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REVIEW

Advances in device-based treatment of heart failure with preserved ejection fraction: evidence from clinical trials

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a group of clinical syndromes that exhibit a remarkably heterogeneous phenotype, characterized by symptoms and signs of heart failure, left ventricular diastolic dysfunction, elevated levels of natriuretic peptides, and an ejection fraction greater than or equal to 50%. With the aging of the population and the escalating prevalence of hypertension, obesity, and diabetes, the incidence of HFpEF is progressively rising. Drug therapy options for HFpEF are currently limited, and the associated high risk of cardiovascular mortality and heart failure rehospitalization significantly impact patients' quality of life and longevity while imposing a substantial economic burden on society. Recent research indicates that certain device-based therapies may serve as valuable adjuncts to drug therapy in patients with specific phenotypes of HFpEF, effectively improving symptoms and quality of life while reducing the risk of readmission for heart failure. These include inter-atrial shunt and greater splanchnic nerve ablation to reduce left ventricular filling pressure, implantable heart failure monitor to guide diuresis, left atrial pacing to correct interatrial dyssynchrony, cardiac contractility modulation to enhance cardiac calcium handling, as well as renal denervation, baroreflex activation therapy, and vagus nerve stimulation to restore the autonomic imbalance. In this review, we provide a comprehensive overview of the mechanisms and clinical evidence pertaining to these devices, with the aim of enhancing therapeutic strategies for HFpEF.

Keywords Baroreflex activation therapy; Heart failure with preserved ejection fraction; Implantable heart failure monitor; Interatrial shunt; Renal denervation; Vagus nerve stimulation

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Introduction

Heart failure (HF) has the same 5-year mortality risk as malignancies and is the most common reason for hospitalization in individuals aged 65 and over.[1] According to the left ventricular ejection fraction (LVEF), the 2021 European HF guidelines classify HF into HF with reduced ejection fraction (HFrEF) (LVEF ≤40%), HF with mildly reduced ejection fraction (HFmrEF) (LVEF 41–49%), and HF with preserved ejection fraction (HFpEF) (LVEF ≥50%).[2] The 2022 American HF guidelines place a simultaneous emphasis on the trajectory of LVEF and categorize HF into four subtypes: HFrEF, HFmrEF, HFpEF, and HF with improved ejection fraction.[3] HFpEF constitutes approximately 50% of all cases of HF, and its prevalence continues to increase due to an aging population and the growing incidence of hypertension, diabetes, and obesity. However, effective drugs for treating HFpEF have been scarce until now. With the landmark results of the EMPEROR-Preserved (Outcome Trial of Empagliflozin in Patients with chronic heart failure with preserved ejection fraction) trial, gliflozins, also known as the sodium-glucose cotransporter 2 inhibitors, have become the first class of medications validated by randomized controlled trials (RCTs) to improve outcomes for HFpEF[4] and received a class II a treatment recommendation in the 2022 American HF guidelines.[5] Despite this, the morbidity and mortality of HFpEF remain unacceptably high, which spurs investigators to develop a range of devices to correct the abnormal haemodynamics of HFpEF and alleviate the associated symptoms.

Despite the intricate pathogenesis and heterogeneous phenotypes of HFpEF, left ventricular diastolic dysfunction and elevated filling pressure are widely recognized as common haemodynamic abnormalities in all cases of HFpEF, which are closely linked to patient symptoms and prognosis. Therefore, current device therapies are designed to mitigate left atrial pressure or pulmonary capillary wedge pressure (PCWP) through various means.[6] These devices include (i) inter-atrial shunt for left atrial decompression; (ii) implantable PCWP monitor to guide diuresis; (iii) left atrial pacing for interatrial dyssynchrony; (iv) splanchnic ablation for favourable volume redistribution; (v) cardiac contractility modulation to improve cardiac calcium handling; and (vi) renal denervation, baroreflex activation therapy, and vagus nerve stimulation to restore the autonomic imbalance. In this review, we summarized the clinical evidence of these devices to enrich the therapeutic approaches of HFpEF.

Inter-atrial shunt

Despite heterogeneity in the aetiology and pathophysiology of HFpEF, left atrial pressure (LAP) overload has been identified as a common cause of HFpEF-related exercise intolerance. Therefore, establishing an artificial inter-atrial shunt that relies on a pressure gradient to drain blood from the left heart to the right heart can effectively reduce LAP both at rest and during exercise. This approach has shown promising results in relieving symptoms and improving clinical outcomes for patients with HFpEF, making it a potential therapeutic option.[7,8] To date, several atrial shunt devices, including the interatrial shunt device [IASD] [Corvia Medical, Inc], the V-wave shunt [V-Wave Ltd], and the atrial flow regulator [Occlutech]), have been developed to reduce LAP by artificially constructing access from the left atrium to the right atrium.[9] Consisting of a nitinol frame and an 8 mm central channel, the IASD is currently the most extensively researched inter-atrial shunt in HFpEF/HFmEF patients. The REDUCE LAP-HF (REDUCe Elevated Left Atrial Pressure in Patients with Heart Failure) was the first open-label, single-arm, phase 1 trial designed to investigate the effect of IASD in 64 patients with symptomatic HFpEF (LVEF $\geq$40%) and elevated PCWP ($>$15 mmHg at rest and $>$25 mmHg during exercise). Results showed that the device was well tolerated, with significant improvements in exercise haemodynamics, 6-min walk distance (6MWD), and Minnesota Living With Heart Failure Questionnaire (MLWHFQ) score at 6 months.[10] These observations were corroborated by the randomized, sham-controlled, phase 2 REDUCE LAP-HF I trial, which demonstrated a favourable mechanistic impact of IASD on exercise PCWP compared with the sham control group at 1-month after randomization.[11] At 1 year, the IASD remained patent in all patients, with no significant differences in major adverse cardiac, cerebrovascular, and renal events. Moreover, patients with the IASD placement showed a trend for improved New York Heart Association (NYHA) functional class and reduced HF hospitalization.[12] However, the phase 3 REDUCE LAP-HF II trial involving 626 symptomatic HF patients with LVEF $\geq$40% and elevated resting or exercise PCWP failed to confirm better outcomes for IASD in cardiovascular death, non-fatal ischaemic stroke, first and recurrent HF events, and health status compared with a sham procedure. Even more unexpectedly, prespecified subgroup analysis showed that IASD was associated with more frequent HF events in those with pulmonary artery systolic pressure greater than 70 mmHg at 20 W bicycle exercise, right atrial volume index $>$29.7 mL/m^2, and male sex. Nonetheless, an exploratory post hoc analysis suggested that IASD may be beneficial in patients with a peak exercise PVR $<$ 1.74 Wood units.[13] Likewise, Borlaug and colleagues also reported that the presence or absence of 'latent' pulmonary vascular disease (defined as exercise PVR $\geq$ 1.74 WU) significantly affected patients' response to atrial shunt. Specifically, while atrial shunt may be detrimental to patients with 'latent' pulmonary vascular disease, it may prove beneficial for those without such conditions.[14] The V-wave shunt is a self-expanding nitinol frame covered with porcine pericardial tissue, shaped like an hourglass. In a single-arm open-label study involving 38 patients with HFrEF and HFpEF, the implantation of the first-generation V-Wave system was deemed both safe and feasible, resulting in significant improvements in NYHA functional class, quality of life (QOL), and 6MWD. However, after 12 months, a high incidence of shunt stenosis or occlusion resulted in loss of efficacy.[15] The ongoing RELIEVE-HF trial (NCT03499236) aims to enrol 500 patients to evaluate the safety and efficacy of the second-generation V-wave shunt in advanced HF, irrespective of LVEF. The atrial flow regulator (AFR) is a self-expandable double-disc wired mesh with a central penetration that enables inter-atrial shunting. The Pilot Study to Assess Safety and Efficacy of a Novel Atrial Flow Regulator in Heart Failure Patients (PRELIEVE) was an open-label, prospective, non-randomized, first-in-man study investigating the feasibility of AFR implantation up to 1-year follow-up in patients with HFrEF or HFpEF. The findings indicated that the AFR device in patients with HF was both feasible and safe and was associated with improved NYHA class, 6MWD, Kansas City Cardiomyopathy Questionnaire (KCCQ), PCWP, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in some but not all patients[16] (see *Table 1*). The Pomeranian atRial flOw reguLatOr iN conGestive hEart failuRe (PROLONGER) study was designed to establish invasive and noninvasive parameters capable of predicting a favourable response to AFR therapy in patients with HF.[17] Regardless of the type of atrial shunt used, it is crucial to determine which HF population will benefit most from it and assess the long-term patency rate of the device.[18] Future trials should also address issues related to post-implantation anti-

Table 1 Clinical evidence for the use of inter-atrial shunt in HFpEF

Author or trial name	Investigational device	Design	Inclusion criteria	Sample size	Follow-up	Primary efficacy and safety outcome
REDUCE LAP-HF[10]	Interatrial shunt device	Phase 1, open-label, single-arm trial	Symptomatic HFpEF (LVEF ≥40%) and elevated PCWP (>15 mmHg at rest and >25 mmHg during exercise).	64	6 months	The device was well tolerated, with significant improvements in exercise haemodynamics, 6MWD, and MLWHFQ score
REDUCE LAP-HF I[11]	Interatrial shunt device	Phase 2, randomized, parallel-group, blinded multicentre trial	NYHA III or ambulatory IV HF, LVEF ≥40%, exercise PCWP ≥25 mmHg, and PCWP-right atrial pressure gradient ≥5 mmHg.	IASD (n = 22) and control (n = 22)	1 month	IASD resulted in a greater reduction in PCWP compared with sham control
REDUCE LAP-HF II[13]	Interatrial shunt device	Phase 3, randomized, multicentre, blinded, sham-controlled trial	Symptomatic HF patients with LVEF ≥40% and elevated resting or exercise PCWP	IASD (n = 314) and control (n = 312)	12 months	There were no differences between groups in cardiovascular death, non-fatal ischaemic stroke, first and recurrent HF events, and health status
Rodés-Cabau et al.[15]	V-wave shunt	Single-arm open-label study	NYHA III and IV	38 (8 with HFpEF)	12 months	There was a significant improvement in NYHA functional class, QOL, and 6MWD, however, there was a high incidence shunt stenosis or occlusion.
AFR-PRELIEVE[16]	Atrial flow regulator	Open-label, prospective, non-randomized, first-in-man study	Symptomatic heart failure NYHA class III or IV and PCWP ≥15 mmHg at rest or ≥25 mmHg at exercise irrespective of LVEF	36 (20 with LVEF ≥40%)	12 months	AFR device was both feasible and safe and was associated with improved NYHA class, 6MWD, KCCQ, PCWP, and NT-proBNP in some individuals

Abbreviations: 6MWD, 6-min walk distance; AFR, atrial flow regulator; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; QOL, quality of life.

thrombotic therapy for IASD, the impact of right heart volume overload, and the potential increased risk of paradoxical stroke.[19,20]

Implantable heart failure monitor

Volume overload remains a primary contributor to the exacerbation of HFpEF. The conventional approach for assessing volume status relies on non-invasive and intermittent monitoring of symptoms, degree of lower limb oedema, body weight, and urine volume. Continuous monitoring of intracardiac pressures reveals that elevated LV filling pressure occurs 1–2 weeks before the onset of dyspnoea and signs of oedema in patients with HF, providing a more sensitive indicator of volume overload and predicting HF deterioration.[21] In recent years, there is growing evidence that pulmonary artery (PA) pressure-guided management of HF by the CardioMEMS HF system, where PA pressure is remotely monitored by a wireless PA sensor implanted in the left inferior pulmonary artery to guide diuresis, further reduces the hospitalization for HF compared with conventional treatment strategy.[22] The CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients) trial enrolled 550 individuals with NYHA functional class III HF, irrespective of the LVEF, and a history of HF hospitalization a year ago, and divided them randomly to the experiment group (n = 270) or the control group (n = 280), with the haemodynamic monitoring data from the CardioMEMS PA sensor was only available in the experiment group. After 6 months of randomization, HF events in the experiment group were reduced by 28% compared with those in the control group (hazard ratio, HR, 0.72; 95% confidence interval, CI, 0·60–0·85; P = 0·0002), and 99% patients had no device or system-related complications.[23] A prespecified subgroup analysis of 119 patients with LVEF ≥40% in the CHAMPION study (62 cases in the experiment group and 57 cases in the control group) showed that, after 17.6 months of follow-up, haemodynamically guided management reduced risk for HF hospitalization by 50% compared with standard HF management (HR, 0.50; 95% CI, 0.35–0.70; $P < 0.0001$). Notably, the reduction in hospitalization for HF was more pronounced in patients with LVEF ≥50%, reaching 70% (HR, 0.30; 95% CI, 0.18–0.48; $P < 0.0001$).[24] Based on the CHAMPION results, the Food and Drug Administration (FDA) approved CardioMEMS for the treatment of patients with HFpEF and HFrEF in 2014.[25] After approval of CardioMEMS, a real-world study involving 1200 patients with NYHA functional class III HF (46.8% with preserved EF) and a prior HF hospitalization within 12 months showed that haemodynamically guided management significantly reduced HF hospitalization by 57% and all-cause hospitalization by 27% compared with 1 year before procedure. The benefit was consistent across baseline LVEF, and more than 99% of patients were free of device-related complications or sensor failure.[26] The GUIDE-HF (haemodynamic-GUIDEed management of Heart Failure) trial extended the indication for CardioMEMS implantation to earlier HF populations. The trial included 1000 patients with all LVEF, NYHA functional classII-IV HF, and either a recent hospitalization for HF or increased B-type natriuretic peptides (BNP). All patients were implanted with CardioMEMS, and the haemodynamic data were available and unavailable in the experiment group (n = 497) and control group (n = 503), respectively. At 12 months of follow-up, the primary outcomes of all-cause mortality and readmission for HF were not reduced in the experiment group compared with the control group. However, a prespecified pre-COVID-19 analysis showed that haemodynamically guided HF management strategies significantly reduced the composite endpoint of HF events and all-cause mortality by 19% (P = 0.049) and the risk for HF hospitalization by 28% (P = 0.007).[27] According to the results of the GUIDE-HF study, the FDA has approved the implantation of CardioMEMS for earlier HF patients, including NYHA class II HF patients with prior hospitalization or elevated BNP.[28] A retrospective analysis of 29 patients with HFpEF (LVEF ≥ 45%) showed that CardioMEMS improved not only pulmonary artery diastolic pressures but also metabolic markers including body weight, body mass index, systolic blood pressure, high-density lipoprotein, and triglycerides 6 months after implantation.[29] Recently, the first open-label, randomized controlled trial conducted in Europe consistently confirmed that implantation of CardioMEMS for haemodynamic monitoring, in addition to standard treatment, resulted in further improvement of quality of life and reduction of heart failure hospitalizations among patients with moderate-to-severe heart failure[30] (see *Table 2*). For clinical use, the latest HF guidelines gave a class IIb recommendation for CardioMEMS implantation in selected HF patients to reduce the risk of HF hospitalization.[3] Future trials are warranted to investigate the potential of CardioMEMS implantation in HF in the post-COVID-19 era, particularly in reducing cardiovascular mortality.

Left atrial pacing

Echocardiographic studies have shown that interatrial dyssynchrony is common in patients with HFpEF and is associated with decreased left atrial function and worsening clinical symptoms, suggesting that amelioration of interatrial dyssynchrony may be a potential treatment target for HFpEF.[31–33] Left atrial pacing is performed using specially designed coronary sinus leads to stimulate the middle and distal coronary sinus region, initially for atrial tachyarrhythmias and more recently for atrial resynchronization in HFpEF

Table 2 Clinical evidence for the use of implantable heart failure monitor in HFpEF

Author or trial name	Investigational device	Design	Inclusion criteria	Sample size	Follow-up	Primary efficacy and safety outcome
CHAMPION[24]	CardioMEMS	Prospective, single-blinded, randomized controlled clinical trial	LVEF ≥40%	62 cases in the experiment group and 57 cases in the control group	17.6 months	Reduction in hospitalization for HF was more pronounced in patients with LVEF ≥50%, reaching 70%
CardioMEMS post-approval study[26]	CardioMEMS	Real-world study	Patients with NYHA III HF and a prior HF hospitalization within 12 months	1200 (46.8% with preserved LVEF)	One year	Haemodynamically guided management significantly reduced HF hospitalization by 57% and all-cause hospitalization by 27% compared with 1 year before procedure
GUIDE-HF[27]	CardioMEMS	Multicentre, randomized single-blind	Patients with all LVEF, NYHA class II–IV HF, and either a recent hospitalization for HF or increased BNP	1000	12 months	Prespecified pre-COVID-19 analysis showed that haemodynamically guided HF management strategies significantly reduced the composite endpoint of HF events and all-cause mortality by 19% and the risk for HF hospitalization by 28%
Alam A et al.[29]	CardioMEMS	Retrospective cohort study	LVEF ≥45%	29	6 months	Haemodynamically guided HF management improved not only pulmonary artery diastolic pressures but also metabolic markers including body weight, body mass index, systolic blood pressure, high-density lipoprotein, and triglycerides
MONITOR-HF[30]	CardioMEMS	Open-label, randomized trial	Chronic HF of NYHA III and a previous HF hospitalization, irrespective of LVEF	CardioMEMS-HF group (n = 176) and control group (n = 172)	48 months	Haemodynamic monitoring substantially improved QOL and reduced heart failure hospitalization.

Abbreviations: BNP, B-type natriuretic peptides; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QOL, quality of life.

patients.[34] In 2013, a pilot study conducted by Laurent and colleagues enrolled six patients with severe HFpEF with interatrial conduction delay (defined as P wave duration >120 ms in lead II) to evaluate the potential benefits of left atrial pacing. The result showed that left atrial pacing significantly improved the 6MWD, mitral A-wave duration, and E/A and E/e' ratio after 3 months of active pacing.[35] Importantly, after 1 week of pacing inactivation, a significant decrease in 6MWD happened with an on/off response. In addition, recent studies have found that left atrial pacing at about 125 beats per minute could lead to beneficial cardiac remodelling and reduced left ventricular end-diastolic volume and filling pressure in anaesthetised patients with hypertensive heart disease-associated HFpEF and in pigs with concentric LV hypertrophy and fibrosis.[36,37] It is believed that these benefits from left atrial permanent pacing open a new avenue for the treatment of HFpEF. More recently, the myPACE (Personalized Pacing: A New Paradigm for Patients With Diastolic Dysfunction or Heart Failure With Preserved Ejection Fraction) trial showed that, among patients with stage B and C HFpEF and pacemakers, moderately accelerated, personalized pacing was well tolerated and improved QOL, NT-proBNP, physical activity, and atrial fibrillation compared with conventional care at 1-year follow-up.[38] However, the RAPID-HF (Efficacy Study of Pacemakers to Treat Slow Heart Rate in Patients With Heart Failure) trial, a randomized, double-blind, cross-over study conducted in 29 patients with HFpEF/HFmEF and chronotropic incompetence, indicate that atrial pacing did not significantly improve cardiac output, exercise capacity, QOL score, and serum NT-proBNP levels in these patients and was associated with an increase in adverse events[39] (see *Table 3*). In the future, larger RCTs with extended follow-up periods are warranted to further investigate the efficacy and safety of left atrial pacing for HFpEF.

Table 3 Clinical evidence for the use of left atrial pacing in HFpEF

Author or trial name	Investigational device	Design	Inclusion criteria	Sample size	Follow-up	Primary efficacy and safety outcome
Laurent G et al.[35]	NA	A pilot study	HFpEF with interatrial conduction delay	6	3 months	6MWD, mitral A-wave duration, and E/A and E/e' ratio were improved.
Silverman DN et al.[36]	NA	NA	A history of paroxysmal AF undergoing elective radiofrequency ablation with an LV EF ≥ 50%	12 controls and 10 patients with HFpEF	NA	The volume loss was about twice as much in the HFpEF group
myPACE[38]	NA	Blinded randomized clinical trial	stage B and C HFpEF	Left atrial pacing (n = 50) or usual care (n = 57)	12 months	Improved MLHFQ scores, NT-proBNP, physical activity, and atrial fibrillation compared with conventional care
RAPID-HF[39]	NA	Single-centre, double-blind, randomized, crossover trial	Symptomatic HFpEF and chronotropic incompetence	29	16 weeks	Atrial pacing did not significantly improve cardiac output, exercise capacity, QOL score, and serum NT-proBNP levels in these patients and was associated with an increase in adverse events

Abbreviations: 6MWD, 6-min walk distance; AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living With Heart Failure Questionnaire; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QOL, quality of life.

Splanchnic ablation for volume management

Besides fluid retention, inappropriate volume redistribution characterized by blood transfer from the visceral bed to the central circulation has been proposed as a major driver of increased cardiac filling pressures and exercise intolerance in HFpEF.[40] The majority of the body's blood is stored in the splanchnic venous bed, which is regulated by sympathetic nerves through the greater splanchnic nerve (GSN) to control its relaxation and contraction.[41] Preclinical evidence has suggested that stimulation of the right GSN resulted in significantly increased arterial, central venous, and pulmonary arterial pressures.[42] On the contrary, temporary or permanent GSN blockade may confer a haemodynamic benefit in the setting of HF independent of ejection fraction.[43,44] The first-in-human study of the right GSN blockade by thora-

coscopic surgery in 10 HFpEF patients showed reduced cardiac filling pressure during exercise and improved QOL and NYHA class at 12 months of follow-up.[45] However, adverse events associated with the procedure itself have prompted the development of a less invasive, endovascular, transvenous procedure known as splanchnic ablation for volume management (SAVM). The first-in-human study of SAVM using the Axon ablation system in 11 HFpEF patients showed that the procedure was safe and resulted in sustained improvements in NT-proBNP, health status, and 6MWD over a 12-month follow-up period.[46] The ongoing randomized, sham-controlled, phase 2 clinical trial REBALANCE-HF (Endovascular Ablation of the Right Greater Splanchnic Nerve in Subjects Having HFpEF) was designed to enrol 80 patients for transvenous SAVM at 20 centres in the United States. Inclusion criteria included ejection fraction ≥50% and elevated PCWP ≥25 mmHg during exercise. Early findings from the initial 18 patients indicate that, 1 month following SAVM intervention, there was a significant reduction of 7.5 mmHg ($P < 0.01$) in mean PCWP during exercise at 20 W, with an improvement of at least one NYHA class observed in 33% of patients. Additionally, the overall score on the KCCQ increased by 22.1 points. Three non-serious device/procedure-related adverse events were recorded[47] (see *Table 4*). These results collectively suggest that modulation of splanchnic bed capacitance via GSN ablation offers a potential treatment strategy for HFpEF. However, the long-term safety and efficacy of GSN ablation, as well as which HFpEF subtypes benefit the most, warrants further investigation.[48]

Cardiac contractility modulation

Cardiac contractility modulation (CCM) is a novel device that provides non-excitatory, high-voltage, and long-duration electrical pulses during the absolute refractory period of the cardiac cycle through two pacing electrodes connected to the right ventricular septum, thereby reversing cardiac remodelling and improving cardiac function without increasing myocardial oxygen consumption.[49,50] The mechanisms of CCM may be related to the improvement of cardiac calcium handling and modification of HF pathological gene profile. Several clinical studies have shown that CCM safely and effectively improved physical tolerance as determined by peak oxygen uptake (VO_2) and QOL as determined by the MLWHFQ score, and reduced cardiac death and HF hospitalization in patients with HFrEF.[51–53] In 2019, an expert consensus of the European Society of Cardiology approved CCM by the Optimizer Smart device for the treatment of chronic HF patients who had an LVEF of 25–45% and narrow QRS (<130 ms) and remained symptomatic despite receiving guideline-directed medical therapy.[54] However, unlike the clear evidence for CCM use in HFrEF, there is little clinical

Table 4 Clinical evidence for the use of splanchnic ablation for volume management in HFpEF

Author or trial name	Investigational device	Design	Inclusion criteria	Sample size	Follow-up	Primary efficacy and safety outcome
Málek F et al.[45]	Thoracoscopic surgery	Single-arm, open-label, prospective trial	NYHA III, LVEF >40%, PCWP ≥15 mmHg at rest or ≥25 mmHg with supine cycle ergometry	10	12 months	At 3 months post-GSN ablation, patients demonstrated a reduction in 20 W exercise PCWP. At 12 months, improvements were seen in NYHA class and QOL assessed with MLWHFQ
Fudim M et al.[46]	Axon ablation system	Open-label, single-arm	NYHA II or III, LVEF ≥50%, and elevated PCWP at rest or with exercise.	11	12 months	KCCQ score, 6MWD and NT-proBNP were improved compared with baseline.
Ongoing REBALANCE-HF[47]	Axon ablation system	Prospective, multicentre randomized, sham control, double blinded	LVEF ≥50% and elevated PCWP ≥25 mmHg during exercise	18 patients enrolled into the roll-in, open-label arm	1 month	At 1 month, the mean PCWP at 20 W exercise decreased, NYHA class improved by at least one class in 33% of patients and KCCQ score improved by 22.1 points.

Abbreviations: GSN, greater splanchnic nerve; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living With Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; QOL, quality of life.

evidence for CCM use in HFpEF. Subgroup analysis of the FIX-HF-5 (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure) trial suggested that HF patients with LVEF 35–45% had more significant improvement in peak VO_2 and MLWHFQ score compared with those with LVEF 25–34% at 6 months after CCM implantation.[55] The CCM-REG prospective registry study also showed that patients with baseline LVEF of 35–45% had a better 3 years survival benefit than those with LVEF of 25–34% after the CCM procedure.[56] The greater benefit of CCM in patients with a higher LVEF range suggests that CCM may be suitable for HFpEF. In 2016, Tschöpe C et al first reported an overall symptomatic, functional, and histological improvement in two female HFpEF patients (LVEF of 50% and 47%, respectively) treated with CCM for 3 months.[57] The CCM-HFpEF (CCM in Heart Failure With Preserved Ejection Fraction, NCT03240237) trial is a prospective, multicenter, single-arm, pilot study assessing the efficacy and safety of CCM therapy in HFpEF patients with NYHA class II or III. A total of 47 patients (LVEF of 59 ± 4.4%) were enrolled and followed up to 24 weeks after CCM device implantation. The results showed that CCM significantly improved patients' health status as determined by the KCCQ overall score by 18.0 points ($P < 0.001$). In addition, CCM was generally safe, with 93.6% of patients experiencing no device-related complications.[58] The randomized, quadruple-blind, sham-controlled, 1500-patient AIM HIGHer (Assessment of CCM in HF With Higher Ejection Fraction) trial is underway to validate the potential impacts of CCM on cardiovascular death and HF hospitalization in HFpEF patients (see *Table 5*).

Renal denervation

Although renal denervation (RDN) has been proven effective in treating refractory hypertension,[59] its efficacy in HF, particularly HFpEF, remains uncertain due to insufficient evidence. Current literature suggests that sympathetic nerve activation is present in patients with HFpEF, similar to those with HFrEF.[60] This phenomenon is often associated with the pathological process of common co-morbidities of HFpEF, such as hypertension, atrial fibrillation, metabolic syndrome, chronic kidney disease, and pulmonary hypertension.[61] RDN can enhance the function of remote organs, including the heart, skeletal muscle, vasculature, and lungs by reducing renal afferent and efferent sympathetic tone. This improvement in organ function collectively enhances exercise capacity and QOL for patients with HFpEF.[61] Therefore, RDN may be a promising therapeutic option for HFpEF. However, clinical trials on the effects of RDN in HFpEF are few and inconsistent. Brandt et al. first reported that RDN significantly reduced LV mass and improved diastolic function at 6 months in 46 patients with refractory hypertension, while no signifi-

Table 5 Clinical evidence for the use of cardiac contractility modulation in HFpEF

Author or trial name	Investigational device	Design	Inclusion criteria	Sample size	Follow-up	Primary efficacy and safety outcome
Tschöpe C et al.[57]	NA	Case report	NYHA class II–III, LVEF of 50% and 47%, respectively	2	3 months	Overall symptomatic, functional, and histological improvement
CCM-HFpEF[58]	OPTIMIZER™ Smart Mini System	Prospective, multicentre, single-arm, pilot study	NYHAII or III, LVEF of 59 ± 4.4%	47	24 weeks	The KCCQ overall score improved by 18.0 points; 93.6% of patients experiencing no device-related complications
Ongoing AIM HIGHer	OPTIMIZER™ Smart Mini System	Prospective, multicentre, randomized, quadruple-blind, sham-controlled	HF with an LVEF ≥40% and ≤60%	1500 participants	18 months	NA

Abbreviations: KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NA, not applicable; NYHA, New York Heart Association.

cant changes were observed in control patients.[62] However, the first randomized, open-controlled trial to evaluate the effectiveness of RDN in HFpEF patients was terminated early due to recruitment difficulties (only 25 HFpEF patients were randomized 2:1 to receive RDN or medication). The trial was inadequate in its ability to detect whether RDN improved QOL (MLWHFQ score), exercise function, BNP, and cardiac remodelling at 12 months, although RDN improved VO_2 peak and E/e' at 3 months.[63] Kresoja KP et al. retrospectively analysed cardiac magnetic resonance imaging and echocardiogram data from 164 hypertensive patients undergoing RDN procedure, of whom 99 were HFpEF patients. After RDN treatment, LV diastolic stiffness and LV filling pressures as well as NT-proBNP were improved in patients with HFpEF, suggesting RDN might be a promising therapy for patients with HFpEF and uncontrolled arterial hypertension.[64] Whether the efficacy of RDN for HFpEF depends on its effect on lowering blood pressure and heart rate remains controversial. Schirmer SH et al. found that the improvement of LV hypertrophy and diastolic function by RDN after 6 months was unrelated to a reduction in systolic blood pressure and heart rate, suggesting a direct effect of RDN on changes in the cardiac phenotype.[65] However, in a 1-year follow-up of 190 patients with refractory hypertension and paroxysmal atrial fibrillation treated with RDN, Xu and colleagues documented that RDN only improved diastolic function in those with decreased mean arterial pressure and heart rate.[66] Future RCTs are warranted to further address which phenotypes of patients respond better to RDN, the long-term efficacy, and safety of RDN in HFpEF treatment, and the mechanism of action involved. The ongoing UNLOAD-HFpEF (Renal Denervation to Treat Heart Failure With Preserved Ejection Fraction) trial is the first randomized, sham-controlled double-blind pilot trial that will further address the role of RDN in HFpEF (see *Table 6*).

Table 6 Clinical evidence for the use of renal denervation in HFpEF

Author or trial name	Investigational device	Design	Inclusion criteria	Sample size	Follow-up	Primary efficacy and safety outcome
RDT-PEF[63]	Medtronic Symplicity Spyral™	Phase II, single-centre, prospective, randomized, controlled, open-label and blinded end-point trial	NYHA class II–III, LVEF ≥50%	RDN (n = 17), control (n = 8)	12 months	No differences between groups at 12 months for MLWHFQ score, VO_2 on exercise, BNP, E/e', left atrial volume index or LV mass index
Kresoja KP et al.[64]	Medtronic Symplicity Spyral™ or and ultrasound RDN (Paradise, ReCor Medical, Palo Alto, CA).	Single-centre, retrospective observational study	NA	99	NA	LV diastolic stiffness and LV filling pressures as well as NT-proBNP decreased
Ongoing UNLOAD-HFpEF	Ultrasound RDN (Paradise, ReCor Medical, Palo Alto, CA)	Single-centre, randomized, sham-controlled double-blind	NYHA class II or III, LVEF ≥55%	68	6 months	NA

Abbreviations: BNP, B-type natriuretic peptides; LV, left ventricular; LVEF, left ventricular ejection fraction; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RDN, renal denervation; VO_2, peak oxygen uptake.

Baroreflex activation therapy

Baroreceptor dysfunction is a prevalent pathophysiological feature in most cases of HF and closely links to LV impairment regardless of LVEF.[67] Baroreflex activation therapy (BAT) chronically stimulates carotid baroreceptors to reduce centrally mediated sympathetic outflow and increase parasympathetic activity, thereby counteracting sympathetic overactivation and parasympathetic withdrawal associated with HF. The HOPE4HF (Hope Heart Failure Study) and BeAT-HF (Baroreflex Activation for Heart Failure) trials showed that, compared with GDMT alone, BAT with the Barostim Neo system plus GDMT significantly improved the 6MWD, MLWHFQ-rated QOL, NYHA functional class, and NT-proBNP in patients HFrEF (LVEF ≤35%) with NYHA functional class III, and were associated with a trend of

reduced hospital days for HF. The safety of BAT was also demonstrated, with over 94% of patients having no major neurologic, cardiovascular, or procedure-related events.[68,69] Based on these results, the BAT with the second-generation Barostim Neo system is approved by the FDA for symptomatic HF patients with NYHA functional class III, LVEF less than or equal to 35%, NT-proBNP less than 1600 pg/mL and no indication for cardiac resynchronization therapy.[70] A patient-level meta-analysis suggested that BAT improved exercise capacity, NYHA class, and QOL in GDMT-treated patients with NYHA class II/III HFrEF.[71] However, evidence regarding the use of BAT in HFpEF remains lacking. Results from feasibility studies in 21 subjects with normal LVEF showed that after 12 months, BAT delivered by the first-generation Rheos System reduced blood pressure and improved 6MWD and LV mass in patients with refractory hypertension and symptomatic HFpEF.[72,73] Clemmer et al. utilized HumMod, a comprehensive physiological model, to simulate HFpEF and predict the dynamic changes in blood pressure, cardiac structure, and sympathetic nerve activity (SNA) during baroreflex activation. The results showed that simulating baroreflex activation for a period of 6 months led to reduced LV mass, lowered blood pressure, decreased cardiac SNA, and restoration of β1-adrenergic activity. Notably, the improvement in LV mass was weakened when renal SNA suppression was blocked during BAT, suggesting that BAT primarily enhances cardiac structure and function by inhibiting renal SNA.[74] The BAROSTIM THERAPY In Heart Failure With Preserved Ejection Fraction (NCT02876042) is an ongoing registry to evaluate the feasibility and effectiveness of BAT in patients with HFpEF combined with refractory hypertension (see *Table 7*).

Vagus nerve stimulation

Inflammation is thought to be one of the main causes and therapeutic targets of HFpEF. Vagus nerve stimulation (VNS), which sends electrical pulses to the vagus nerve via an implantable device, has been shown to relieve proinflammatory states and improve cardiac remodelling. Schwartz and colleagues first reported the feasibility of long-term VNS in eight patients with HFrEF, showing improvements in functional status, QOL, and LV volume after implantation of a vagus stimulator.[75] However, three larger clinical trials, including ANTHEM-HF (Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure), INOVATE-HF (INcrease Of VAgal TonE in CHF), and NECTAR-HF (Neural Cardiac Therapy for Heart Failure), have failed to consistently validated the prognosis-improving effects of VNS in patients with HFrEF.[76–78] The reason may be in part related to the different stimulus strengths and duty cycles of VNS in these clinical trials.[79] The recently published ANTHEM-HFpEF (Autonomic Regulation Therapy to Enhance Myocardial Function in

Table 7 Clinical evidence for the use of baroreflex activation therapy in HFpEF

Author or trial name	Investigational device	Design	Inclusion criteria	Sample size	Follow-up	Primary efficacy and safety outcome
Bisognano JD et al.[72]	Rheos System	Multicentre, prospective, randomized, controlled, open-label and blinded end-point trial	Drug-resistant HTN with systolic blood pressure ≥160 mmHg and stable medication of ≥3 anti-HTN drugs	21	12 months	Significant reduction in mitral A-wave velocity, left atrial dimension, and LVMI.
Ongoing BAROSTIM THERAPY	BAROSTIM NEO™ System	A post-market registry	Resistant hypertension and HFpEF	70	6 months	NA

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HTN, hypertension; LVMI, left ventricular mass index; NA, not applicable.

Table 8 Clinical evidence for the use of vagus nerve stimulation in HFpEF

Author or trial name	Investigational device	Design	Inclusion criteria	Sample size	Follow-up	Primary efficacy and safety outcome
ANTHEM-HFpEF[80]	LivaNova VNS Therapy® system	Open-label interventional study	HFpEF or HFmrEF, NYHA class II–III, and LVEF ≥40%.	52	12 months	VNS showed good tolerance and was associated with significant improvements in NYHA class, 6MWD, QOL, autonomic tone and cardiac electrical stability.
Tran et al.[83]	Transcutaneous electrical nerve stimulation unit	Prospective, randomized, double-blind, 2 × 2 cross-over study.	Patients with diastolic dysfunction and preserved LVEF	24	During stimulation	LV global longitudinal strain improved by 1.8 ± 0.9% during active LLTS compared with sham stimulation
Stavrakis et al.[84]	The Parasym device (Parasym, London, UK)	A pilot, sham-control, double-blind, randomized clinical trial	HFpEF patients and at least two additional co-morbidities (obesity, diabetes, hypertension, or age ≥65 years)	Active, n = 26; sham, n = 26	3 months	LV global longitudinal strain, tumour necrosis factor-α level, and QOL were significantly improved after treatment with LLTS

Abbreviations: 6MWD, 6-min walk distance; HFmrEF, HF with mildly reduced ejection fraction; HFpEF, HF with preserved ejection fraction; LLTS, Low-level tragus stimulation; LV, left ventricular; NYHA, New York Heart Association; QOL: quality of life.

Heart Failure With Preserved Ejection Fraction) trial first investigated the safety and feasibility of chronic VNS in 52 patients with HFpEF/HFmrEF. At the 1-year follow-up, VNS showed good tolerance and was associated with significant improvements in NYHA class, 6MWD, QOL, autonomic tone, and cardiac electrical stability, although it did not alter cardiac mechanical function.[80] Low-level tragus stimulation (LLTS) is a non-invasive method of percutaneous VNS that has been demonstrated to reduce cardiac inflammation and fibrosis and improve LV diastolic function in a rat model of HFpEF.[81,82] Tran et al. showed for the first time that LLTS can acutely improve the global longitudinal strain of LV in HFpEF patients by regulating autonomic tone.[83] Subsequently, a pilot, sham-control, double-blind, randomized clinical trial evaluated the effects of chronic LLTS on cardiac function, exercise capacity, and inflammation in HFpEF patients with a predominantly inflammatory-metabolic phenotype. Fifty-two HFpEF patients and at least two additional co-morbidities (obesity, diabetes, hypertension, or age ≥65 years) were included (active, n = 26; sham, n = 26). The results showed that the LV global longitudinal strain, tumour necrosis factor-α level, and QOL were significantly improved after treatment with LLTS for 3 months. Of note, the decreases in tumour necrosis factor-α were associated with improvements in the LV global longitudinal strain, suggesting that patients with a proinflammatory state may benefit more from LLTS[84] (see *Table 8*). Future studies are warranted to elucidate the effectiveness of VNS on distinct phenotypes of HFPEF and to investigate how to optimize stimulation parameters, such as intensity, duration, and frequency, for augmenting the therapeutic potential of VNS.[85]

Conclusion and future perspectives

Device-based therapy of HFpEF is an emerging field of research, most of which is still in the initial stage at present. Overall, the clinical evidence of phase 3 RCTs is few, the follow-up period is short, and the endpoints are mostly NYHA class, 6MWD, QOL, and biomarkers of HF, rather than cardiovascular death or HF hospitalization. Therefore, the effectiveness of these devices still needs to be further demonstrated. Among these devices, the clinical evidence of inter-atrial shunt, implantable heart failure monitors and baroreflex activation therapy is relatively well established. The IASD gained CE Mark approval in 2016, becoming the world's first transcatheter device for the treatment of HFpEF, and the CardioMEMS and Barostim Neo systems have also been approved by the FDA for use in selected HF patients. The fact that CardioMEMS has received aIIb recommendation in current guidelines for selected heart failure patients, with the aim of reducing heart failure hospitalizations, is also encouraging. However, in phase III clinical trials, the primary endpoint for both IASD and CardioMEMS were neutral and

only showed benefits in certain subgroups. Therefore, further research is needed to determine which phenotypes of HFpEF will benefit the most. Mechanically, both inter-atrial shunt and splanchnic ablation improve haemodynamics and reduce PCWP. Renal denervation and vagus nerve stimulation may be options for HFpEF patients with sympathetic overactivation and a predominantly inflammatory-metabolic phenotype, respectively. There may also be a place for baroreflex activation therapy in HFpEF patients combined with refractory hypertension. Of course, left atrial pacing for interatrial dyssynchrony and cardiac contractile regulation to improve cardiac calcium may also be potential treatment strategies for HFpEF, but the current clinical evidence is relatively weak. In the future, it is believed that these devices may play a more important role in the treatment of HFpEF with the improvement of the technology itself, the precision of the inclusion of the HFpEF population, and the extension of the follow-up period. In addition, further evidence is needed to determine whether complex interventions involving multiple HFpEF devices are safe and provide additive benefits in HFpEF patients.[19] Finally, healthcare professionals should overcome the stereotype that device therapy is exclusively applicable to HFrEF and adopt a more proactive approach in utilizing some of the devices that have demonstrated efficacy in improving surrogate endpoints of HFpEF in RCTs.

Author contributions

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Conflict of interest

The authors declare that they have no conflicts of interest.

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