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REVIEW

New Perspectives in the Treatment of Acute and Chronic Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Acute and chronic heart failure with reduced ejection fraction (HFrEF) is a major public health problem, studies showing a 25% survival rate at 5 years after hospitalization. If left untreated, it is a common and potentially fatal disease. In recent years, the medical and device therapies of patients with HFrEF have significantly improved. The aim of our review is to provide an evidence-based update on new therapeutic strategies in acute and chronic settings, to prevent hospitalization and death in patients with HFrEF. We performed a systematic literature search on PubMed, EMBASE, and the Cochrane Database of Systemic Reviews, and we included a number of 23 randomized controlled trials published in the last 30 years. The benefit of beta-blockers and renin-angiotensin-aldosterone system inhibitors in patients with HFrEF is well known. Recent developments, such as sodium-glucose cotransporter 2 inhibitors, vericiguat, transcatheter mitral valve repair, wireless pulmonary artery pressure monitor and cardiac contractility modulation, have also proven effective in improving prognosis. In addition, other new therapeutic agents showed encouraging results, but they are currently being studied. The implementation of personalized disease management programs that directly target the cause of HFrEF is crucial in order to improve prognosis and quality of life for these patients.

Keywords: heart failure with reduced ejection fraction, drug treatment, device treatment, acute management, chronic management, quality of life

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INTRODUCTION

Acute and chronic heart failure (HF) is one of the most important cardiovascular diseases, considering the increasing morbidity and mortality rate.[1,2] It is also the most frequent cardiovascular reason for hospital admission among people older than 60 years of age.[3–5] The mortality rate of patients with chronic HF at one year is 7.2%, and the one-year hospitalization rate is 31.9%.[6,7] Over the last several decades, there have been important advances in the treatment of HF; new medications and devices are being used in clinical practice in order to prevent hospitalization and death, and also to improve the quality of life.

According to the value of left ventricular ejection fraction (LVEF), HF may be classified into three categories: HF with reduced ejection fraction (HFrEF, with LVEF ≤40%), HF with midrange ejection fraction (LVEF 41–49% and diastolic dysfunction), and HF with preserved

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ejection fraction (LVEF ≥50% and diastolic dysfunction).[1,8] Approximately 50% of patients with HF have a reduced LVEF.[6]

The appearance of several new medications that involve neurohormone inhibition of the sympathetic nervous system, the angiotensin receptor neprilysin, and the renin-angiotensin-aldosterone system, and also device therapies, was associated with a reduction in the hospitalization and mortality rates of patients with HFrEF.[7–9] More recently, some randomized clinical trials have demonstrated an important reduction of mortality and cardiovascular events in these patients by using dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor,[10] vericiguat, an oral soluble guanylate cyclase stimulator,[11] and omecamtiv mecarbil, a selective cardiac myosin activator.[12] Given the benefits seen in these recently published clinical trials, all these new drugs have been included in the next updated HF guidelines, this year.

Despite all these therapeutic advances in the management of patients with HFrEF,[13–18] almost 50% of patients with ventricular dysfunction die within five years, and approximately 40% of them die in the first year after hospitalization for HF, in most of the cases by sudden cardiac death.[19–22] Considering the high mortality rates related to cardiac dysfunction and also the recent advancements in medical and device therapies of patients with HFrEF, the aim of our systematic review is to provide an evidence-based update on recent advances and perspectives in the context of treatment, in acute and chronic settings.

We performed a systematic literature search of PubMed, EMBASE, and the Cochrane Database of Systemic Reviews for randomized controlled trials on medical and device therapies of patients with HFrEF. We filtered the results for randomized controlled trials published in English between January 1, 1990, and August 1, 2020. The following search terms were included: HF with reduced ejection fraction, HFrEF, medical therapeutics, device therapies, hospitalization, death, and randomized trials. We also reviewed the most recent guidelines on HF of the European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American Heart Association (AHA). The studies included in this systematic review were considered eligible if they were (a) randomized clinical trials; (b) included patients with HF with reduced ejection fraction (LVEF ≤40%); (c) compared drug or device therapy with placebo, no medication or standard medical therapy, with at least 12 weeks of follow-up; (d) provided data about all-cause mortality, sudden cardiac death, cardiovascular death, cardiovascular/HF hospitalization, worsening HF event. A number of 23 studies were included in this review, and the results were stratified according to the drug treatment or device treatment for patients with HF with reduced ejection fraction.

DRUG TREATMENT

1. BETA-BLOCKERS

Considering the important role of sympathetic nervous system activation in the pathogenesis of HF, its suppression with beta-blockers has demonstrated beneficial effects in reducing all-cause and cardiovascular mortality. Bisoprolol, carvedilol, or metoprolol succinate should be administered in all patients with HFrEF if they are not contraindicated or there is no intolerance, considering that they decrease all-cause mortality, sudden cardiac death, and hospitalization.[23–26]

Guidelines recommend the use of beta-blockers for all patients with stable, symptomatic HFrEF, in order to reduce HF hospitalization and death. In patients with significant bradycardia, second- or third-degree atrioventricular block (without a cardiac pacemaker), and bronchial asthma, beta-blockers are contraindicated, but in patients with stable chronic obstructive lung disease they are usually not.[1,8]

The initial and target doses of beta-blockers should be selected according to the clinical status of the patient and blood pressure values.[27] Dose adjustment should be performed once every 1–2 weeks, with the aim to achieve the maximum tolerated dose after 3–6 months of treatment.

2. ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS)

Various studies have demonstrated that ACE inhibitors and ARBs improve clinical outcomes and reduce all-cause mortality in patients with HFrEF in the range of 20% to 30% (Table 1).[28–37] ACE inhibitors and ARBs are indicated for patients with HFrEF unless contraindicated: patients with angioedema during previous administration of a drug from these classes, those who are pregnant or plan to become pregnant, or patients with bilateral artery stenosis.[6,38,39] It is estimated that almost a quarter of patients treated with ACE inhibitors develop a dry cough, independent of the dose. In this case, it is recommended to replace the ACE inhibitor with an ARB.[40,41]

3. MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRAS)

Given the inappropriate activation of the renin-angiotensin-aldosterone system in patients with HFrEF, treatment with MRAs improved clinical outcomes in these patients. The benefit of MRAs in addition to a HF treatment regimen has been demonstrated only in few multicenter, large-sized studies such as the Randomized Aldactone Evaluation Study (RALES) trial,[42] the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[43] and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).[44] MRAs demonstrated a 15% to 30% reduction in mortality and a 15% to 40% reduction in HF hospitalizations in patients with HFrEF after a minimum monitoring period of 16 months, even in patients with myocardial infarction. MRAs should be added to the treatment regimen of patients with LVEF ≤35% and persistent NYHA classes II to IV symptoms, despite ACE inhibitors/ARB/angiotensin receptor-neprilysin inhibitors (ARNI) and beta-blocker therapy.[45-47] It is absolutely necessary to monitor kidney function and serum potassium one week after initiation of treatment or dose adjustment, then monthly for the first three months, every three months for a year, and then every 6 months.[48]

4. HYDRALAZINE AND ISOSORBIDE DINITRATE

The African-American Heart Failure Trial (A-HeFT) demonstrated that for Black patients with advanced HF, the addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy, including neurohormone blockers, significantly reduced mortality and HF hospitalization.[49]

5. IVABRADINE

Despite the strong evidence supporting the efficacy of beta-blockers in patients with HFrEF, some patients cannot tolerate them due to their undesirable hemodynamic effects. Ivabradine selectively blocks the funny channel (If) current and reduces the heart rate in patients with sinus rhythm, without influence on blood pressure, being used for the treatment of patients with HFrEF and LVEF ≤35%.[50,51] In the Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT), a randomized, placebo-controlled trial, ivabradine reduced HF mortality and HF hospitalization.[52] Thus, ivabradine is indicated in patients who remain symptomatic, with a heart rate of at least 70 beats per minute, despite treatment with a maximally tolerated dose of beta-blockers, ACE inhibitors, ARBs and MRAs.[53–55] In summary, the adequate reduction of the resting heart rate to 60 beats per minute or lower should be one of the primary goals of therapy in HFrEF patients. Since achieving this target heart rate with beta-blockers alone is difficult in the majority of patients with HFrEF, combining ivabradine is an effective alternative approach.[56]

6. ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI)

ARNI combines an angiotensin II type 1 receptor blocker and an inhibitor of neprilysin, the enzyme that promotes the degradation of atrial and brain natriuretic peptides.[57]

The efficacy of ARNI was demonstrated in the Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure (PRADIGM-HF) trial. Compared to enalapril, sacubitril/valsartan reduced hospitalization for HF and cardiovascular mortality (Table 1).[58]

The current ESC guidelines recommend sacubitril/valsartan for patients who have no contraindications and who remain symptomatic despite treatment with an ACE inhibitor or ARB, a beta-blocker and a MRA.[1]

The ACE inhibitor should be stopped at least 36 hours before the first intake of sacubitril/valsartan, because their simultaneous intake may cause accumulation of bradykinin and secondary occurrence of severe angioedema.

7. NEW DRUG THERAPIES

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

SGLT2 inhibitors increase urinary excretion of glucose in the renal tubules, natriuresis and osmotic diuresis, which can lead to blood pressure reduction, weight loss, improve glycemic control and insulin sensitivity.[59,60] Also, it has been reported that SGLT2 inhibitors have cardioprotective effects and improve prognosis in HFrEF, probably by improving cardiac metabolism, inflammation, and fibrosis.[59,61,62] Considering these beneficial effects of SGLT2 inhibitors, the 2019 guidelines of the ESC on diabetes, prediabetes, and cardiovascular diseases,[63] the 2019 Heart Failure Association (HFA) position paper on the role and safety of new glucose-lowering medications,[64] and the HFA clinical practice update on HF[65] sustain that empagliflozin, dapagliflozin, and canagliflozin can be used to prevent HF hospitalization in patients with type 2 diabetes mellitus.

TABLE 1. Clinical trials of medical therapies for patients with heart failure and reduced ejection fraction

Study	Patients	Follow-up (months)	End point	HR (95% CI)	Results
Beta-blockers					
CIBIS II[23]	LVEF ≤35% NYHA III/IV	15.6	All-cause mortality Sudden cardiac death	0.66 (0.54–0.81) 0.56 (0.39–0.80)	Bisoprolol has a significant mortality benefit in stable heart-failure patients, independent of the severity or cause of heart failure.
USCP[25]	LVEF ≤35%	12	All-cause mortality CV hospitalization	0.65 (0.39–0.80) 0.38 (0.18–0.53)	Carvedilol reduces the risk of death and cardiac hospitalization in patients with heart failure who receive treatment with digoxin, diuretics and an angiotensin-converting-enzyme inhibitor.
MERIT-HF[24]	LVEF ≤40% NYHA II–IV	12	All-cause mortality Deaths from HF	0.66 (0.53–0.81) 0.51 (0.33–0.79)	Metoprolol improves survival, reduces the need for hospitalizations due to worsening heart failure, improves NYHA functional class, and has beneficial effects on well-being of patients with symptomatic heart failure.
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers					
SOLVD[30]	LVEF ≤35% NYHA II–IV	48	All-cause mortality CV death or hospitalization	0.61 (0.05–0.26) 0.26 (0.18–0.34)	Enalapril reduces the incidence of heart failure, the heart failure hospitalizations and the risk of death, among patients with asymptomatic left ventricular dysfunction.
ATLAS[31]	LVEF ≤30% NYHA II–IV	46	All-cause mortality All-cause hospitalization	0.92 (0.82–1.03) 0.88 (0.82–0.96)	Patients with heart failure should not be maintained on very low doses of an ACE inhibitor (unless these are the only doses that can be tolerated) and the difference in efficacy between intermediate and high doses of an ACE inhibitor is very small.
CHARM[32]	LVEF ≤40% NYHA II–IV	34	CV mortality HF hospitalization	0.70 (0.60–0.81) 0.80 (0.66-0.96)	Candesartan significantly reduces all-cause mortality, cardiovascular death, and HF hospitalizations when added to standard therapies.
Mineralocorticoid receptor antagonists					
RALES[42]	LVEF ≤35% and NYHA IV, within the six months before enrolment	24	All-cause mortality HF hospitalization	0.70 (0.60-0.82) 0.65 (0.54–0.77)	Spironolactone, in addition to standard therapy, substantially reduces the risk of morbidity and death among patients with severe heart failure.
EPHESUS[43]	Patients with HF and LVEF ≤40%, at 3 to 14 days after AMI	16	All-cause mortality CV death, CV hospitalization	0.85 (0.75–0.96) 0.87 (0.79–0.95)	Eplerenone, in addition to optimal medical therapy, reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and HF.
EMPHASIS-HF[44]	LVEF ≤35% NYHA II	21	All-cause mortality CV death, HF hospitalization	0.76 (0.61–0.94) 0.63 (0.54–0.74)	Eplerenone reduces the risk of death and hospitalization among patients with systolic heart failure and mild symptoms.
Hydralazine and Isosorbide Dinitrate					
A-HeFT[49]	Black patients with NYHA III or IV, with dilated ventricles	10	All-cause mortality HF hospitalization	p = 0.02 p = 0.001	The addition of a fixed dose of isosorbide dinitrate plus hydralazine to standard therapy is efficacious and increases survival among black patients with advanced HF.
Ivabradine					
SHIFT[52]	Symptomatic HF and LVEF ≤35%, sinus rhythm with HR ≥70 bpm	22.9	All-cause mortality Death from HF HF hospitalization	p = 0.092 0.74 (0.58-0.94) 0.74 (0.66–0.83)	Heart-rate reduction with ivabradine reduces the cardiovascular death or hospital admission for worsening heart failure.

Angiotensin receptor-neprilysin inhibitor					
PARADIGM-HF[58]	LVEF ≤40% NYHA II–IV	27	All-cause mortality HF hospitalization	0.84 (0.76–0.93) 0.81 (0.71–0.89)	Sacubitril/valsartan is superior to enalapril in reducing the risks of death and of hospitalization for HF.
Sodium-glucose cotransporter 2 inhibitors					
DAPA-HF[10]	LVEF ≤40% NYHA II–IV	18.2	CV death Worsening HF	0.82 (0.69–0.98) 0.74 (0.65–0.85)	The risk of worsening HF or death from cardiovascular causes is lower among patients who receive dapagliflozin, regardless of the presence or absence of diabetes.
Oral soluble guanylate cyclase stimulator					
VICTORIA[11]	LVEF ≤45% NYHA II–IV	10.8	CV death HF hospitalization	0.90 (0.82–0.98) 0.90 (0.81–1.00)	The incidence of death from cardiovascular causes or hospitalization for HF is lower among patients with high-risk HF who receive vericiguat.

ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; bpm, beats per minute; CV, cardiovascular; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

Oral soluble guanylate cyclase stimulator

Vericiguat is an oral soluble guanylate cyclase stimulator, used to reduce the risk of HF hospitalization and cardiovascular death. The Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial evaluated the efficacy and safety of vericiguat in patients with a reduced ejection fraction and chronic HF with recent decompensated HF.[11] They found that vericiguat reduced the first HF hospitalization and cardiac death over a medium follow-up of 10.8 months. Symptomatic hypotension and syncope occurred in both groups, but there was no statistically significant difference (Table 1).

DEVICE TREATMENT

1. CARDIAC RESYNCHRONIZATION THERAPY AND IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

Since their inception, implantable cardiac devices, such as implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) have proven their effectiveness in improving cardiovascular outcome in HF patients. The selection of patients who might benefit from an ICD or CRT is challenging, considering the undesired effects of these devices such as infections, lead and generator problems, or inappropriate shocks.[18,66]

The current ESC guidelines recommend CRT for symptomatic patients with LVEF ≤35%, despite optimal medical therapy, who have left bundle branch block and a QRS duration ≥130 ms.[1] The use of multimodality imaging, such as late gadolinium enhancement detected by cardiac magnetic resonance and radial strain, demonstrated a higher portion of CRT responders compared with the control group, but the clinical outcomes were similar.[67]

The Cardiac Resynchronization in Heart Failure (CARE-HF) trial demonstrated that, compared with optimal medical therapy, CRT reduces all-cause mortality, the interventricular mechanical delay, the end-systolic volume, and the area of the mitral regurgitant jet. Also, CRT improved the LVEF, symptoms and the quality of life.[68] The benefits of CRT in reducing hospitalization and all-cause mortality were also demonstrated in a subgroup analysis from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial, but only for patients with a QRS duration ≥150 ms and left bundle branch block morphology.[69]

ICD is generally recommended for primary prevention in symptomatic HF patients with LVEF ≤35% despite >3 months of optimal medical therapy, but there are also slightly different indications according to specific cardiac pathologies.[1]

The benefits of ICD in reducing all-cause mortality were demonstrated in patients with ischemic cardiomyopathy in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) trial.[70] On the other hand, in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), these benefits were demonstrated both in patients with ischemic (21% reduction) and nonischemic HF (27% reduction) (Table 2).[71]

2. ATRIAL FIBRILLATION ABLATION IN HEART FAILURE

Considering that atrial fibrillation is the most common arrhythmia in patients with HF and that it can decrease

TABLE 2. Clinical trials of device therapies for patients with heart failure and reduced ejection fraction

Study	Patients	Follow-up (months)	End point	HR (95% CI)	Results
Cardiac resynchronization therapy					
CARE-HF[68]	LVEF ≤35%, NYHA III–IV, QRSd ≥120 ms, sinus rhythm, LVESD ≥30 mm	29	All-cause mortality HF hospitalization	0.64 (0.48–0.85) 0.48 (0.36-0.64)	Cardiac resynchronization improves symptoms and quality of life, reduces complications and the risk of death in patients with HF and cardiac dyssynchrony.
MADIT-CRT[69]	LVEF ≤30%, NYHA I–II, QRSd ≥130 ms, sinus rhythm	29	All-cause mortality or HF hospitalization	0.66 (0.52–0.84)	CRT combined with ICD reduced the risk of heart-failure events in relatively asymptomatic patients with a low ejection fraction and wide QRS complex.
Implantable cardiac defibrillator					
MADIT-II[70]	Prior MI (≥1 month), LVEF ≤30%	20	All-cause mortality	0.69 (0.51–0.93)	Prophylactic implantation of a defibrillator in patients with a prior myocardial infarction and advanced left ventricular dysfunction improves survival.
SCD-HeFT[71]	LVEF ≤35%, NYHA II–III	45	All-cause mortality	0.77 (0.62–0.96)	Single-lead, shock-only ICD therapy reduces overall mortality by 23%, whereas amiodarone has no favourable effect on survival.
Atrial fibrillation ablation in heart failure					
CASTLE-AF[72]	LVEF ≤35%, NYHA II–IV,ICD	37.8	All-cause deathHF hospitalization	0.53 (0.32–0.86) 0.56 (0.37–0.83)	Catheter ablation for atrial fibrillation in patients with heart failure was associated with a significantly lower rate of all-cause death or HF hospitalization than was medical therapy.
Transcatheter mitral valve repair					
MITRA-FR[75]	LVEF: ≥15 and ≤40%; NYHA II–IV; Moderate to severe mitral regurgitation	12	All-cause mortality HF hospitalization	1.11 (0.69–1.77) 1.13 (0.81–1.56)	The rate of death or unplanned hospitalization for heart failure 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.
COAPT[76]	LVEF: ≥20 and ≤50%; NYHA II–IV; Moderate to severe mitral regurgitation; LVESD ≤70 mm	24	All-cause mortality HF hospitalization	0.62 (0.46–0.82) 0.53 (0.40–0.70)	Transcatheter mitral-valve repair resulted in a lower rate of hospitalization for HF and lower all-cause mortality than medical therapy alone, among patients who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy.
Remote monitoring					
CHAMPION[77]	NYHA III	18	All-cause mortality HF hospitalization	0.68 (0.45–1.02) 0.72 (0.59–0.88)	Pulmonary artery pressure-guided HF management reduces morbidity and mortality in patients with NYHA III on guideline-directed medical therapy.
Cardiac contractility modulation					
FIX-HF-5C2[81]	LVEF: ≥25 and ≤45%; NYHA III–IV; Not eligible for CRT	24	Change of peak VO_2 (mL/kg/min) NYHA improvement by at least 1 functional class	1.72 (95% BCI, 1.02–2.42) 83.1% vs. 42.7% (p <0.001)	The 2-lead system is safe and improves peak VO2 and NYHA, with less device-related adverse effects as the 3-lead system.

BCI, Bayesian credible interval; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardiac defibrillator; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MI, myocardial infarction; NYHA, New York Heart Association; peak VO2, peak oxygen consumption; QRSd, QRS duration on electrocardiogram

LVEF and cause symptoms of HF, atrial fibrillation ablation may be considered in symptomatic HFrEF patients, despite optimal medical therapy.[1] CASTLE-AF (Catheter Ablation for Atrial Fibrillation with Heart Failure) is a recently published trial that demonstrated the beneficial effect of atrial fibrillation ablation in HFrEF patients (Table 2).[72] In patients ≥65 years or with more than one risk factor for stroke, this beneficial effect was not shown in the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial.[73] The utility of atrioventricular junction ablation followed by CRT in patients with HF and symptomatic atrial fibrillation, but who are not candidates for atrial fibrillation ablation or in those who have failed to respond to this treatment, was demonstrated in the Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy (APF-CRT) trial. Even if it included a small number of patients, this strategy was associated with a decreased rate of HF-related morbidity and mortality and improved quality of life.[74]

3. TRANSCATHETER MITRAL VALVE REPAIR

It is known that functional mitral regurgitation, often encountered in HFrEF, is a predictor of mortality.[1] Because the surgical risk of HFrEF combined with mitral regurgitation is high, the percutaneous correction of functional mitral regurgitation is actively studied. A recent study, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR), that compared percutaneous mitral valve repair using the MitraClip device with medical therapy vs. medical therapy alone, found no differences in mortality and HF hospitalization rates.[75] Conversely, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated a significant reduction of HF hospitalization (35.8% vs. 67.9%; HR 0.53 [95% CI 0.40–0.70]) and all-cause mortality (29.1% vs. 46.1%; HR 0.62 [95% CI 0.46–0.82]) compared with medical therapy alone, within 2 years of follow-up (Table 2).[76]

4. REMOTE MONITORING

Wireless pulmonary artery pressure monitors in patients with persistent NYHA class III symptoms following hospitalization for acute HF is one of the most active fields in the management of HF, in order to guide the treatment. The CardioMEMS Heart Sensor Allowing Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial demonstrated that hemodynamic monitoring with a wireless implantable pulmonary artery pressure monitoring device significantly reduces hospitalizations for HF, over a mean follow-up period of 18 months (Table 2).[77]

5. CARDIAC CONTRACTILITY MODULATION (CCM)

In recent years, a new therapy that delivers high amplitude biphasic pulses to the right ventricular septum during the absolute refractory period of the myocardium – cardiac contractility modulation (CCM) – has become available. The system delivers, through a small implantable pulse generator, biphasic pulses, modulating the strength of the contraction of the myocardium by generating non-excitatory impulses. The therapy is delivered for a total of 7 to 12 hours, at regular intervals throughout the day. Thus, the CCM system modulates the strength of the myocardium contraction rather than the rhythm, as is the case of pacemaker or defibrillator devices.[78]

CCM has been studied in several randomized studies, in patients with symptomatic HF on optimal medical therapy and with a QRS duration <130 ms and EF <45%, thus being ineligible for CRT. Collectively, the results indicated that CCM improves quality of life, LVEF, indexes of diastolic function, NYHA classification, 6 min walk test (6MWT) distance, and peak oxygen consumption (peak VO2) during cardiopulmonary stress testing.[78–80] The FIX-HF-5C2 study evaluated the safety and effectiveness of a 2-lead system (eliminating the atrial lead) compared with the 3-lead system and demonstrated that the 2-lead system effectively delivers a comparable number of CCM signals (including in patients with atrial fibrillation) as the 3-lead system, is equally safe and improves peak VO_2 and New York Heart Association classification with less device-related adverse effects (0% vs. 8%; p = 0.03) (Table 2).[81]

CCM is applicable for patients with NYHA class II or III symptoms, a normal QRS, a LVEF ≥20%, peak VO_2 ≥10 mL/kg/min, and fewer than 10,000 ventricular ectopic beats or bigeminies per day.[80]

Table 2. Clinical trials of device therapies for patients with heart failure and reduced ejection fraction

NEW THERAPEUTIC AGENTS THAT ARE CURRENTLY BEING STUDIED

1. OMECAMTIV MECARBIL

Omecamtiv mecarbil is a selective cardiac myosin activator and a myotrope that increases cardiac function and decreases ventricular volumes, with no increase of

the calcium level or oxygen use in cardiomyocytes, as is the case with standard inotropic agents.[12,82,83] It also decreases the heart rate and N-terminal pro-B-type natriuretic peptide in patients with HFrEF.[84] Results from phase 2 trials were very promising, and therefore there are major expectations for the Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) study, which is a phase 3 clinical trial. It is a double-blind, placebo-controlled trial that included patients with class II, III or IV HF, a LVEF of 35% or less, elevated natriuretic peptides, and either current hospitalization for HF or history of hospitalization or emergency department visit for HF within a year of screening.[12] Its main objective is to evaluate if omecamtiv mecarbil can improve symptoms, prevent HF events, and delay cardiovascular death in patients with chronic HF. The trial's estimated date of completion is 2021.

2. ULARITIDE

Ularitide is a synthetic form of urodilatin, a human natriuretic peptide, produced by distal tubules of the kidney, collecting duct cells as a response to increased blood pressure. Ularitide increases diuresis and natriuresis, produces vasodilation, and inhibits the renin-angiotensin-aldosterone system.[85,86] In a phase 1 study, ularitide reduced the pulmonary capillary wedge pressure (PCWP) and the systemic vascular resistance, and also improved the systolic function in patients with acute HF. SIRIUS I, a phase 2 study, evaluated the clinical value of ularitide and demonstrated that it improved the PCWP, reduced N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels, and relieved dyspnea, without affecting kidney function.[86] Therefore, these studies indicate that ularitide may have beneficial hemodynamic effects in patients with HF, but further phase 3 studies on patients with chronic HFrEF are needed.

3. SERELAXIN

Serelaxin is a synthetic recombinant of relaxin, a peptide structurally similar to insulin, which can increase plasma volume and cardiac output, and decrease blood pressure and vascular resistance.[87,88] In phase 1 trials, serelaxin has been shown to be safe and tolerable; it increased renal plasma flow and natriuresis, reduced PCWP and vascular resistance, and improved the cardiac index.[89] These promising results initiated a phase 2 study which demonstrated that serelaxin improved dyspnea and reduced cardiovascular death or readmission due to heart or renal failure in patients with acute cardiac failure.[90]

The results from phases 1 and 2 trials were followed by phase 3 trials such as the Recombinant Human Relaxin-2 for Treatment of Acute Heart Failure (RELAX-AHF) trial. According to the results from this study, serelaxin had no significant effect on readmission for renal or heart failure, but was associated with a 47% reduction of HF worsening and a 37% reduction of all-cause and cardiovascular 180-day mortality.[91]

4. TOLVAPTAN

In HF, reduced cardiac output and blood pressure determine an activation of baroreceptors and of the renin-angiotensin-aldosterone system, which will increase arginine vasopressin levels. Tolvaptan is an oral vasopressin type 2 receptor antagonist that increases aquaresis, without changes in the excretion of electrolytes.[92–94] Also, compared with standard diuretics, it increases serum sodium levels in patients with hyponatremia and has only a slight tendency to affect renal function.[93,94] In a phase 3 placebo-controlled study, the efficacy and safety of tolvaptan was evaluated in treating HF patients with volume overload, despite the use of conventional diuretics. The results of this study demonstrated a reduction of HF symptoms, an increase in diuresis, and a decrease of body weight.[95]

Currently, several device therapies for the management of patients with HFrEF are under study. The Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF) phase 1 study demonstrated that a transcatheter interatrial shunt device reduces pulmonary capillary wedge pressure at 1 month in patients with HF and LVEF ≥40%.[96] Recent phase 2 and 3 trials evaluated the effect of vagus nerve stimulation in symptomatic patients with HFrEF, but they failed to show a significant improvement of clinical outcomes and left ventricular diameters.[97,98]

The results of these studies regarding the aforementioned new therapeutic agents for the treatment of HF are promising, but they require further research before they can be used as efficacious therapeutic agents.

CONCLUSIONS AND PERSPECTIVES

Heart failure with reduced ejection fraction is a major health problem with significant morbidity and mortality. Few areas in medicine have had such a remarkable progress over the past decades, as that observed in the man-

agement of patients with HFrEF. The current management of HFrEF has changed significantly in recent years, with the advent of many new drugs and devices that have been shown to improve the quality of life and to reduce the mortality of these patients. Understanding the mechanisms responsible for each patient's clinical status is crucial in order to apply a therapeutic strategy that directly targets the cause of the hemodynamic compromise.

CONFLICT OF INTEREST

We declare that there is no conflict of interest.

REFERENCES

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129-2200. doi: 10.1093/eurheartj/ehw128.
2. Choi HM, Park MS, Youn JC. Update on heart failure management and future directions. Korean J Intern Med. 2019;34:11-43. doi: 10.3904/kjim.2018.428.
3. Rossignol P, Hernandez AF, Solomon SD, Zannad F. Heart failure drug treatment. Lancet. 2019;393:1034-1044. doi: 10.1016/S0140-6736(18)31808-7.
4. Braunwald E. Heart failure. JACC Heart Fail. 2013;1:1-20. doi: 10.1016/j.jchf.2012.10.002.
5. Zannad F. Rising incidence of heart failure demands action. Lancet. 2018;391:518-519. doi: 10.1016/S0140-6736(17)32873-8.
6. Murphy SP, Ibrahim NE, Januzzi JL. Heart failure with reduced ejection fraction: a review. JAMA. 2020;324:488-504. doi: 10.1001/jama.2020.10262.
7. Virani SS, Alonso A, Benjamin EJ, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2020 update: a report from the American Heart Association. Circulation. 2020;141:e139-e596. doi: 10.1161/CIR.0000000000000757.
8. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137-e161. doi: 10.1016/j.cardfail.2017.04.014.
9. Yancy CW, Januzzi JL Jr, Allen LA, et al. 2021 Update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77:772-810. doi: 10.1016/j.jacc.2020.11.022.
10. McMurray JJV, Solomon SD, Inzucchi SE, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381:1995-2008. doi: 10.1056/NEJMoa1911303.
11. Armstrong PW, Pieske B, Anstrom KJ, et al. VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med. 2020;382:1883-1893. doi: 10.1056/NEJMoa1915928.
12. Teerlink JR, Diaz R, Felker GM, et al. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: rationale and design of GALACTIC-HF. JACC: Heart Fail. 2020;8:329-340. doi: 10.1016/j.jchf.2019.12.001.
13. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet. 2019; 393:61-73. doi: 10.1016/S0140-6736(18)32484-X.
14. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. J Am Coll Cardiol. 2018;72:351-366. doi: 10.1016/j.jacc.2018.04.070.
15. Azevedo PS, Polegato BF, Minicucci MF, Paiva SA, Zornoff LA. Cardiac remodelling: concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment. Arq Bras Cardiol. 2016;106:62-69. doi: 10.5935/abc.20160005.
16. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling-concepts and clinical implications: a consensus paper from an international forum on cardiac remodelling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol. 2000;35:569-582. doi: 10.1016/s0735-1097(99)00630-0.
17. Doenst T, Nguyen TD, Abel ED. Cardiac metabolism in heart failure: implications beyond ATP production. Circ Res. 2013;113:709-724. doi: 10.1161/CIRCRESAHA.113.300376.
18. Normand C, Kaye DM, Povsic TJ, Dickstein K. Beyond pharmacological treatment: an insight into therapies that target specific aspects of heart failure pathophysiology. Lancet. 2019;393:1045-1055. doi: 10.1016/S0140-6736(18)32216-5.
19. Tarone G, Balligand JL, Bauersachs J, et al. Targeting myocardial remodelling to develop novel therapies for heart failure: a position paper from the Working Group on Myocardial Function of the European Society of Cardiology. Eur J Heart Fail. 2014;16:494-508. doi: 10.1002/ejhf.62.
20. Kehat I, Molkentin JD. Molecular pathways underlying cardiac remodelling during pathophysiological stimulation. Circulation. 2010;122:2727-2735. doi: 10.1161/CIRCULATIONAHA.110.942268.
21. Tomasik A, Nowalany-Kozielska E. Pharmacological treatment of left ventricular remodelling: recent trial results. Clin Invest. 2015;5:767-776. doi: 10.1172/JCI41329.
22. Marrow BA, Cook SA, Prasad SK, McCann GP. Emerging techniques for risk stratification in nonischemic dilated cardiomyopathy: JACC review topic of the week. J Am Coll Cardiol. 2020;75:1196-1207. doi: 10.1016/j.jacc.2019.12.058.
23. Lechat P, Brunhuber KW, Hofmann R, et al. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9-13. doi.org/10.1016/S0140-6736(98)11181-9.
24. Hjalmarson Å, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). JAMA. 2000;283:1295-1302. doi: 10.1001/jama.283.10.1295.

25. Packer M. US Carvedilol Heart Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med. 1996;334:1349-1355. doi: 10.1056/NEJM199605233342101.
26. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344:1651-1658. doi: 10.1056/NEJM200105313442201.
27. Fröhlich H, Torres L, Täger T, et al. Bisoprolol compared with carvedilol and metoprolol succinate in the treatment of patients with chronic heart failure. Clin Research Cardiol. 2017;106:711-721. doi: 10.1007/s00392-017-1115-0.
28. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667-1675. doi: 10.1056/NEJMoa01071.
29. Swedberg K, Kjekshus J, CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). Am J Cardiol. 1988;62: 60A-66A. doi: 10.1016/s0002-9149(88)80087-0.
30. Yusuf S, Pitt B, Davis CE, Hood WBJr, Cohn JN, SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;27:685-691. doi: 10.1056/NEJM199209033271003.
31. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation. 1999;100:2312-2318.
32. Young JB, Dunlap ME, Pfeffer MA et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation. 2004;110:2618-2626. doi: 10.1161/01.CIR.0000146819.43235.A9.
33. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol. 2017;14:30-38. doi: 10.1038/nrcardio.2016.163.
34. Mărănducă MA, Tărniceru CC, Carasevici E, Cojocaru E. Interaction between angiotensin II, hypertension and inflammation in rat kidney. The Medical-Surgical Journal. 2015;119:791-797. doi: 10.1016/j.phrs.2017.03.017.
35. Bauersachs J, Jaisser F, Toto R. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. Hypertension. 2015;65:257-263. doi: 10.1161/HYPERTENSIONAHA.114.04488.
36. Berliner D, Bauersachs J. New drugs: big changes in conservative heart failure therapy? Eur J CardioThorac Surg. 2019;55:i3-i10. doi: 10.1093/ejcts/ezy421.
37. Li H, Duan Y, Chen B, et al. New pharmacological treatments for heart failure with reduced ejection fraction (HFrEF): A Bayesian network meta-analysis. Medicine. 2020;99:e18341. doi: 10.1097/MD.0000000000018341.
38. Berliner D, Hallbaum M, Bauersachs J. Current drug therapy for heart failure with reduced ejection fraction. Herz. 2018;43:383-391. doi: 10.1007/s00059-018-4712-4.
39. Van der Meer P, Gaggin HK, Dec GW. ACC/AHA versus ESC guidelines on heart failure: JACC guideline comparison. J Am Coll Cardiol. 2019;73:2756-2768. doi: 10.1016/j.jacc.2019.03.478.
40. Reis Filho JRDAR, Cardoso JN, Cardoso CMDR, Pereira-Barretto AC. Reverse cardiac remodelling: a marker of better prognosis in heart failure. Arq Bras Cardiol. 2015;104:502-506. doi: 10.5935/abc.20150025.
41. Hussein AA and Wilkoff BL. Cardiac implantable electronic device therapy in heart failure. Circulation Res. 2019;124:1584-1597. doi: 10.1161/CIRCRESAHA.118.313571.
42. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341:709-717. doi: 10.1056/NEJM199909023411001.
43. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309-1321. doi: 10.1056/NEJMoa030207.
44. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364:11-21. doi: 10.1056/NEJMoa1009492.
45. Rossignol P, Cleland JG, Bhandari S, et al. Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. Circulation. 2012;125:271-279. doi: 10.1161/CIRCULATIONAHA.111.028282.
46. Rossignol P, Dobre D, McMurray JJ, et al. Incidence, determinants, and prognostic significance of hyperkalaemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Circ Heart Fail. 2014;7:51-58. doi: 10.1161/CIRCHEARTFAILURE.113.000792.
47. Vardeny O, Claggett B, Anand I, et al. Incidence, predictors, and outcomes related to hypo- and hyperkalaemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. Circ Heart Fail. 2014;7:573-579. doi: 10.1161/CIRCHEARTFAILURE.114.001104.
48. Maisel A, Xue Y, van Veldhuisen DJ, et al. Effect of spironolactone on 30-day death and heart failure rehospitalization (from the COACH study). Am J Cardiol. 2014;114:737–742. doi: 10.1016/j.amjcard.2014.05.062.
49. Taylor AL, Ziesche S, Yancy C, African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049-2057. doi: 10.1056/NEJMoa042934.
50. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L. Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (SHIFT). Eur J Heart Fail. 2010;12:75-81. doi: 10.1093/eurjhf/hfp154.
51. Fox K, Ford I, Steg PG, et al. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet. 2008;372:817-821. doi: 10.1016/S0140-6736(08)61171-X.
52. Swedberg K, Komajda M, Böhm M, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875-885. doi: 10.1016/S0140-6736(10)61198-1.
53. Orasanu G, Al-Kindi SG, Oliveira GH. Ivabradine in management of heart failure: a critical appraisal. Curr Heart

Fail Rep. 2016;13:60-69. doi: 10.1007/s11897-016-0276-x.
54. Sattar Y, Samani EN, Zafrullah FNU, Latchana S, Patel NB. Ivabradine in congestive heart failure: patient selection and perspectives. Cureus. 2019;11:e4448. doi: 10.7759/cureus.4448.
55. Tondi L, Fragasso G, Spoladore R, et al. Real-life indications to ivabradine treatment for heart rate optimization in patients with chronic systolic heart failure. J Cardiovasc Med. 2018;19:351-356. doi: 10.2459/JCM.0000000000000661.
56. Thorup L, Simonsen U, Grimm D, Hedegaard ER. Ivabradine: current and future treatment of heart failure. Basic Clin Pharmacol Toxicol. 2017;121:89-97. doi: 10.1111/bcpt.12784.
57. Agnetti G, Piepoli MF, Siniscalchi G, Nicolini F. New insights in the diagnosis and treatment of heart failure. BioMed Res Intern. 2015;2015:265260. doi: 10.1155/2015/265260.
58. McMurray JJ, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993-1004. doi: 10.1056/NEJMoa1409077.
59. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZ. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. Circulation. 2017;136:1643-1658. doi: 10.1161/CIRCULATIONAHA.117.030012.
60. Ahmed HM, Khraishah H, Cho L. Cardioprotective anti-hyperglycaemic medications: a review of clinical trials. Eur Heart J. 2018;39:2368-2375. doi: 10.1093/eurheartj/ehx668.
61. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. JAMA Cardiol. 2017;2:1025-1029. doi: 10.1001/jamacardio.2017.2275.
62. Verma S, McMurray JJ. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018;61:2108-2117. doi: 10.1007/s00125-018-4670-7.
63. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). Eur Heart J. 2020;41:255-323. doi: 10.1093/eurheartj/ehz486.
64. Seferović PM, Fragasso G, Petrie M, et al. Sodium–glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2020;22:1495-1503. doi: 10.1002/ejhf.1954.
65. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;21:1169-1186. doi: 10.1002/ejhf.1531.
66. Stevenson LW, Desai AS. Selecting patients for discussion of the ICD as primary prevention for sudden death in heart failure. J Card Fail. 2006;12:407-412. doi: 10.1016/j.cardfail.2006.06.001.
67. Sommer A, Kronborg MB, Nørgaard BL, et al. Multimodality imaging-guided left ventricular lead placement in cardiac resynchronization therapy: a randomized controlled trial. Eur J Heart Fail. 2016;18:1365-1374. doi: 10.1002/ejhf.530.
68. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352:1539-1549. doi: 10.1056/NEJMoa050496.
69. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361:1329-1338. doi: 10.1056/NEJMoa0906431.
70. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346:877-883. doi: 10.1056/NEJMoa013474.
71. Bardy GH. Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352:225-237. doi: 10.1056/NEJMoa043399.
72. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med. 2018;378:417-427. doi: 10.1056/NEJMoa1707855.
73. Tofield A. The CABANA trial: a first glance at an important study. Eur Heart J. 2018;39:2767-2768. doi: 10.1093/eurheartj/ehy379.
74. Brignole M, Pokushalov E, Pentimalli F, et al. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. Eur Heart J. 2018;39:3999-4008. doi: 10.1093/eurheartj/ehy555.
75. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 2018;379:2297-2306. doi: 10.1056/NEJMoa1805374.
76. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med. 2018;379:2307-2318. doi: 10.1056/NEJMoa1806640.
77. Givertz MM, Stevenson LW, Costanzo MR, CHAMPION Trial Investigators. Pulmonary artery pressure-guided management of patients with heart failure and reduced ejection fraction. J Am Coll Cardiol. 2017;70:1875-1886. doi: 10.1016/j.jacc.2017.08.010.
78. Kadish A, Nademanee K, Volosin K, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. Am Heart J. 2011;161:329-337. doi: 10.1016/j.ahj.2010.10.025.
79. Abraham WT, Kuck KH, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. JACC Heart Fail. 2018;6:874-883. doi: 10.1016/j.jchf.2018.04.010.
80. Kuschyk J, Nägele H, Heinz-Kuck K, et al. Cardiac contractility modulation treatment in patients with symptomatic heart failure despite optimal medical therapy and cardiac resynchronization therapy (CRT). Int J Cardiol. 2019;277:173-177. doi: 10.1016/j.ijcard.2018.10.086.
81. Wiegn P, Chan R, Jost C, et al. Safety, performance, and efficacy of cardiac contractility modulation delivered by the 2-lead optimizer smart system: The FIX-HF-5C2 Study. Circulation: Heart Fail. 2020;13:p.e006512. doi: 10.1161/CIRCHEARTFAILURE.119.006512.
82. Tariq S, Aronow WS. Use of inotropic agents in treatment of systolic heart failure. Intern J Mol Sci. 2015;16:29060-29068. doi: 10.3390/ijms161226147.
83. Planelles-Herrero VJ, Hartman JJ, Robert-Paganin J, Malik FI, Houdusse A. Mechanistic and structural basis for activation of cardiac myosin force production by omecamtiv mecarbil. Nat Commun. 2017;8:1-10. doi: 10.1038/s41467-017-00176-5.

84. Psotka MA, Teerlink JR. Direct myosin activation by omecamtiv mecarbil for heart failure with reduced ejection fraction. Handb Exp Pharmacol. 2017;243:465-490. doi: 10.1007/164_2017_13.
85. Anker SD, Ponikowski P, Mitrovic V, Peacock WF, Filippatos G. Ularitide for the treatment of acute decompensated heart failure: from preclinical to clinical studies. Eur Heart J. 2015;36:715-723. doi: 10.1093/eurheartj/ehu484.
86. Kentsch M, Ludwig D, Drummer C, Gerzer R, Müller-Esch G. Haemodynamic and renal effects of urodilatin bolus injections in patients with congestive heart failure. Eur J Clin Investing. 1992;22:662-669. doi: 10.1093/eurheartj/ehu484.
87. Ghosh RK, Banerjee K, Tummala R, Ball S, Ravakhah K, Gupta A. Serelaxin in acute heart failure: most recent update on clinical and preclinical evidence. Cardiovasc Ther. 2017;35:55-63. doi: 10.1111/1755-5922.12231.
88. Bathgate RA, Halls ML, van der Westhuizen ET, Callander GE, Kocan M, Summers RJ. Relaxin family peptides and their receptors. Physiol Rev. 2013;93:405-480. doi: 10.1152/physrev.00001.2012.
89. Dschietzig T, Teichman S, Unemori E, et al. Intravenous recombinant human relaxin in compensated heart failure: a safety, tolerability, and pharmacodynamic trial. J Cardiac Fail. 2009;15:182-190. doi: 10.1016/j.cardfail.2009.01.008.
90. Teerlink JR, Metra M, Felker GM, et al. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. Lancet. 2009;373:1429-1439. doi: 10.1016/S0140-6736(09)60622-X.
91. Teerlink JR, Cotter G, Davison BA. RELAXin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013;381:29-39. doi: 10.1016/S0140-6736(12)61855-8.
92. Inomata T, Ikeda Y, Kida K, Kanagawa Aquaresis Investigators. Effects of additive tolvaptan vs. increased furosemide on heart failure with diuretic resistance and renal impairment-results from the K-STAR Study. Circulation. 2017;82:159-167. doi: 10.1253/circj.CJ-17-0179.
93. Pose A, Almenar L, Gavira JJ, et al. Benefit of tolvaptan in the management of hyponatraemia in patients with diuretic-refractory congestive heart failure: the SEMI-SEC project. ESC Heart Fail. 2017;4:130-137. doi: 10.1002/ehf2.12124.
94. Uemura Y, Shibata R, Takemoto K, et al. Safety and efficacy of long-term use of tolvaptan in patients with heart failure and chronic kidney disease. Circ J. 2017;81:1736-1738. doi: 10.1253/circj.CJ-17-0554.
95. Kinugawa K, Sato N, Inomata T, et al. Efficacy and safety of tolvaptan in heart failure patients with volume overload. Circ J. 2014;78:844-852. doi.org/10.1253/circj.CJ-66-0093 .
96. Feldman T, Mauri L, Kahwash R, et al. Transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction (REDUCE LAP-HF I [reduce elevated left atrial pressure in patients with heart failure]): a phase 2, randomized, sham-controlled trial. Circulation. 2018;137:364-375. doi: 10.1161/CIRCULATIONAHA.117.032094.
97. De Ferrari GM, Stolen C, Tuinenburg AE. Long-term vagal stimulation for heart failure: Eighteen month results from the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) trial. Intern J Cardiol. 2017;244:229-234. doi: 10.1016/j.ijcard.2017.06.036.
98. Gold MR, Van Veldhuisen DJ, Hauptman PJ, et al. Vagus nerve stimulation for the treatment of heart failure: the INOVATE-HF trial. J Am Coll Cardiol. 2016;68:149-158. doi: 10.1016/j.jacc.2016.03.525.