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Cardiovascular Diabetology

REVIEW

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Reappraisal on pharmacological and mechanical treatments of heart failure

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Abstract

Heart failure (HF) is a highly frequent disorder with considerable morbidity, hospitalization, and mortality; thus, it invariably places pressure on clinical and public health systems in the modern world. There have been notable advances in the definition, diagnosis, and treatment of HF, and newly developed agents and devices have been widely adopted in clinical practice. Here, this review first summarizes the current emerging therapeutic agents, including pharmacotherapy, device-based therapy, and the treatment of some common comorbidities, to improve the prognosis of HF patients. Then, we discuss and point out the commonalities and areas for improvement in current clinical studies of HF. Finally, we highlight the gaps in HF research. We are looking forward to a bright future with reduced morbidity and mortality from HF.

Keywords: Heart failure, Pharmacotherapy, Devices, Treatment, Management, Prognosis, Comorbidities

Background

In the past half-century, significant progress has been made in the prevention, diagnosis, and management of cardiovascular diseases. Cardiovascular mortality in developed countries has been reduced by 2/3. The mortality of people with acute coronary syndromes (ACS), valvular, and congenital heart disease, arrhythmia and hypertension has been significantly reduced, with the exception of heart failure (HF). HF is a clinical syndrome that mainly manifests as pulmonary congestion and vena cava congestion, resulting from abnormal cardiac structure and/or function [1]. HF is not an independent disease, but a terminal stage in the development of heart disease. Many diseases can cause HF. In addition to cardiomyopathy and valvular heart disease, cardiogenic diseases also include endocardial or pericardial abnormalities and heart rate (HR) or rhythm disorders. The 2016 guidelines update the classification of HF according to ejection fraction values, including HF with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) [2]. HF has become a global health burden and affects an estimated 26 million individuals worldwide with a prevalence of approximately 1–2% [3]. The lifetime risk of developing HF is approximately one in five for a 40-year-old in Europe and North America. A total of 74% of HF patients have at least one complication, and such patients are more likely to develop further deterioration of the disease, leading to high hospitalization for HF (HHF) rates and mortality. There is no controversy that HF is currently becoming a preventable and curable disorder based on evidence-based findings [2]. However, the prognosis of advanced HF is worse than that of partial solid tumours and myocardial infarction (MI). There is growing appreciation that the choice of therapy creates exciting new opportunities to improve overall and personalized care, to the individual patient [4]. This review about the reappraisal on pharmacological and mechanical treatments of HF tries to give a compact overview of novel and/or vital trials (Fig. 1) to contribute to a more comprehensive knowledge of this disease.

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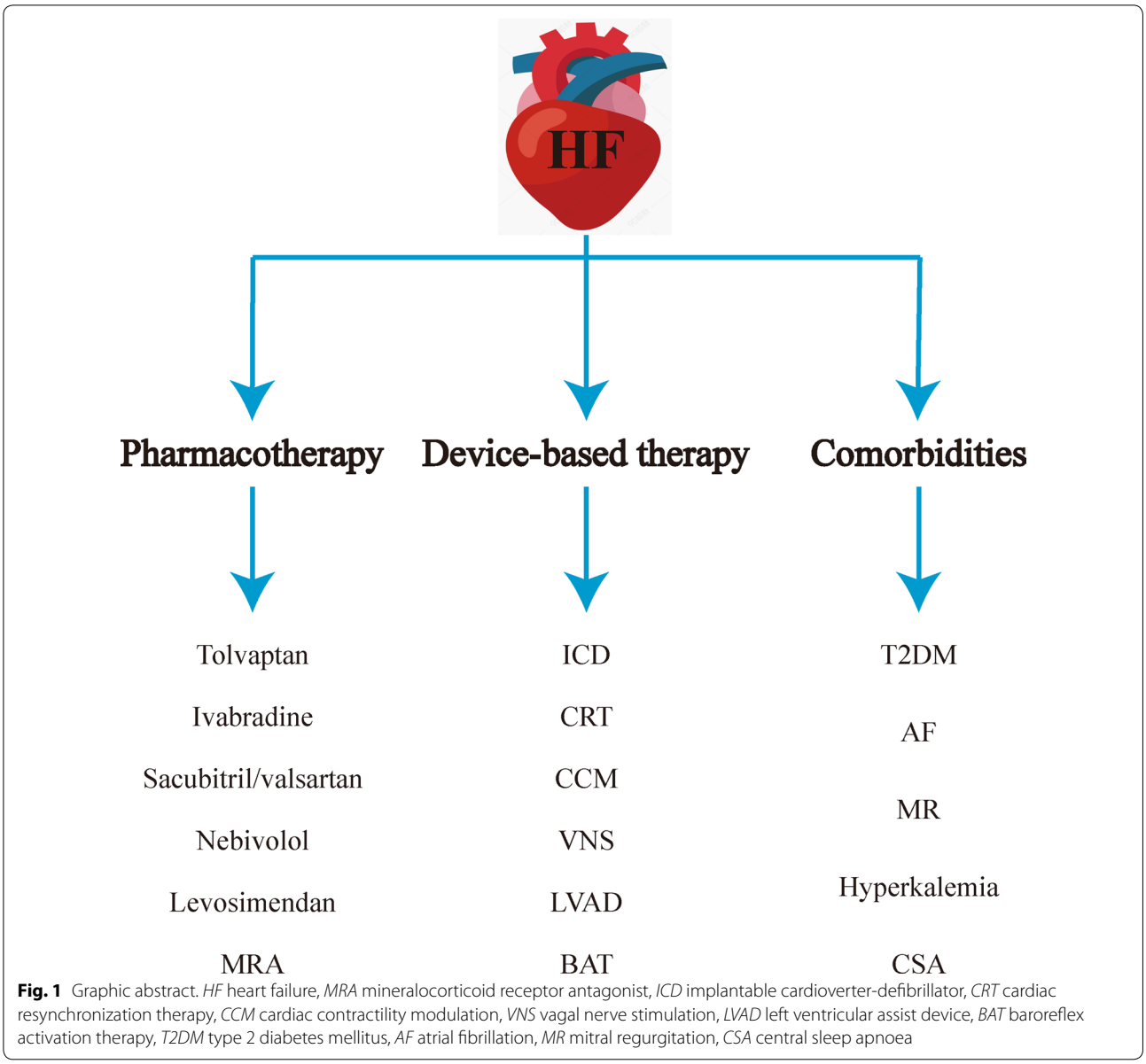

Fig. 1 Graphic abstract. *HF* heart failure, *MRA* mineralocorticoid receptor antagonist, *ICD* implantable cardioverter-defibrillator, *CRT* cardiac resynchronization therapy, *CCM* cardiac contractility modulation, *VNS* vagal nerve stimulation, *LVAD* left ventricular assist device, *BAT* baroreflex activation therapy, *T2DM* type 2 diabetes mellitus, *AF* atrial fibrillation, *MR* mitral regurgitation, *CSA* central sleep apnoea

Pharmacotherapy

Tolvaptan

Diuretics are often used in acute HF (AHF) since they can significantly relieve the discomfort of patients, but their side effects are mainly related to electrolyte abnormalities and a deterioration of renal function [5]. Tolvaptan is an oral, selective vasopressin V2 receptor antagonist that induces water excretion and sodium retention. At present, it is often used to treat hypervolemic or isovolumic hyponatraemia with HF, liver cirrhosis and SIADH [6]. Tolvaptan has been shown in many studies to reduce volume load, stabilize haemodynamics, and improve hyponatraemia without affecting renal function. Its application has been recommended by the guidelines for HF [1, 7]. The TACTICS-HF study found that tolvaptan add-on therapy did not improve congestion in AHF [8]. Other studies also indicated that tolvaptan does not affect HR or blood pressure while reducing fluid retention. In addition, in patients with AHF accompanied by renal insufficiency, tolvaptan also has significant benefits [9, 10]. Tolvaptan had no significant effect on potassium or renal function, and it improved the prognosis of AHF patients [11]. EVEREST indicated that the addition of tolvaptan for AHF treatment improved physician-assessed signs and symptoms (including dyspnoea, orthopnoea, fatigue, jugular venous distension, rales, and pedal

oedema) during hospitalization without serious adverse short- or long-term effects, but it not reduce long-term cardiovascular morbidity and mortality [12]. In addition to AHF, SECRET and QUEST found that tolvaptan was also effective in chronic HF (CHF) patients. The results from METEOR hold that tolvaptan had no effect on the left ventricular (LV) end-diastolic volume but a significant favourable effect on the composite of mortality and HHF [13]. Tolvaptan corrects hyponatraemia, a predictor of HF. Moreover, tolvaptan produces encouraging changes in filling pressure and significantly increases urine volume in decompensated HF.

Ivabradine

HR is a modifiable risk factor in HF, and HR acceleration is an independent predictor of the vulnerable phase for HF. In individuals with markedly depressed LV function, the acute administration of ivabradine, the first specific sinus node If channel inhibitor, is well tolerated, effectively reduces HR, markedly increases stroke volume and preserves cardiac output. The results from the SHIFT trial support ivabradine in combination with standard treatment for HF to further improve the symptoms and long-term prognosis [14], and age does not limit the appropriate use of ivabradine [15]. Ivabradine was approved for patients with HF after this trial [7, 16]. The results from INTENSIFY and ETHIC-AHF showed that patients with HF who received early treatment with ivabradine and had better HR control showed significantly improved symptoms of HF and cardiac function. In addition, the early combined use of ivabradine was associated with increased doses of beta-blockers [17], improving exercise tolerance and the quality of life (QoL) [18].

Sacubitril/valsartan

Sacubitril/valsartan is a dual inhibitor of the angiotensin II receptor and neprilysin. PARADIGM-HF demonstrated that sacubitril/valsartan was preferable to enalapril in lowering the risks of mortality and HHF [19, 20] and led to better health-related QoL in surviving patients [21]. In addition, treatment with sacubitril/valsartan may not only reduce the requirement for loop diuretics [22] but also effectively prevent clinical progression [23] relative to enalapril in HFrEF. These findings of sacubitril/valsartan with stunning interest laid the foundation forrecommendations in guidelines [2, 7, 16]. PIONEER-HF further confirmed the necessity of early use of sacubitril/valsartan in HFrEF [24], and the reduction in N-terminal pro-B-type natriuretic peptide (NT-pro BNP) concentration was weakly yet significantly correlated with reverse cardiac remodelling at 12 months [25]; however, sacubitril/valsartan showed no better reduction in central aortic stiffness than enalapril in HFrEF [26]. An analysis of the TRANSITION study indicated that sacubitril/valsartan has promising results in patients who are naïve to angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) treatment [27] as well as in patients with de novo HFrEF [28]. Patients in both PIONEER-HF and TRANSITION studies did not use ACEIs/ARBs prior to the initiation of sacubitril/valsartan, suggesting that sacubitril/valsartan and enalapril have similar efficacy and safety in such patients. After seeing significant results in HFrEF, sacubitril/valsartan began to be used in HFpEF studies. In HFpEF patients, the impact of sacubitril/valsartan on NT-pro BNP, left atrial volume, NYHA functional classification and eGFR was independent of SBP reduction [29, 30], but there is no consistent conclusion about clinical events [31]. Studies have revealed that sacubitril/valsartan acts directly on cardiac fibroblasts to prevent maladaptive cardiac fibrosis and dysfunction [32]. Large-sample, multicentre prospective clinical studies are needed to confirm these findings.

Nebivolol

Large randomized trials have shown that beta-blockers reduce mortality and HHF in HF patients. SENIORS showed that nebivolol (beta1-blocker, NO-releasing activity) is an effective and well-tolerated treatment for HF in elderly patients regardless of ejection fraction [33–35], a subgroup analysis showed nebivolol was less effective in those patients with diabetes [36], and the benefits of nebivolol appeared to be related to the maintenance dose achieved [37]. Nebivolol users had a lower HHF than carvedilol users among concurrent HF and chronic obstructive pulmonary disease patients [38]. Nebivolol might improve cardiac function in HFrEF patients [39], but it did not improve exercise capacity in patients with HFpEF [40]. A pharmacological characteristics study found that lung diffusion and exercise performance (the former likely due to lower interference with β2-mediated alveolar fluid clearance) were higher in patients who received nebivolol [41]. Thankfully, studies involving nebivolol included HF patients, regardless of ejection fraction, but we still need hard endpoint data.

Levosimendan

In LIDO, levosimendan, a positive inotropic drug with vasodilator effects, improved haemodynamic performance and lowered mortality for up to 180 days compared with dobutamine in severe, low-output HF patients [42]. In the later SURVIVE, levosimendan did not significantly reduce all-cause mortality at 180 days or affect any secondary clinical outcomes, despite an initial reduction in plasma B-type natriuretic peptide (BNP) [43].

REVIVE demonstrated that intravenous levosimendan provided rapid and durable symptomatic relief but was associated with an increased risk of adverse cardiovascular events [44]. LevoRep, a prospective, randomized, double-blind, placebo-controlled, multicentre, parallel-group trial, indicated that intermittent ambulatory treatment with levosimendan in patients with advanced HF did not significantly improve functional capacity or the QoL compared with placebo [45]. Another study showed that levosimendan significantly and safely improved LVEF and the reduced NT-pro BNP of refractory HF in elderly patients [46]. LION-HEART, a multicentre, double-blind, randomized, parallel-group, placebo-controlled trial, found that intermittent administration of levosimendan to outpatients with advanced systolic HF reduced plasma concentrations of NT-pro BNP, worsening of health-related QoL and HHF [47]. For patients with HF complicated by acute MI (AMI), levosimendan treatment improved contractility in post-ischaemic myocardium and was well tolerated without any increase in arrhythmias but with more episodes of hypotension [48]. LEAF studied short-term intravenous infusion of levosimendan, which appears to be more effective than placebo for treating patients with HF complicated by AMI [49]. The result of this confusion may be that the composite endpoint events are not uniform, and LAICA [50] and LeoDOR [51] are warranted to confirm those findings.

Mineralocorticoid receptor antagonists (MRAs)

Eplerenone is safe and improves clinical outcomes among HFrEF patients in EMPHASIS-HF [52, 53], even in subgroups at high risk of developing hyperkalaemia or worsening renal function [52, 54, 55], and may prevent re-admission when initiated soon after HHF or ACS in patients with systolic HF and mild symptoms [53]. Even moderate prolongation of QRS duration, baseline heart rate, and hypokalaemia were associated with a high risk of worse outcomes in HFrEF, and eplerenone was similarly effective, irrespective of QRS duration/morphology [56], baseline heart rate [57], and hypokalaemia [58]. Moreover, eplerenone improved outcomes in HFrEF patients with and without abdominal obesity [59]. Eplerenone was well-tolerated in Japanese patients with HFrEF and showed results consistent with those reported in the EMPHASIS-HF [60]. In EPHESUS, eplerenone reduced hospitalizations and mortality in HFrEF/HEpEF [61], regardless of percutaneous coronary intervention [62]. However, no relevant studies support the hypothesis that eplerenone has a significantly beneficial effect on glucose homeostasis in patients with HFrEF and either glucose intolerance or diabetes [63].Finerenone was well tolerated and induced a 30% or greater decrease in NT-proBNP levels in a similar proportion of patients to eplerenone [64], and finerenone was well tolerated in Japanese patients in ARTS-HF Japan [65].

In TOPCAT, spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or HHF in HFpEF patients [66]. However, a post hoc analysis demonstrated possible clinical benefits with spironolactone in patients with HFpEF from the Americas [67]. The potential efficacy of spironolactone was greatest at the lower end of the LVEF spectrum [68], and spironolactone was not associated with alterations in cardiac structure or function [69]. In Aldo-DHF, spironolactone improved LV diastolic function but did not affect maximal exercise capacity, patient symptoms, or the QoL in patients with HFpEF [70]. However, HFpEF patients are resistant to the beneficial effects of spironolactone on LV diastolic dysfunction [71]. In older adults with stable compensated HFpEF, spironolactone was well tolerated and reduced blood pressure, but it did not improve exercise capacity, the QoL, LV mass, or arterial stiffness [72, 73]. For AHF patients, spironolactone was well tolerated, but it did not improve the primary or secondary efficacy end points [74].

MRAs decrease morbidity and mortality in patients with HF [75]. But the current source of evidence is mainly eplerenone and finerenone for HFrEF, and mainly spironolactone for HFpEF, which might help clinicians in their treatment decisions. The improved LV function observed in those trials is contradictory, and further investigation in larger populations is required. For the uncertainty of spironolactone in the treatment of AHF, EARLIER [76] may give us more inspiration. Additional comparative studies are also required to comprehensively characterize the clinical relevance of the pharmacological differences between MRAs.

Device-based therapy

In addition to novel, optimized pharmacotherapeutic regimens, interventional and surgical methods have also made remarkable progress in recent decades.

Implantable cardioverter-defibrillators (ICDs)

ICDs are included among the recommendations for non-surgical device treatment of HFrEF in the guidelines [2]. An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF, and an LV ejection fraction (LVEF) $\leq 35\%$ despite ≥ 3 months of optimal medical therapy, ischaemic heart disease (unless they have had an MI in the prior 40 days) or dilated cardiomyopathy, provided they are expected to survive substantially longer than 1 year with good functional status. SCD-HeFT indicated that ICDs reduced the risk of sudden death in HFrEF patients

without diabetes, irrespective of aetiology [77]. In addition, in DANISH, a randomized controlled trial, prophylactic ICD implantation in patients with HFrEF not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care [78]. Rates of sudden death declined substantially over time among ambulatory patients with HFrEF who were enrolled in clinical trials [79], a finding that is consistent with a cumulative benefit of evidence-based medications on this cause of death, which might reduce the absolute effect of ICDs on mortality. ICDs have changed the landscape of sudden death prevention in HFrEF; moreover, sudden death accounts for ~20% of deaths in HFpEF [80]. If ICDs are to be applied to HFpEF, there must be a coordinated effort to identify and select high-risk patients [81]. We need more evidence about indications for the use of ICDs in specific subgroups (HFmrEF/HFpEF) and the optimal selection of ICD candidates.

Cardiac resynchronization therapy (CRT)

CRT improves cardiac performance in appropriately selected patients, improves symptoms, and well-being and reduces morbidity and mortality [82, 83]. Theerefore, CRT is also among the recommendations for non-surgical device treatment of HFrEF in the guidelines [2]. CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration $\geq$ 130 ms and left bundle branch block QRS morphology and in those with an LVEF $\leq$ 35% despite optimal medical therapy in order to improve symptoms and reduce morbidity and mortality in patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree atrioventricular block in order to reduce morbidity. The CRT studies involved a different range of LVEF, less than 30% in RAFT [84] and MADIT-CRT [85], less than 40% in REVERSE [86], and less than 50% in BLOCK-HF [87]. In other words, relatively few patients with an LVEF of 35–40% have been randomized, and an individual participant data meta-analysis fortunately suggests no diminution of the effect of CRT in this group [83]. Most other trials have compared defibrillators with CRT to ICDs, and a few have compared pacemakers with CRT to backup pacing. To date, the evidence suggests that no difference in mortality was observed between defibrillators with CRT and pacemakers with CRT [78]. Furthermore, it is important to note that not all patients respond favourably to CRT [82], and QRS morphology or duration may act as a predictor of response to CRT. Trials for HF may be warranted, although this intervention may be useful only for some highly selected patient groups.

Cardiac contractility modulation (CCM)

CCM is safe, improves exercise tolerance and the QoL in HF patients with ejection fractions between 25% and 45% and narrow QRS complex, and leads to fewer HHF [88–90]. CCM is likely to be cost-effective, provided that the treatment benefit can be maintained beyond the duration of the existing clinical trial follow-up [91]. Current studies indicate that CCM can be used as one of the treatment options for HF patients with a normal QRS complex, but the long-term safety and effectiveness of CCM still need further follow-up studies.

Vagal nerve stimulation (VNS)

Vagal nerve stimulation as delivered in the NECTAR-HF trial for a 6-month period failed to demonstrate a significant effect on primary and secondary endpoint measures of cardiac remodelling and functional capacity in symptomatic HF patients (LVEF $\leq$ 35%), but quality-of-life measures showed significant improvement [92]. Later, 18-month results showed that although a favourable long-term safety profile was found, improvements in the efficacy endpoints were not seen with VNS, and a new technique for the detection of acute HR responses to VNS suggests that the recruitment of nerve fibres responsible for HR changes was substantially lower in NECTAR-HF than in preclinical models [93]. The ANTHEM-HF trial showed chronic open-loop autonomic regulation therapy via left- or right-sided VNS continued to be feasible and well-tolerated in patients with HFrEF [94], and improvements in cardiac function and HF symptoms were seen after 6 months of VNS and were maintained at 12 months [95]. INOVATE-HF, a multinational, randomized trial involving 85 centres including 707 patients with chronic symptomatic HF (LVEF $\leq$ 40%), indicated that VNS did not reduce the rate of death or HF events [96]. Given the inconsistencies in the results so far, more methodologically sound trials are warranted.

LV assist devices (LVADs)

The use of an LVAD as a bridge-to-transplantation strategy can potentially improve patient survival while waiting for transplantation and allow better allocation of donor hearts [97], but now patients with chronic, refractory HF despite medical therapy can be treated with a permanent implantable LVAD [98]. Despite experiencing more frequent adverse events (such as bleeding and worsening HF), LVAD patients improved more in survival with improved functional status, health-related QoL and depression [99]. Preoperative patient optimization using extracorporeal life support improves outcomes of interagency registry for mechanical-assisted circulatory

support level I patients receiving a permanent LVAD [100]; however, fewer data are available for longer-term outcomes.

Baroreflex activation therapy (BAT)

Increased sympathetic and decreased parasympathetic activity contribute to HF symptoms and disease progression. BAT results in a centrally mediated reduction of sympathetic outflow and increased parasympathetic activity. A study showed that BAT was safe and improved functional status, the QoL, exercise capacity, N-terminal pro-brain natriuretic peptide, and possibly the burden of HHF in HFrEF patients with guideline-directed medical therapy [101]. These effects were most pronounced in patients not treated with CRT [102] and were not major differences between patients with and without coronary artery disease [103]. A later study provided evidence that BAT in HFrEF not only improves haemodynamic and clinical profiles but also exerts profound sympathoinhibitory effects, allowing an almost complete restoration of physiological levels of sympathetic neural function [104].

Comorbidities and concomitant medical therapy

Type 2 diabetes mellitus (T2DM)

T2DM is common in patients with HF and is associated with considerable morbidity and mortality [105, 106]. There are many glucose-lowering agents used in patients with HF, showing mixed results. Enhanced recognition of those patients would help guide therapeutic decisions.

Sodium-glucose cotransporter-2 inhibitors (SGLT-2is)

The initiation of SGLT-2is, underscoring the potential benefit and risks [107], was related to a lower risk of cardiovascular events, including HHF and death in the cardiovascular disease population [108, 109]. In a cohort, SGLT-2i use compared with dipeptidyl peptidase-4 inhibitor (DPP4i) use was associated with a reduced risk of HF [110]. The promising results of SGLT-2is may be related to the upregulation of the renin-angiotensin-aldosterone system [111]. EMPA-REG OUTCOME [112] is recognized by international guidelines as a landmark study [113]. In the empagliflozin group, there were significantly lower rates of HHF [114], which were achieved by improving diastolic stiffness and hence diastolic function [115] as well as attenuating cardiac fibrosis and improving ventricular haemodynamics [116]. In a real-world population similar to those included in the DECLARE-TIMI 58 study, dapagliflozin was safe and resulted in lower event rates of HHF and cardiovascular mortality than other glucose-lowering drugs [117]. DAPA-HF determined that dapagliflozin lowered the risk of worsening HF or death from cardiovascular causes, added to conventional therapy, in a broad spectrum of HFrEF [118, 119]. Canagliflozin reduced HHF with no statistical evidence of heterogeneity of the treatment effect across the primary and secondary prevention groups [120]. In addition, a number of randomized trials (such as DELIVERED, PRESERVED-HF, and EMPEROR-PRESERVED) are underway to explore the efficacy of SGLT-2is in HFpEF patients. However, because the patients in these studies did not demonstrate any HF-related manifestations or the degree of HF was very low at baseline, any recommendation of SGLT2is for the treatment of HF should be cautious. The current COAPT study included HFrEF and HFmrEF patients, and it is expected to answer this question.

Significant advances have recently occurred in the treatment of T2DM, with evidence of SGLT-2is showing either neutral or beneficial cardiovascular effects. A subanalysis of trials addressing HF treatment in the general population has shown that all HF therapies are similarly effective regardless of T2DM [121]. EMPA-REG OUTCOME demonstrated that patients with T2DM and cardiovascular disease who received empagliflozin, compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care [112, 122, 123]. The first interim analysis from EMPRISE showed that compared with sitagliptin, the initiation of empagliflozin was associated with a decreased risk of HHF among patients with T2DM as treated in routine care, with and without a history of cardiovascular disease [124]. In patients with T2DM who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin robustly resulted in a lower rate of cardiovascular death or HHF [125, 126], and subgroup analysis showed that dapagliflozin reduced HHF in patients with and without HFrEF [127]. Another prospective multicentre trial showed the beneficial effect of dapagliflozin on LV diastolic functional parameters for T2DM patients with HF [128]. CREDENCE and CANVAS supported that canagliflozin significantly reduced major cardiovascular events in patients with T2DM and cardiovascular disease [129–131]. Similarly, in patients with T2DM and a history of HF, canagliflozin reduced the risk of cardiovascular death or HHF [132]. Nevertheless, the evidence of the therapeutic effect of SGLT-2is on patients with HF and T2DM is still insufficient, and long-term clinical testing is needed.

Glucagon-like peptide-1 (GLP-1)

Abnormal myocardial metabolism has been documented in the HF population, with reduced fatty acid oxidation and myocardial insulin resistance [133, 134]. GLP-1 increases myocardial insulin sensitivity and has

a cardioprotective nature [135–137]. Previous small-sample, retrospective studies showed that GLP-1 was associated with favourable effects that GLP-1 significantly improved LV function, functional status, and the QoL [138]; and that GLP-1 reduced the risk of HHF, all-cause hospitalization, and death in T2DM [139]. Another study involving 32 T2DM patients with a history of CHF provided evidence that treatment with liraglutide is associated with improvements in cardiac function and functional capacity [140]. However, in LEADER, the rate of the primary composite outcome in the time-to-event analysis (the first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke) among patients with T2DM and high cardiovascular risk was lower with liraglutide than with placebo, whereas the number of HHF was reduced non-significantly in the active arm [141]. Moreover, the unfavourable results observed in LEADER are not stand-alone findings. LIVE, a randomized, double-blinded, placebo-controlled multicentre trial, determined that although the GLP-1 analogue liraglutide did not affect LV systolic function compared with placebo in stable CHF patients with and without T2DM, treatment with liraglutide was associated with an increase in HR and more serious cardiac adverse events [142]. The FIGHT trial, a multicentre, double-blind, placebo-controlled randomized clinical trial of HFrEF, revealed that the use of liraglutide did not lead to greater post-hospitalization clinical stability [143]. In SUSTAIN 6, involving 3297 patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal MI, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide [144, 145].

In summary, the results of the body of existing evidence do not support the use of liraglutide or semaglutide in HF with T2DM, and LIVE points out the potential harmful effect of liraglutide in this population. Importantly, the safety of these powerful GLP-1 analogues in patients with T2DM and documented HF remains uncertain. Therefore, further studies are needed to assess the risks and benefits of liraglutide and semaglutide in this particular subgroup of diabetic patients.

DPP4is

TECOS, a randomized, double-blind study assigned 14,671 patients with T2DM and cardiovascular disease, revealed that sitagliptin, a DPP4i, use did not affect the risk of major adverse cardiovascular events, HHF, or other adverse events [146, 147]. Another DPP4i, saxagliptin, increased HHF, independent of ischaemic events. SAVOR-TIMI 53 assigned 16,492 patients with T2DM who had a history of, or were at risk for, cardiovascular events to receive saxagliptin or placebo and followed them for a median of 2.1 years [148]. VIVIDD indicated that compared with placebo, vildagliptin had no major effect on LVEF, but it did lead to an increase in LV volumes in T2DM and HFrEF patients [149]. A secondary analysis of HF and related outcomes with linagliptin versus placebo in CARMELINA, a cardiovascular outcomes trial that enrolled participants with T2DM and atherosclerotic cardiovascular disease and/or kidney disease, demonstrated that linagliptin did not affect the risk of HHF or other selected HF-related outcomes, including among participants with and without a history of HF, across the spectrum of kidney disease, and independent of previous LVEF [150]. A multicentre, double-blind, randomized, placebo-controlled, parallel group, phase III study that assigned 4202 patients with T2DM and established cardiovascular disease indicated that omarigliptin did not increase the risk of cardiovascular death, nonfatal MI, nonfatal stroke or HHF and was generally well tolerated [151].

As treatment with DPP4is exerts no clinically meaningful effects on BNP and NT-proBNP [152], serial monitoring of NT-proBNP in patients with T2DM and ischaemic heart disease may be useful for the identification of patients at highest risk for HF [153]. More evidence is needed regarding the safety of DPP4i in patients with HF and T2DM.

Atrial fibrillation (AF)

AF and HF are co-evolving epidemics [154]. HF promotes AF, and AF exacerbates HF, which is a vicious circle, and effective treatment is necessary. HF-ACTION illustrated that AF in patients with CHF was associated with older age, reduced exercise capacity at baseline, and a higher overall rate of clinical events [155]. Among HF patients with a history of AF, those with paroxysmal AF were at greater risk of HHF and stroke than those with persistent or permanent AF [156]. AF at enrolment was associated with increased cardiovascular risk in HFpEF patients in the TOPCAT study, and AF was associated with an increased risk of morbidity and mortality [157]. In those special groups, the initiation of digoxin treatment was independently associated with higher mortality [154, 158]. AATAC showed that catheter ablation (CA) of AF was superior to amiodarone in achieving freedom from AF at long-term follow-up and reducing unplanned hospitalization and mortality in patients with HF and persistent AF [159]. CASTLE-AF also discovered that CA was associated with a significantly lower rate of a composite end point of death from any cause or HHF than medical therapy [160]. One study suggested that it may be safe to discontinue oral anticoagulation in post-ablation patients under diligent monitoring, in the absence

of AF recurrence, a history of ischaemic stroke/transient ischaemic attack/systemic embolism, and diabetes mellitus [161, 162], but evidence is lacking in patients with HF and AF. The choice of optimal treatment strategies for patients with both AF and HF is increasingly difficult, given that results from trials of pharmacological rhythm control are arguably obsolete in the age of CA. Restoring sinus rhythm by CA seems successful. In addition to GENETIC-AF [163], long-term studies to examine the effect on HHF, stroke, and death are warrannted.

Mitral regurgitation (MR)

In patients who have HFrEF, severe secondary MR is associated with a poor prognosis [164]. The MITRA-FR trial showed that among patients with severe secondary MR, the rate of death or unplanned HHF at 1 year did not differ significantly between patients who underwent percutaneous mitral-valve repair in addition to receiving medical therapy and those who received medical therapy alone [165]. The same goes for the 24-month outcome from the MITRA-FR trial [166]. Instead, the COAPT trial concluded that among patients with HF and moderate-to-severe or severe secondary MR who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, transcatheter mitral-valve repair resulted in a lower rate of HHF and lower all-cause mortality within 24 months of follow-up than medical therapy alone, and the rate of freedom from device-related complications exceeded a prespecified safety threshold [167]. We are looking forward to more similar research, such as RESHAPE-HF-2, MATTERHORN, EVOLVE-HF and CLAMP [168], to explore whether percutaneous mitral-valve repair improves clinical outcomes in this patient population.

Hyperkalaemia

Chronic kidney disease (CKD) in HF increases the risk of hyperkalaemia [169]. The PEARL-HF trial holds that patiromer (a non absorbed, orally administered, potassium-binding polymer) prevented hyperkalaemia and was relatively well tolerated in patients with HF and a history of hyperkalaemia, resulting in the discontinuation ofrenin-angiotensin-aldosterone system (RAAS) inhibitors and/or beta-adrenergic blocking agents, or in CKD patients with an estimated glomerular filtration rate of < 60 mL/min receiving standard therapy and spironolactone (25–50 mg/day) [170]. In patients with a clinical diagnosis of HF, diabetes, CKD, and hyperkalaemia on RAAS inhibitors, patiromer was well tolerated and effective for hyperkalaemia treatment over 52 weeks [171], as shown in results from AMETHYST-DN. In addition, new evidence is available from Patiromer-204, an open-label study, in which patiromer followed by individualized titration maintained serum potassium within the target range in the majority of patients with HF and CKD, all of whom were uptitrated to spironolactone 50 mg/day. Patiromer was well tolerated, with a low incidence of hyperkalemia, hypokalaemia, and hypomagnesemia [172]. Lokelma was well-tolerated in patients with stable CKD and hyperkalaemia [173] and in those with predialysis hyperkalaemia with end-stage renal disease undergoing adequate hemodialysis [174]. Lokelma enables substantial RAAS inhibitors to change while achieving normokalaemia [175]. However, no new evidence is available for lokelma in the field of HF. We need more evidence (PRIORITIZE HF and DIAMOND) to further confirm this.

Central sleep apnoea (CSA)

Periodic breathing with CSA is common in HF and is associated with poor QoL and increased risk of morbidity and mortality [176]. Adaptive servo-ventilation had no significant effect on the primary end point in patients who had HFrEF and predominantly CSA, but all-cause and cardiovascular mortality were both increased with this therapy, as seen in results from SERVE-HF [177]. The use of chronic transvenous phrenic nerve stimulation appeared to be safe and feasible in HF patients with CSA [178–180]. This approach may represent a novel therapy for CSA and warrants further prospective, randomized, controlled trials.

Discussion

HF is an important cardiovascular disease because of its increasing prevalence, significant morbidity, high mortality, and rapidly expanding health-care costs. According to the Global Burden of Diseases, Injuries, and Risk Factors Study 2017, there are more than 60 million HF patients worldwide [181]. As the life expectancy of the population increases and our ability to diagnose and treat cardiovascular diseases such as ACS increases, it is estimated that these numbers will continue to increase [182]. It is estimated that the lifetime risk of HF in adults ranges from 20 to 45% [183]. The risk of rehospitalization and cardiovascular death for HF hospitalized patients is increased [184]. One in 8 deaths results from HF, with a mortality rate of up to 50% within 5 years of diagnosis [184]. In addition to the heavy burden of disease, HF also brings a large economic burden. The total global cost of HF was estimated at 108 billion dollars in 2012 [185], and this number is expected to increase significantly over time. In the United States, the cost of HF is expected to increase by 127% by 2030 [184].

HF has underlying causes, pathophysiological complexities, and concomitant comorbidities, which make both diagnosis and treatment particularly challenging. Coupled with rising risk factors such as hypertension, T2DM,

and obesity, HF requires more consideration by medical staff and patients and their families. Here, we have summarized the treatments of and corresponding key trials in HF (Table 1). However, looking at HF as a life-limiting syndrome makes it possible to provide multidisciplinary patient-centred care focused on both extending survival when possible and achieving the best possible QoL.

Challenges and limitations in the current treatment of HF

We are making progress, but it has been extraordinarily slow. Over the past three decades, with the passage of time, the clinical treatment of HF has continued to increase. Although the mortality rate of HF has shown a downward trend, it is still at a high level. Numerous studies have shown that patients with HF still have a high residual risk despite many approved, guideline-recommended treatments [19, 119]. Therefore, under the conventional drug treatment of intervention in the RAAS and sympathetic nervous system (Fig. 2), the management of HF cannot be met. Diuretics, ACEIs/ARBs, and beta-blockers are the three standard treatments recommended in the guidelines for the treatment of HF. In addition, sacubitril/valsartan is also widely used in clinical practice, but the recommendations for the drug are slightly different among different guidelines [2, 7]. Since 2013, the guidelines have focused on underlying conditions, which may contribute to diastolic dysfunction, such as hypertension and AF. By 2016, the diagnosis of HF had become more sophisticated, but the diagnosis and theatments of HFmrEF/HFpEF are more challenging than those of HFrEF. Mortality rates in HFpEF patients are higher than in age- and comorbidity-matched non-HF controls and lower than in HFrEF patients [81], and sudden death accounts for ~20% of deaths in HFpEF [80]. Indeed, the management of HFpEF remains problematic due to the paucity of data on the clinical benefits of current therapies, which focus on symptom relief and the reduction of HHF by controlling fluid retention and managing risk factors and comorbidities [81]. PARADIGM-HF [19] triggered hope for the potential benefit of sacubitril/valsartan in HFpEF. However, these hopes were dashed by PARAGON-HF [31]. PARAGON-HF directed

Table 1 Summary of treatments and corresponding key trials

Treatments	Key trials
Pharmacotherapy	
Tolvaptan	TACTICS-HF [8], AQUAMARINE [9, 10], Shirakabe et al. [11], EVEREST [12], SECRET, QUEST, METEOR [13]
Ivabradine	SHIFT [14, 15], INTENSIFY, ETHIC-AHF, Bagriy et al. [17], CARVIVA HF [18]
Sacubitril/valsartan	PARADIGM-HF [19–23], PIONEER-HF [24, 25], EVALUATE-HF [26], TRANSITION [27, 28], PARAMOUNT [29, 30], PARAGON-HF [31]
Nebivolol	SENIORS [33–37], Sessa et al. [38], Brehm et al. [39], ELANDD [40], CARNEBI [41]
Levosimendan	LIDO [42], SURVIVE [43], REVIVE [44], LevoRep [45], Zhang et al. [46], LION-HEART [47], LEAF [48], Jia et al. [49], LAICA [50], Leodor [51]
MRA	Eplerenone: EPHESUS [75], EMPHASIS-HF [52–59], J-EMPHASIS-HF [60], EPHESUS [61, 62], EARLIER [76] Finerenone: ARTS-HF [64], ARTS-HF Japan [65] Spironolactone: TOPCAT [66–69, 201], Aldo-DHF [70, 71], Upadhya et al. [72], ATHENA-HF [74]
Device-based therapy	
ICD	SCD-HeFT [77], DANISH [78].
CRT	RAFT [84], MADIT-CRT [85], REVERSE [86], BLOCK-HF [87]
CCM	FIX-HF-5 [88, 89, 91], Borggrefe et al. [90].
VNS	NECTAR-HF [92, 93], ANTHEM-HF [94, 95], INOVATE-HF [96]
LVAD	ROADMAP [99], INTERMACS [100].
BAT	HOPE4HF [101], Zile et al. [102], Halbach et al. [103], Raffaella et al. [104]
Comorbidities	
T2DM	SGLT-2i: Empagliflozin EMPA-REG OUTCOME [112, 114, 122], EMPRISE [124]; Dapagliflozin: DECLARE-TIMI 58 [117, 125–127], Soga et al. [128]; DAPA-HF [118, 119]; Canagliflozin: CANVAS [120, 131, 132], CREDENCE [129, 130]. GLP-1: Liraglutide: LEADER [141], LIVE [142], and FIGHT [143]; Semaglutide: SUSTAIN-6 [144] DPP4i: Sitagliptin: TECOS [146, 147]; Saxagliptin: SAVOR-TIMI 53 [148]; Vildagliptin: VIVIDD [149]; Linagliptin: CARMELINA [150]; Omarigliptin: Gantz et al. [151]
AF	ENGAGE AF-TIMI 48 [154], HF-ACTION [155], PARADIGM-HF/ATMOSPHERE [156], TOPCAT [157], ARISTOTLE [158], AATAC [159], CASTLE-AF [160], GENETIC-AF [163]
MR	MITRA-FR [165, 166], COAPT [167]
Hyperkalemia	Patiromer: PEARL-HF [170], AMETHYST-DN [171], Patiromer-204 [172] Lokelma: Stephen et al. [173], DIALIZE [174], ZS-005 [175]
CSA	SERVE-HF [177], Ponikowski et al. [178], Pilot [179], Zhang et al. [180]

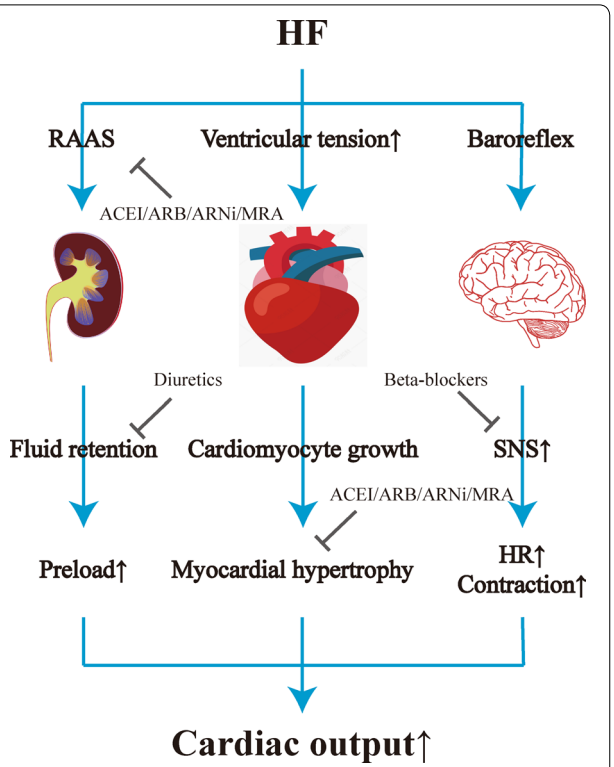

Fig. 2 The conventional drug treatment of HF. *HF* heart failure, *RAAS* renin-angiotensin-aldosterone system, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNi* angiotensin receptor-neprilysin inhibitor, *MRA* mineralocorticoid receptor antagonist, *SNS* sympathetic nervous system, *HR* heart rate

us to design trials to test whether a borderline EF is a signal of potential benefit from therapy targeting HFrEF and HFpEF simultaneously [186]. To date, a high-quality clinical trial specifically designed for HFpEF is still lacking, whether it is pharmacotherapy or device-based therapy. Some results on HFpEF have been obtained only through subgroup analysis. Moreover, no prospective trial has been conducted in patients with HFmrEF to date. All analyses are based on post hoc analyses from HFrEF and/or HFpEF trials, with inclusion criteria that included patients now classified as HFmrEF.

In view of increasing interest in diabetes in HF, glucose-lowering agents merit further study in this context. In studies about SGLT-2is, many of the patients included did not have HF even at baseline, and studies focused on HF may be urgent. Additionally, these sources of evidence are the results of randomized double-blind placebo comparisons, and the long-term prognosis is still controversial. Therefore, long-term clinical follow-up and methodologically sound, positive drug control trials are needed to show more valuable information on glucose-lowering agents.

Future directions in finding novel treatments for HF

HFmrEF/HFpEF is a highly heterogeneous disease both in mechanism and in clinical practice, which may be the reason why many conventional HF treatments fail to achieve good results. The most appropriate strategies for the treatment of HFmrEF/HFpEF have not been defined [187], and we have to consider shifting our attention to less well-investigated hypotheses. The PARAGON-HF [31] study confirmed that sacubitril/valsartan did not improve outcomes in HFpEF, but benefits were found in some special populations, which suggests that we need to find a target-based HFpEF typing method to implement targeted and accurate treatment. Moreover, we need more dedicated studies composed of HFpEF patients, rather than analyses of patient subgroups derived from preexisting trials, which introduce confounding biases and generalization difficulties.

Exciting research into new biological targets is currently underway. The activation of the cyclic guanosine monophosphate pathway is among those avenues, with several studies examining the roles of udenafil and BAY1021189 in the treatment of HFpEF [188]. In SOCRATES-REDUCED, among patients with worsening chronic HFrEF, compared with placebo, vericiguat, an oral soluble guanylate cyclase stimulatoror, did not have a statistically significant effect on changes in NT-pro BNP levels but it was well-tolerated [189]. In SOCRATES-PRESERVED, vericiguat also did not change NT-pro BNP levels and left atrial volume, but it was well-tolerated and associated with improvements in the QoL in patients with HFpEF [190]. Based on the results of SOCRATES-REDUCED [189] and SOCRATES-PRESERVED [190], VICTORIA [191], a multicentre, randomized, double-blind, placebo-controlled trial of the efficacy and safety of the oral soluble guanylate cyclase stimulator vericiguat was carried out among a broadly generalizable high-risk population of three unique clinical strata of patients with worsening chronic HFrEF despite very good HF therapy [192]. The latest results showed that the incidence of death from cardiovascular causes or HHF was lower among those who received vericiguat than among those who received placebo [193]. In addition, the REDUCE LAP-HF study, an open-label, single-arm, phase I study designed to assess the performance and safety of a transcatheter interatrial shunt device in patients older than 40 years of age with symptoms of HFpEF despite pharmacological therapy, showed that the implantation of an interatrial shunt device is feasible, seems to be safe, reduces left atrial pressure during exercise, and could be a new strategy for the management of HFpEF [194].

In addition to T2DM, MR, hyperkalaemia, and CSA, HF is also fraquently associated with other diseases, including anaemia, poor renal function, iron deficiency,

etc., which is also a direction that needs our continuous exploration. Emphasis should be given to the understanding of comorbidities. SCD-HeFT indicated that ICDs reduced the risk of sudden death in HFrEF patients without diabetes but not in patients with T2DM [77]. There are many trials on HF combined with diabetes, and we urgently need to include this specific population at the beginning of the trials, not through subgroup analysis or post hoc analysis, especially for SGLT-2is. SAFE-IRON-HF and SLEEP-HF were well-positioned to evaluate patients with HF complicated by mild iron deficiency anaemia or sleep disordered breathing.

Exercise is seen as a diagnostic and prognostic tool as well as a therapeutic intervention in CHF [195]. Several trials have shown that exercise is beneficial for CHF [196–200], not only improving functional capacity and the QoL but also reducing the risk of rehospitalization, even showing a tendency towards better survival rates. Moreover, both poor and intermediate self-reported physical activity were associated with a higher risk of HHF and mortality [201]. Peak oxygen uptake and the 6-min walk test may be suitable surrogate end points for the treatment effect of exercise on mortality and the QoL in HF. Different exercise programmes (intensity, frequency) also need further research. Future studies should aim to achieve a consensus on the definition of outcomes and the uniformity of exercise programmes and promote the reporting of a core set of HF data.

Moreover, drug interactions may be important because this is an actual problem in HF due to the inclusion of new drugs in treatment. There is a lack of research on device-based therapy for HF combined with other diseases. This large gap also needs to be filled.

Robust evidence from prospective studies is lacking for most therapies and additional studies will provide further insights into these patient populations. Equally important, however, is the standardization of research protocols (more standardized diagnostic approaches, homogenous exclusion criteria, and HFmrEF/HFpEF-dedicated cohort analyses), the application of which may help improve our understanding of the disease and translate into better outcomes. There is an urgent need to develop evidence-based treatment algorithms that not only alleviate the symptoms of patients and reduce the burden of hospitalization but also, more importantly, increase the QoL and prolong life when possible and in accordance with patient preferences. Although the path to the treatment of HFmrEF/HFpEF is still full of obstacles, we are seeing light at the end of the tunnel.

Conclusions

Although HF frequently exists, there are still numerous unanswered questions about the pathophysiology, symptomatology, diagnosis, and prognosis. We have barked up this tree for a few decades; it is time to move on. More systematic research is urgently needed to answer these unresolved issues and to provide treatments that can improve the QoL and reduce adverse clinical outcomes in the rapidly expanding number of patients with HF, especially HFmrEF/HFpEF.

Abbreviations

ACEI: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; AHF: Acute heart failure; AMI: Acute myocardial infarction; ARB: Angiotensin receptor blocker; BAT: Baroreflex activation therapy; BNP: B-type natriuretic peptide; CA: Catheter ablation; CCM: Cardiac contractility modulation; CHF: Chronic heart failure; CKD: Chronic kidney disease; CRT: Cardiac resynchronization therapy; CSA: Central sleep apnoea; DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP-1: Glucagon-like peptide-1; HF: Heart failure; HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; HHF: Hospitalization for heart failure; HR: Heart rate; ICD: Implantable cardioverter-defibrillator; LV: Left ventricular; LVAD: Left ventricular assist device; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; MR: Mitral regurgitation; MRA: Mineralocorticoid receptor antagonist; NT-pro BNP: N-terminal pro-B-type natriuretic peptide; QoL: Quality of life; RAAS: Renin-angiotensin-aldosterone system; T2DM: Type 2 diabetes mellitus; VNS: Vagal nerve stimulation.

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Authors' contributions

BL and NG conceived, designed, or planned the idea. All authors collected and read the literature. BL drafted the manuscript. NG revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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