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Current treatment for heart failure with reduced ejection fraction

A systematic review of the new therapies

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Abstract

Introduction: heart failure with reduced ejection fraction has a growing therapeutic arsenal. Thus, the indications for each therapy must be refined.

Methods: a systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, to update the systematic search performed in the development of the “Clinical Practice Guidelines for Prevention, Diagnosis, Treatment and Rehabilitation” (CPG) of the Colombian Ministry of Health.

Results: six new clinical trials were found which substantially modify the main recommendations of the CPG. Angiotensin receptor antagonists combined with neprilysin inhibitors (ARNI), sodium-glucose cotransporter 2 (SGLT2) inhibitors, betablockers and mineralocorticoid receptor antagonists (MRA) are now the main core of treatment for patients with heart failure with reduced ejection fraction. Other therapeutic options should be considered after beginning and titrating the doses of these four medications.

Discussion: given the robustness of the evaluating studies, the proposed practical scheme, as the central core with four fundamental therapeutic strategies, will improve the treatment of patients with heart failure and allow the stepwise inclusion of other alternatives, plotted as orbits, to impact on other individual outcomes. (*Acta Med Colomb* 2021; 46. DOI: <https://doi.org/10.36104/amc.2021.2108>).

Keywords: heart failure, epidemiology, mortality.

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Introduction

Heart failure (HF) is a clinical syndrome characterized by typical signs and symptoms in addition to the objective evidence of a structural or functional abnormality of the heart (1). It is associated with significant morbidity and mortality, with one-year mortality rates of 7.2% and hospitalization rates of 31.9% in patients with chronic HF, and these outcomes increasing to 17.4% mortality and 43.9% hospitalization in patients with acute HF (2). Five-year survival is 56.7% (95% CI 54-59.4%) and 10-year survival is 34.9% (95% CI 24-46.8%) (3).

Traditionally, left ventricular ejection fraction (LVEF) has been the most commonly used classification method, due to its practical implications for determining an appropriate treatment strategy, although over the last few years the measurement of global longitudinal strain and myocardial contraction fraction have gained ground (4). The European Society of Cardiology classifies it in three categories accord-

ing to LVEF: HF with preserved LVEF when it is equal to or greater than 50%, HF with mildly reduced LVEF if it is 40-49%, and HF with reduced LVEF (HF-rLVEF) when it is less than 40% (5).

Heart failure with preserved and mid-range LVEF has no specific evidenced-based treatment to date, and its treatment is aimed at managing risk factors and controlling comorbidities (1, 2, 5), while HF-rLVEF has clearly evidence-based treatments with an increasingly broad therapeutic arsenal, and currently even offers new treatment paradigms (6). Thus we, in this systematic review of the literature, deal with the current treatment of HF-rLVEF.

Data collection

The study design is a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (7). The systematic search performed in drafting the “Clinical Practice

Guidelines for the Prevention, Diagnosis, Treatment and Rehabilitation of Heart Failure in People Over the Age of 18, Classification B, C and D" (1) was updated.

Objective

The population, intervention, control, and outcome (PICO) questions were:

1. In patients over the age of 18 with HF-rLVEF, does pharmacological or interventional treatment or treatment with devices decrease the combined primary outcome - mortality and hospitalizations for any cause or for cardiovascular causes - compared with a placebo or active treatment or not using them?

Eligibility criteria

Studies were selected by two investigators, and differences were resolved by consensus. The included studies were randomized clinical trials which compared the use of pharmacological or interventional treatment or devices in HF-rLVEF (defined as LVEF less than 40%) with placebo, active treatment or, in the case of devices, with not using them, and which reported relevant combined outcomes: mortality from any cause or cardiovascular mortality, hospitalizations for any cause or for HF. The baseline characteristics and the outcomes evaluated were extracted from each study.

Search strategy

A systematic search was performed in the following bibliographic databases: PubMed, Embase, CENTRAL, DARE, Epistemonikos, SciELO, LILACS and OpenGrey, along with the web pages of clinical trial registries such as Clinical-Trials. The manual search included international cardiology congress pages, web sites and cardiology electronic media like Twitter from institutions such as the European Society of Cardiology, the American Heart Association, the Canadian Cardiovascular Society and the American College of Cardiology, as well as primary studies included in these societies' clinical practice guidelines and those of the National Institute for Health Care Excellence (NICE) and meta-analyses. The update included studies in English from January 2014 to December 2020.

A general and manual search was performed including the following terms: *"heart failure" or "congestive heart failure" or "left ventricular dysfunction" or "reduced ejection fraction" or "systolic heart failure" and "treatment" "management" or "drug therapy" and randomized controlled trial or controlled clinical trial or randomized or randomly or trial"*.

Statistical analysis

In line with the individual characteristics of the included studies, the heterogeneity among them and the fact that they act as complementary therapies, the study group consensus was to perform a systematic review rather than a meta-analysis. The individual papers were analyzed according to

their baseline characteristics and defined outcomes, which are presented in tables for comparison. The risk of bias was assessed using the strategy proposed by Cochrane, and the fragility index was calculated for new studies along with a comparison with the classic studies using the outcome of mortality from any cause. The fragility index is defined as the minimum number of events that would have to change to a "non-event" status in order to change from a significant to a nonsignificant result, as evidence of the robustness of the studies, since many of these depend on a difference of three or fewer events; its interpretation shows that the smaller the index, the more fragile the result (8).

Results

The systematic and manual search recovered 1,424 results, of which only original clinical trials were analyzed, excluding publications analyzing individual subgroups or secondary outcomes or subrogates. New studies of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) or beta blockers were not recovered, nor were new studies of mineralocorticoid receptor antagonists (MRAs) or ivabradine.

The risk of bias for the six new studies analyzed was considered to be low for all the evaluated aspects: generation of the allocation sequence, allocation concealment, blinding of participants and personnel, blinding of outcomes, incomplete outcomes and selective reporting (Table 1).

The fragility index shows robust results for sacubitril/valsartan for both the primary combined outcome as well as for cardiovascular death, death from a cardiovascular source and hospitalization for HF. For dapagliflozin, the results are robust for the primary combined outcome and hospitalization for HF. The empagliflozin study showed robust results for the primary combined outcome and hospitalization for HF; for sotagliflozin it is robust for the primary outcome; and vericiguat and omecamtiv mecarbil had very low fragility indices, especially the latter one (Table 2).

A comparative analysis of the classic and new studies was performed for the outcome of mortality (Table 3). The results showed estimates below 1 in almost all cases, except for valsartan, losartan and omecamtiv mecarbil. Those with a 95% CI above 1 were valsartan and candesartan in the CHARM Added trial, losartan in ELITE II and HEAAL, carvedilol in ANZ, nebivolol, digoxin, ivabradine vericiguat, empagliflozin, omecamtiv mecarbil and sotagliflozin. The fragility indices were robust for beta blockers, spironolactone and sacubitril/valsartan.

Pharmacological treatment

Angiotensin converting enzyme (ACE) inhibitors

The ACE inhibitors decrease the concentration of angiotensin II and aldosterone, increase renin release and the concentration of angiotensin (9-12), decrease the plasma concentration of epinephrine, norepinephrine and vasopressin, and increase the production of bradykinin (10, 13, 14).

The CONSENSUS Trial (15) with enalapril was the first drug (1986) to show reduced mortality in HF, in patients in New York Heart Association (NYHA) class IV. Six-month mortality significantly reduced in the group receiving enalapril (44% vs. 26%). Since then, many studies have shown that RAAS inhibitors reduce morbidity and mortality in HF-rLVEF, with reductions in mortality from all causes ranging from 20-30% (16-20).

Angiotensin II receptor blockers (ARBs)

The clinical trial results indicate that ARBs are not superior to ACE inhibitors, but are an alternative for patients with intolerance. Clinical trials have evaluated the efficacy not only of losartan (OPTIME-ELITE II), but also of valsartan (Val-HeFT) and candesartan (CHARM) in patients with HF, in terms of cardiovascular morbidity and mortality (21-24). However, they have not been able to surpass the ACE inhibitors in consistently reducing morbidity and mortality; their main advantage lies in a better tolerance. Their use as an alternative treatment is based on the results of the CHARM-Alternative study in patients with symptomatic HF and LVEF <40% who were not taking ACE inhibitors due to intolerance. In these patients, the use of candesartan achieved a significant reduction in both mortality and the number of hospitalizations for HF (25).

Beta blockers

Beta blockers should be part of the treatment of all chronic, stable patients, and they should be started early after compen-

sating patients with acute, newly diagnosed HF (1, 5). They have proven benefits, regardless of the etiology of the HF. These include symptom relief and improved quality of life, reduced risk of hospitalization and incidence of sudden death, as well as improved survival. In addition, they have significant effects on reverse ventricular remodeling, with LVEF recovery (26-30). Beta blocker treatment should be used with caution in patients with borderline BP, recent inotrope treatment or NYHA functional class IV.

A recent meta-analysis raises questions about the effect of beta blockers on patients with HF and atrial fibrillation (AF), as they have a different impact in these patients than in patients with a sinus rhythm (31). The recent RATE AF clinical trial shows that digoxin, compared with bisoprolol, has similar effectivity, but with fewer adverse events (32).

Mineralocorticoid receptor antagonists (MRAs)

The MRAs (spironolactone and eplerenone) reduce the aldosterone escape phenomenon, contribute to the RAAS block (33-35) and reduce mortality by 15 to 30%. Furthermore, they decreased hospitalizations for HF by 15 to 40% in three randomized clinical trials (RALES, EMPHASIS, EPHEsus) (36-38), in patients with chronic HF-rLVEF, including patients who had had a myocardial infarction, excluding patients with a baseline serum creatinine greater than 2.5 mg/dL (or an estimated glomerular filtration rate [GFR] <30 mL/min/1.73 m²) or a serum potassium level >5.0 mEq/L.

Table 1. Risk of bias in the clinical trials.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
PARADIGM HF	Low	Low	Low	Low	Low	Low
DAPA HF	Low	Low	Low	Low	Low	Low
VICTORIA	Low	Low	Low	Low	Low	Low
EMPEROR REDUCED	Low	Low	Low	Low	Low	Low
GALACTIC HF	Low	Low	Low	Low	Low	Low
SOLOIST WHF	Low	Low	Low	Low	Low	Low

Table 2. Fragility index for all the outcomes in the new trials included.

Fragility index	PARADIGM HF Active treatment/ superiority LCZ696/ enalapril	DAPA HF Placebo/superiority Dapagliflozin/placebo	VICTORIA Placebo/superiority Vericiguat/placebo	EMPEROR R Placebo/superiority Empagliflozin/placebo	GALACTIC HF Placebo/superiority Omecamtiv/placebo	SOLOIST WHF Placebo/superiority Sotagliflozin/placebo
Primary outcome	118	62	8	50	1	72
Cardiovascular death	66	5	0	0	0	0
Total death	49	8	0	0	0	0
Hospitalization for heart failure	54	43	0	50	0	NA

Table 3. Comparison of the fragility index of classic HF trials.

Study	Total mortality	Estimated 95% CI	Fragility index
CONSENSUS	1 year • 36 vs. 52%	RR 0.69 (0.52-0.91)	7
SOLVD T	2 years • 35.1 vs. 39.7%	RR 0.84 (0.74-0.95)	10
Val-HeFT	2 years • 19.7 vs. 19.4%	RR 1.02 (0.88-1.18)	0
CHARM Alternative	3 years • 26.1 vs. 29.1%	aHR 0.83 (0.7-0.99)	0
CHARM Added	3.5 years • 29.5 vs. 32.4%	HR 0.89 (0.77-1.02)	0
ELITE II	1.5 years • 17.7 vs. 15.9 %	HR 1.13 (0.95-1.35)	0
HEAAL	4.7 years • 33 vs. 34.8 %	HR 0.94 (0.84-1.04)	0
CIBIS II	1.3 years • 12 vs. 17%	HR 0.66 (0.54-0.81)	37
MERIT HF	1 year • 7.2 vs. 11%	RR 0.66 (0.53-0.81)	34
COPERNICUS	10.4 m • 11.4 vs. 18.5%	RR 0.66 (0.53-0.81)	30
ANZ CARVEDILOL	1.6 years • 9.7 vs. 12.5%	RR 0.76 (0.44-1.32)	0
COMET	5 years • 34 vs. 40%	HR 0.83 (0.74-0.93)	33
SENIORS	1.75 years • 15.8 vs. 18.1%	HR 0.88 (0.71-1.08)	0
RALES	2 years • 35 vs. 46%	RR 0.70 (0.6-0.82)	54
EMPHASIS HF	1.75 years • 12.5 vs. 15.5%	HR 0.76 (0.62-0.93)	5
DIG	3 years • 34.8 vs. 35.1%	RR 0.99 (0.91-1.07)	0
A-HeFT	10 m • 6.2 vs. 10.2%	HR 0.57 (no CI) RR 0.63 (0.41-0.96)	3
SHIFT	2 years • 16 vs. 17%	HR 0.9 (0.8-1.02)	0
PARADIGM	2.25 years • 17 vs. 19.8%	HR 0.84 (0.76-0.93)	49
DAPA HF	18.2 m • 11.6 vs. 13.9%	HR 0.83 (0.71 to 0.97)	8
VICTORIA	10.8 m • 20.3 vs. 21.2%	HR 0.95 (0.84-1.07)	0
EMPEROR R	16 m • 13.4 vs. 14.2%	HR 0.92 (0.77 to 1.10)	0
GALACTIC HF	21.8 m • 25.9 vs. 25.9%	HR 1.00 (0.92 to 1.09)	0
SOLOIST WHF	9 m • 13.5 vs. 16.3%	HR 0.82 (0.59-1.14)	0

Recent evidence, using indirect comparison, suggests greater survival benefits with a starting strategy using the three agents compared with conventional therapy (39). New drugs such as finerenone have shown benefits in a Phase 2 trial (ARTS-HF) and in type 2 diabetic patients with chronic kidney disease (40-41).

Angiotensin receptor-neprilysin inhibitors (ARNIs)

Initially, as a complement to the neurohormonal block, an attempt was made to raise natriuretic peptide levels with nesiritide and carperitide, with discouraging results (42-45). Subsequently, isolated neprilysin inhibition was attempted with racecadotril, candoxatrilat and ecdotril, which was unsuccessful, as their effect was rapidly lost (46). The next step was to use a new group known as vasopeptidase inhibitors which have a dual mechanism, inhibiting neutral

endopeptidases (such as neprilysin) and ACE (omapatrilat). The OVERTURE trial showed noninferiority compared with enalapril, but a greater number of patients with angioedema [24 (0.8%) vs. 14 (0.5%)] (47), due to neprilysin degrading aminopeptidase P which, like ACE, degrades bradykinin.

Finally, sacubitril (a neprilysin inhibitor) was combined with an ARB-II (valsartan), which was tested in the PARADIGM HF trial (48) in patients with LVEF <35%, with proven tolerance to ACE inhibitors or ARBs, NYHA ≥II, elevated natriuretic peptides, systolic arterial pressure (SAP) > 100 mmHg, GFR > 30 mL/min/1.73m² and potassium ≤5.2 mEq/L. Sacubitril/valsartan showed superiority in doses of 200 mg every 12 hours, compared with enalapril at 10 mg every 12 hours, in cardiovascular mortality, including sudden death and worsening HF (HR 0.8, CI 0.73-0.87) and hospitalizations for HF (HR 0.79, CI 0.71-0.89).

Table 4. Comparison of the new HF treatments. Baseline characteristics.

Variable	PARADIGM HF Active treatment/superiority LCZ696/enalapril	DAPA HF Placebo/superiority DAPA/placebo	VICTORIA Placebo/superiority Vericiguat/placebo	EMPEROR R Placebo/superiority Empagliflozin/placebo	GALACTIC HF Placebo/superiority Omecamtiv/placebo	SOLOIST WHF Placebo/superiority Sotagliflozin/placebo
Group	ARNI	ISGLT2	SGCE	ISGLT2	CMA	ISGLT2
Year	2014	2019	2020	2020	2020	2020
Median follow up	27 months	18 months	11 months	16 months	21.8 months	9 months
Sample size	4,187/4,212	2,373/2,371	2,526/2,524	1,863/1,867	4,120/4,112	608/614
Design	RCT	RCT	RCT	RCT	RCT	RCT
Age (years)	63.8 ± 11.5/63.8 ± 11.3	66.2 ± 11/66.5 ± 10.8	67.5 ± 12.2/67.2 ± 12.2	67.2 ± 10.8/66.5 ± 11.2	64.5 ± 11.3/64.5 ± 11.4	69 (63–76)/70 (64–76)
Average GFR	68 ± 20/68 ± 20	66 ± 19.6/65.5 ± 19.3	61.3 ± 27/61.7 ± 27.3	61.8 ± 21.7/62.2 ± 21.5	58.7 (43.8–73.7)/58.8 (44.3–74.3)	49.2 (39.5–61.2)/50.5 (40.5–64.6)
Ejection fraction (%)	29.6 ± 6.1/29.4 ± 6.3	31.2 ± 6.7/30.9 ± 6.9	29 ± 8.3/28.8 ± 8.3	27.7 ± 6.0/27.2 ± 6.1	26.6 ± 6.3/26.5 ± 6.3	35 (28–47)/35 (28–45)
Ischemic (%)	59.9/60.1	55.5/57.3	59.8/56.8	52.8/50.7	53.2/54	
NYHA I/II/III/IV (%)	4.3/71.6/23.1/0.8; 5/69.3/24.9/0.6	0/67.7/31.5/0.8; 0/67.4/31.7/1.0	0/58.6/40/1.4; 0.1/59.3/39.4/1.2	0/75.1/24.4/0.5; 0/75/24.4/0.6	0/53.3/43.7/3; 0/52.8/44.1/3	Hospitalized + IV diuretic
Hypertension (%)	70.9/70.5		79.3/79	72.4/72.3		
Diabetes (%)	34.7/34.6	41.8/41.8	48.6/45.3	49.8/49.8	40.1/40.3	Type 2 100%
Atrial fibrillation (%)	36.2/37.4	38.6/38	43.5/46.4	35.6/37.8	27.8/26.7	
Beta blocker (%)	93.1/92.9	96/96.2	93.2/93	94.7/94.7	94.2/94.4	92.8/91.4
Aldosterone antagonist (%)	54.2/57	71.5/70.6	69.3/71.4	70.1/72.6	77.6/77.8	66.3/62.7
ACE inhibitor/ARB (%)		84.5/82.8	73.3/73.6	70.5/68.9	87/87	82/83
Sacubitril/valsartan (%)		10.5/10.9	14.3/14.7	18.3/20.7	19.9/19	15.3/18.2
ICD	14.9/14.7	26.2/26.1	27.6/27.9	31.0/31.8	32.2/31.3	
CRT	7/6.7	8/6.9	14.7/14.6	11.8/11.9	14.4/13.8	
NT-proBNP pg/mL	1,631/1,594	1,428/1,446	2,803.5/2,821	1,887/1,926	1,977/2,025	1,816/1,741

The PIONEER HF trial (49) proved the safety of beginning this drug in uncompensated HF in patients with LVEF <40%, BNP ≥400 ng/L or NT-proBNP ≥1,600 ng/L, no inotrope requirement in the last 24 hours, nor use of vasodilators, SAP <100 mmHg or increased diuretics in the last six hours. Sacubitril/valsartan showed superiority at a dose of 200 mg every 12 hours compared with enalapril at doses of 10 mg every 12 hours, with regard to decreased NT-ProBNP levels and a reduction in 30-day readmissions as a secondary outcome.

Subsequently, the TITRATION trial was performed to determine the safety of conservative (standard) titration or condensed (aggressive) titration of the dose, with good results in both arms (50). Similarly, the TRANSITION trial (51) showed that initiating sacubitril/valsartan before or after discharge did not affect the achievement of the target dose. Finally, the PROVE HF study (52) found a weak, but statistically significant, relationship between NT-ProBNP levels and the change in LVEF, since the bioavailability of

valsartan in the ARNI is 50% greater than that of valsartan alone, which means that 400 mg of the combination contains ~203 mg of valsartan, equivalent to 320 of valsartan sold alone; in addition, it has proven cost-effectiveness (Tables 4-6) (19).

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

Beginning in 2016, with the publication of the EMPERG-OUTCOME (53) study which found a reduction in hospitalization for HF in patients with diabetes mellitus (DM) receiving empagliflozin treatment, there has been a growing interest in the effect of this group of medications on HF treatment. The proposed mechanism of action of SGLT-2 inhibitors is, first of all, natriuresis and glucosuria which, in addition to decreasing preload and postload, decreases interstitial edema which is related to ventricular hypertrophy, although this effect is neutralized around week 12 of treatment (54). The second proposed effect is decreased BP, secondary to decreased sympathetic tone through direct

Table 5. Comparison of the new HF treatments. Outcomes.

Outcome	PARADIGM HF Active treatment/superiority LCZ696/enalapril	DAPA HF Placebo/superiority DAPA/placebo	VICTORIA Placebo/superiority Vericiguat/placebo	EMPEROR R Placebo/superiority Empagliflozin/placebo	GALACTIC HF Placebo/superiority Omecamtiv/placebo	SOLOIST WHF Placebo/superiority Sotagliflozin/placebo
Primary combined (% HR, events per 100 patient years)	21.8/26.5 HR 0.80 (0.73-0.87)	16.3/21.2 HR 0.74 (0.65-0.85) 11.6/15.6	35.5/38.5 HR 0.90 (0.82-0.98) 33.6/37.8	19.4/24.7 HR 0.75 (0.65-0.86) 15.8/21.0	37/39.1 HR 0.92 (0.86-0.99) 24.2/26.3	40.3/ 57.8 HR 0.67 (0.52-0.85) 51/76.3
CV death	13.3/16.5 HR 0.80 (0.71-0.89)	9.6/11.5 HR 0.82 (0.69-0.98) 6.5/11.5	16.4/17.5 HR 0.93 (0.81-1.06) 12.9/13.9	10/10.8 HR 0.92 (0.75-1.12) 7.6/8.1	19.1/19.4 HR 1.01 (0.92-1.11) 10.9/10.8	8.4/ 9.5 HR 0.84 (0.58-1.22) 10.6/12.5
First hospitalization for heart failure	12.8/15.6 HR 0.79 (0.71-0.89)	9.7/13.4 HR 0.70 (0.59-0.83) 6.9/9.8	27.4/29.6 HR 0.90 (0.81-1.0) 25.9/29.1	13.2/18.3 HR 0.69 (0.59-0.81) 10.7/15.5	27.7/28.7 HR 0.95 (0.87-1.03) 18/19.1	
Total hospitalization	39.7/43.5 HR 0.88 (0.82-0.94)			HR 0.85 (0.75-0.95)	28.6/30.1 HR 0.93 (0.86-1) 18.7/20.3	
Total death	17/19.8 HR 0.84 (0.76-0.93)	11.6/13.9 HR 0.83 (0.71-0.97) 7.9/9.5	20.3/21.2 HR 0.95 (0.84-1.07) 16/16.9	13.4/14.2 HR 0.92 (0.77-1.10) 10.1/ 10.7	25.9/25.9 HR 1 (0.92-1.09) 14.4/14.4	10.7/ 12.4 HR 0.82 (0.59-1.14) 13.5/16.3
KCCQ change	“-2.9±0.36/-4.63±0.36” HR 1.64 (0.63-2.65)	6.1±18.6/3.3±19.2 HR 1.18 (1.11-1.26)		5.8±0.4/4.1±0.4 HR 1.7 (0.5-3.0)	5.8±0.3/6.3±0.3 -0.5 (-1.4 to 0.5)	17.7/13.6
Kidney worsening	2.2/2.6 HR 0.86 (0.65-1.13)	1.2/1.6 HR 0.71 (0.44-1.16) 0.8/1.2		1.6/3.1 HR 0.50 (0.32-0.77)		

inhibition of noradrenaline synthesis by blocking renal tyrosine hydroxylase (55). The third mechanism is decreased cardiomyocyte glucose consumption in favor of the use of fatty acids and ketones which, besides being more energy efficient, have the ability to decrease oxidative stress (56). Finally, although there are several ideas to explain improved contractility through calcium metabolism, direct blocking of the NHE1 receptor by SGLT-2 inhibitors and the subsequent reduction in intracellular sodium and calcium, as

well as increased mitochondrial calcium, has the greatest evidence (56).

Their clinical effect has been proven in recent years in patients without DM; thus, the DEFINE HF (57) study found that patients with LVEF <40%, NYHA II-III, elevated natriuretic peptides and GFR $\geq 30\text{mL/min/1.73m}^2$ dapagliflozin at 10 mg/day was superior to placebo in decreasing the dual co-primary outcome which included reducing NT-proBNP levels by at least 20% and increasing the Kansas scale by

Table 6. Comparison of the new HF treatments. Adverse events.

Adverse event	PARADIGM HF Active treatment/ superiority LCZ696/enalapril	DAPA HF Placebo/superiority DAPA/placebo	VICTORIA Placebo/superiority Vericiguat/placebo	EMPEROR R Placebo/superiority Empagliflozin/placebo	GALACTIC HF Placebo/superiority Omecamtiv/placebo	SOLOIST WHF Placebo/superiority Sotagliflozin/placebo
Symptomatic hypotension (%, p)	14/9.2 p<0.001	0.3/0.5	9.1/7.9 p=0.12			6/4.9
Hypoglycemia						1.5/0.3
Renal adverse event	3.3/4.5 p<0.007	6.5/7.2 p=0.36	2.1/2.2			
Hypercalemia	16.1/17.3 p=0.15	0.1/0.2	4.4/5.6			
Cough	11.3/14.3 p<0.001		4.4/4.2			
Angioedema	0.4/0.2					
Volume depletion		7.5/6.8 P=0.4				
Syncope			4/3.5 p=0.30			
Urinary tract infection						4.8/5.1
Diarrhea						6.1/3.4
Anemia			7.6/5.7			
Ischemic cardiac event					4.9/4.6	
Severe ventricular arrhythmia					2.9/3.1	

≥ 5 points (OR 1.8 CI 1.03-3.06), although there were no differences in the other co-primary outcome of the average NT-proBNP levels at 6-12 weeks.

Later, the DAPA-HF (58) trial showed that in patients with LVEF $<40\%$ and NYHA $\geq$ II with elevated natriuretic peptides, despite being on optimal therapy, with GFR ≥ 30 mL/min/1.73m², SAP > 95 mmHg, and without type 1 DM, dapagliflozin was superior at 10 mg/day compared with placebo in the combined outcome of worsening HF (unplanned hospitalization or an urgent visit to the emergency room for intravenous therapy) or cardiovascular death (HR 0.74 CI 0.65-0.85).

The EMPEROR REDUCED (59) study randomized patients with LVEF $<30\%$, NYHA $\geq$ II, and elevated natriuretic peptides (in cases with LVEF between 30 and 40%, hospitalizations for HF in the previous year or very high peptide levels were also required), despite being on optimal therapy, with a GFR ≥ 20 mL/min/1.73m² and SAP >100 mmHg. In this study, empagliflozin proved to be superior at 10 mg/day compared with placebo in decreasing hospitalizations for HF or cardiovascular death (HR 0.75 95% CI 0.65-0.86).

Finally, the SOLOIST WHF study in type 2 diabetic patients with decompensated HF randomly assigned stabilized patients, before or within three days of discharge, to 200 mg of sotagliflozin (increasing to 400 mg, depending on side effects) versus placebo. After a median nine-month follow up, it significantly decreased the combined primary outcome (HR 0.67 95% CI 0.52-0.85). This study offers an interesting perspective by suggesting that early initiation of treatment has important effects and, furthermore, the effect is maintained in patients with an LVEF $\geq 50\%$, which suggests a promising effect for patients with HF with a slightly reduced and preserved fraction (60), as suggested by the results of the recent EMPEROR PRESERVED (N Engl J Med 2021 DOI: 10.1056/NEJMoa2107038/10.1056) study.

Although, given the consistency of the described evidence, it could be deduced that this is a group effect, the results of the VERTIS CV (61) trial raised doubts in this regard, since the use of ertugliflozin in patients with type 2 diabetes was unable to show superiority to the placebo, but did show non-inferiority, although the population of HF patients included did not exceed 25%. A subsequent report with the prespecified analysis of HF-related events suggested a reduction in hospitalization for HF (RR 0.70 95% CI 0.56-0.87) and the combined outcome of hospitalization for HF/cardiovascular death (RR 0.83 95% CI 0.72-0.96) (62).

Ivabradine

Ivabradine inhibits the sinus node's pacemaker activity by selectively blocking the hyperpolarization channels known as the "funny" (I_f) channels, decreasing the heart rate of patients with a sinus rhythm without affecting arterial pressure, cardiac contractility or intracardiac conduction (30). Among the studies found on this treatment is the initial background in the BEAUTIFUL (63) study on patients with coronary disease and ventricular dysfunction (LVEF $<40\%$), which

found no difference between ivabradine and placebo in the primary outcome (HR 1 95% CI 0.91-1.1) nor in the secondary outcomes which made up the combined primary outcome. However, in the subgroup analysis, in patients with a baseline heart rate ≥ 70 bpm, it reduced the incidence of hospitalization for myocardial infarction and coronary revascularization, although it did not decrease the primary objective nor overall mortality (64).

The SHIFT (65) study was conducted in patients with chronic HF and LVEF $\leq 35\%$, sinus rhythm and a resting heart rate ≥ 70 bpm. Ivabradine had an impact on the primary outcome of cardiovascular death or hospitalization for HF (HR 0.82 95% CI 0.75-0.90), as well as the outcomes related to HF (hospitalization for HF HR 0.74 95% CI 0.66-0.83; and death from HF HR 0.74 95% CI 0.58-0.94).

Patients treated with ivabradine have an average heart rate reduction of 8 bpm, while a meta-analysis of patients with HF-rLVEF with beta blockers showed a reduction of 12 bpm (66). Cullington et al. (67) showed that the proportion of patients for whom the addition of ivabradine would be indicated according to the SHIFT trial criteria dropped from 19.4% of the total at the initial visit to only 9% at the 12-month follow up, after adequately adjusting the beta blocker dose.

Hydralazine and isosorbide dinitrate

The evidence for the clinical usefulness of hydralazine and isosorbide dinitrate comes initially from the V-HeFT I trial, which compared three treatments: placebo, prazosin, or isosorbide dinitrate and hydralazine. After two years, there was a 34% reduction in the primary outcome of cumulative mortality in the hydralazine and isosorbide dinitrate group compared with placebo ($p=0.028$, 95% CI 4-54%) (68). Subsequently, the V-HeFT II study compared hydralazine combined with isosorbide dinitrate to enalapril; at two years, there was a significantly higher reduction in mortality from all causes in the enalapril group (ARR 6%, $p=0.016$) and the differences in mortality between the two groups were not sustained at 2.5 years (ARR 5.4%, $p=0.08$), improved peak oxygen consumption and LVEF in the hydralazine-isosorbide dinitrate group compared with enalapril early on, as part of the secondary results (69).

The AHeFT study was carried out based on observations which suggested a greater benefit in African Americans. This study randomized 1,050 black patients with HF in functional class III/IV and ventricular dilation to receive a fixed dose of hydralazine and isosorbide dinitrate ($n=518$) compared to placebo ($n=532$) in addition to standard medical care. The study was ended early when it showed that hydralazine combined with isosorbide dinitrate resulted in significantly lower mortality compared with placebo (6.2% vs. 10.2%, $p=0.02$). The outcome of side effects was also better in the intervention group, with a 43% reduction in death from any cause (HR 0.57; $p=0.01$), 33% reduction in the rate of first hospitalizations for HF (16.4% vs. 22.4%, $p=0.01$), and improved quality of life (70).

Vericiguat

Vericiguat is an oral, soluble guanylate cyclase stimulator which increases cyclic GMP activity, a second messenger involved in regulating cardio-renal and metabolic protective mechanisms. The SOCRATES-REDUCED study randomized 456 patients with HF with LVEF <45% and one recent decompensation episode (<4 weeks). A total of 377 patients finished treatment and there was no difference between the baseline and 12-week NT-proBNP levels between the group treated with vericiguat and the placebo group, with adequate tolerance and no differences in adverse events, with a linear relationship between the dose of vericiguat used and the degree of NT-proBNP reduction (71).

The VICTORIA study involved 5,050 patients with high-risk HF-rLVEF (40% in NYHA functional class III), severe impairment of systolic ventricular function (mean LVEF of 29%), with elevated natriuretic peptides and recent decompensation (80% within the last three months) to receive oral vericiguat with a target dose of 10 mg per day, compared with placebo plus guideline-directed treatment. The study showed a modest reduction in the primary outcome of cardiovascular death or first hospitalization for HF (35.5% vs. 38.5%, HR 0.9 [95% CI, 0.82-0.98, $p=0.02$]), derived mainly from the effect on hospitalizations for HF or any cause, with no impact on cardiovascular deaths or total deaths. Mean follow up was 10.8 months. Due to its vasodilating properties, there was symptomatic hypotension in 9.1% of the patients compared with 7.9% in the placebo group ($p=0.12$) and syncope in 4% compared with 3.5% in the placebo group ($p=0.30$) (72).

Omecamtiv mecarbil

Omecamtiv mecarbil is a selective cardiac myosin activator which increases contractility by binding to an allosteric site, for a faster transition from weak to strong binding, increasing the number of myosin heads bound to an actin filament, generating more strength. In addition, stabilization of the baseline status reduces ATP turnover in the absence of an interaction with actin, which improves energy efficiency.

The Phase 3 GALACTIC HF trial in 8,256 patients with chronic HF with LVEF $\leq 35\%$ compared omecamtiv mecarbil with placebo and showed a reduction in the primary outcome of HF-related events or cardiovascular death (HR 0.92 95% CI 0.86-0.99), with no impact on cardiovascular mortality or quality of life assessed with the Kansas questionnaire. Despite its modest effect in the total group, the finding of the differential impact according to LVEF, with a median cut-off $\leq 28\%$ generates an interesting hypothesis which should be tested in a subsequent clinical trial (73).

Digoxin

Digoxin, a sodium-potassium ATPase pump inhibitor (74) was evaluated in the DIG study in 6,800 patients with HF and LVEF <45%. The study showed no differences in mortality [34.8% vs. 35.1% (RR 0.99 95% CI 0.91-1.07,

$p=0.08$)], but there was a reduction in total hospitalization and hospitalization for decompensated HF [26.8% vs. 34.7% (RR 0.72 95% CI 0.66-0.79, $p=0.001$)]. An analysis of secondary outcomes showed that digoxin had the tendency to reduce deaths attributable to worsening HF [RR 0.88 (95% CI, 0.77-1.01, $p=0.06$)] (75). The prespecified subgroup analysis of high-risk patients (NYHA III-IV, LVEF < 25%, cardiothoracic ratio > 55%) after two years of follow up showed a reduction in the outcome of hospitalization and death from any cause (76).

A Cochrane review showed that digoxin does not reduce mortality from all causes nor from HF, but it does reduce HF symptoms and readmissions by 32% [OR 0.68 (95% CI 0.61-0.75, $p < 0.00001$)]. The benefits were greater in patients with greater LVEF impairment (<25%) or NYHA functional class III/IV. A subgroup analysis by serum digoxin concentrations showed that patients with levels between 0.5 and 0.8 ng/mL had a 20% reduction in deaths from all causes (HR 0.8 [95% CI 0.68-0.94, $p=0.005$]). There were more arrhythmia complications in patients with serum digoxin levels >1.2 ng/mL, especially in patients with kidney disease, who require close monitoring (77).

Diuretics

Their use is mainly based on small, controlled clinical trials in which they have proven to be well tolerated and to alleviate congestion, improving edemas and reducing body weight (78). Likewise, changes in neurohormonal parameters associated with congestion have been shown (63). Loop diuretics are preferred (furosemide, bumetanide, torsemide), although thiazides may be added in diuretic-resistant patients, as well as potassium-sparing diuretics (3, 25). The main adverse events associated with their use are fluid and electrolyte disorders and renal dysfunction (79); the long-term effect on outcomes is unclear (80).

Studies of other treatment options for managing congestion, such as arginine vasopressin antagonists, have shown no impact on clinical outcomes, although they do increase urine volume and decrease weight (81, 82).

Treatment of comorbidities and devices

Other types of therapies exist, including iron supplementation, management of atrial fibrillation, implantable automatic defibrillators, cardiac resynchronization, cardiac contractility modulation, mitral clips, CardioMEMS and ventricular assist devices which have proven beneficial in specific groups of patients, after optimizing what is considered to be standard treatment (83-129) (Annex 1).

Discussion

Given the current evidence, the papers published especially during the last year, the GPC recommended heart failure algorithm should be updated to introduce new therapies, considering the magnitude of the treatment benefit and that the effect could be considered to be separate from each of

the medication groups, supported by the studies' subgroup analyses.

The consistency of studies with ARNI place it as the treatment of choice, replacing ACE inhibitors/ARBs, and reserving these for a few cases, specifically patients who do not tolerate ARNI treatment due to hypotension. Likewise, the SGLT-2 inhibitors, together with the already positioned beta blockers and MRAs complement this first-line therapy. The results with other new medications such as vericiguat and omecamtiv mecarbil are modest and they should be reserved for only a few cases which are not stabilized using standard treatment. The risk of bias was considered to be low in all the items.

The fragility index analysis comparing the classical strategies with the new ones showed robust results for beta blockers, spironolactone and sacubitril/valsartan, and weak results for ACE inhibitors, ARBs, vericiguat and omecamtiv mecarbil, although it should be noted that this may be affected by factors such as the expected effect size, the number

of events and the study's power (130).

The proposal was designed as a decision circle with a central nucleus including what is considered to be the pillar of HF treatment (Figure 1), which is enlarged according to certain variables which may be considered or introduced into treatment, according to the clinical progress.

The central nucleus is organized hierarchically to highlight the fundamental pillars of treatment and provide a general recommendation for initiating and titrating doses according to monitoring and the patient's clinical progress, supported by the mentioned studies. The next orbit contains the interventions to be used after reaching the goals of the basic nucleus which contains four strategies, whose evidential strength is differentiated based on the support of designed clinical trials, the affected outcome and the variables to be considered for its use.

The suggestion is to begin in step one with ARNI (Figure 2); the only available one to date is the sacubitril/valsartan

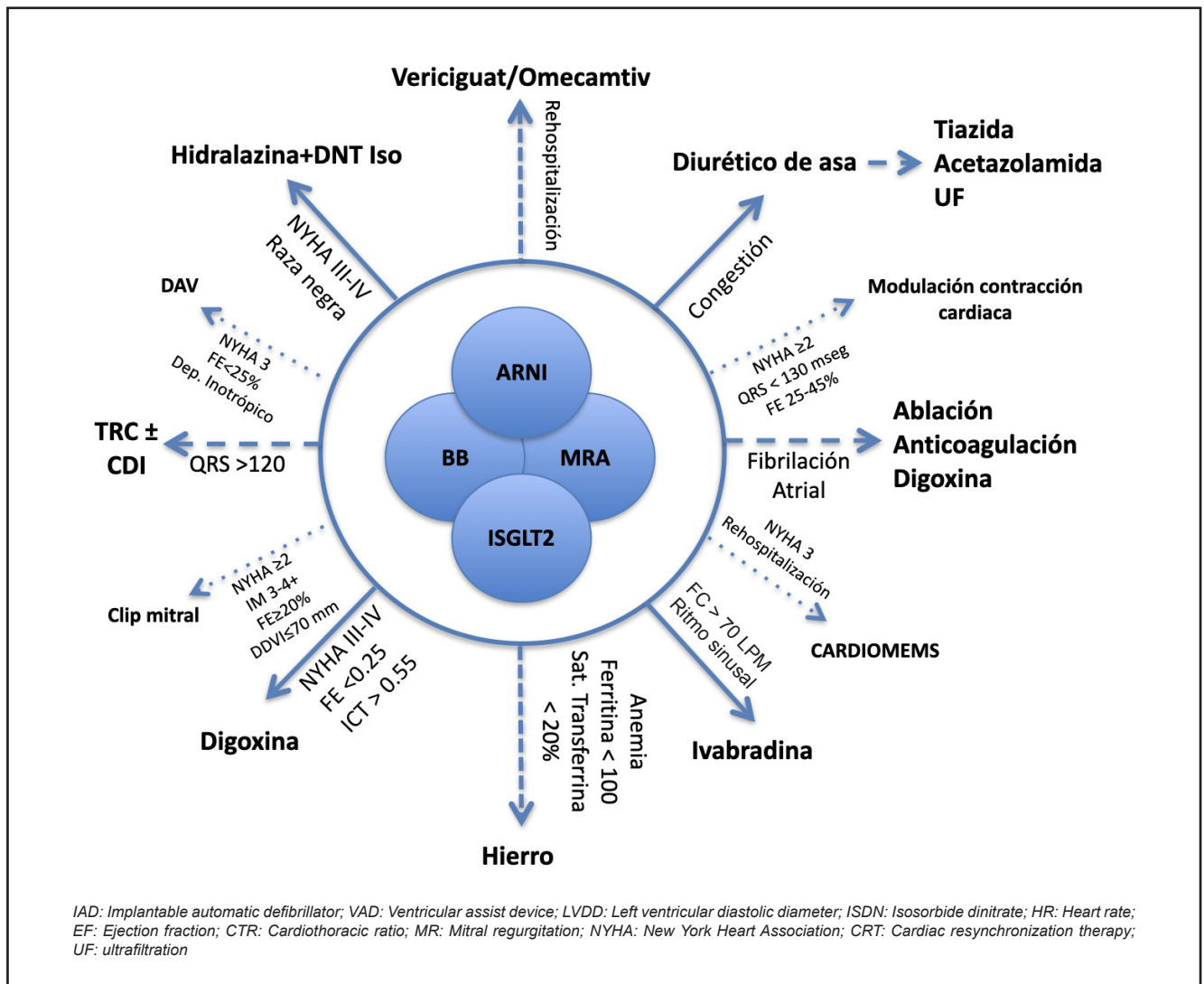


Figure 1. Decision circle for managing HF-rLVEF.

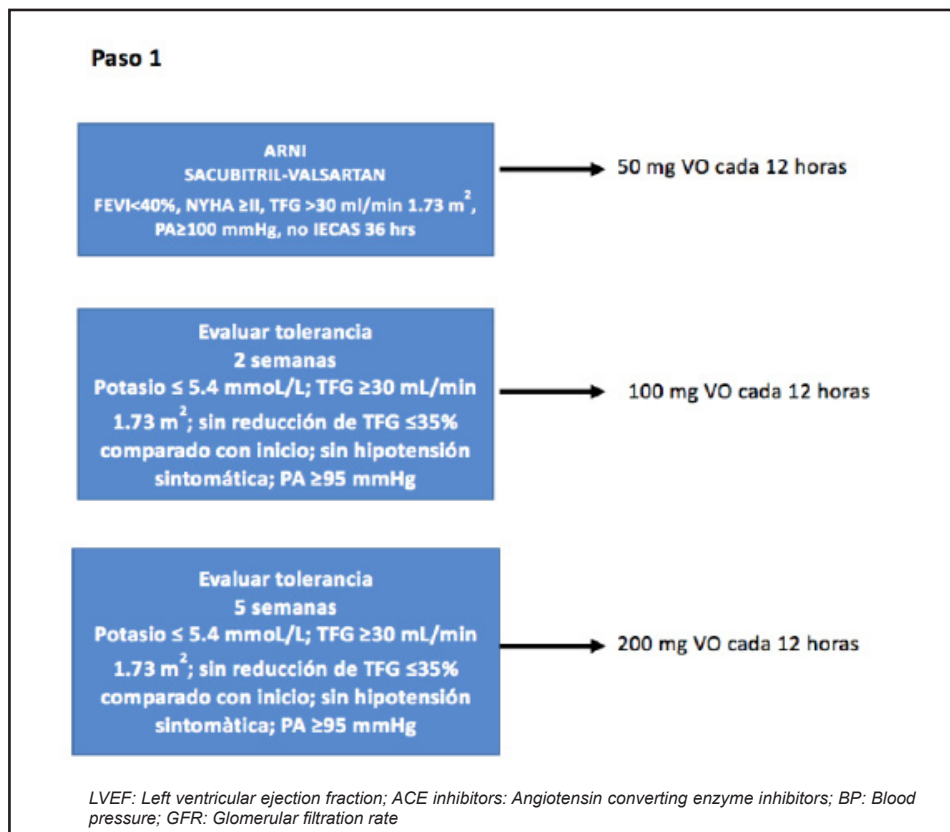


Figure 2. HF treatment. Step 1.

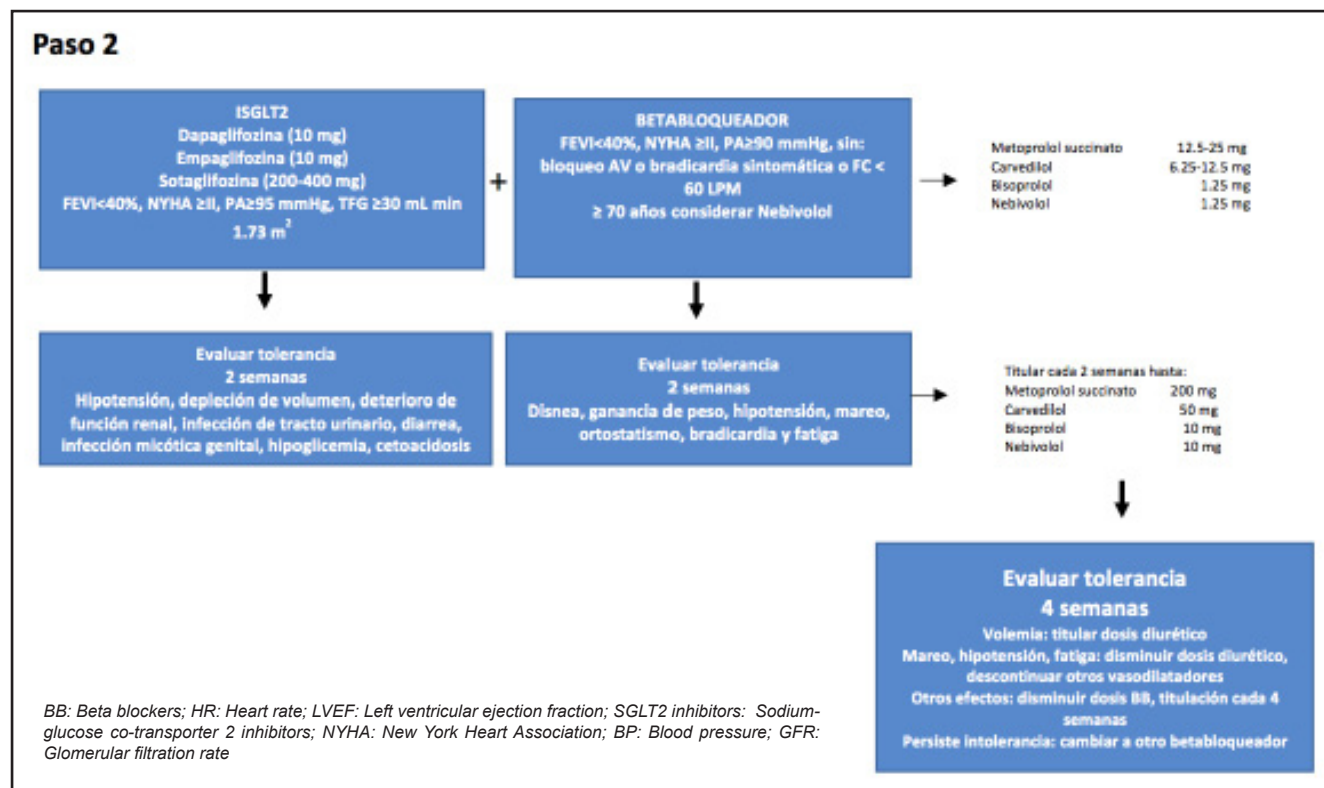


Figure 3. HF treatment. Step 2.

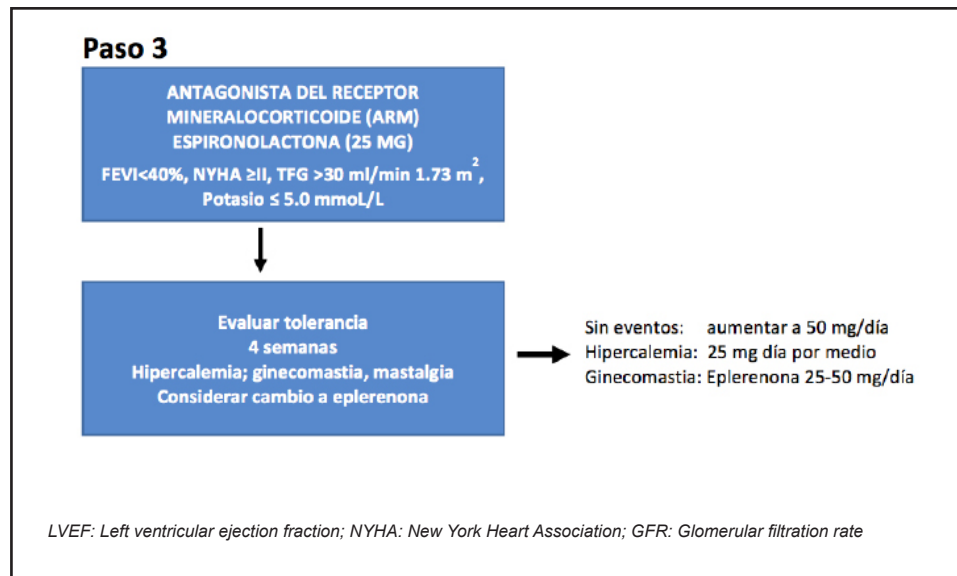


Figure 4. Heart failure treatment. Step 3

combination. In step 2, SGLT-2 inhibitors plus the beta blocker (Figure 3), and, finally, the MRA (Figure 4).

It is important to highlight that the algorithm is conceived in order to begin these treatments, considered to be pillars, early; and that the suggested titration may be modified according to the patient's clinical condition, although it is expected that the use of these recommendations will improve tolerance and adherence, in general, and that low doses of all the groups may be prescribed, to be subsequently increased according to the set sequence of steps (131).

Other therapies, such as cardiac rehabilitation, including an exercise program, vaccination and palliative care should be used concomitantly, ideally within a structured Heart Failure Clinic program. Patients who remain symptomatic despite the use of this strategy should be referred to a heart transplant group for assessment, especially if they are between 18 and 70 years old; have an NYHA functional status III or IV; a peak oxygen consumption (VO_2 max) ≤ 14 mL/kg/minute or, with beta blockers, ≤ 12 mL/kg/minute, in patients < 50 years old add VO_2 max $\leq 50\%$ of the expected (predicted) value and in a submaximal test (RER < 1.05) use the slope of the ventilatory equivalent of CO_2 > 35 on the cardiopulmonary stress test; and are classified as high risk according to the *Heart Failure Survival Score* or have < 80% expected one-year survival on the *Seattle Heart Failure Model* scale (132).

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Anexo

Tratamiento de comorbilidades

Suplementación de hierro

La deficiencia de hierro está estrechamente relacionada con la gravedad de la FC y se asocia a un mayor riesgo de muerte, independientemente de la presencia de anemia (83), peor clase funcional, pobre capacidad máxima al esfuerzo y peor calidad de vida (84, 85). La deficiencia de hierro afecta al 50% de los pacientes con FC (86).

La administración intravenosa de hierro se ha estudiado específicamente en dos estudios aleatorizados (FAIR-HF y CONFIRM-HF) (87, 88) en pacientes con FC y déficit de hierro demostraron que el hierro carboximaltosa intravenoso mejora el estado general de los pacientes, la calidad de vida y la clase funcional de la NYHA. Como objetivo secundario, se observó una reducción significativa de la hospitalización por empeoramiento de la FC. El reciente ensayo AFFIRM AHF en 1132 pacientes con hospitalización por FC aguda y asociada a deficiencia de hierro, demostró impacto sobre el desenlace combinado de hospitalizaciones totales por FC y muerte de origen cardiovascular, aunque casi exclusivamente a expensas de la reducción en las hospitalizaciones (57.2 pacientes/año vs 72.5 pacientes/año) (89, 90).

Fibrilación auricular

Se reporta una prevalencia de FA del 4.2% en pacientes NYHA I y hasta el 49.8% en pacientes NYHA IV (91). El desarrollo de FA en esta población se asocia a un peor pronóstico, asociándose con un aumento significativo de la mortalidad global (OR 1.4, IC 1.32-1.48) (92); en todos los pacientes con disfunción ventricular y FA está indicada la anticoagulación dado que la presencia de FC confiere un aumento de 1.7-2.6 veces en el riesgo fenómenos embólicos (93). Para el control de la respuesta ventricular se pueden emplear betabloqueadores, digoxina y como último recurso amiodarona. Los calcioantagonistas no dihidropiridínicos están contraindicados. A pesar de que no ha sido estudiado específicamente, en estos pacientes se propone una meta de frecuencia cardíaca entre < 100-110 latidos por minuto (94).

Aunque ciertos betabloqueadores tienen claro beneficio sobre la mortalidad en FC-FEVIr, el beneficio de esta terapia parece atenuarse en los pacientes que de manera concomitante presentan FA. Así, estudios muestran que los betabloqueadores disminuyen la mortalidad del paciente en ritmo sinusal (HR 0.73, IC 0.67-0.8) pero no en ritmo de FA (0.97, IC 0.83-1.14). A pesar de esto, los betabloqueadores son seguros y algunos estudios sugieren que podría haber un efecto benéfico por lo que se recomienda su uso (95); como alternativa puede utilizarse la digoxina con menores

efectos secundarios de acuerdo con los resultados del ensayo RATE-AF (32).

El aislamiento eléctrico de venas pulmonares es una alternativa atractiva; el estudio CASTLE-AF encontró que los pacientes con FEVI < 35% y FA con pobre respuesta al tratamiento que se asignaron a ablación por catéter tuvieron una disminución en el desenlace combinado de muerte u hospitalización por FC al compararse con la terapia estándar (HR 0.62, IC 0.43-0.87) (96); sin embargo, el efecto solo pudo ser manifiesto después de dos años de seguimiento. Estudios adicionales en esta área son necesarios para definir el papel definitivo de esta terapia.

Tratamiento con dispositivos

Desfibrilador automático implantable (DAI)

La causa de muerte en el paciente con FC varía según la clase funcional (97). En NYHA II, 64% de las muertes son de origen súbito y 12% por progresión de la FC; mientras que la mayoría de las muertes en NYHA IV son secundarias a progresión de la enfermedad (56%). Así, la mayoría de los estudios evaluando el papel del DAI han incluido pacientes sintomáticos NYHA II/III. En NYHA IV se desaconseja el uso de esta terapia (recomendación clase III) dado que esta población fue excluida de la mayoría de los estudios y que su pronóstico es pobre sin trasplante cardíaco (98).

El uso del DAI está recomendado para prevención primaria en pacientes con FEVI <35% luego de tres meses de tratamiento cuando se tiene una expectativa de vida superior a un año. El MADIT I fue el primer estudio en evaluar esta intervención. En éste, pacientes con cardiopatía isquémica, FEVI <35% y episodios de taquicardia ventricular no sostenida, tuvieron una reducción en la mortalidad con el uso de DAI (HR 0.46; IC 0.26-0.82) (99). En el MADIT II, los pacientes con cardiopatía isquémica y FEVI <30% que fueron asignados a DAI, tuvieron una menor mortalidad global a dos años (14.2% vs 19.8%; HR 0.69, IC 0.51-0.93) (100).

El uso de DAI en cardiopatía no isquémica tiene una evidencia menos sólida, aunque hay estudios que avalan su uso (101). El 50% de la población incluida en el SCD-HeFT tenía una cardiopatía no isquémica. En este ensayo, pacientes con FEVI <35% y clase funcional NYHA II/III se asignaron a placebo, amiodarona o DAI. El uso de DAI se asoció a una reducción en el riesgo de muerte (HR 0.77, IC 0.62-0.96) sin haber diferencias en el subanálisis según la etiología de la FC.

Por otro lado, el estudio DANISH incluyó paciente específicamente de origen no isquémico. Aunque en el

estudio, hubo diferencias en el desenlace secundario de muerte súbita (HR 0.5, IC 0.31-0.82), no hubo diferencias en el desenlace primario de mortalidad (HR 0.87, IC 0.68-1.12) (102).

Terapia de resincronización cardíaca (TRC)

La disincronía ventricular es un hallazgo frecuente en los pacientes con FC. Aunque existen diferentes maneras para estimar la misma, la duración del QRS sigue siendo el método más adecuado. Un QRS prolongado (>120 milisegundos) es un hallazgo frecuente en el paciente con FC (28% de los casos) (103). La TRC busca mejorar la disincronía electromecánica mediante la estimulación biventricular e impacta de manera favorable la FEVI, el remodelamiento cardíaco, el grado de insuficiencia mitral y los niveles de NTproBNP (104). Además, algunos estudios han demostrado beneficio en desenlaces de mortalidad y hospitalización por FC (104-106).

La FEVI, la duración del QRS, la morfología del bloqueo de rama y la clase funcional son los parámetros empleados para definir la necesidad de TRC. El COMPANION, evaluó la utilidad de la TRC en pacientes NYHA III/IV, con FEVI <35% y QRS >120 milisegundos. Este estudio comparó de manera aleatoria los grupos de manejo farmacológico, TRC, o TRC con DAI. El uso de TRC disminuyó de manera significativa el desenlace combinado de muerte y hospitalización (HR 0.81; IC 0.69-0.96). En el análisis por subgrupos, no hubo beneficio de la intervención en presencia de bloqueos diferentes a rama izquierda (105).

El estudio MADIT-CRT incluyó pacientes con FEVI <30%, QRS >130 milisegundos y una clase funcional NYHA I/II. Los pacientes se asignaron a TRC con DAI vs DAI de manera aislada. El ensayo encontró que los pacientes asignados a TRC con DAI tenían un menor desenlace combinado de muerte o eventos asociados a FC (17.2% vs 25.3%, HR 0.66; IC 0.52-0.84). En el análisis por subgrupos se encontró que las personas con QRS <150 milisegundos no tenían un beneficio de la intervención (HR 1.06, IC 0.74-1.52) (106).

Modulación de la contractilidad cardíaca

La modulación de la contractilidad cardíaca consiste en la estimulación eléctrica con señal bifásica, de alto voltaje y larga duración de la pared septal del ventrículo derecho durante el periodo refractario absoluto; la señal no produce una nueva contracción, sino que influencia la biología del miocardio en falla. Esto resulta en un incremento de la contractilidad cardíaca sin aumentar el consumo de oxígeno y genera remodelado reverso. Después de completar con éxito un estudio doble ciego y doble cruzado en Europa (FIX-HF-4) (107) y un estudio piloto en los Estados Unidos (108) se diseñó el estudio FIX-HF-5 para estudiar prospec-

tivamente la seguridad y eficacia de la modulación de la contractilidad cardíaca en pacientes con FC con síntomas NYHA III o IV y FEVI <35% (109). Se incluyeron 428 pacientes, alcanzando el desenlace primario de seguridad (una evaluación de no inferioridad de la combinación de mortalidad por todas las causas y hospitalizaciones por todas las causas). Sin embargo, el desenlace primario de eficacia, que consistía en un análisis de los respondedores de los cambios en el umbral anaeróbico ventilatorio en las pruebas de esfuerzo cardiopulmonar, no se cumplió. Un análisis de subgrupos preespecificado mostró efectos significativos del tratamiento en los desenlaces primarios y secundarios (incluido el VO₂ pico y el cuestionario Minnesota Living With Heart Failure Questionnaire) en pacientes con FEVI que oscilaban entre el 25% y el 45% (110). Con base en estos hallazgos se diseñó el estudio confirmatorio FIX-HF-5C (111), con el fin de confirmar prospectivamente la eficacia de la modulación de contractilidad cardíaca en pacientes con FEVI 25%-45%, encontrando mejoría en la tolerancia al ejercicio y la calidad de vida en el grupo especificado de pacientes con FC, y menores hospitalizaciones por FC.

Clip mitral

Se sabe que en los pacientes con FC e insuficiencia mitral secundaria hasta el 62% habrán muerto a cinco años (112-114). En este escenario surge, como una modificación a la técnica ideada por Alfieri en 1991, el reparo borde a borde por método percutáneo, más conocido como MitraClip®, con el objetivo de obtener las presuntas ventajas de la reducción de la insuficiencia mitral funcional, mediante un método menos invasivo como es la implantación con catéter percutáneo.

Los estudios clínicos en este escenario han sido contradictorios así en el estudio MITRA-FR (115) en pacientes con FEVI 15-40% y NYHA ≥II a pesar de tratamiento óptimo con insuficiencia mitral secundaria con volumen regurgitante ≥30 cc u orificio regurgitante ≥20 mm², los cuales no fuesen candidatos quirúrgicos no se logró demostrar la superioridad del MitraClip® aunado al manejo médico frente al manejo médico exclusivo en disminución de hospitalización por FC o muerte cardiovascular; en contraposición, en el estudio COAPT (116) pacientes con FEVI 20-50% y NYHA ≥II a pesar de tratamiento óptimo con insuficiencia mitral secundaria clasificada como 3+ o 4+, los cuales no fuesen candidatos quirúrgicos se demostró la superioridad del MitraClip® aunado al manejo médico frente al manejo médico exclusivo en disminución de hospitalización por FC (HR 0.53 IC 0.40- 0.70) o muerte (HR 0.62 IC 0.46-0.82).

Estos hallazgos generaron el concepto de regurgitación mitral proporcionada y desproporcionada, en el cual se

plantea que existen pacientes cuya regurgitación mitral secundaria es proporcional al grado de dilatación ventricular por lo que en teoría responderían a terapias para reducir el volumen de fin de diástole ventricular izquierdo, en contraposición a otro grupo cuya severidad de la regurgitación es desproporcionada con respecto al volumen ventricular, por lo que se beneficiarían de intervenciones dirigidas a la válvula mitral (117-118); la propuesta es bastante seductora y ha sido aceptada hasta ahora, aunque sigue generando controversia (119), por lo que es importante estar atentos a nueva evidencia.

Por lo anteriormente expuesto, se puede considerar que en aquellos pacientes con FEVI 20-50% con un diámetro de fin de diástole del ventrículo izquierdo ≤ 70 mm con presión arterial pulmonar ≤ 70 mmHg, que persistan en NYHA $\geq$ II a pesar de tratamiento óptimo y que tengan regurgitación mitral secundaria severa, el uso de MitraClip® estaría indicado (120).

CardioMEMS

La vigilancia remota de las variables hemodinámicas es un campo actual de investigación, de especial interés entre los pacientes con síntomas graves o FC avanzada. De forma convencional los DAI y TRC proporcionan información y alertas remotas que conducen a ajustes en el tratamiento del paciente. El dispositivo CardioMEMS, mide variables hemodinámicas en la arteria pulmonar y envía información de manera remota, su uso en pacientes con FC clase funcional NYHA III, se asoció con una reducción en el riesgo de hospitalizaciones por FC (HR 0.72 IC95% 0.59-0.88), con una presentación de complicaciones que no superaba el 1%, resultados reproducidos en el estudio MEMES HF (121), que se mantienen a un año de seguimiento (122). A pesar de tener aprobación por entidades regulatorias, las recomendaciones de las

sociedades científicas son débiles dada la incertidumbre generada por el diseño de los estudios mencionados y por su costo-efectividad (123, 124).

Asistencia ventricular

El estudio clásico fue el REMATCH publicado en 2001 incluyó pacientes con FC avanzada con contraindicación para trasplante, el cual demostró reducción de mortalidad comparado con placebo (RR 0.52 IC 95% 0.34-0.78) (125). Los desarrollos posteriores se centraron en mejorar el tamaño, la biocompatibilidad, durabilidad y disminuir la tasa de infecciones, pasando por dispositivos de segunda generación como el Heart Mate II, hasta llegar a los actuales, de tercera generación, con flujo continuo generado por bombas centrífugas como el Heart Ware y el Heart Mate III.

El ADVANCE trial con el dispositivo Heart Ware demostró supervivencia de 86% al año de seguimiento (126); posteriormente el ENDURANCE Trial demostró no inferioridad comparado con otros dispositivos de asistencia ventricular, con menor tasa de disfunción o falla del dispositivo, pero con aumento de la tasa de eventos cerebrovasculares y similar ganancia en calidad de vida (127). Finalmente, el MOMENTUM 3 Trial con el dispositivo Heart Mate 3 demostró superioridad con respecto a los dispositivos convencionales en cuanto a supervivencia y libre de enfermedad cerebrovascular o necesidad de reemplazo o remoción por disfunción a los dos años de seguimiento (RR 0.84 IC 95% 0.78-0.91) (128).

Por lo anterior el soporte mecánico circulatorio a largo plazo debe ser considerado en pacientes con estado funcional NYHA III-IV a pesar de manejo médico óptimo, con FEVI $\leq 25\%$ y al menos otro criterio como: clasificación INTERMACS 2-4, dependencia de inotrópicos, disfunción de órgano progresiva, VO_2 pico < 12 ml/Kg/minuto o dependencia de soporte mecánico temporal (129).

