Advances in management of heart failure

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ABSTRACT

Heart failure is increasing in prevalence in many countries with aging populations. Fortunately, remarkable scientific advances have been made in the past few years that have led to new treatments and improved prognosis for patients with heart failure. This review examines these changes with a focus on the diagnosis and medical management of heart failure. The changes include the increase to four foundational drug classes (pillars of therapy) now recommended for patients with heart failure and reduced left ventricular ejection fraction, use of sodium-glucose cotransporter-2 inhibitors for those with a higher ejection fraction, and the importance of rapid initiation of life prolonging therapies once a diagnosis of heart failure has been made. Device management and other non-drug management have also evolved with the publication of new clinical trials. The review emphasizes evidence published since the recent heart failure guidelines of the European Society of Cardiology and American College of Cardiology/American Heart Association/Heart Failure Society of America in 2021 and 2022. Additional studies are needed to determine how best to implement these new interventions in clinical practice.

Introduction

Heart failure is a common and growing health and economic burden for many of the world's communities. This growth is pronounced in societies with aging populations. Advances in heart failure care have been dramatic over recent years, including new drugs, devices, and diagnostic care strategies. Clinical guidelines published within the past few years have included many of these changes, but even these recent guidelines are already out of date in their recommendations for treatment and diagnosis. In light of this rapidly changing scientific evidence base, we provide an up-to-date review of the most important aspects of heart failure care.

Sources and selection criteria

We searched PubMed and the Cochrane Database of Systematic reviews for articles published between January 2015 and 7 July 2023 to identify new randomized controlled trials (RCTs) and large cohort studies of treatments and diagnostic strategies for heart failure. We also identified epidemiologic studies published from 2020 to 2023. We included older studies to provide context. We focused on studies not included in the recent European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines from 2021 and 2022.[1 2] We prioritized RCTs over observational data when reviewing interventions. We did not consider case reports or case series in our review.

Epidemiology

The Global Burden of Disease Study estimated that 57 million people were living with heart failure in 2019.[3 4] Although this number has been increasing in countries with aging populations, the age standardized rate has fallen from 7.7 per 1000 in 2010 to 7.1 per 1000 in 2019.[3 4] The change over time in the age adjusted prevalence from 2009 to 2019 (an average 0.3% decline per year during this period) has not been linear, with rates initially falling but then increasing by 0.6% per year between 2016 and 2019.[3 4] The reason for this change in prevalence is unclear and requires further investigation. An increase in hospital admissions for heart failure has been noted for young adults (age 18-45) in the US, with rates increasing from 1.8 per 10 000 in 2013 to 2.5 per 10 000 in 2018.[5]

Large differences in prevalence are noted across global regions for both men and women (fig 1).[3 4] The region with the highest prevalence of heart failure includes the high income countries of North America, and the lowest prevalence was in central Asia. An estimated 3% of the US population will have heart failure by 2030.[6] The largest declines in age adjusted rates were noted in high income countries of North America and Australasia regions.

Survival

Survival following a diagnosis of heart failure is poor and is highly influenced by age. In the UK, survival approaches 80% at five years for people aged 45-64 but is closer to 20% at five years for those aged ≥85.[7] Fortunately, survival rates have

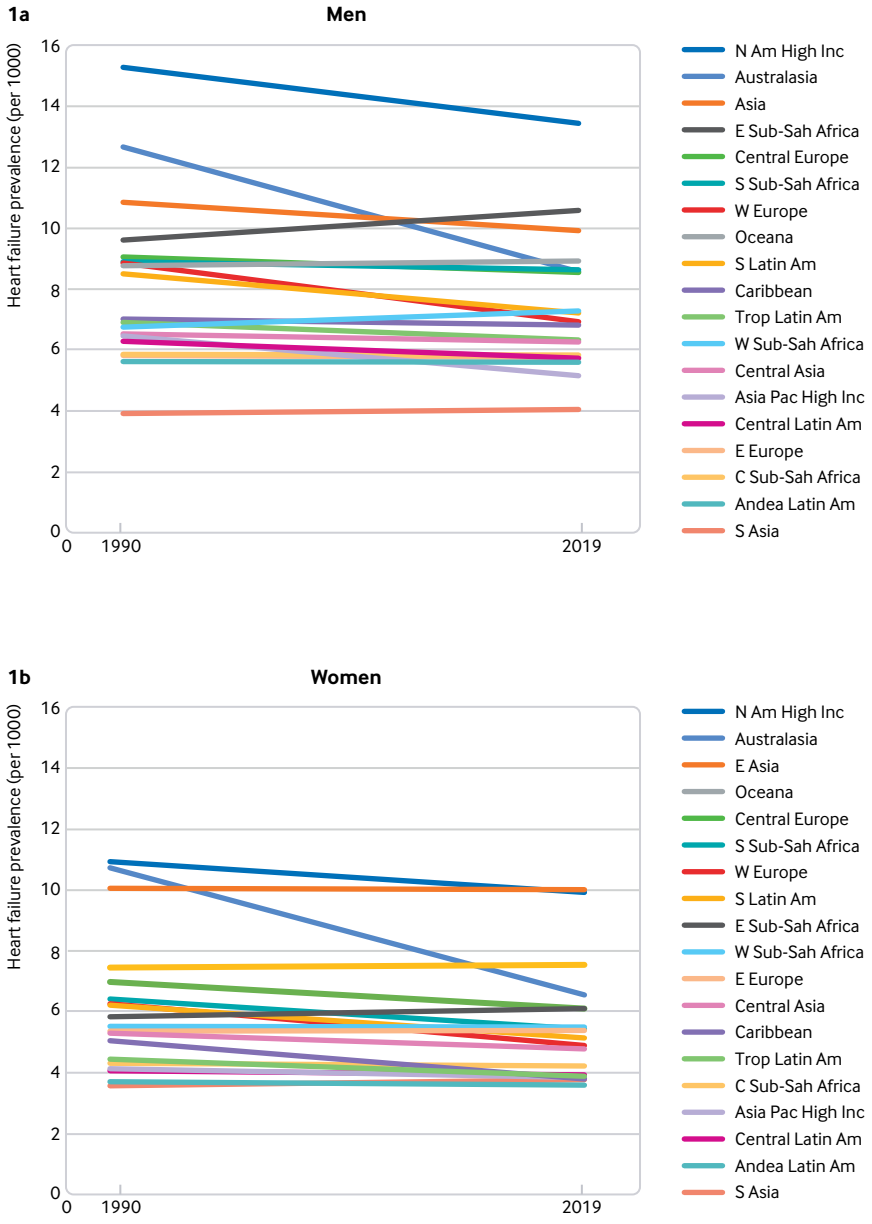

Fig 1 | Country specific, age adjusted prevalence of heart failure from 1990 to 2019 in men (top) and women (bottom). Estimates are from the Global Burden of Disease Study[3 4]

improved since 2000, particularly among younger patients.[7]

Although overall survival is an important outcome, it reflects the combined effects of all the patient's conditions. The incremental impact of heart failure on survival is difficult to discern, as most patients with heart failure have multiple comorbidities. Years of life lost due to heart failure can be estimated by examining survival relative to actuarial estimates of life expectancy. Data from the UK have shown that heart failure is associated with a 2.4-fold greater loss of time alive than observed in the age and sex matched general population over 10 years.[8] Length of life lost with heart failure varies from five months (women) to one year (men) for people with no comorbidities and from three years (women) to 4.5 years (men) for those with three or more comorbidities.[8]

The impact of covid-19 on the incidence of heart failure is uncertain but may be substantial. Studies from the US Veterans Affairs healthcare system have suggested that covid-19 is associated with an increased risk of cardiovascular events including death, myocardial infarction, and stroke.[9 10]

Prevention, screening, and identification of heart failure

Heart failure can be largely prevented or delayed with optimal control of risk factors.[11 12] Uncontrolled hypertension remains the most common risk factor for incident heart failure.[13 14] Optimal blood pressure control is associated with a 40% reduction in heart

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failure events,[15] and multiple therapies for comorbid conditions reduce the risk of progression to heart failure including sodium-glucose cotransporter-2 (SGLT2) inhibitors, which reduce the risk of incident heart failure in patients with diabetes mellitus.[16-18] Among patients with chronic kidney disease, both SGLT2 inhibitors and finerenone (in those with diabetes) reduce the risk of incident heart failure.[19 20]

Several clinical risk models can identify patients at high risk for progression to heart failure.[21-24] Concentrations of natriuretic peptide (B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP)) are also elevated among patients at high risk of incident heart failure or asymptomatic systolic dysfunction.[25-27] In the STOP-HF (St Vincent's Screening to Prevent Heart Failure) study, patients with a cardiovascular risk factor were screened using BNP. Patients with elevated concentrations had echocardiography and collaborative cardiology and primary care management. This led to a reduction in subsequent left ventricular systolic dysfunction and emergency hospital admissions for cardiovascular reasons.[28] Similar results were confirmed in a trial among patients with diabetes mellitus.[29] Since these trials, additional treatment options are now available to prevent incident heart failure among people at high risk.[1 2] Expanding natriuretic peptide screening could lead to earlier diagnosis and treatment, substantially reducing the morbidity of heart failure.

Given that heart failure is a progressive condition with high early morbidity, prompt recognition is critical. In the UK, more than 80% of first diagnoses of heart failure are made in the hospital, and more than 40% of these patients have symptoms that should promote earlier assessment.[30] Women were noted to take six times longer to receive a diagnosis of heart failure and were twice as likely to be misdiagnosed.[31] Similar patterns of delayed diagnosis of heart failure have been noted in the US and Canada.[32-34] Minimizing the morbidity of heart failure requires increased awareness among patients and primary care clinicians, as well as additional strategies to facilitate disease recognition.

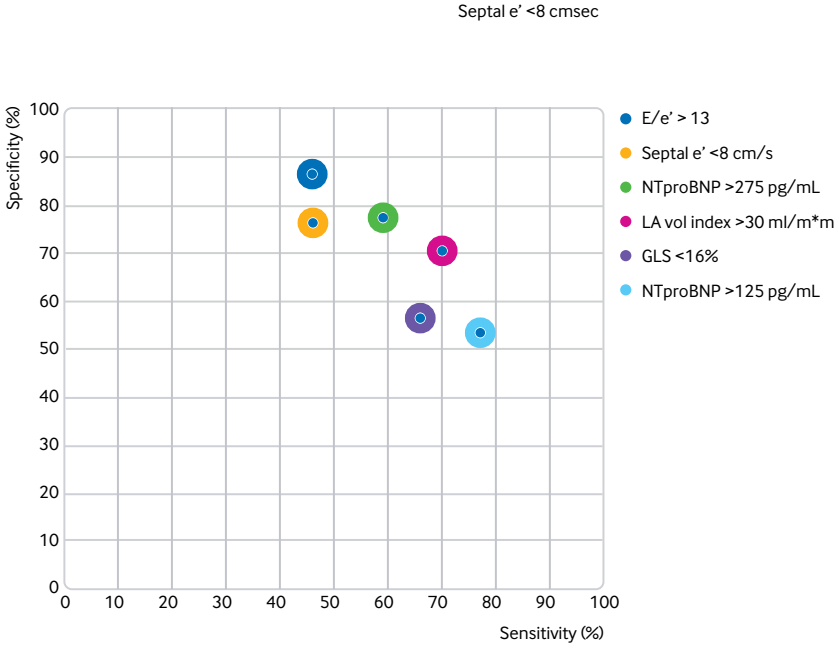

Fig 2 | Test characteristics for common non-invasive tests of increased left ventricular filling pressure. No single test threshold has both sensitivity and specificity above 70%.[10] E/e'=early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; GLS=global longitudinal strain; LA=left atrium; NT-proBNP=N-terminal pro B-type natriuretic peptide

Diagnosis

The diagnosis of heart failure requires the presence of symptoms consistent with cardiac dysfunction along with evidence of either significantly reduced left ventricular systolic function (≤40%) or increased filling pressures. This is now incorporated into the recently published universal definition of heart failure.[35] Heart failure is categorized into three groups based on the left ventricular ejection fraction (LVEF): heart failure with reduced ejection fraction (HFrEF) if the LVEF is ≤40%; heart failure with mildly reduced ejection fraction (HFmrEF) if the LVEF is 41-49%, and heart failure with preserved ejection fraction (HFpEF) if the LVEF is ≥50%. Patients with LVEF >40% require additional evidence of increased filling pressures (at rest or with exercise) to establish a diagnosis of heart failure.

Diagnosis of HFpEF

The diagnosis of HFpEF is particularly challenging, as determining increased filling pressure can be difficult. Most definitions of HFpEF exclude patients with heart failure symptoms due to valve disease, arrhythmia, pericardial constraint, or high cardiac output. Although invasive testing with cardiac catheterization is the gold standard for determining elevated left ventricular filling pressures, the diagnosis can be made non-invasively. Unfortunately, no single non-invasive test result has both a high sensitivity and a high specificity (fig 2).

Accordingly, clinical scores have been created using the results from multiple tests to diagnose HFpEF. These include H2FPEF (Heavy, 2 or more Hypertensive drugs, atrial Fibrillation, Pulmonary hypertension (pulmonary artery systolic pressure >35 mm Hg), Elder age >60, elevated Filling pressures, E/e' >9)[36] and HFA-PEFF (Heart Failure Association—Pre-test assessment; Echocardiography and natriuretic peptide score; Functional testing; Final etiology).[37] A recent evaluation found that these two scores have similar prognostic value, although 28% of patients had discordant findings (HFpEF diagnosed by only one of the algorithms).[38]

Perhaps as important as making the diagnosis of heart failure is determining whether the patient will benefit from therapy for HFpEF. Thus, clinicians can use the enrollment criteria from clinical trials showing benefit to make a diagnosis of HFpEF. The two clinical trials of SGLT2 inhibitors that showed benefit for patients with HFpEF used the following enrollment criteria: New York Heart Association

(NYHA) II-IV symptoms, treatment with a diuretic, an NT-BNP >300 pg/mL if sinus rhythm (>600 or >900 pg/mL if atrial fibrillation), and evidence of structural heart disease (left atrial enlargement, left ventricular hypertrophy), in the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial, or a recent hospital admission for heart failure.[39 40]

Determining the cause of heart failure

Determining the underlying cause of heart failure symptoms is an important second step after making a diagnosis, as some conditions have specific treatments.[1 2] Additional testing beyond echocardiography is often needed, and although routine screening with cardiac magnetic resonance (CMR) imaging is not clearly beneficial,[41] selected use of CMR often provides useful information. The patterns of late gadolinium enhancement and certain T1 and T2 techniques may suggest a diagnosis of non-compaction, myocarditis, or Chagas disease, as well as infiltrative cardiomyopathies including amyloidosis, iron overload, sarcoidosis, and Fabry disease.[1 2] Patients with dilated cardiomyopathy and those with significant hypertrophy on echocardiography may be most likely to benefit from CMR.

Four medication pillars of HFrEF therapy

For patients with heart failure and a reduced left ventricular ejection fraction to ≤40% (HFrEF), four classes of drugs are now known to improve survival.[1 2] These are renin-angiotensin system inhibitors including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) or angiotensin receptor/neprilysin inhibitors (ARNI); β blockers; mineralocorticoid receptor antagonists (MRAs); and SGLT2 inhibitors (table 1; fig 3). Using the relative risk reduction from the clinical trials, it has been estimated that the combination of the four pillars of HFrEF therapy will lead to a 73% relative risk reduction in mortality and a number needed to treat of four to prevent a death compared with no treatment.[42]

ARNI

The combination of an ARB and a neprilysin inhibitor is now recommended as one of the pillars of HFrEF therapy. The PARADIGM-HF (Prospective Comparison of ARN Inhibitors with ACE Inhibitors to Determine Impact on Global Mortality and Morbidity in HF) trial randomized 8442 patients with HFrEF. It found a 20% reduction in cardiovascular death or admission to hospital for heart failure with sacubitril and valsartan compared with enalapril (hazard ratio 0.80, 95% confidence interval 0.73 to 0.87).[43] Sacubitril/valsartan was also associated with a significant reduction in symptoms, as measured by the Kansas City Cardiomyopathy Clinical Summary Score (hazard ratio 1.64, 0.63 to 2.65).[43] A second RCT was conducted in patients admitted to hospital with heart failure (PIONEER-HF58: Comparison of Sacubitril-Valsartan vs Enalapril on Effect of N-Terminal Pro–Brain Natriuretic Peptide [NT-proBNP] in Patients Stabilized From an Acute HF Episode).[44] This trial in 881 patients showed a reduction in NT-proBNP concentrations (ratio of change 0.71, 95% confidence interval 0.63 to 0.81) for patients starting sacubitril/valsartan during hospital admission compared with those treated with enalapril. Safety was also demonstrated, with no significant differences in worsening renal function, hyperkalemia, and symptomatic hypotension. The 2022 US Heart Failure Guideline now recommends ARNI as the first line agent with ACE inhibitor or ARB alone for patients unable to take ARNI.[2] Use of ARNI along with an ACE inhibitor is contraindicated.

No benefit with ARNI was observed for patients with advanced heart failure defined as NYHA class IV symptoms or patients taking chronic inotropic therapy.[45] The LIFE (LCZ696 in Advanced HF) study randomized 335 patients with advanced heart failure and found that after 24 weeks of treatment, changes in NT-proBNP were not clearly different between patients treated with sacubitril/valsartan and those treated with valsartan alone (ratio of change 0.95, 0.84 to 1.08).

SGLT2 inhibitors

This new class of drugs (sodium-glucose cotransporter-2 inhibitors) was originally designed to improve glycemic regulation in diabetes but was found to also improve cardiac outcomes, including the prevention of heart failure. Subsequent trials in patients with reduced LVEF have consistently shown a significant reduction in hospital admissions due to heart failure, with several also showing a reduction in cardiovascular mortality.[46] Accordingly, this class (for example, dapagliflozin and empagliflozin) is now one of the four pillars of HFrEF therapy.

Sotagliflozin is a combined SGLT1 and SGLT2 inhibitor, and whether it should be placed in the same

Table 1 | Life prolonging medications for heart failure with reduced left ventricular ejection fraction[42]

Treatment	Background therapy for treatment and control groups	Relative risk reduction (death)*	NNT to prevent 1 death at 3 years*
ACEi/ARB	No other life prolonging medication	17	26
β blocker	ACEi (>90%)	34	9
MRA	ACEi (≥90%); β blockers 10%	30	6
ARNI	ACEi (100%: active control); β blockers (>90%); MRAs (>50%)	16	27
SGLT2i	ACEi/ARB/ANRI (90%); β blockers (>90%); MRAs (>70%)	17	22

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor/neprilysin inhibitor; MRA=mineralocorticoid receptor antagonist; SGLT2i=sodium-glucose cotransporter-2 inhibitor; NNT=number needed to treat.
*From Bassi et al, *JAMA Cardiology* 2020.[42]

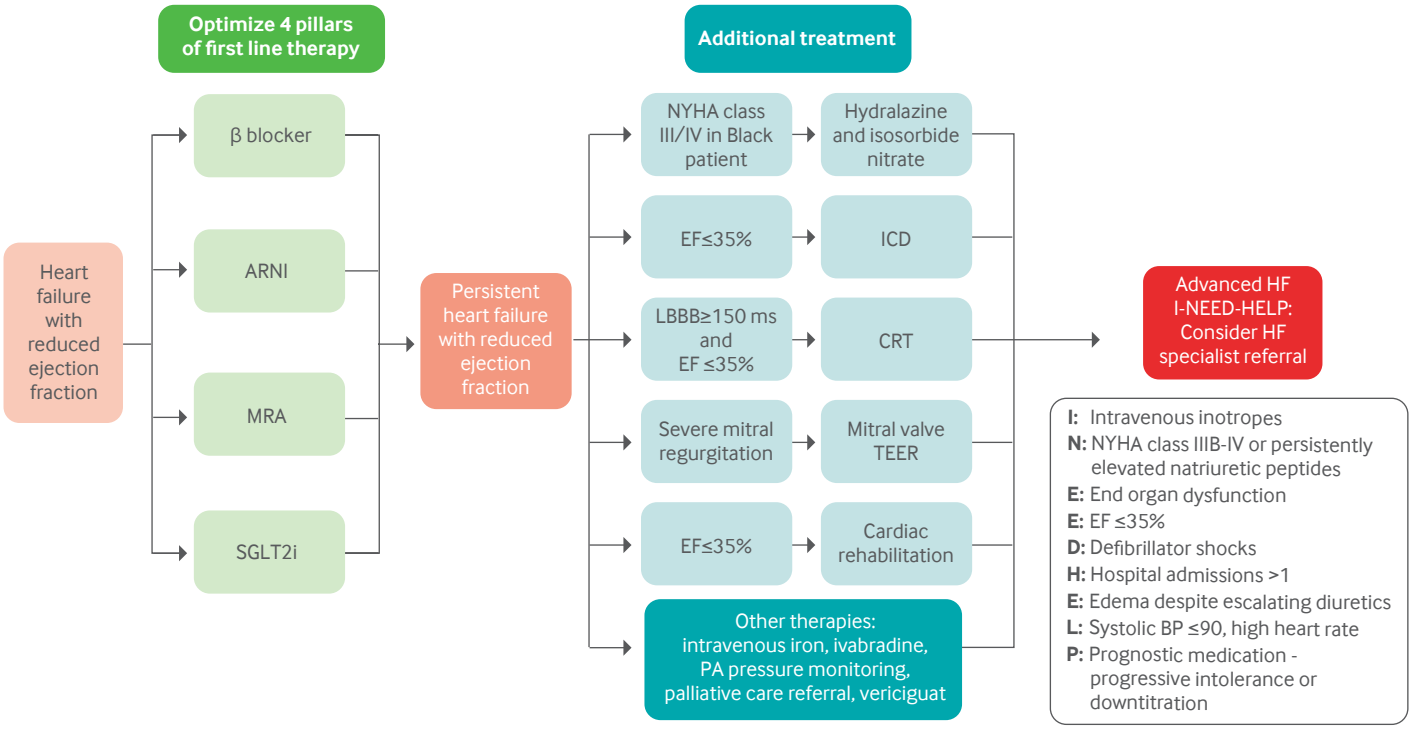

Fig 3 | Schematic of treatment for heart failure with reduced ejection fraction. ARNI=angiotensin receptor/neprilysin inhibitor therapy; BP=blood pressure; CRT=cardiac resynchronization therapy; EF=ejection fraction; HF=heart failure; ICD=implantable cardiac defibrillator; LBBB=left bundle branch block; MRA=mineralocorticoid receptor antagonist; NYHA=New York Heart Association; PA=pulmonary artery; SGLT2i=sodium glucose linked cotransporter 2 inhibitor; TEER=transcatheter edge-to-edge repair

class as purer SGLT2 inhibitors is unclear. In a study in 1222 patients with diabetes and recent hospital admission for heart failure, initiation of sotagliflozin before or shortly after discharge reduced death from cardiovascular causes and hospital admissions and urgent visits for heart failure compared with placebo (hazard ratio 0.67, 0.52 to 0.84).[47] A second study randomized 10584 patients with diabetes and renal dysfunction, 20% of whom had heart failure, to sotagliflozin or placebo. The combined endpoint of cardiovascular death, hospital admission for heart failure, and urgent visits for heart failure was reduced by sotagliflozin, with similar effects for patients with and without heart failure (hazard ratio 0.74, 0.63 to 0.88).[48] The 2021 ESC guideline has grouped sotagliflozin with the SGLT2 inhibitors in its recommendations for patients with heart failure and diabetes.[1] The drug was only recently approved in the US and thus was not eligible for inclusion in the ACC/AHA/HFSA 2022 guideline.[2]

Importance of rapid initiation of therapy

The importance of rapid initiation of life prolonging heart failure medication is now recognized owing to results from the Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF) trial.[49] This multicenter study with 1078 patients from 87 hospitals in 14 countries examined rapid up-titration of guideline directed medication after an admission for acute heart failure. The intervention group had their medications up-titrated to 100% of recommended doses within two weeks of discharge. The primary endpoint of 180 day readmission to hospital due to heart failure or all cause death was reduced by an absolute percentage of 8.1% (95% confidence interval 2.9% to 13.2%) with rapid titration. We note that the STRONG-HF trial was conducted before SGLT2 inhibitors became standard of care for HFrEF therapy.

Further evidence of the benefit of rapid initiation comes from the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial.[50] Among 4744 patients in this trial, the time to clinical benefit was surprisingly fast with a significant reduction in cardiovascular death or worsening heart failure observed by 28 days after randomization to dapagliflozin compared with placebo (hazard ratio 0.51, 95% confidence interval 0.28 to 0.94).[50] Similarly, in 1222 patients treated with sotagliflozin compared with placebo,[47] the time to a sustained and significant reduction in the primary endpoint was 27 days (hazard ratio 9.62, 0.39 to 0.99). However, the time to benefit was twice as long for patients with heart failure and preserved ejection fraction.[51]

Although the goal is to initiate all four drug classes in a timely manner, the optimal order and timing of initiation remains controversial. Investigators have modeled the potential benefit of different strategies based on how quickly benefits were observed in

clinical trials.[52] They found that a strategy of starting with SGLT2 inhibitors and MRAs should lead to the greatest improvement in outcome. Other authors advocate for a more rapid approach, starting all four drugs at low doses together.[53] Starting drugs rapidly in combination may be the quickest way to reach recommended doses, although it also may increase the risk of temporary side effects (for example, hypotension or elevated creatinine). Side effects may lead clinicians and patients to assume a permanent drug intolerance and reduce the chances that the patient is ultimately treated with all four recommended classes. The patient's condition may indicate the appropriate drug to use first. For example, an SGLT2 inhibitor or MRA may be the appropriate first drug in those with borderline low blood pressure. Additional studies are needed to determine which initiation strategy leads to the optimal sustained use of recommended treatments. Strategies for implementation of guideline directed medical therapy have been recently reviewed.[54]

Diuretics

Although diuretics are a mainstay of treatment for patients with signs or symptoms of congestion, they have not been shown to improve mortality.[2 55] The efficacies of two loop diuretics were compared in the TRANSFORM-HF trial of 2859 patients who were randomized to furosemide or torsemide.[56] The primary outcome of all cause death was similar for the two loop diuretics (hazard ratio with torsemide treatment 1.02, 0.89 to 1.18).

Recently, the efficacy of intravenous acetazolamide in addition to intravenous loop diuretics was examined in the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial.[57] Among 519 patients with heart failure, greater decongestion was seen in the group randomized to acetazolamide (successful decongestion within three days: 42.2% *v* 30.5%; P<0.001). In the Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) trial, 239 patients were randomized to a thiazide diuretic or placebo in addition to a loop diuretic.[58] The addition of the thiazide significantly increased decongestion but with an increase in serum creatinine. Together, the ADVOR and CLOROTIC trials suggest that add-on diuretic therapy can improve decongestion compared with loop diuretics alone, although long term safety is uncertain.[57 58]

Treatment of patients with improved ejection fraction

LVEF will improve from below 40% to above 40% during follow-up in about 15% of patients.[59] Some will even have a normalization of their LVEF (>50%). Although this improvement may imply recovery, a randomized trial of 51 patients with predominantly familial/idiopathic dilated cardiomyopathy found that discontinuing medication in those with apparent recovery of left ventricular function (LVEF >50%, NT-proBNP <250 ng/L, normalized left ventricular volume) led to relapses of heart failure in 46% (95% confidence interval 29% to 67%) at six months compared with 0% in those continuing medication (P=0.0001).[60] Accordingly, the ACC/AHA/HFSA guideline was revised in 2022 to use the term "improved" instead of "recovered" when the LVEF increases from ≤40% to >40%.[2]

Continued HFrEF treatments are recommended for patients whose LVEF improves, although whether dose escalation or additional medications are beneficial once symptoms have resolved and LVEF has improved remains uncertain. In rare cases, withdrawal of therapy will succeed without relapse of heart failure. These patients with truly recovered LVEF include those whose cardiomyopathy is the result of a toxin, tachycardia, or other insult that has been eliminated. Unfortunately, being certain of the cause of cardiomyopathy is often difficult, and any attempt at withdrawal should be gradual with close follow-up and should be done only in selected cases in which heart failure has a specific and reversible cause.

Treatment of HFmrEF and HFpEF

As noted above, an LVEF of 41-49% is mildly reduced (HFmrEF) whereas patients with an LVEF ≥50% are considered to have preserved ejection fraction (HFpEF). These labels apply only to patients who have not previously had an LVEF ≤40% (these are referred to as heart failure with improved ejection fraction). SGLT2 inhibitors are recommended as the first line medication for patients with mildly reduced or preserved LVEF on the basis of the two trials that enrolled many patients with an LVEF >40%.[39 40]

Of the other treatments for HFrEF, ARNI, ACE inhibitors, ARBs, and MRAs are second line therapies as the evidence for benefit is much weaker than for patients with HFrEF. Accordingly, MRAs and ACE inhibitors/ARBs/ARNI have a class 2B recommendation for HFmrEF and HFpEF in guidelines for patients with mildly reduced or preserved LVEF.[2]

Of note, β blockers are not recommended for patients with HFpEF (2B recommendation for HFmrEF).[2] Lack of benefit for HFpEF was noted in a meta-analysis of randomized trials of β blockers, which reported a non-significant trend toward increased cardiovascular and all cause mortality in patients with preserved LVEF and sinus rhythm (hazard ratio 1.70, 0.78 to 4.10).[61]

LVEF and benefit of medical therapy

LVEF can be difficult to quantify with echocardiography, but it has been routinely used to determine eligibility for clinical trials in heart failure. Given the growing evidence for treatment benefit in patients with higher LVEF levels, some authors have questioned the continued use of the LVEF to classify patients with heart failure. Multiple drug therapies have been tested across the ejection fraction spectrum: β blockers, ACE inhibitors/ARBs, ARNI, MRAs, and SGLT2 inhibitors. Traditionally, trials

have stratified patients on the basis of LVEF ≤40% or >40%. However, most therapies have shown a benefit at higher thresholds than the traditional cutoff of reduced LVEF at 40%. For β blockers, a reduction in cardiovascular mortality was observed with LVEF <50%.[61] For MRA therapy, a larger treatment benefit is more likely for patients with LVEF 41-49% than with LVEF ≥50%.[62] The treatment benefit of sacubitril/valsartan was observed with LVEF <60%.[63] For SGLT2 inhibitor therapy, the relative treatment effect was similar across the LVEF spectrum.[64] Overall, these results suggest that the LVEF thresholds for systolic dysfunction used in treatment trials may benefit from reclassification but that LVEF will remain important for determining optimal management.

The association of LVEF with the benefit of early initiation and titration was evaluated in a sub-study of the STRONG-HF trial.[65] This study showed the consistency of the rapid implementation of guideline based medical therapy across the entire spectrum of LVEF after an admission for heart failure.

Other drug treatments

Several additional medications can be used to improve outcomes among patients with HFrEF. This section discusses several of these therapies: hydralazine/isosorbide dinitrate therapy, ivabradine, vericiguat, intravenous iron, and glucagon-like peptide-1 receptor agonists. We discuss their evidence and contemporary role.

Hydralazine/isosorbide dinitrate therapy

The combination of hydralazine and isosorbide dinitrate is a guideline recommended therapy for self-identified Black patients with HFrEF with NYHA class III or IV heart failure despite treatment with optimal medical therapy as described above.[1 2] The combination therapy causes both arterial and venous vasodilation in addition to nitrous oxide augmentation that may have remodeling benefits.[66] A-HeFT (African-American Heart Failure Trial) randomized 1050 self-identified Black patients to hydralazine/isosorbide dinitrate therapy versus placebo. Patients receiving hydralazine/isosorbide dinitrate therapy had a 43% relative reduction in death over a mean follow-up of 10 months (10.2% *v* 6.2%; P=0.02).[67] However, rates of treatment and adherence to hydralazine/isosorbide dinitrate therapy are low.[68 69] This may be due to multiple factors, including the difficulty of adhering to a three times daily medication and concerns about a race based indication. Additionally, the effectiveness of combined hydralazine and isosorbide nitrate therapy among non-Black patients remains unclear.[65] Although hydralazine/isosorbide dinitrate therapy remains an important tool for reducing morbidity among Black patients with HFrEF, we believe that it should remain a second line therapy for patients with persistent HFrEF after optimization of the four pillars described above (fig 4).

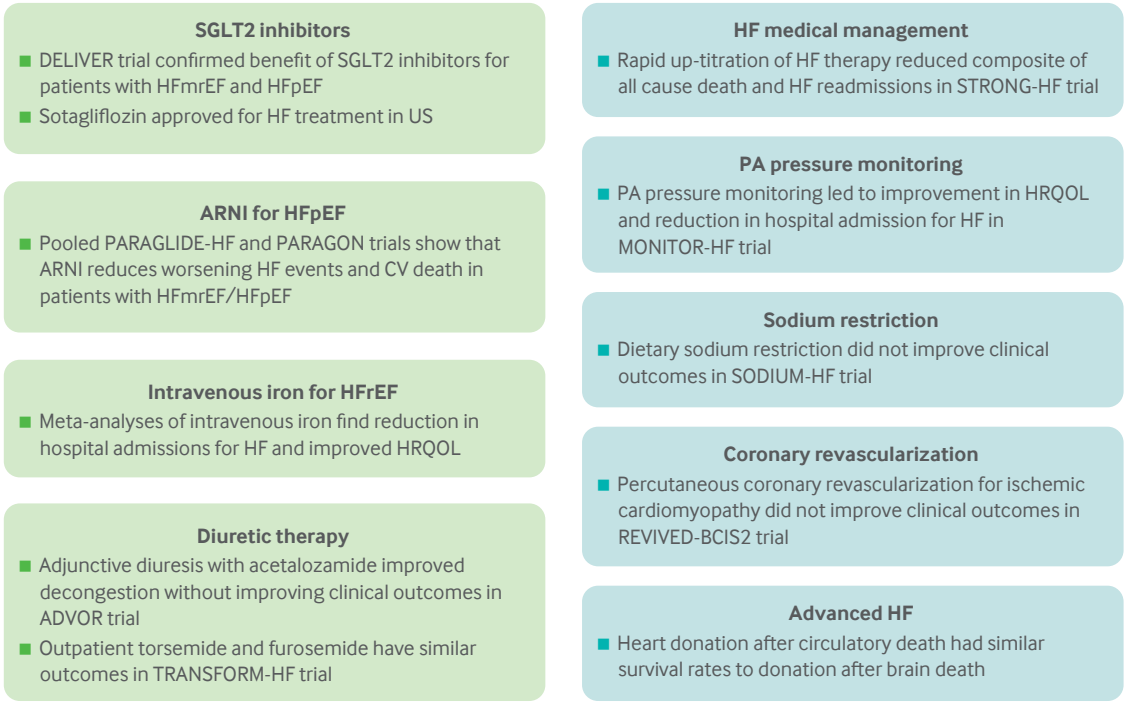

Fig 4 | Updates in heart failure since the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America and 2021 European Society of Cardiology heart failure guidelines.[1 2] Of note, angiotensin receptor/neprilysin inhibitor (ARNI) may not be beneficial in patients with a left ventricular ejection fraction >60%.[63] CV=cardiovascular; HF=heart failure; HFmrEF=heart failure with mildly reduced ejection fraction; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; HRQOL=health related quality of life; PA=pulmonary artery; SGLT2=sodium-glucose cotransporter-2

Ivabradine

Ivabradine inhibits the channel responsible for the cardiac pacemaker current, *I*(*f*), in the sinus node.[70] In SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial), among 6558 patients with HFrEF with sinus rhythm and a heart rate ≥70 bpm, ivabradine led to an 18% relative reduction (hazard ratio 0.82, 0.75 to 0.90) compared with placebo in the composite outcome of cardiovascular death and hospital admission for heart failure.[71] However, only 26% of patients were taking a target dose of β blocker therapy. Given the substantial benefit of β blocker therapy, patients with HFrEF should first have their β blocker dose optimized before initiation of ivabradine therapy.

Vericiguat

Vericiguat is a novel heart failure medication that stimulates soluble guanylate cyclase and up-titrates the nitric oxide signaling pathway promoting vasodilation and reduced cardiac remodeling. In the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial, 5050 patients with HFrEF with recent hospital admission or intravenous diuretic treated with vericiguat versus placebo had a 10% relative reduction (hazard ratio, 0.83 to 0.98) in the risk of cardiovascular death or hospital admission for heart failure.[72] However, patients in the highest quarter of natriuretic peptide concentrations were less likely to benefit from vericiguat compared with placebo.[73] Although vericiguat was effective among a high risk HFrEF cohort, the smaller magnitude of benefit has rendered it a second line therapy for patients at high risk following optimization of the four pillars described above.

Intravenous iron infusion

Multiple studies have shown that iron deficiency and anemia are associated with increased mortality and decreased exertional capacity.[74 75] Several trials have shown that intravenous iron reduces the risk of hospital admission for heart failure and improves patient reported health status among patients with HFrEF.[76-80] Unfortunately, these effects have not been reproduced with oral iron administration.[81] These findings emphasize the importance of screening for iron deficiency and intravenous repletion; hospital admissions for heart failure are an ideal opportunity for screening and intervention.

Glucagon-like peptide-1 receptor agonists

Similarly to SGLT2 inhibitors, glucagon-like peptide-1 receptor agonists (GLP1RA) were initially developed to improve glycemic control among patients with diabetes mellitus. In a meta-analysis of eight trials with cardiovascular outcomes evaluating GLP1RA among patients with type 2 diabetes mellitus, GLP1RA reduced the risk of cardiovascular death (hazard ratio 0.87, 0.80 to 0.94) and hospital admission for heart failure (0.89, 0.82 to 0.98).[82] However, the prevalence of heart failure at baseline was between only 9% and 24% across these trials.[83]

GLP1RA were subsequently shown to be potent therapies for weight loss among obese patients without diabetes mellitus.[84 85] In the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial, semaglutide versus placebo was found to significantly reduce the composite outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke among patients with existing atherosclerotic cardiovascular disease who were overweight or obese but without diabetes mellitus. Among enrolled patients, 24% had chronic heart failure at baseline.

Given the high prevalence of both diabetes mellitus and obesity among patients with heart failure, the potential benefits of GLP1RA warrant optimism. The Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction (STEP-HFpEF) trial evaluated the effect of semaglutide versus placebo on patient reported health status among 529 non-diabetic patients with ejection fraction ≥45%, obesity, and evidence of impaired health status (Kansas City Cardiomyopathy Questionnaire (KCCQ) score of <90) at baseline. Participants treated with semaglutide had on average a 7.8 (95% confidence interval 4.8 to 10.9) greater increase in their KCCQ score than patients treated with placebo, in addition to a significant 20.3 m larger improvement in their six minute walk distance.

Concern persists regarding the use of GLP1RA among patients with HFrEF. In a pooled analysis of two GLP1RA trials including patients with HFrEF, treatment with GLP1RA increased hospital admissions for heart failure.[86] Existing data support the use of GLP1RA among patients with obesity and HFpEF, but additional data on the safety and efficacy among patients with HFrEF is needed.

Devices and invasive therapies

Pulmonary artery pressure monitoring

The CardioMEMS device is an ambulatory pulmonary artery pressure monitor. Ambulatory pulmonary artery pressure monitoring can be used to guide adjustment of medication (for example, loop diuretics) and monitor for signs of decompensation. In the initial CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association (NYHA) Class III Heart Failure Patients) trial, the CardioMEMS device reduced hospital admissions for heart failure and improved patient reported health status among 550 patients with heart failure irrespective of LVEF and a previous admission for heart failure (hazard ratio 0.72, 0.60 to 0.85).[87] Although the GUIDE-HF (hemodynamic-GUIDEed management of Heart Failure) trial failed to show a reduction in hospital admissions for heart failure (1022 patients; hazard ratio 0.88, 0.74 to 1.05), the subsequent MONITOR-HH (remote hemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure) trial found an improvement in patient reported

health status and a reduction in admissions for heart failure with pulmonary artery pressure monitoring (348 patients; improvement in KCCQ overall summary score of 7.1 (95% confidence interval 1.5 to 12.8).[88 89] A meta-analysis of the three trials estimated a 30% reduction in hospital admissions for heart failure with pulmonary artery pressure monitoring (hazard ratio 0.70, 0.58 to 0.86).[90] When considering implementation of pulmonary artery pressure monitoring, it is critical to remember that the effectiveness of any remote monitoring interventions is dependent on the downstream responses to abnormal readings. Maximizing the effectiveness of hemodynamic monitoring requires establishment of workflows to promote active monitoring and appropriate interventions for abnormal hemodynamics.

Implantable cardiac defibrillators and cardiac resynchronization therapy

Implantable cardiac defibrillators (ICDs) and cardiac resynchronization therapy (CRT) remain mainstays of HFrEF therapy.[1 2] Although multiple trials have illustrated the survival benefit with ICD therapy for patients with HFrEF, the more recent DANISH (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) trial did not find a significant reduction in all cause mortality among 556 patients with non-ischemic cardiomyopathy (hazard ratio 0.87, 0.68 to 1.12).[91] However, patients under the age of 70 did have a survival benefit with ICD therapy. This likely reflects the fact that ICD therapy prevents only sudden cardiac death; as the competing risk of non-cardiovascular death increases (for example, increasing age) or the risk of sudden cardiac death decreases (for example, non-ischemic cardiomyopathy or effective medical therapy), the absolute benefit of ICD therapy decreases.[92] However, despite improvements in medical therapy, sudden cardiac death remains frequent among patients with HFrEF.[93] The shared decision making around ICD implantation should incorporate not only the patient's preference but also estimates of an individual patient's expected benefit.[92 94 95]

CRT has shown the greatest benefit in patients with a wide QRS (≥150 ms, typically in a left bundle branch block pattern). CRT has traditionally relied on biventricular pacing. Conduction system pacing is a novel approach of pacing the His bundle or left bundle branch.[96] Small studies have suggested that conduction system pacing may be a potential alternative to promoting ventricular synchrony.[97-100] Ongoing trials are testing whether this strategy leads to similar clinical outcomes to traditional CRT via coronary sinus pacing.

Mitral transcatheter edge-to-edge repair

HFrEF is often accompanied by severe secondary mitral regurgitation (often described as posterior leaflet restriction on the echocardiography report), which is associated with increased risk of mortality and hospital admission.[101 102] Mitral regurgitation often improves with optimal medical therapy and positive ventricular remodeling.[103] For patients with persistent severe mitral regurgitation, repair of the mitral valve via transcatheter edge-to-edge repair (TEER) is a potential therapy. Two trials of mitral valve TEER had discordant results. In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial in 614 patients, mitral TEER led to a 47% reduction in hospital admission for heart failure (hazard ratio 0.53, 0.40 to 0.70) and reduced all cause mortality by 38% (0.62, 0.46 to 0.82).[104] However, the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial showed no reduction in mortality or hospital admission for heart failure with mitral valve TEER (304 patients; odds ratio 1.16, 0.73 to 1.84).[105] The discordant results may be due to the degree of mitral regurgitation in relation to the severity of cardiomyopathy. Greater mitral regurgitation in relation to the degree of left ventricular dilation (disproportionate mitral regurgitation) may be more likely to benefit from mitral valve repair.[106] In addition, MITRA-FR did not require optimization of guideline based medical therapy before the procedure.

Revascularization

Coronary artery bypass grafting (CABG) for patients with severe coronary artery disease has been shown to improve outcomes compared with medical therapy,[107] but the early studies showing benefit typically did not include patients with significantly reduced ejection fraction. In addition, medical therapy has advanced substantially since these trials were conducted. In response to these concerns, the Surgical Treatment for Ischemic Heart Failure (STICH) trial randomized 1212 patients with an ejection fraction ≤35% and coronary artery disease amenable to CABG or medical therapy.[108] The primary outcome of all cause mortality was not significantly lower with CABG (hazard ratio 0.86, 0.72 to 1.04). However, the secondary outcome of death from any cardiovascular cause or hospital admission with heart failure showed a benefit with CABG (hazard ratio 0.74, 0.64 to 0.85), and current guidelines recommend bypass grafting if severe disease suitable for bypass is present and the LVEF is <35%.[2]

The potential benefit of revascularization with percutaneous coronary intervention was recently evaluated in the Revascularization for Ischemic Ventricular Dysfunction (REVIVED) trial.[109] This study found that among 700 patients with extensive coronary artery disease amenable to percutaneous coronary intervention and viable myocardium, the intervention did not improve mortality or hospital admission compared with usual care (hazard ratio 0.99, 0.78 to 1.27). This study is consistent with previous randomized evaluations suggesting that using viability to target revascularization does not improve outcome.[110]

Treatment of advanced heart failure

Heart failure can be a progressive condition despite optimal therapy, and appropriate timing of referral to heart failure specialists is important.[111] The I-NEED-HELP acronym provides potential triggers for that referral.[112]

Clinical outcomes with left ventricular assist device (LVAD) therapy have continued to improve over time. An improvement in post-implantation survival to more than 50% at five years has been seen, in addition to a reduction in rates of stroke and gastrointestinal bleeding.[113] After recall of the Heartware LVAD, the HeartMate 3 centrifugal flow left ventricular assist device is the only available durable LVAD. In the MOMENTUM 3 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3) trial, the HeartMate 3 had lower rates of reoperation, pump thrombosis, stroke, and gastrointestinal bleeding than the HeartMate 2 axial flow pump.[114]

Heart transplant remains the cornerstone of therapy for patients with stage D heart failure. The median survival after heart transplant now exceeds 12 years.[115] The ability to effectively transplant hearts from hepatitis C positive donors and following circulatory arrest has increased the potential donor pool.[116 117] Improvements in donor preservation have also allowed sharing of potential donors across greater distances.[118]

Non-drug, non-device therapies

Sodium and fluid restriction

Restricting dietary sodium intake is commonly recommended to reduce symptoms of heart failure. However, limited data are available to support such restriction. The SODIUM-HF (Study of Dietary Intervention under 100 mmol in Heart Failure) trial randomized 806 patients to a low sodium diet of less than 1500 mg/day or usual care. It found similar rates of cardiovascular hospital admission, cardiovascular emergency department visit, or all cause death (hazard ratio 0.89, 0.63 to 1.26).[119] Of note, patients with a low sodium diet had higher patient reported health status. The US cardiovascular disease guidelines continue to recommend dietary sodium restriction among patients with and without heart failure.[2 120] However, potential concerns include that excessive sodium restriction may contribute to poor nutrition or may exacerbate deleterious neurohormonal activation.[121] Although moderating sodium intake may be reasonable, focusing on optimization of therapies shown to improve outcomes should be prioritized.

Fluid restriction in heart failure has also been tested in several randomized trials. A meta-analysis of six trials found that liberal fluid consumption did not increase readmssions due to heart failure or all cause mortality.[122] Accordingly, heart failure guidelines now state that the benefit of fluid restriction is uncertain or note the gap in evidence for its effectiveness.[1 2]

Cardiac rehabilitation

Cardiac rehabilitation has generally been reserved for patients with heart failure with reduced LVEF or those who undergo cardiovascular surgery (for example, CABG). The REHAB-HF (Rehabilitation Therapy in Older Acute Heart Failure Patients) trial found that dedicated rehabilitation improved physical functioning for older patients admitted to hospital with heart failure regardless of LVEF.[123] A participant level meta-analysis of 13 randomized trials in 3990 participants found (at 12 months of follow-up; most patients had HFrEF) an improvement in six minute walk distance (mean 21.0 (95% confidence interval 1.57 to 40.4) m) and Minnesota Living With Heart Failure score (mean improvement 5.9, 1.0 to 10.9).[124] Additional trials are under way to evaluate the benefit of rehabilitation strategies for patients with HFpEF.

Measuring patient reported outcomes in heart failure

Without treatment, heart failure not only substantially increases the risk of mortality but also impairs quality of life.[125] Improving health related quality of life is an important goal of heart failure treatment. Multiple therapies have been shown to significantly improve quality of life on the basis of patient reported health status (table 2).[87 134 140-145] The two most commonly used measures of patient reported health status in treatment trials have been the KCCQ and the Minnesota Living with Heart Failure Questionnaire.[146 147]

Although patient reported health status has been commonly measured in clinical trials, it is rarely used in clinical practice. However, multiple studies have shown that not only is patient reported health status often discordant with the clinician's assessment but it also has a higher concordance with objective functional testing than does the NYHA classification.[148 149] Patient reported health status is also a strong predictor of hospital admission and death.[150-155] Therefore, the call to incorporate routine measurement of patient reported health status into clinical care is increasing.[2 156 157] Theoretically, this could improve clinicians' understanding of patients' health status and guide improved shared decision making. Limited data support the potential utility and acceptability of routine assessment of patient reported health status in clinical care,[158-160] but no data are available on the clinical impact of such a strategy. Additionally, the challenges of effectively implementing data collection within the electronic health record remain.[161]

Equity

Inequitable outcomes for health conditions among different groups often exist within societies, and heart failure is no exception. Data from the US suggest race/ethnicity differences in the incidence of and survival with heart failure.[162 163] The cause of disparities in outcome is multifactorial, and these are often driven as much or more by social determinants of health than by differences in patient management.[163 164] A

Table 2 | Heart failure therapies with evidence of improvement in patient reported heart failure health status

Treatment	Measure	Mean difference from pivotal trials* (95% CI)	Mean follow-up (months)
Heart failure with reduced ejection fraction			
ARB	MLHFQ	Val-HeFT: −1.8†[126]	23
ARNI (*v* ACEi)	KCCQ-OS	PARADIGM-HF: 1.3 (0.2 to 1.6)[127]	8
SGLT2i	KCCQ-OS	DAPA-HF: 2.3†[128]	8
		EMPEROR-Reduced: 1.5 (0.3 to 2.7)[129]	12
Hydralazine nitrate	MLHFQ	A-HeFT: −2.9†[67]	10
Ivabradine	KCCQ-OS	SHIFT: 2.4 (0.9 to 3.9)[130]	12
Intravenous iron	KCCQ-OS	AFFIRM-AHF: 3.0 (0.3 to 5.6)[131]	6
Cardiac resynchronization therapy	MLHFQ	CARE-HF: −10.6 (−8.1 to −13.1)[132]	3
	KCCQ	MADIT-CRT: 1.5†[133]	30
Mitral TEER	KCCQ-OS	COAPT: 5.1 (1.5 to 8.6)[134]	12
Exercise training	KCCQ-OS	HF-ACTION: 5.2 (4.4 to 6.0)[135]	
Heart failure with mildly reduced or preserved ejection fraction			
MRA	KCCQ-OS	TOPCAT: 1.5†‡[136]	4
SGLT2i	KCCQ-OS	EMPEROR-Preserved: 1.6 (0.8 to 2.4)[137]	12
		DELIVER: 2.1 (1.3 to 2.9)[138]	8
Heart failure across ejection fraction spectrum			
PA pressure monitoring	MLHFQ	CHAMPION: −4†[87]	6
	KCCQ-OS	MONITOR-HF: 7.1 (1.5 to 12.8)[89]	12
Salt restriction	KCCQ-OS	SODIUM-HF: 3.4 (0.8 to 60)[119]	12
Other heart failure populations			
Tafamidis for cardiac amyloid	KCCQ-OS	ATTR-CM: 13.7 (9.5 to 17.8)[139]	30

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; ARNI=angiotensin receptor/neprilysin inhibitor; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary Score; MLHFQ=Minnesota Living with Heart Failure Questionnaire; MRA=mineralocorticoid receptor antagonist; PA=pulmonary artery; SGLT2i=sodium-glucose cotransporter 2 inhibitor; TEER=transcatheter edge-to-edge repair.
*Higher KCCQ-OS score and lower MLHFQ score represent better patient reported health status. For KCCQ and MLHFQ, patient should notice five point difference (minimally important clinical difference). Data in table do not provide population distribution, indicating fraction with score >5.
†95% confidence intervals not available.
‡Based on adjusted analysis.

recent analysis from the US found similar use of drug treatments known to prolong survival for patients with heart failure across race and ethnicity groups.[165] Inequitable treatment rates have been observed for device therapies, such as CRT, and therapies for advanced heart failure; these may reflect not only bias but also the critical role of access to care in promoting improved equity.[166-168] A focus beyond treatment differences is needed if overall health is to be improved. Improving representation in clinical trials is important to improve our ability to provide appropriate customized care to all patients with heart failure.[169]

Guidelines

Several clinical guidelines have been published recently including the ESC (2021) and ACC/AHA/HFSA (2022) guidelines.[1 2] Important differences in guideline recommendations are rare and largely due to differences in the published evidence that occurred between publication. For example, the 2022 ACC/AHA/HFSA guideline includes a 2A recommendation for SGLT2 inhibitors for patients with HFmrEF and HFpEF following the publication of a large clinical trial showing outcome benefit.[2 40] Important studies that were published after these guidelines include a second randomized trial showing benefit of SGLT2 inhibitors in patients with an LVEF >40%,[39] the STRONG-HF trial showing benefit of rapid initiation and titration of medications for those with HFrEF,[49] and a trial showing that pulmonary pressure monitoring using the CardioMEMS device improved outcome.[89] Future guidelines will likely incorporate the trial results into revised recommendations. Figure 4 shows a summary of new evidence published since the 2022 ACC/AHA/HFSA and 2021 ESC heart failure guidelines.[1 2] An update to the 2021 ESC guideline was recently published,[170] and this incorporates new clinical trials of SGLT2 inhibitors, finerenone, and intravenous iron therapy.

Emerging treatments

Continued progress in treatment remains critical given the residual morbidity for patients with heart failure. Omecamtiv mecarbil is a cardiac myosin activator that improves cardiac contractility. In the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure) trial, 8258 patients with HFrEF who received omecamtiv mecarbil showed an 8% relative reduction (0.92, 0.86 to 0.99) in the risk of cardiovascular death or heart failure event (hospital admission or urgent visit).[171] The benefit was driven by the difference in heart failure events. Multiple secondary analyses have illustrated larger therapeutic benefit among patients with more severe heart failure based on LVEF, systolic blood pressure, NYHA class, or natriuretic peptides.[172-175] Omecamtiv mecarbil is not available as it was denied approval by the US Food and Drug Administration and is still pursuing approval in Europe.

Several trials will help to clarify the role of existing heart failure therapies. The VICTOR trial is evaluating the efficacy of vericiguat among patients with heart failure who have not had a recent worsening heart

failure event (clinicaltrials.gov: NCT05093933). The DECISION trial is testing the efficacy and safety of digoxin at low serum concentrations (NCT03783429). Given the controversy of the TOPCAT trial findings, two ongoing trials are evaluating the efficacy of spironolactone among patients with heart failure with LVEF ≥40% (NCT04727073; NCT02901184).

Many novel therapies for heart failure are under evaluation in clinical trials. These include multiple trials of finerenone among patients with heart failure across the ejection fraction spectrum (NCT04435626; NCT06033950; NCT06024746). The SUMMIT trial will evaluate the effect of tirzepatide, another GLP1RA, among patients with HFpEF and obesity (NCT04847557). Other ongoing studies are testing anti-inflammatory therapies among patients with HFmrEF/HFpEF (NCT05636176; NCT04986202).

Non-drug care of patients with heart failure also continues to evolve. The CABA-HFPEF trial is testing catheter ablation among patients with heart failure with LVEF ≥40% and atrial fibrillation (NCT05508256). Multiple ongoing trials are evaluating tricuspid valve interventions among patients with severe tricuspid regurgitation.

Conclusion

The management of patients with heart failure has changed markedly in the past several years, with evidence for four life prolonging classes of drugs for patients with reduced LVEF and the benefit of SGLT2 inhibitors for those with mildly reduced and preserved LVEF. Device management and other non-drug management have evolved as results from new clinical trials are published. Identification of appropriate candidates for treatment requires accurate diagnosis, which can be challenging for patients with heart failure and preserved ejection fraction. Additional questions remain—in particular, how best to implement these new treatment recommendations into clinical practice.

GLOSSARY OF ABBREVIATIONS

- ACC—American College of Cardiology
- ACE—angiotensin converting enzyme
- AHA—American Heart Association
- ARB—angiotensin receptor blocker
- ARNI—angiotensin receptor/neprilysin inhibitor
- BNP—B-type natriuretic peptide
- CABG—coronary artery bypass grafting
- CMR—cardiac magnetic resonance
- CRT—cardiac resynchronization therapy
- ESC—European Society of Cardiology
- GLP1RA—glucagon-like peptide-1 receptor agonists
- HFmrEF—heart failure with mildly reduced left ventricular ejection fraction
- HFpEF—heart failure with preserved left ventricular ejection fraction
- HFrEF—heart failure with reduced left ventricular ejection fraction
- HFSA—Heart Failure Society of America
- HRQOL—health related quality of life
- ICD—implantable cardioverter defibrillator
- KCCQ—Kansas City Cardiomyopathy Questionnaire
- LVAD—left ventricular assist device
- LVEF—left ventricular ejection fraction
- MRA—mineralocorticoid receptor antagonists
- NYHA—New York Heart Association
- RCT—randomized controlled trial
- SGLT2—sodium-glucose cotransporter-2
- TEER—transcatheter edge-to-edge repair

QUESTIONS FOR FUTURE RESEARCH

- Does the order of initiation of medications for heart failure with reduced left ventricular ejection fraction affect the ability to achieve sustained treatment with all four pillars of therapy?
- Does the simultaneous initiation of medications increase or decrease the probability of sustained drug treatment?
- What are the benefits of medications in addition to sodium-glucose cotransporter-2 inhibitors for patients with heart failure with preserved left ventricular ejection fraction?
- Which patients should receive a trial of medication withdrawal if their symptoms resolve and their left ventricular function becomes normal?

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We obtained input from patient representatives/advocates as this manuscript was prepared. The feedback was helpful in defining the specific topics covered. In particular, the patient representatives/advocates highlighted the importance of including a discussion relating to equity.

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