so far.

Heart failure with preserved ejection fraction medical treatment

First recognised in the 1980s and initially termed “diastolic HF,” HFpEF accounts for approximately half of all hospital admissions for HF, is associated with substantial morbidity and

229 mortality, and is increasing in prevalence.³⁹ The definition, pathophysiology, and aetiology of
230 HFpEF have been subject to controversy and debate, and consensus among experts is still rare.
231 Nevertheless, most current guidelines agree that the minimum requirements for the diagnosis of
232 HFpEF are signs and symptoms of HF and a relatively preserved EF.⁹ What constitutes
233 “preserved” has evolved, and initially encompassed the entire EF range above the reduced range,
234 generally considered an LVEF of $\leq 40\%$.
235 Patients with HFpEF tend to be older than those with HFrEF, and the prevalence of this disorder
236 is increasing as the population ages.⁴⁰ Moreover, HFpEF is associated with more comorbidities
237 than those with HFrEF,⁴¹ including hypertension, diabetes, atrial fibrillation, anaemia and
238 chronic obstructive pulmonary disease, and the attributable risk associated with these
239 comorbidities increases as EF rises.⁴² The high prevalence of comorbidities in HFpEF has
240 contributed to the notion that HFpEF may not exist as an independent entity, but may simply be a
241 collection of comorbidities. The concept is countered by the substantially higher event rates in
242 patients with HFpEF than in patients with these comorbidities but without HF.⁴³ While
243 ambulatory patients with HFpEF have substantially lower morbidity and mortality than patients
244 with HFrEF,⁴⁴ the subsequent hospitalisation and mortality rates in hospitalised patients with
245 HFpEF is comparable to that in patients with HFrEF.⁴⁵
246 The primary pathophysiologic abnormality in HFpEF is generally considered to be an inability to
247 provide adequate cardiac output at rest or with exercise or to do so only in the setting of elevated
248 filling pressures,⁴⁶ as is the case with HFrEF. Indeed, elevation in left sided filling pressure is
249 thought to be the sine qua non of HFpEF and has traditionally been thought secondary to
250 abnormalities of diastolic function. However, it has become increasingly recognised that
251 abnormalities of diastolic function are common in the elderly and present in many individuals

without HF.⁴⁷ Moreover, abnormalities of systolic function are prevalent in and related to outcomes in patients with HFpEF.^{48,49} Some patients with HFpEF have either rest or exercise induced elevation in pulmonary pressures.⁵⁰ Other pathophysiologic mechanisms that have been implicated include chronotropic incompetence,⁵¹ abnormalities of ventricular-vascular coupling,⁵² and abnormalities of renal function.⁵³

Several aetiologic molecular mechanisms have been postulated in HFpEF.⁵⁴ Diseases like hypertension and diabetes, known precursors of HFpEF, are associated with myocardial intracellular fibrosis and increased collagen deposition and turnover.⁵⁵ Abnormal phosphorylation of the spring-like titin protein, responsible for restoring the sarcomere to its resting state, has been implicated.⁵⁶ It has recently been shown that patients with obesity-related HFpEF display unique pathophysiological features, including greater biventricular remodeling, volume overload, more right ventricular dysfunction, greater ventricular interaction and pericardial restraint, worse exercise capacity, more profound hemodynamic derangements, and impaired pulmonary vasodilation. These distinctions suggest that obesity may be considered as a specific HFpEF phenotype.⁵⁷ Interestingly, a randomized trial comparing exercise only, diet only, combined exercise and diet, to a control group for 20 weeks, in 100 older obese HFpEF patients showed that caloric restriction diet or aerobic exercise training increased peak oxygen consumption..⁵⁸ Increased adiposity also contributed to worse NYHA functional class in HFpEF.^{59,60} Initially healthy subjects with elevated waist circumference have a higher long-term diastolic dysfunction risk.⁶¹ Several laboratories have suggested obesity (and comorbidities such as chronic kidney disease) lead to a systemic pro-inflammatory state, and generation of reactive oxygen species limits nitric oxide availability to myocytes, resulting in reduced cGMP production and ultimately decreasing protein kinase G activity which may result in hypertrophy

and myocyte stiffness.⁶² More specifically, obesity may lead to the accumulation and inflammation of epicardial adipose tissue, which may impair the electrophysiological properties and distensibility of the myocardium. It has recently been hypothesized that epicardial adipose tissue is a transducer which could be targeted by therapeutic interventions aimed at decreasing its accumulation and inflammation (e.g. statins, metformin, SGLT-2 inhibitors, mineralocorticoid receptor antagonists).⁶³ Despite strong support for several hypotheses, the aetiological factors responsible for HFpEF are likely to be multifactorial and more precise etiologic phenotyping is essential for the identification of novel therapies. Indeed, because of phenotypic diversity in HFpEF, personalized therapeutic strategies are proposed, which may be adapted to combinations of clinical presentations and risk predispositions⁶⁴.

Both treatment of HFpEF and the ability to test new therapies in HFpEF requires accurate diagnosis of the disorder. In addition to signs and symptoms of HF and documentation of a preserved EF, most guidelines and consensus documents recommend that other diagnostic criteria be incorporated when considering this disorder, including echocardiographic evidence of diastolic abnormalities or elevation in NP.⁶⁵ Both of these increase the likelihood that patients truly have HF, yet neither are sufficient for the diagnosis and can be abnormal in patients without HF.

Several clinical outcomes trials have been performed in patients with HFpEF yet none have met their primary endpoint (Table 1).⁶⁶⁻⁷⁰ All of these trials have thus far assessed inhibitors of the RAAS, either ACE Inhibitors,⁶⁷ angiotensin receptor blockers,^{66,68} or MRAs.⁶⁹ In CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity)-Preserved,⁶⁶ candesartan was associated with a 11% non-significant reduction in cardiovascular death or HF hospitalisation, although post-hoc analyses suggested a significant reduction in total

hospitalisations.⁷¹ The TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) comparing spironolactone to placebo, based on the success of MRAs in HFrEF and the likelihood that myocardial fibrosis plays a role in the pathophysiology of HFpEF, failed to meet its primary endpoint, with an 11% non-significant reduction in cardiovascular death or HF hospitalisation. Nevertheless, after unblinding it was noted that patients enrolled in one specific region (Russia and Republic of Georgia) had substantially lower event rates than those enrolled in United States, Canada, Argentina and Brazil, suggesting that many patients in that region may not have had HF.⁷² The 18% nominally significant risk reduction of the primary outcome in the remaining regions has encouraged some to believe that if properly tested, spironolactone would improve outcomes in HFpEF. For instance, the latest US guidelines state that “In appropriately selected patients with HFpEF (with EF $\geq$ 45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate $>$ 30 mL/min, creatinine $<$ 2.5 mg/dL, potassium $<$ 5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalization”¹¹.

Therapeutic approaches other than RAAS inhibition have been tested in HFpEF, including several that have targeted the nitric oxide pathway but did not show any benefit.⁷³⁻⁷⁵ Despite data suggesting the importance of cGMP in HFpEF and a relative reduction in intracellular cGMP, the soluble guanylate cyclase stimulator vericiguat was ineffective in lowering NT-proBNP or improving left atrial size in HFpEF,⁷⁶ although there were significant improvements in quality of life measures. However, data from cardiovascular outcome trials data are lacking. In the only positive phase 2 trial in HFpEF, sacubitril/valsartan was superior to valsartan in reducing NT-proBNP, improving left atrial size and NYHA class.⁷⁷ These findings provided the rationale for the ongoing PARAGON-HF (Efficacy and Safety of LCZ696 Compared to

Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction, NCT01920711) outcomes trial comparing sacubitril/valsartan to valsartan in 4822 patients with HFpEF, defined as LVEF $\geq 45\%$, elevation in NP and evidence of structural heart disease, which is expected to report in 2019.⁷⁰ More recently, the results of EMPA-REG and CANVAS (Canagliflozin Cardiovascular Assessment Study) provided the rationale for an outcomes trial in HFpEF with the SGLT-2 inhibitor empagliflozin (Table 1).^{78,79} Finally, spironolactone for HFpEF is being retested in two separate trials (NCT02901184 and SPIRIT-DHF [Spironolactone in the treatment for diastolic heart failure]).

It is obviously of paramount importance to rule out other causes of symptoms, including ischaemic heart disease, overt lung disease, hypertrophic cardiomyopathy, or infiltrative cardiomyopathies that could mimic signs and symptoms of HFpEF but which may have specific alternative therapies. In the absence of evidence-based therapy, treatment of HFpEF remains empiric and based on management of symptoms and comorbidities.⁸⁰ Although the benefits of diuretic use in HFpEF has not been rigorously proven in clinical trials, treatment of congestion with diuretics remains the mainstay of therapy (as described above) and appears to improve symptoms. It also appears prudent to control ventricular rates in patients with AF, particularly because elevated heart rates are associated with reduced ventricular filling time, but whether rhythm control is beneficial in HFpEF remains unclear. Finally, as mentioned above, current US guidelines recommend consideration of spironolactone.¹¹ Recognizing the challenges and uncertainty in establishing a definitive diagnosis in many cases, probability score-based diagnostic algorithms have most recently been proposed, where patients are assessed for the probability of having HFpEF based on routine clinical and echocardiographic features.⁸¹

Acutely decompensated heart failure treatment

Acute HF is a common cause of hospitalisation among individuals >65 years of age globally.⁸²⁻⁸⁵

These acute events are associated with poor short and long-term prognosis in terms of survival and rehospitalisation.⁸⁶⁻⁸⁹ The pathophysiology of AHF is multifactorial, with many potential precipitating factors (e.g., acute coronary syndrome, arrhythmia, hypertension, renal impairment, infection, non-adherence), some of them (acute coronary syndrome or infection) being associated with an increased mortality.⁹⁰

Treatment approaches are aimed at treating the underlying cause (which is often not known) and relieving symptoms. Despite intensive investigation in prospective, randomised trials, no therapies for acute HF have been shown to improve clinical outcomes.⁹¹ In the absence of therapies that prolong survival or reduce morbidity, the goal of initial therapy is to stabilise the patient and decrease congestion to produce symptomatic relief and to decrease the potential for organ impairment secondary to congestion.⁹² Specific therapies depend on the individual patient's clinical presentation. Most patients present with evidence of congestion and normal or elevated systolic blood pressure ("wet and warm") and are treated with intravenous diuretics and vasodilators.^{9,89,93} A smaller proportion present with hypoperfusion where inotropes or vasopressors may be considered in patients with systolic blood pressure <90 mmHg.⁹ Once the patient is stable, the most important long-term intervention for patients with AHF may be to optimise medical management prior to discharge⁹⁴ and plan for early post-discharge follow-up, ideally in a HF disease management programme if available.⁹⁵

Many factors have been proposed to explain the lack of efficacy of acutely administered therapies on clinical outcome in patients with AHF, including patient heterogeneity, multiple pathophysiologic mechanisms, generally rapid response to standard care (i.e., diuretics) in most

patients, and the low likelihood that short-term administration of a therapy can impact long-term outcomes.^{91,96} Future trials should apply the lessons learned from past trials to design study protocols, select candidate therapies, and identify target patient populations.⁹⁷

New drugs in research and development

Promising agents are now in phase 3 outcome trials (Table 2), and many new compounds, most targeting new molecular mechanisms, are currently in early clinical development (Table 3).

Enabling life saving pharmacological therapy with multidisciplinary management.

It is recommended that optimisation of available symptom-alleviating and life- saving HFrEF pharmacological treatments should be pursued when patients are discharged. Observational studies show however that this is simply not the case and that prescriptions filled upon discharge have the highest chance of being unchanged, months after discharge. Therefore, unfortunately, evidence-based therapies are not being optimally implemented within the current health care systems resulting in life-saving drugs under-prescription and under-dosing in HFrEF. The monitoring of creatinine and potassium after an MRA prescription is also poor both in the US⁹⁸ and in EU.⁹⁹

More broadly, the recognition of HF as a complex disorder with multiple co-morbidities and different strategies for improving health, multidisciplinary management has become a foundation of care (Figure 3). Systems of care that include multidisciplinary management have been shown to reduce HF hospitalisation and improve survival in patients discharged from the hospital.^{100,101} In France, a regional HF-disease management programme (DMP) (ICALOR programme) was established in 2006 in Lorraine,^{102,103} applying all major components of recommended DMPs as

per European Society of Cardiology guidelines. The ICALOR programme was proven to decrease cost-effectively both HF hospitalizations and all-cause mortality stabilizing HF hospitalization rate progression in Lorraine,^{102,103} whereas those observed overall in France progressed continually. This benefit stopped right after the unfortunate programme interruption.¹⁰¹

To deliver successful programs, it is important to have close collaboration and a team-oriented approach to HF care across the different domains of a health care system. Cardiologists and HF nurses need to coordinate with general practitioners and primary care physicians. The HF team should include clinical pharmacists who review and focus on complex pharmacological treatments that may have important drug-drug or drug-disease interactions to consider. Dieticians and exercise physiologists counsel patients on establishing everyday habits that support a healthy lifestyle for HF and other preventive care strategies. Social workers are also critical team members and ensure patients have appropriate access to resources. Psychologists can guide patients through anxiety or depression, which are common in patients with HF. This integrated care team approach shifts clinical management towards a proactive system as opposed to a reactive system.

A key focus of multidisciplinary teams is to prevent readmission after a HF hospitalisation. Patients enter a vulnerable period early post-discharge. Throughout the hospitalisation, a multidisciplinary team should address potential aetiologies of the worsening HF event, develop preventive strategies for future events, and coordinate post-discharge care. Systems with early physician follow-up after discharge are associated with lower 30-day readmission rates.¹⁰⁴ Heart failure is a life-long condition, monitoring strategies for patients with HF continue to shift towards a more proactive care model. By continuously monitoring a patient's condition, early

identification of worsening HF may be possible and followed by targeted interventions. In addition, monitoring strategies can identify potential problems that need to be addressed such as potassium management (hyper or hypokalemia)¹⁰⁵ a major hurdle toward RAASi implementation in HFrEF, as described above.

Telemedicine programs that remotely monitor symptoms and other parameters such as weight have had variable results.¹⁰⁶ While meta-analysis suggests clinical benefits,¹⁰⁷ large clinical trials have not shown consistently demonstrated benefits. Some of the neutral trials failed to couple the monitoring effort with a structured disease management practice which could systematically review and respond to the monitored data. Others have pointed out that there is limited value to monitoring alone, without a well-conceptualized, systematic process of integrating and acting upon the information. As new technology evolves integrating multiple sensors, patient self-reported health status, and seamless home to clinic monitoring systems, it is possible that more consistent benefits may be achieved.¹⁰⁸ Implantable devices with integrated physiological signals and sensors designed to alert when patients are higher risk for hospitalisation for HF may provide actionable data for future telemedicine programs.¹⁰⁹ Ongoing trials are testing whether alert management with specific treatment protocols may achieve improved outcomes. Priorities for research to continue advancement of lifestyle interventions such as exercise and application of monitoring technologies for patients with HF are outlined in Box 1.

Heart failure prevention

Prevention is likely the best mechanism to combat HF and its associated clinical and societal burdens.² Heart failure is often a preventable cardiovascular syndrome. Reducing blood pressure

lowers the risk of 'new onset' HF by as much as 40%, similar to the effect of lowering blood pressure on stroke and greater than the effect of lowering blood pressure on the risk of MI.^{110,111} Diabetes mellitus may contribute to HF development, although glycaemic control or choice of glucose lowering therapy in patients with type 2 diabetes mellitus has not until recently been associated with HF prevention, and may have actually led to worsening heart failure (e.g. with glitazones). However, beyond glycaemic control, some inhibitors of sodium-glucose co-transporter 2 (SGLT-2) improve clinical outcomes, including hospitalisation for HF, in patients with type 2 diabetes and pre-existing cardiovascular disease or cardiovascular risk factors.¹¹²⁻¹¹⁴ In primary and secondary cardiovascular prevention trials, statins may reduce the rate of HF hospitalisation¹¹⁵. Smoking, excessive alcohol consumption, sedentary lifestyle, and obesity are all associated with the development of cardiovascular disease. Moreover, adherence to healthy lifestyle factors, no smoking, regular exercise, normal weight, moderate alcohol intake, and consumption of breakfast cereal and fruits and vegetables was found associated with a lower risk of developing HF in a database from 20,900 men from the Physicians' Health Study who were apparently healthy at baseline.¹¹⁶ Furthermore, recent observational data in 11,351 participants in the ARIC (Atherosclerosis in the Community) study showed that maintaining recommended activity levels was associated with the lowest HF risk, while initiating and increasing physical activity, even in late middle age, were also linked to lower HF risk. The authors concluded that "augmenting physical activity may be an important component of strategies to prevent HF".¹¹⁷ However, HF prevention in these observational data may be the result of better control of risk factors and prevention of ischemic heart disease. In patients with ischaemic heart disease, angiotensin converting enzyme (ACE) inhibitors delay the onset of HF and reduce cardiovascular mortality.¹¹⁸

Identification of mechanistic therapeutic targets (e.g., cardiac remodelling, inflammation, fibrosis, diastolic dysfunction, vascular dysfunction) may be a more effective approach for HF prevention in the future. Mechanistic bioprofiling of patients (i.e., selecting subgroups of patients based on biomarker profiles indicative of underlying mechanisms associated with HF risk) and subsequently matching prevention strategies to mechanistic biotargets may be a promising approach to the development of specific HF prevention strategies.¹¹⁹

Conclusion

There are few areas in medicine where progress has been as remarkable as that observed with drug therapy of chronic HFrEF over the last three decades. Unfortunately, no such evidence basis exists for HFpEF or acute heart failure, beyond management of cardiovascular risk factors. Therefore, notwithstanding improving outcome in prevalent HF, delaying or preventing HF has become increasingly important in patients at-risk for HF and should be prioritised in future research programmes. It is also of paramount importance to prevent chronic HF from worsening and necessitating hospital admission for acute HF. Implementation of disease management programmes possibly including modern monitoring technology may in our opinion help achieve this objective.

Acknowledgements

Funding source: none

The authors acknowledge the contributions of Wendy Gattis Stough, PharmD for editing and assistance with the preparation of the manuscript. Dr. Stough was funded by CHRU Nancy.

Patrick Rossignol and Faiez Zannad are supported by the French National Research Agency (Fight HF programme ANR-15-RHU-0004 and GEENAGE Impact programme Lorraine University d'Excellence).

Declaration of Interests

Rossignol: Personal fees (consulting) from Novartis, Relypsa, AstraZeneca, Grünenthal, Stealth Peptides, Fresenius, Vifor Fresenius Medical Care Renal Pharma, Vifor and CTMA; lecture fees from Bayer and CVRx; cofounder of CardioRenal

Hernandez: Dr. Hernandez has received research grants from Amgen, AstraZeneca, Boehringer Ingelheim, BristolMyersSquibb, Daiichi, GlaxoSmithKline, Janssen, Luitpold, Merck, NIH/NHLBI, Novartis, PCORI, Portola, and has consulted for Amgen, AstraZeneca, Bayer, Boston Scientific, Merck, Novartis, Pfizer

Solomon: Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Celladon, Gilead, GlaxoSmithKline, Ionis Pharmaceuticals, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, Theracos, and has consulted for Alnylam, Amgen, AstraZeneca, Bayer, BMS, Corvia, Cytokinetics, Gilead, GSK, Ironwood, Merck, Novartis, Pfizer, Roche, Takeda, Theracos

498

499 Zannad: Personal fees for Steering Committee membership and/or consultancy from Amgen,

500 Janssen, Bayer, Novartis, Boston Scientific, Resmed, Takeda, General Electric, Boehringer

501 Ingelheim, AstraZeneca, CVRx, Quantum Genomics, Relypsa, and ZS Pharma; Founder of

502 Cardiovascular Clinical Trialists (CVCT) and of CardioRenal

503

Figure Legends

Figure 1. Heart Failure Presentation at a Glance, depicting the spectrum of HF patient population presentation

Figure 2. Decrement of mortality associated with mild to moderate and severe HFrEF in major outcome trials

Results of random effect network meta-analysis for all-cause mortality: hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; and MRA, mineralocorticoid receptor antagonist.

Reprinted with permission from: Burnett H, Earley A, Voors AA, Senni M, McMurray JJV, Deschaseaux C, Cope S. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction. A network meta-analysis. *Circulation Heart Failure* 2017;10:e003529²⁶ (<https://doi.org/10.1161/CIRCHEARTFAILURE.116.003529>)

Figure 3. Heart failure multidisciplinary and multi-technology enabled care

Heart failure care is evolving into a more patient-centered, multidisciplinary and multi-technology management program. Patients will have more personalised health recommendations based on their underlying condition, comorbidities and social environment. Continuous monitoring will be enabled by remote, wireless technology at the home to detect early signals of worsening of heart failure as well as to reinforce self-management of heart failure. When early signals detect a potential worsening, remote management can alter care and/or have rapid in-

527 clinic treatment. As a last step, patients can come into the hospital for more intensive
528 management with the plans to have early follow-up after discharge to ensure stability.

529

530

References

- 534 1. Braunwald E. Heart failure. *JACC Heart Fail* 2013; **1**: 1-20.
- 535 2. Zannad F. Rising incidence of heart failure demands action. *Lancet* 2018; **391**(10120):
536 518-9.
- 537 3. Bergethon KE, Ju C, DeVore AD, et al. Trends in 30-Day Readmission Rates for Patients
538 Hospitalized With Heart Failure: Findings From the Get With The Guidelines-Heart
539 Failure Registry. *Circ Heart Fail* 2016; **9**(6).
- 540 4. Maggioni AP, Dahlstrom U, Filippatos G, et al. EURObservational Research Programme:
541 regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-
542 HF Pilot). *Eur J Heart Fail* 2013; **15**(7): 808-17.
- 543 5. Tromp J, Tay WT, Ouwerkerk W, et al. Multimorbidity in patients with heart failure from
544 11 Asian regions: A prospective cohort study using the ASIAN-HF registry. *PLoS Med*
545 2018; **15**(3): e1002541.
- 546 6. Damasceno A, Mayosi BM, Sani M, et al. The causes, treatment, and outcome of acute
547 heart failure in 1006 Africans from 9 countries. *Arch Intern Med* 2012; **172**(18): 1386-94.
- 548 7. Dokainish H, Teo K, Zhu J, et al. Global mortality variations in patients with heart
549 failure: results from the International Congestive Heart Failure (INTER-CHF)
550 prospective cohort study. *Lancet Glob Health* 2017; **5**(7): e665-e72.
- 551 8. Crespo-Leiro MG, Anker SD, Maggioni AP, et al. European Society of Cardiology Heart
552 Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences
553 across regions. *Eur J Heart Fail* 2016; **18**(6): 613-25.
- 554 9. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and
555 treatment of acute and chronic heart failure: The Task Force for the diagnosis and
556 treatment of acute and chronic heart failure of the European Society of Cardiology
557 (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of
558 the ESC. *Eur Heart J* 2016; **37**(27): 2129-200.
- 559 10. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management
560 of heart failure: executive summary: a report of the American College of Cardiology
561 Foundation/American Heart Association Task Force on practice guidelines. *Circulation*
562 2013; **128**(16): 1810-52.
- 563 11. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the
564 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the
565 American College of Cardiology/American Heart Association Task Force on Clinical
566 Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;
567 **70**(6): 776-803.
- 568 12. Van Aelst LNL, Arrigo M, Placido R, et al. Acutely decompensated heart failure with
569 preserved and reduced ejection fraction present with comparable haemodynamic
570 congestion. *Eur J Heart Fail* 2018; **20**(4): 738-47.
- 571 13. Girerd N, Seronde MF, Coiro S, et al. Integrative Assessment of Congestion in Heart
572 Failure Throughout the Patient Journey. *JACC Heart Fail* 2018; **6**(4): 273-85.
- 573 14. Harjola VP, Parissis J, Brunner-La Rocca HP, et al. Comprehensive in-hospital
574 monitoring in acute heart failure: applications for clinical practice and future directions
575 for research. A statement from the Acute Heart Failure Committee of the Heart Failure

- Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2018; doi:10.1002/ehf.1204.
15. Ibrahim NE, Januzzi JL, Jr. The Future of Biomarker-Guided Therapy for Heart Failure After the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) Study. *Curr Heart Fail Rep* 2018; **15**(2): 37-43.
16. Felker G, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: A randomized clinical trial. *JAMA* 2017; **318**(8): 713-20.
17. Costanzo MR, Ronco C, Abraham WT, et al. Extracorporeal Ultrafiltration for Fluid Overload in Heart Failure: Current Status and Prospects for Further Research. *J Am Coll Cardiol* 2017; **69**(19): 2428-45.
18. Houston BA, Kalathiya RJ, Kim DA, Zakaria S. Volume Overload in Heart Failure: An Evidence-Based Review of Strategies for Treatment and Prevention. *Mayo Clin Proc* 2015; **90**(9): 1247-61.
19. Colin-Ramirez E, Ezekowitz JA. Salt in the diet in patients with heart failure: what to recommend. *Curr Opin Cardiol* 2016; **31**(2): 196-203.
20. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011; **377**(9766): 658-66.
21. Zannad F, Rossignol P. Cardiorenal syndrome revisited. *Circulation* 2018; **submitted, under review**.
22. Gerber Y, Weston SA, Berardi C, et al. Contemporary trends in heart failure with reduced and preserved ejection fraction after myocardial infarction: a community study. *Am J Epidemiol* 2013; **178**(8): 1272-80.
23. Bonow RO, Leon MB, Doshi D, Moat N. Management strategies and future challenges for aortic valve disease. *Lancet* 2016; **387**(10025): 1312-23.
24. Nishimura RA, Vahanian A, Eleid MF, Mack MJ. Mitral valve disease--current management and future challenges. *Lancet* 2016; **387**(10025): 1324-34.
25. Rodes-Cabau J, Taramasso M, O'Gara PT. Diagnosis and treatment of tricuspid valve disease: current and future perspectives. *Lancet* 2016; **388**(10058): 2431-42.
26. Burnett H, Earley A, Voors AA, et al. Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction: A Network Meta-Analysis. *Circ Heart Fail* 2017; **10**(1): e003529.
27. Shen L, Jhund PS, Petrie MC, et al. Declining Risk of Sudden Death in Heart Failure. *N Engl J Med* 2017; **377**(1): 41-51.
28. Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2017; **19**(11): 1414-23.
29. Ouwerkerk W, Voors AA, Anker SD, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J* 2017; **38**(24): 1883-90.
30. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care* 2015; **21**(11 Suppl): S212-20.

31. Rossignol P, Menard J, Fay R, Gustafsson F, Pitt B, Zannad F. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy. *J Am Coll Cardiol* 2011; **58**(19): 1958-66.
32. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J* 2011; **32**(7): 820-8.
33. Eschaliel R, McMurray JJ, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure). *J Am Coll Cardiol* 2013; **62**(17): 1585-93.
34. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; **37**(38): 2893-962.
35. Ferreira JP, Girerd N, Alshalash S, Konstam MA, Zannad F. Antithrombotic therapy in heart failure patients with and without atrial fibrillation: update and future challenges. *Eur Heart J* 2016; **37**(31): 2455-64.
36. Zannad F, Greenberg B, Cleland JG, et al. Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. *Eur J Heart Fail* 2015; **17**(7): 735-42.
37. Anker SD, Comin CJ, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**(25): 2436-48.
38. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015; **36**(11): 657-68.
39. Komajda M, Lam CS. Heart failure with preserved ejection fraction: a clinical dilemma. *Eur Heart J* 2014; **35**(16): 1022-32.
40. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355**(3): 251-9.
41. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; **355**(3): 260-9.
42. Wolsk E, Claggett B, Kober L, et al. Contribution of cardiac and extra-cardiac disease burden to risk of cardiovascular outcomes varies by ejection fraction in heart failure. *Eur J Heart Fail* 2018; **20**(3): 504-10.
43. Campbell RT, McMurray JJ. Comorbidities and differential diagnosis in heart failure with preserved ejection fraction. *Heart Fail Clin* 2014; **10**(3): 481-501.
44. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005; **112**(24): 3738-44.

45. Shah KS, Xu H, Matsouaka RA, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol* 2017; **70**(20): 2476-86.
46. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation* 2011; **123**(18): 2006-13.
47. Shah AM, Claggett B, Kitzman D, et al. Contemporary Assessment of Left Ventricular Diastolic Function in Older Adults: The Atherosclerosis Risk in Communities Study. *Circulation* 2017; **135**(5): 426-39.
48. Shah AM, Claggett B, Sweitzer NK, et al. Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. *Circulation* 2015; **132**(5): 402-14.
49. Kraigher-Krainer E, Shah AM, Gupta DK, et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2014; **63**(5): 447-56.
50. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol* 2009; **53**(13): 1119-26.
51. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation* 2006; **114**(20): 2138-47.
52. Mohammed SF, Borlaug BA, Roger VL, et al. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. *Circ Heart Fail* 2012; **5**(6): 710-9.
53. Gori M, Senni M, Gupta DK, et al. Association between renal function and cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur Heart J* 2014; **35**(48): 3442-51.
54. Lam CSP, Voors AA, de Boer RA, Solomon SD, van Veldhuisen DJ. Heart failure with preserved ejection fraction: from mechanisms to therapies. *Eur Heart J* 2018; doi: **10.1093/eurheartj/ehy301**.
55. Krum H, Elisk M, Schneider HG, et al. Relation of peripheral collagen markers to death and hospitalization in patients with heart failure and preserved ejection fraction: results of the I-PRESERVE collagen substudy. *Circ Heart Fail* 2011; **4**(5): 561-8.
56. Hamdani N, Franssen C, Lourenco A, et al. Myocardial titin hypophosphorylation importantly contributes to heart failure with preserved ejection fraction in a rat metabolic risk model. *Circ Heart Fail* 2013; **6**(6): 1239-49.
57. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. *Circulation* 2017; **136**(1): 6-19.
58. Kitzman DW, Brubaker P, Morgan T, et al. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *JAMA* 2016; **315**(1): 36-46.
59. Dalos D, Mascherbauer J, Zotter-Tufaro C, et al. Functional Status, Pulmonary Artery Pressure, and Clinical Outcomes in Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol* 2016; **68**(2): 189-99.
60. Kitzman DW, Shah SJ. The HFpEF Obesity Phenotype: The Elephant in the Room. *J Am Coll Cardiol* 2016; **68**(2): 200-3.

61. Chau K, Girerd N, Magnusson M, et al. Obesity and metabolic features associated with long-term developing diastolic dysfunction in an initially healthy population-based cohort. *Clin Res Cardiol* 2018; **10.1007/s00392-018-1259-6**.
62. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013; **62**(4): 263-71.
63. Packer M. Epicardial Adipose Tissue May Mediate Deleterious Effects of Obesity and Inflammation on the Myocardium. *J Am Coll Cardiol* 2018; **71**(20): 2360-72.
64. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. *Circulation* 2016; **134**(1): 73-90.
65. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007; **28**(20): 2539-50.
66. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; **362**(9386): 777-81.
67. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; **27**(19): 2338-45.
68. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359**(23): 2456-67.
69. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**(15): 1383-92.
70. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. *JACC Heart Fail* 2017; **5**(7): 471-82.
71. Rogers JK, Pocock SJ, McMurray JJ, et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. *Eur J Heart Fail* 2014; **16**(1): 33-40.
72. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015; **131**(1): 34-42.
73. Hoendermis ES, Liu LC, Hummel YM, et al. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. *Eur Heart J* 2015; **36**(38): 2565-73.
74. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2013; **309**(12): 1268-77.
75. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2015; **373**(24): 2314-24.
76. Pieske B, Maggioni AP, Lam CSP, et al. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOLuble guanylate Cyclase

- stimulator in heart failure patients with PRESERVED EF (SOCRATES-PRESERVED) study. *Eur Heart J* 2017; **38**(15): 1119-27.
77. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012; **380**(9851): 1387-95.
78. Fitchett D, Butler J, van de Borne P, et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME(R) trial. *Eur Heart J* 2018; **39**(5): 363-70.
79. Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018; doi: **10.1161/CIRCULATIONAHA.118.034222**.
80. Redfield MM. Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2016; **375**(19): 1868-77.
81. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure with Preserved Ejection Fraction. *Circulation* 2018; doi: **10.1161/CIRCULATIONAHA.118.034646**.
82. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**(8): 891-975.
83. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013; **6**(3): 606-19.
84. Christ M, Stork S, Dorr M, et al. Heart failure epidemiology 2000-2013: insights from the German Federal Health Monitoring System. *Eur J Heart Fail* 2016; **18**(8): 1009-18.
85. Omersa D, Farkas J, Erzen I, Lainscak M. National trends in heart failure hospitalization rates in Slovenia 2004-2012. *Eur J Heart Fail* 2016; **18**(11): 1321-8.
86. Solomon SD, Dobson J, Pocock S, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007; **116**(13): 1482-7.
87. Kristensen SL, Jhund PS, Kober L, et al. Comparison of outcomes after hospitalization for worsening heart failure, myocardial infarction, and stroke in patients with heart failure and reduced and preserved ejection fraction. *Eur J Heart Fail* 2015; **17**(2): 169-76.
88. Crespo-Leiro MG, Anker SD, Maggioni AP, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016; **18**(6): 613-25.
89. Chioncel O, Mebazaa A, Harjola VP, et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017; **19**(10): 1242-54.
90. Arrigo M, Gayat E, Parenica J, et al. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail* 2017; **19**(2): 201-8.
91. Ferrari R, Bueno H, Chioncel O, et al. Acute heart failure: lessons learned, roads ahead. *Eur J Heart Fail* 2018; **20**(5): 842-50.

92. Harjola VP, Mullens W, Banaszewski M, et al. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2017; **19**(7): 821-36.
93. Mebazaa A, Yilmaz MB, Levy P, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail* 2015; **17**(6): 544-58.
94. Gayat E, Arrigo M, Littnerova S, et al. Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study. *Eur J Heart Fail* 2018; **20**(2): 345-54.
95. Cheema B, Ambrosy AP, Kaplan RM, et al. Lessons learned in acute heart failure. *Eur J Heart Fail* 2018; **20**(4): 630-41.
96. Packer M. Acute Heart Failure Is an Event Rather Than a Disease: Plea for a Radical Change in Thinking and in Therapeutic Drug Development. *JACC: Heart Failure* 2018; **6**(1): 73-5.
97. Mebazaa A. Acute Heart Failure Deserves a Log-Scale Boost in Research Support: Call for Multidisciplinary and Universal Actions. *JACC: Heart Failure* 2018; **6**(1): 76-9.
98. Cooper LB, Hammill BG, Peterson ED, et al. Consistency of Laboratory Monitoring During Initiation of Mineralocorticoid Receptor Antagonist Therapy in Patients With Heart Failure. *JAMA* 2015; **314**(18): 1973-5.
99. Nilsson E, De Deco P, Trevisan M, et al. A real-world cohort study on the quality of potassium and creatinine monitoring during initiation of mineralocorticoid receptor antagonists in patients with heart failure. *Eur Heart J Qual Care Clin Outcomes* 2018; **10.1093/ehjqcco/qcy019**.
100. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. *J Am Coll Cardiol* 2004; **44**(4): 810-9.
101. Alla F, Agrinier N, Lavielle M, et al. Impact of the interruption of a large heart failure regional disease management programme on hospital admission rates: a population-based study. *Eur J Heart Fail* 2018; doi: **10.1002/ejhf.1193**.
102. Laborde-Casterot H, Agrinier N, Zannad F, et al. Effectiveness of a multidisciplinary heart failure disease management programme on 1-year mortality: Prospective cohort study. *Medicine (Baltimore)* 2016; **95**(37): e4399.
103. Agrinier N, Altieri C, Alla F, et al. Effectiveness of a multidimensional home nurse led heart failure disease management program--a French nationwide time-series comparison. *Int J Cardiol* 2013; **168**(4): 3652-8.
104. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. *JAMA* 2010; **303**(17): 1716-22.
105. Sarwar CM, Papadimitriou L, Pitt B, et al. Hyperkalemia in Heart Failure. *J Am Coll Cardiol* 2016; **68**(14): 1575-89.
106. Anker SD, Koehler F, Abraham WT. Telemedicine and remote management of patients with heart failure. *Lancet* 2011; **378**(9792): 731-9.

107. Yun JE, Park JE, Park HY, Lee HY, Park DA. Comparative Effectiveness of Telemonitoring Versus Usual Care for Heart Failure: A Systematic Review and Meta-analysis. *J Card Fail* 2018; **24**(1): 19-28.
108. Fraiche AM, Eapen ZJ, McClellan MB. Moving Beyond the Walls of the Clinic: Opportunities and Challenges to the Future of Telehealth in Heart Failure. *JACC Heart Fail* 2017; **5**(4): 297-304.
109. Boehmer JP, Hariharan R, Devecchi FG, et al. A Multisensor Algorithm Predicts Heart Failure Events in Patients With Implanted Devices: Results From the MultiSENSE Study. *JACC Heart Fail* 2017; **5**(3): 216-25.
110. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362**(9395): 1527-35.
111. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment. 6. Prevention of heart failure and new-onset heart failure--meta-analyses of randomized trials. *J Hypertens* 2016; **34**(3): 373-84; discussion 84.
112. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373**(22): 2117-28.
113. Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018; **10.1161/CIRCULATIONAHA.118.034222**.
114. Butler J, Hamo CE, Filippatos G, et al. The potential role and rationale for treatment of heart failure with sodium-glucose co-transporter 2 inhibitors. *Eur J Heart Fail* 2017; **19**(11): 1390-400.
115. Preiss D, Campbell RT, Murray HM, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. *Eur Heart J* 2015; **36**(24): 1536-46.
116. Djousse L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure. *JAMA* 2009; **302**(4): 394-400.
117. Florido R, Kwak L, Lazo M, et al. Six-Year Changes in Physical Activity and the Risk of Incident Heart Failure: ARIC Study. *Circulation* 2018; **137**(20): 2142-51.
118. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006; **368**(9535): 581-8.
119. Ferreira JP, Machu JL, Girerd N, et al. Rationale of the FIBROTARGETS study designed to identify novel biomarkers of myocardial fibrosis. *ESC Heart Fail* 2018; **5**(1): 139-48.
120. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005; **112**: e154-e235.
121. Ziaeian B, Fonarow GC. The Prevention of Hospital Readmissions in Heart Failure. *Prog Cardiovasc Dis* 2016; **58**(4): 379-85.

891 122. Senni M, Gavazzi A, Oliva F, et al. In-hospital and 1-year outcomes of acute heart failure
892 patients according to presentation (de novo vs. worsening) and ejection fraction. Results
893 from IN-HF Outcome Registry. *Int J Cardiol* 2014; **173**(2): 163-9.

894 Short Panel:

895 **Heart failure presentation**

- 896 • Patients at high risk for HF (i.e., those with hypertension, diabetes mellitus,
897 atherosclerotic disease, obesity) but without structural heart disease or HF symptoms are
898 considered Stage A in the development of HF.¹²⁰
- 899 • Stage B describes the development of asymptomatic structural heart disease (i.e. previous
900 myocardial infarction [MI], left ventricular remodeling, left ventricular hypertrophy,
901 reduced EF, asymptomatic valvular disease).¹²⁰
- 902 • Stage C HF reflects symptomatic patients who should receive optimal medical therapy
903 unless contraindicated.^{9,10,120} Symptoms are non-specific and dominated by shortness of
904 breath and fatigue, leading to reduced functional capacity assessed by clinical scores
905 (NYHA classification I to IV) and 6-minute walk distance or other ergometric tests. The
906 most common signs of HF are related to congestion, whether vascular or interstitial,
907 pulmonary (e.g., rales, pleural effusion) or peripheral (e.g. leg oedema, jugular vein
908 dilatation, and, in more severe cases, liver enlargement and ascites). ~~Stage C patients may~~
909 ~~be relatively stable on GDMT, but ultimately progression of the disease is marked by~~
910 ~~episodes of acute decompensation, which can be precipitated by several cardiovascular~~
911 ~~and non-cardiovascular factors.~~
- 912 • Acute decompensation is accompanied by distressing symptoms of congestion and the
913 potential for end-organ (i.e., cardiac, liver, kidney) damage.¹³ Hospitalisations for HF
914 carry a poor prognosis. Among patients hospitalised in the United States for HF from
915 2008 to 2010, 67·4% experienced a readmission and 35·8% died within one year of the
916 index hospitalisation.¹²¹ Data from Europe show consistent results.¹²²

- Patients with refractory symptoms despite optimal implementation of best medical care are considered Stage D.¹²⁰ These patients should be considered for additional interventions (e.g., mechanical circulatory support, transplant evaluation), but these therapies are beyond the scope of this review.

924 BOX: Research priorities

- 925 • Randomized evidence that lifestyle modifications delay per se the onset of HF and reduce
926 cardiovascular mortality
- 927 • Identification of mechanistic therapeutic targets to prevent and treat HFrEF and HFpEF
- 928 • Defining the best monitoring strategies to monitor decongestion/re-congestion
- 929 • Identification of the most effective components of disease management programs
- 930 • The incorporation of digital self-management tools and patient facing applications for heart
931 failure management
- 932 • The use of external (wearables) and internal sensors to identify early signals of worsening
933 heart failure including remote imaging and the protocols for managing heart failure with
934 worsening signals
- 935 • Understanding whether virtualisation of clinical management of heart failure may be
936 automated and the benefits or risks for medication titration or alteration based on multiple,
937 integrated electronic data streams from home and clinic
- 938 • Understanding whether population management systems can be used for managing and
939 monitoring patients with heart failure using new data science methods such as machine
940 learning

941

942

Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction

Trial	N	Treatment arms	Key Inclusion criteria	Primary Endpoint	Findings
CHARM-Preserved ⁶⁶	3023	Candesartan vs. placebo	NYHA class II-IV, prior CV hospitalisation	Time to first cardiovascular death or heart failure hospitalisation	Primary outcome HR 0·89 (0·77, 1·03), p = 0·12
PEP-CHF ⁶⁷	850	Perindopril vs. placebo	Clinical diagnosis of DHF with ≥signs/symptoms of HF, ≥2 of the following: Left atrial enlargement/LVH/Impaired LV filling/Atrial fibrillation	Time to first all-cause death or heart failure hospitalisation	Primary outcome HR 0·92 (0·70, 1·21), p = 0·55
I-PRESERVE ⁶⁸	4128	Irbesartan vs. placebo	NYHA class II-IV + any corroborating evidence (e.g., HF sign), LVH or	Time to first all-cause death or cardiovascular hospitalisation	Primary outcome HR 0·95 (0·86, 1·05), p = 0·35

Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction (continued)

Trial	N	Treatment arms	Key Inclusion criteria	Primary Endpoint	Findings
			LAE considered optional corroborating evidence, HFH required unless in NYHA class III-IV		
TOPCAT⁶⁹	3445	Spironolactone vs. placebo	Signs and symptoms of HF, elevated NP, or HFH	Time to first cardiovascular death, heart failure hospitalisation or resuscitated sudden death	Primary outcome HR 0·89 (0·77, 1·04), p = 0·14
PARAGON-HF⁷⁰	~4800	Sacubitril/valsartan vs. valsartan	NYHA class II-IV, elevated NT-proBNP (depending on timing of prior heart failure hospitalisation and atrial fibrillation status),	Cardiovascular death or total heart failure hospitalisation (first and recurrent)	Ongoing, fully recruited

Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction (continued)

Trial	N	Treatment arms	Key Inclusion criteria	Primary Endpoint	Findings
			structural heart disease (left atrial enlargement or left ventricular hypertrophy)		
EMPEROR-Preserved (NCT03057951)	~4126	Empagliflozin vs. placebo	NYHA class II-IV heart failure, EF > 40%, elevated NT-proBNP (depending on atrial fibrillation status), structural heart disease (left atrial enlargement or LVH) or documented HF hospitalisation	Time to first cardiovascular death or heart failure hospitalisation	Ongoing

CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; CV, cardiovascular; DHF, diastolic heart failure; EF, ejection fraction; EMPEROR, Empagliflozin outcome trial in patients with chronic heart failure with reduced

Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction (continued)

ejection fraction; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction Study; LV, left ventricular; LVH, left ventricular hypertrophy; NP, natriuretic peptides; NT-proBNP, N-terminal B-type natriuretic peptide; NYHA, New York Heart Association; PARAGON-HF, Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; PEP-CHF, Perindopril for Elderly People with Heart Failure; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

Table 2. Ongoing Heart Failure with Reduced Ejection Fraction Outcome Trials

Trial	Number of patients	Treatments	Key inclusion criteria	Primary endpoint
COMMANDER HF (NCT01877915)	5070	Rivaroxaban vs. placebo (in addition to standard of care for HF and CAD)	Symptomatic HF, episode of decompensated HF within 30 days, LVEF $\leq$ 40%, evidence of significant CAD, BNP $\geq$ 200 pg/mL or NT-proBNP $\geq$ 800 pg/mL	Major acute cardiovascular events (all-cause mortality, MI, stroke)
GALACTIC HF (NCT02929329)	8000	Omecamtiv mecarbil vs. placebo	History of chronic HF, LVEF $\leq$ 35%, NYHA class II-IV, current hospitalisation for HF or within previous year, elevated BNP or NT-proBNP	Time to CV death or first HF event
FAIR-HF2 NCT03036462	1200	Intravenous iron (ferric	Chronic HF, confirmed presence of iron deficiency,	Combined rate of recurrent hospitalisations for HF and CV death

Table 2. Ongoing Heart Failure with Reduced Ejection Fraction Outcome Trials (continued)

Trial	Number of patients	Treatments	Key inclusion criteria	Primary endpoint
		carboxymaltose) vs. placebo	serum haemoglobin 9.5 to 14.0 g/dL	
HEART-FID NCT03037931	3014	Ferric carboxymaltose vs. placebo	Stable HF on maximal tolerated background therapy, LVEF $\leq 35\%$, haemoglobin >9.0 g/dL and <13.5 g/dL (females) or <15.0 (males), serum ferritin <100 ng/mL or 100-300 ng/mL with TSAT $<20\%$, hospitalisation for HF within 12 months or screening NT-proBNP >600 pg/mL or BNP >200 pg/mL (sinus rhythm) or NT-proBNP >1000 pg/mL or	All-cause mortality or HF hospitalisation at 1 year; change in 6-minute walk distance

Table 2. Ongoing Heart Failure with Reduced Ejection Fraction Outcome Trials (continued)

Trial	Number of patients	Treatments	Key inclusion criteria	Primary endpoint
			BNP >400 pg/mL (atrial fibrillation)	
EMPEROR Reduced (NCT03057977)	2850	Empagliflozin vs. placebo	Chronic HFrEF, NYHA class II-IV, elevated NT-proBNP or BNP (at various levels depending on LVEF and cardiac rhythm)	Time to first adjudicated CV death or HF hospitalisation
DAPA-HF (NCT03036124)	4500	Dapagliflozin vs. placebo	HFrEF, LVEF $\leq 40\%$, elevated NT-proBNP, eGFR ≥ 30 ml/min/1.73 m ²	Time to first CV death, hospitalisation for HF, or urgent HF visit
VICTORIA (NCT02861534)	4872	Vericiguat vs. placebo	Chronic HFrEF, NYHA class II-IV, HF hospitalisation within 6 months or intravenous diuretics within 3 months;	Time to first CV death or HF hospitalisation

Table 2. Ongoing Heart Failure with Reduced Ejection Fraction Outcome Trials (continued)

Trial	Number of patients	Treatments	Key inclusion criteria	Primary endpoint
			elevated BNP or NT-proBNP (specific levels dependent on cardiac rhythm) LVEF <45%	

For all trials, all patients on standard background therapy for HF

BNP, B-type natriuretic peptide; CAD, coronary artery disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

Table 3. Candidate drugs under early clinical development in chronic heart failure

Mechanism of action	Drugs
Adenosine A1 partial agonists	Neladenoson dalanate
<u>Aminopeptidase A (APA) inhibitor.</u>	QCG001
<u>Antidiabetics</u>	GLP-1 agonists, SGLT2 inhbitors
Apelin	Apelin, CLR325
Atrial natriuretic peptides	Cenderitide (CD-NP), ANX-042, PL-3994 (NPR-A agonist)
AT1R biased ligands	TVR120027
β 3-agonists	Mirabegron
Cardiac ion channels modulator	Ranolazine (I_{NaL}), GSK2193874, (TRPV4)
IL-1 β recept antagonists	Anakinra
Mitochondrial targeting peptide	MTP-131 (elamipretide), Perhexilene
Mineralocorticoid receptor antagonists	Finerenone, BR-4628109, CS-3150, LY-2623091, MT-3995
Neuregulin-1	GGF (rhNR-1)
Phosphodiesterase inhibitors	ITI-214, CRD-733
Probiotics (GUT microbiome)	Rifaxamin

Table 1. Completed and ongoing outcomes trials in heart failure with preserved ejection fraction(continued)

Mechanism of action	Drugs
sGC stimulator	Riociguat
Selective androgen receptor modulators	GSK2849466
Vasodilators	Urocortins 2 and 3
Vasopressin receptor antagonists	Tolvaptan, Ribuvaptan
Xanthine-oxidase inhibitors	Febuxostat
Uricosurics	Probenecid
Drugs targeting Epigenetics	DNA methyltransferase inhibitors. HDAC inhibitors

Figure 1.

Chronic

III: Marked limitation of physical activity.
Comfortable at rest,
but less than ordinary activity
causes symptoms of HF

IV: Unable to carry on
any physical activity
without symptoms of HF,
or symptoms of HF at rest

II: Slight limitation of physical activity.
Comfortable at rest,
but ordinary physical activity
results in symptoms of HF

I: No limitation of physical
activity.
Ordinary physical activity
does not cause symptoms of HF

**Acutely
Decompensated**

Personalized Health Plan

Remote Monitoring and Management

Enhanced Clinic Support with Rapid Access

Emergency and Hospital Care