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REVIEW

Emerging concepts in heart failure management and treatment: focus on current guideline-directed medical therapy for heart failure with reduced ejection fraction

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Abstract

One of the most relevant and differentiating aspects provided by the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure is the retraction of the historical stepped and vertical pharmacological treatment scheme for heart failure with reduced ejection fraction (HFrEF). Subsequently, it was replaced by an updated algorithm that places four therapeutic families in the same initial horizontal step with an equally high degree of recommendation (class I). In this context, these four pillars, which have demonstrated a significant reduction in mortality and hospitalizations in patients with HFrEF, include (1) angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB)/angiotensin II receptor-neprilysin inhibitors (ARNi), (2) beta blockers, (3) mineralocorticoid receptor antagonists (MRA) and (4) sodium–glucose cotransporter 2 inhibitors (SGLT2is) as the main novelty. This manuscript reviews the current therapeutic algorithm with a special focus on the therapeutic value of adding an MRA (still underused in both clinical trials and real world), changing an ACEi/ARB for an ARNi and incorporating an SGLT2i in patients with HFrEF.

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Keywords: angiotensin II receptor-neprilysin inhibitor, ARNi, dapagliflozin, empagliflozin, heart failure, mineralocorticoid receptor antagonists, MRA, sacubitril/valsartan, sodium–glucose cotransporter type 2 inhibitors, SGLT2i, sodium–glucose cotransporter 2 inhibitors.

Citation

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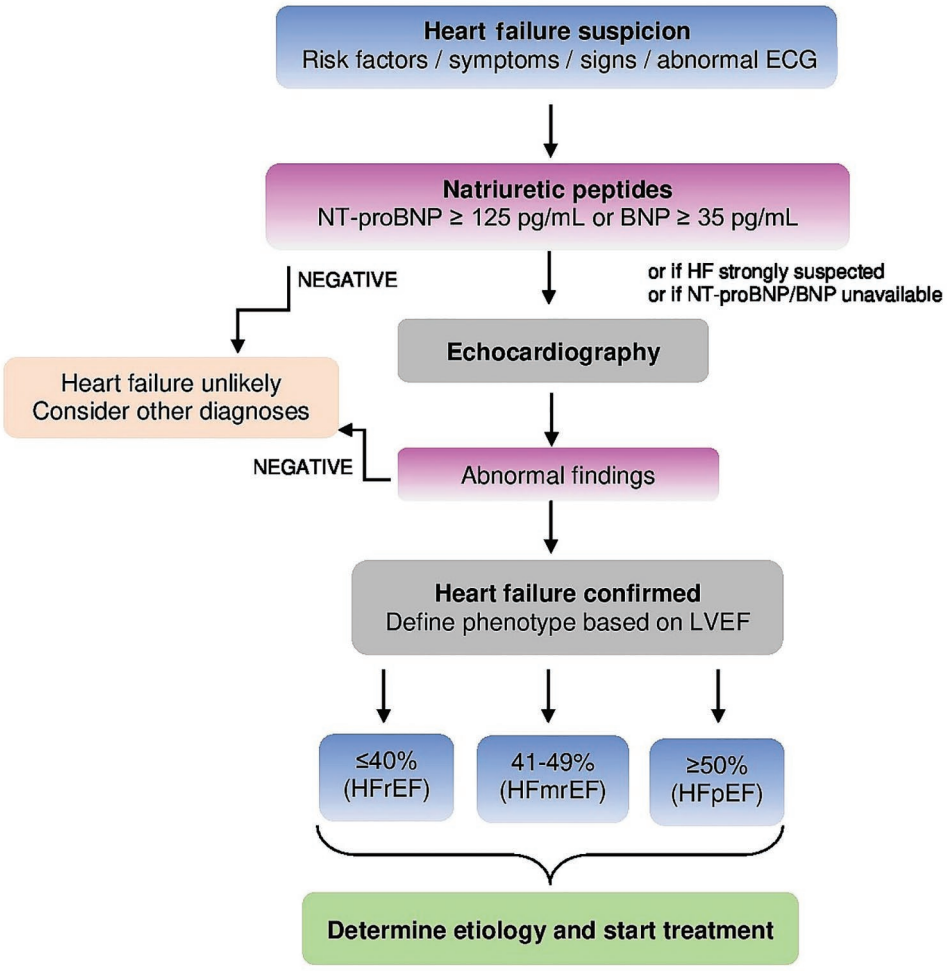
Introduction

In 2021, an update of the European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure was published, replacing the previous version dated 2016.[1,2] This revision introduced the adoption of the universal definition of heart failure (HF), a new phenotypic categorization of HF based on the left ventricular ejection fraction (LVEF) value, the consolidation of natriuretic peptide (NP) levels in its diagnostic algorithm and the implementation of a horizontal therapeutic scheme based on four different medicinal families, all of which have a class I recommendation. HF was thus defined as "*a clinical syndrome consisting of cardinal symptoms such as dyspnoea and fatigue, which may be accompanied by signs such as increased jugular venous pressure, pulmonary crackles and peripheral oedema; it is usually due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise*".[1]

HF with reduced ejection fraction (HFrEF) is considered in symptomatic patients with an LVEF ≤40%, values between 41% and 49% are reserved for HF with mildly reduced ejection fraction (HFmrEF), and values ≥50% are classified as HF with preserved ejection fraction (HFpEF).[1] Another important change lies in the need to determine plasma levels of NP as a previous step to echocardiography (keeping previous cut-off values) in order to rule out the presence of HF (Figure 1).

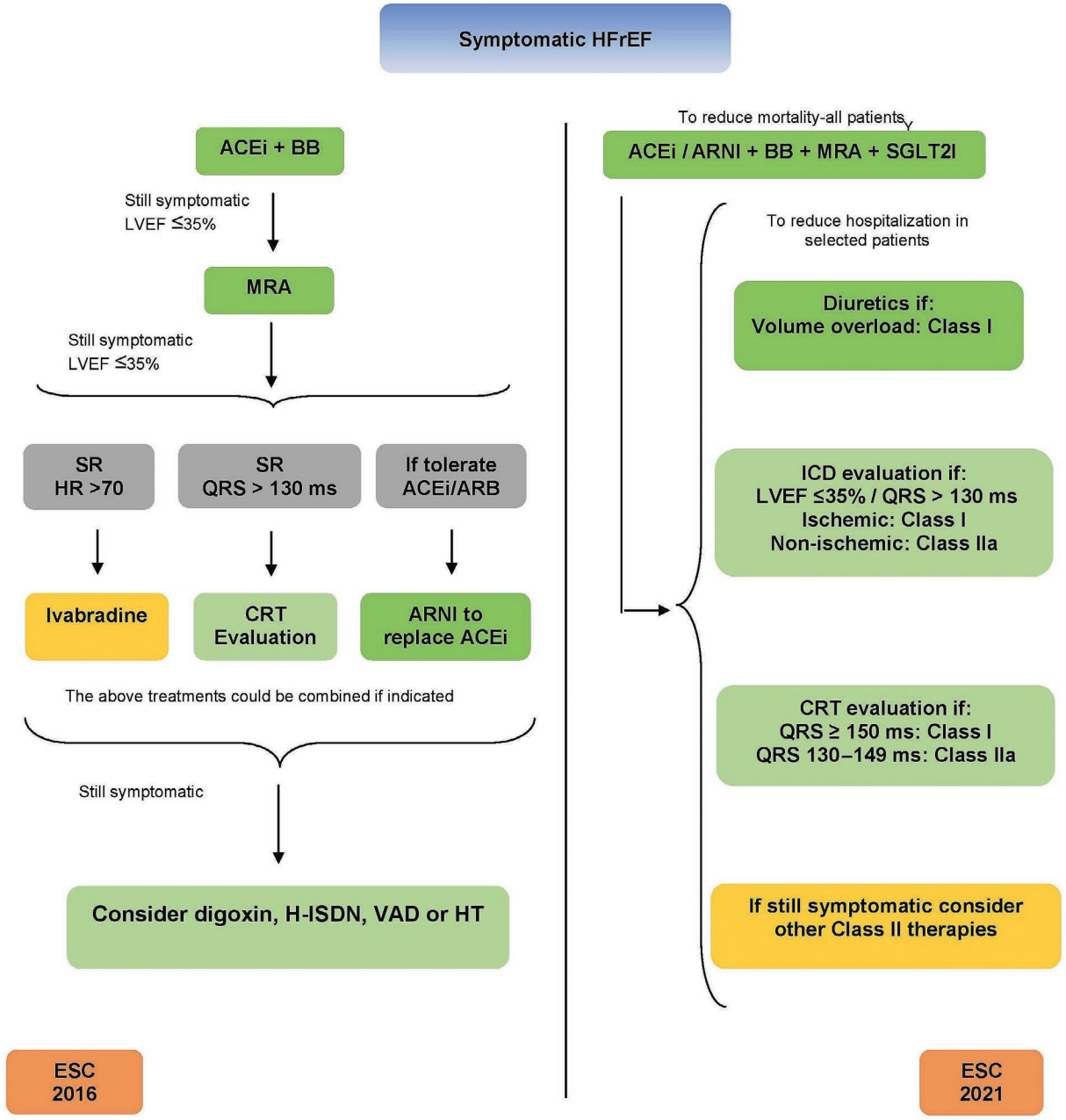
However, the most differentiating aspect of this guideline is the profound modification of the therapeutic algorithm of HFrEF (Figure 2).[1] This change was based on the fact that the previous vertical 'step-by-step' scheme is replaced by a horizontal and quickly simultaneous therapeutic format consisting of four families of agents.[1,2] In this scenario, the optimal current guideline-directed medical therapy (GDMT) to reduce mortality and morbidity in patients with HFrEF is composed of (1) an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNi), (2) beta blockers (BBs), (3) a mineralocorticoid receptor antagonist (MRA) and (4) a sodium–glucose cotransporter 2 inhibitor (SGLT2i).[1] Indeed, the introduction of the SGLT2i family in this therapeutic scheme represents an important novelty because these agents were originally developed as hypoglycaemic agents for the treatment of type 2 diabetes mellitus (T2DM) based on their potent glycosuric effects.[3] However, and subsequently, their benefits were also demonstrated in the entire clinical spectrum of HF (reduction of morbidity and mortality) based on a multiplicity of biological effects (e.g. cardiac, renal, vascular).[4,5] This was evidenced in the DAPA-HF and EMPEROR-Reduced studies in the case of HFrEF[6,7] and in the EMPEROR-Preserved

Figure 1. ESC diagnostic algorithm for heart failure.



BNP, B-type natriuretic peptide; ECG, electrocardiogram; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide.
Adapted from ESC guidelines 2021.[1]

Figure 2. ESC therapeutic algorithms evolution for HFrEF (2016 *versus* 2021).



ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker, ARNI, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; H-ISDN, hydralazine and isosorbide dinitrate; HR, heart rate; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist, SGLT2I, sodium-glucose cotransporter 2 inhibitor.
Adapted from ESC guidelines.[1,2]

study in the case of HFpEF[8] although it should be noted that this study considered an LVEF >40% as preserved.

The adoption of ACEi/ARBs and BBs in the treatment of HF is widespread, universal and beyond any doubt.[1] However, as is explained later, evidence of the use of an MRA in both clinical studies and the real world remains limited even with more than 20 years of favourable studies (Randomized Aldactone Evaluation Study (RALES) study, 1999)[9]. Supporting evidence for the use of sacubitril/valsartan (S/V; which is the only ARNi available) is more recent (PARADIGM-HF, 2014)[10] and its inclusion in contemporary clinical studies remains minimal. Finally, the use of SGLT2i is very recent (DAPA-HF, 2019; EMPEROR-

Reduced, 2020)[6,7] to allow assessment. Therefore, this review aims to assess this current therapeutic algorithm with a special focus on the therapeutic value of adding an MRA, changing an ACEi/ARB for an ARNi and incorporating an SGLT2i as GDMT for patients with HFrEF in a four-pillar scheme (including BBs), which was reasonably called 'The Fantastic 4'.[11]

Review

Mineralocorticoid antagonists

The positive performance of incorporating an MRA in the treatment of HFrEF has been documented in several placebo-controlled randomized studies, including the RALES trial,[9] the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[12] and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)[13] (Table 1).

In the RALES trial (1999), a low dose of spironolactone (25 mg/daily) promoted a significant relative risk reduction (RRR) of both death from all causes (RRR 30%) and cardiac death (RRR 31%) in patients with HF (New York Heart Association [NYHA] functional class III–IV) with an LVEF ≤35%. In addition, there was a significant reduction in heart failure hospitalizations (HFH) (RRR 35%) and in hospitalizations for any cardiac cause (RRR 30%).[9] The EPHESUS trial (2003) showed that the addition of eplerenone (25 mg daily titrated to 50 mg) in patients with HF (LVEF ≤40%) as a consequence of an acute myocardial infarction (3–14 days after) was able to decrease the risk of death from any cause (RRR 15%) and the risk

Table 1. Mineralocorticoid receptor antagonists in clinical trials of heart failure with reduced ejection fraction.

Item	RALES (*n*=1663)	EPHESUS (*n*=6632)	EMPHASIS (*n*=2737)
Study medication	Spironolactone	Eplerenone	Eplerenone
Mean follow-up (months)	24	16	21
Demography			
Mean age (years)	65	64	68
Men (%)	73	72	78
NYHA II/III/IV (%)	0.5/72/27	–	100/0/0
Mean LVEF	25	33	26
ACEi/ARB (%)	95	86	94
Beta blockers (%)	11	75	87
Diuretics (%)	100	60	85
Endpoints			
All-cause death, HR (95% CI)	0.70 (0.60–0.82)	0.85 (0.75–0.96)	0.78 (0.64–0.95)
All-cause hospitalization, HR (95% CI)		0.95 (0.89–1.02)	0.78 (0.69–0.89)
HF hospitalization, HR (95% CI)	0.65 (0.54–0.77)	0.85 (0.74–0.99)	0.61 (0.50–0.75)
Relative risk reduction			
Cardiovascular mortality/HFH, %			37
All-cause mortality, %	30	15	24
Cardiovascular mortality, %	31	17	
Sudden cardiac death, %	29	21	
HFH, %	35	23	42
Safety			
Hyperkalaemia, %	2	1.6	8
Gynaecomastia or breast pain, %	10	0.5	0.7

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HFH, heart failure hospitalization; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.
Table adapted from RALES, EPHESUS and EMPHASIS trials.[9,12,13]

of cardiovascular (CV)-related death or HFH (RRR 13%).[12] Finally, in EMPHASIS-HF (2011), eplerenone (25 mg daily titrated to 50 mg) also reduced (RRR 37%) the primary combined endpoint of death from CV causes and HFH in patients with mild HFrEF (NYHA functional class II) and LVEF ≤35%.[13]

In this context and despite having a level of evidence 1A based on the previously mentioned randomized placebo-controlled studies,[1] the presence of MRAs in both contemporary clinical trials and, especially, in real-world settings is still strikingly less in comparison with other agents with the same level of evidence (ACEi/ARBs or BBs). For example, in clinical trials, MRAs were present in only 54.2% of patients in PARADIGM-HF (S/V arm),[10] 71.5% in DAPA-HF (dapagliflozin arm)[6] and 70.1% in the EMPEROR-Reduced (empagliflozin arm).[7] In real-world settings, MRA utilization is much lower – such as in the Italian ARNO observatory study (n=41,413) conducted from January 2008 to December 2012, in which 65.8%, 52.3% and 42.1% of patients were prescribed ACEi/ARB, BB and MRA, respectively, at HFH discharge.[14] In the prospective ESC-HF Long-Term Registry (observational study) conducted from May 2011 to April 2013, a total of 12,440 patients (40.5% with acute HF and 59.5% with chronic HF) were included. Focusing only on HFrEF outpatients (n=4792), 67% of patients were being treated with an MRA whilst 92% and 93% received an ACEi/ARB or BB, respectively.[15] In a newly available meta-analysis (2022) of real-world HF guideline implementation, the percentage of MRA utilization was found to be considerably lower. Based on 11 studies (since January 2010) including 45,866 patients, MRA use was 47% (95% CI 42–53) whilst ACEi/ARB and BB use was 81% (95% CI 74–86) and 78% (95% CI 70–84), respectively.[16]

This clinical underutilization of MRAs has several underlying reasons, mainly including renal dysfunction, hypotension and hyperkalaemia[17,18]; fortunately, the concomitant use of SGLT2i could improve this safety profile by particularly reducing the risk of hyperkalaemia. In the DAPA-HF study, a total of 3370 individuals (70.1%) were receiving an MRA and, in this setting, mild hyperkalaemia (>5.5 mmol/L) occurred in 182 (11.1%) patients receiving dapagliflozin and in 204 (12.6%) receiving placebo (HR 0.86, 95% CI 0.70–1.05). Concerning moderate/severe hyperkalaemia (>6.0 mmol/L), this was observed in 23 (1.4%) patients in the dapagliflozin arm and 40 (2.4%) given placebo (HR 0.50, 95% CI 0.29–0.85).[19] In the case of EMPEROR-Reduced, 2661 (71%) patients were using an MRA at baseline and mild hyperkalaemia (>5.5 mmol/L) occurred in 164 (9.4%) individuals receiving empagliflozin and in 179 (10.2%) receiving placebo (HR 0.89, 95% CI 0.72–1.09) whereas moderate/severe hyperkalaemia (>6.0 mmol/L) occurred in 42 (2.3%) patients in the empagliflozin arm and in 57 (3.1%) in the placebo arm (HR 0.70, 95% CI 0.47–1.04).[20] Therefore, considering these data, the concomitant use of an SGLT2i could favour greater use of an MRA.

Angiotensin receptor–neprilysin inhibitors

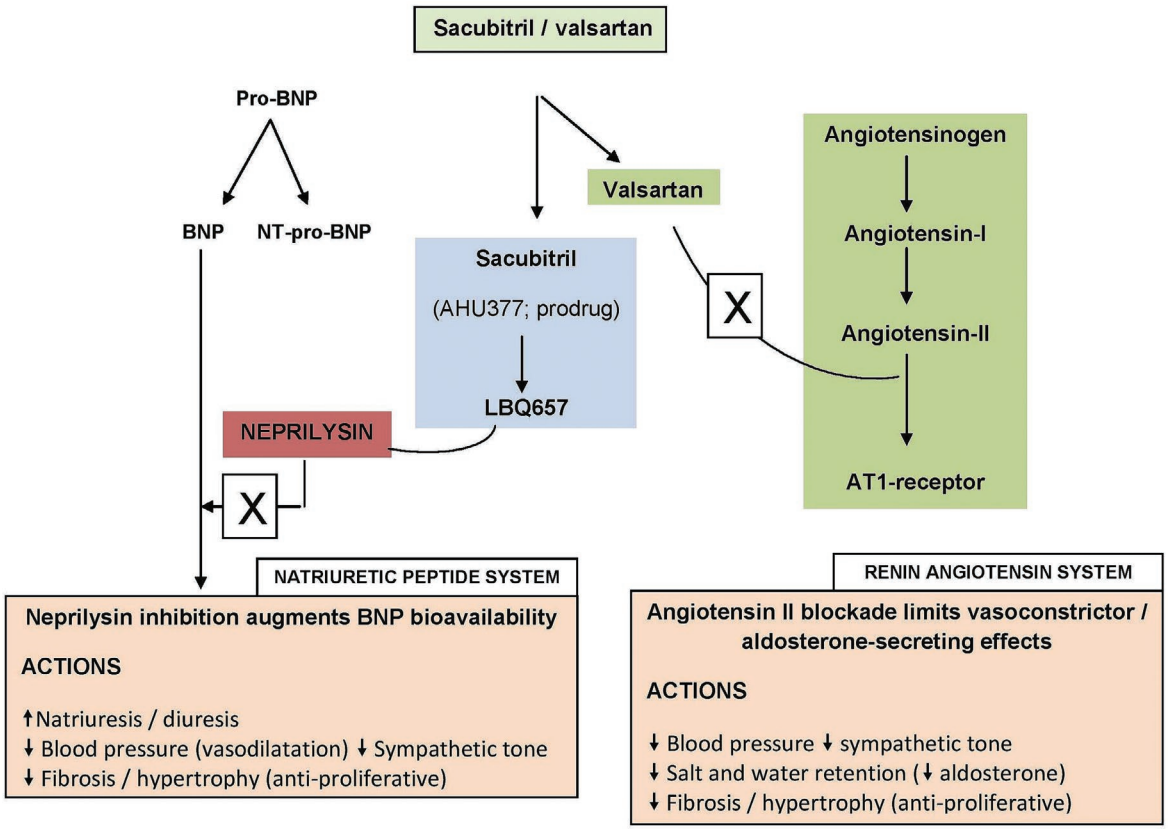
Neprilysin is a neutral endopeptidase that metabolizes different endogenous vasoactive peptides such as NP, bradykinin and adrenomedullin. Neprilysin suppression results in increased availability of NP with the consequent enhancement of its biological actions, such as vasodilation, natriuresis, diuresis, and antifibrotic and remodelling effects, that counteract the negative neurohormonal overactivation of progressive HF (vasoconstriction, sodium retention and maladaptive remodelling) (Figure 3).[21–23]

S/V, which is the combination of a neprilysin inhibitor (sacubitril) and an angiotensin receptor (valsartan),[24] was evaluated (against enalapril) in the PARADIGM-HF trial.[10] In this large double-blind trial, 8442 patients with HFrEF (LVEF ≤40% and mostly NYHA functional class II) were randomized to receive S/V (at a dose of 200 mg twice daily; equivalent 97/103 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy (Table 2). At the time of trial completion (median follow-up of 27 months), the primary outcome (composite of death from CV causes or HFH) was 21.8% in the S/V arm and 26.5% in the enalapril group (p<0.001) and the benefit was steady in all studied subgroups. In comparison with enalapril, S/V also reduced the risk of death from any cause by 16% (p<0.001), the risk of HFH by 21% (p<0.001) and overall mortality (p<0.001)[13] (Table 3). Regarding the safety profile, symptomatic hypotension was more frequent in the S/V arm but, surprisingly, more patients from the enalapril arm ceased study medication due to adverse effects.[10]

Considering the overwhelming results of the PARADIGM-HF trial, S/V was approved for its administration in symptomatic patients with HFrEF and, subsequently, several studies have been published in recent years consolidating its place in therapy.

In the open-label PROVE-HF study, a fall in the levels of N-terminal-prohormone BNP (NT-proBNP) induced by S/V (previously found in PARADIGM-HF) was found accompanied by positive effects on cardiac remodelling in patients with HFrEF (n=794).[25] At 1 year, there was a positive link between changes in the log2-NT-proBNP concentration and numerous echocardiographic measures of cardiac remodelling (p<0.001 for all changes). In this setting, median NT-proBNP levels dropped from 816 to 455 pg/mL whilst LVEF increased by an average of 9.4%. In addition, LV end-systolic volume (LVESV) index, LV end-diastolic volume (LVEDV) index, left atrial volume (LAV) index and the ratio of early diastolic filling/early

Figure 3. Sacubitril/valsartan mode of action.



Sacubitril/valsartan lead to a simultaneous neprylisin inhibition (LBQ657) and AT1 receptor blockade (valsartan) Neprylisin substrates may have biological opposing actions so the benefits of increasing the natriuretic peptides system may be lost by increasing Angiotension-II, so a simultaneous suppression of the RAAS is necessary. Figure only shows effects on BNP but other metabolites are affected.[23,24]

AT1-receptor, Angiotensin II receptor type 1; BNP, brain type natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; Pro-BNP, pro-brain natriuretic peptide; RAAS, renin–angiotensin–aldosterone system.

diastolic annular velocity were reduced by 15.3%, 12.3%, 7.6% and 1.3%, respectively.[25]

The PRIME-HF study revealed that S/V was more efficient (than valsartan) in reducing chronic functional mitral regurgitation in patients with HFrEF (n=118). The primary outcome was a change in the effective regurgitant orifice area of functional mitral regurgitation at 12 months whilst changes in regurgitant volume, LVESV, LVEDV and incomplete mitral leaflet closure were considered secondary endpoints. The reduction in effective regurgitant orifice area was significantly more important in the S/V group in relation to valsartan (-0.058±0.095 *versus* -0.018±0.105 cm^2; p=0.032) and regurgitant volume was also significantly diminished in the S/V group (mean difference -7.3 mL, 95% CI -12.6 to -1.9; p=0.009). Reduction of LVEDV index was also greater in the S/V group (mean difference -7 mL/m^2, 95% CI -13.8 to -0.2; p=0.044) and there were no significant differences regarding the other secondary outcomes.[26]

The EVALUATE-HF study (n=464) was oriented to compare the effects (at 12 weeks) of S/V (*versus* enalapril) on aortic stiffness (primary outcome) and in changes in plasma levels of NT-proBNP and in different echocardiographic measurements, including LVEDV and LVESV indices, LAV index, global longitudinal strain, mitral annular relaxation velocity, mitral E/e' ratio and ventricular-to-vascular coupling ratio. The decrease in aortic characteristic impedance resulted in a non-statistically significant difference against enalapril (p=0.24) but significant differences were observed in LAV index (difference -2.8 mL/m^2; p<0.001), LVEDV index (difference -2.0 mL/m^2; p=0.02), LVESV index (difference -1.6 mL/m^2; p=0.045) and mitral E/e' ratio (difference -1.8; p=0.001). The comparative effect over other secondary outcomes was non-significant, including LVEF (difference 0.6%; p=0.24). Rates of adverse events, including hypotension (1.7% *versus* 3.9%) were similar in both groups.[27] In summary, the combined results of the PROVE-HF, PRIME-HF and EVALUATE-HF studies showed that ARNi-based

therapy is able to improve some key echocardiographic measures of cardiac remodelling.[25–27]

The randomized, multicentre, open-label, parallel-group TRANSITION study evaluated the tolerability and optimal timing of S/V initiation in stabilized patients after an acute HF (AHF) episode (*n*=1002). Basically, the safety of predischarge S/V introduction (≥12 h) *versus* rapid post-discharge (days 1–14) introduction was assessed; of note, 29% of the whole cohort were '*de novo*' patients with HFrEF and 24% had not been previously medicated with ACEi/ARB. The primary endpoint was the proportion of patients reaching 97/103 mg BID target dose after 10 weeks.

The median time at which the first dose of S/V was administered was day -1 in the predischarge group and day +1 in the postdischarge group.

The proportion of predischarge *versus* postdischarge patients who achieved and maintained S/V target doses of 49/51 or 97/103 mg twice daily for ≥2 weeks leading to week 10 was 62.1% *versus* 68.5% (RR 0.91, 95% CI 0.83–0.99) whilst those who in total received any dose of S/V were 86.0% *versus* 89.6% (RR 0.96, 95% CI 0.92–1.01).

It should be highlighted that a similar number of patients in the pre- and postdischarge initiation groups reached the primary outcome (45.4% *versus* 50.7%; RR 0.90, 95% CI 0.79–1.02). The need to discontinue treatment due to a serious adverse event occurred in 7.3% *versus* 4.9% of patients (RR 1.49, 95% CI 0.90–2.46).[28]

The PIONEER study (*n*=881) also investigated the effectiveness and safety of S/V (*versus* enalapril) in patients hospitalized due to AHF. Median time to randomization after admission was 68 h and, at study completion (8 weeks), a statistically significant NT-proBNP reduction (primary endpoint) in the S/V arm was observed (-46.7% *versus* -25.3%; $p<0.001$). In addition, there were no statistically significant differences in rates of symptomatic hypotension, worsening renal function, angioedema or hyperkalaemia between both arms (secondary outcome).[29] In summary, the TRANSITION and PIONEER studies showed the viability and safety of introducing S/V in an acute HFrEF setting.[28,29]

Despite these positive results obtained in different clinical scenarios, including reductions in morbidity and mortality in chronic HFrEF (mainly mild to moderate), decrease of NP, anti-remodelling effects such as functional mitral regurgitation, and AHF onset, the experience in advanced HF remains limited. In this scenario, data from the LIFE study suggest that, unfortunately, S/V is not better than valsartan in significantly reducing NT-proBNP levels measured by its area under the curve (AUC) – its main outcome was the proportional change from baseline in the AUC for NT-proBNP levels measured through week 24.[30]

The LIFE trial was a double-blind randomized clinical study of patients with HFrEF with a 24-week treatment period that randomized 167 individuals to receive S/V and 168 to receive valsartan (all in NYHA class IV). The median NT-proBNP AUC was 1.19 (IQR 0.91–1.64) and 1.08 (IQR 0.75–1.60) in the valsartan and S/V arms, respectively, and the estimated ratio of change in the NT-proBNP AUC was 0.95 (95% CI 0.84–1.08; $p=0.45$). In addition, patients taking S/V exhibited no improvements (*versus* valsartan) in the composite of number of days alive, out of hospital and free from HF events (secondary outcomes).[30]

Finally, the PARADISE-MI trial was a randomized, double-blind, active-comparator study designed to determine the efficacy and safety of S/V (target dose 97/103 mg BID) *versus* ramipril (target 5 mg BID) in patients (*n*=5661) with myocardial infarction (MI).[31] For inclusion, individuals should have had a MI at 0.5 to 7 days before inclusion, LVEF ≤40%, pulmonary congestion and at least one of the following risk factors: age ≥70 years, diabetes mellitus, previous MI, eGFR <60 mL/min/1.73 m^2 (screening), atrial fibrillation, LVEF <30%, Killip class ≥III, or ST-segment elevation MI without reperfusion.[31] Over a median of 22 months, the primary outcome of CV death or incident HF (HFH or outpatient HF) occurred in 11.9% of patients in the S/V group *versus* 13.2% in the ramipril group (HR 0.90, 95% CI 0.78–1.04; $p=0.17$). Death from CV causes occurred in 5.9% of patients in the active arm and in 6.7% in the placebo arm (HR 0.87, 95% CI 0.71–1.08; $p=0.20$) whilst HFH occurred in 7.1% of patients in the S/V arm and in 8.4% in the placebo group (HR 0.84, 95% CI 0.70–1.02; $p=0.17$). Lastly, death from any cause accounted for 7.5% in the S/V arm and 8.5% in the placebo arm (HR 0.88, 95% CI 0.73–1.05; $p=0.16$). Regarding the safety profile, 12.6% of patients in the S/V arm and 13.4% in the ramipril arm had to stop treatment due to an adverse event. In conclusion, and despite the rate of events being lower with S/V compared to ramipril, the results did not reach significance in relation to a reduction in death from CV causes or incidental HF in patients with acute MI.[31]

Finally, it is important to highlight that the use of S/V (first-in-class ARNi) in contemporary clinical trials remains low (but increasing) compared to that of ACEIs/ARBs (Table 2). However, as will be seen in the discussion, the replacement of an ACEI/ARB by an ARNi is more beneficial in terms of HF outcomes.

Sodium–glucose cotransporter 2 inhibitors

As previously mentioned, SGLT2i were originally developed and clinically introduced as hypoglycaemic

Table 2. Contemporary heart failure studies: baseline characteristics.

Main characteristics	PARADIGM-HF (*n*=8442)	DAPA-HF (*n*=4744)	EMPEROR-Reduced (*n*=3730)	SOLOIST-WHF (*n*=1222)
Year	2014	2019	2020	2020
Active arm	S/V (*n*=4187)	Dapagliflozin (*n*=2373)	Empagliflozin (*n*=1863)	Sotagliflozin (*n*=608)
Median follow-up	27 months	16 months	16 months	9 months
Age (years)	63.8	66.2	67.2	69.0
Women, %	21	23.8	23.5	32.6
LVEF, %	29.6	31.2	27.7	35.0
NYHA, %	II, III, IV (71.6/23.1/0.8)	II, III, IV (67.7/31.5/0.8)	II, III, IV (75.1/24.4/0.5)	Hospitalized
Average eGFR, mL/min/1.73 m^2	68	66	6i.8	49.2
NT-proBNP pg/mL	1631	1428	1887	1816
Diabetes	34.7	41.8	49.8	100
Ischaemic aetiology, %	59.9	55.5	52.8	–
Atrial fibrillation, %	36.2	38.6	35.6	–
ACEi/ARB, %	–	84.5	70.5	82.1
S/V	–	10.5	18.3	15.3
BB/MRA, %	93.1/54.2	96/71.5	94.7/70.1	92.8/66.3
ICD/CRT, %	14.9/7.0	26.2/8.0	31/11.8	–

ACEi, angiotensin II converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal-prohormone BNP; NYHA, New York Heart Association; S/V, sacubitril/valsartan.
Table adapted from PARADIGM-HF, DAPA-HF, EMPEROR-Reduced and SOLOIST-WHF trials.[6,7,10,32]

agents (for T2DM) based on their potent glycosuric effects[3] but were subsequently shown to have positive effects on morbidity and mortality in patients with HF in both the setting of reduced[6,7] and preserved LVEF.[6] In this context, the systemic effects of SGLT2i are considered secondary to increased glycosuria and natriuresis. In the first case, by prevention of filtered glucose urinary reabsorption (proximal convoluted tubule), which results in reduction of glucotoxicity, augmented ketone metabolism, and an improvement of β-cell physiology and insulin sensitivity. In turn, these effects are clinically accompanied by reductions in serum glucose and glycated haemoglobin and in fat mass and body weight. In addition, SGLT2 inhibition enhances natriuresis because glucose is associated with sodium and chloride excretion, which implies a mixed diuretic and natriuretic mechanism; in this case, the clinical impact is expressed by reductions in plasma volume, blood pressure, arterial stiffness, albuminuria and glomerular hyperfiltration[4,5] (Figure 4).

SGLT2i exert a multiplicity of direct cardiac effects, including (1) enhancement of myocardial contractility by inhibiting cardiac Na^+/H^+ exchanger (overexpressed in HF) and normalizing sodium and calcium dyshomeostasis, (2) oxidative stress reduction, (3) energy production optimization by inducing autophagy of dysfunctional mitochondria, (4) anti-inflammatory effects by neutralizing pro-inflammatory cytokines and reducing macrophage infiltration, (5) apoptosis reduction mainly by anticaspase activity, (6) antifibrotic and anti-remodelling effects by reducing inflammation, oxidative stress and apoptosis, (7) improvement of the failing heart dysfunctional metabolism by contributing ketone bodies, (8) improving diastolic function by reducing myocardial passive stiffness (phosphorylation of myofilaments regulatory proteins) and (9) improving endothelial function[4,5] (Figure 4).

As previously mentioned, one of the most relevant novelties provided by the ESC 2021 guidelines is the incor-

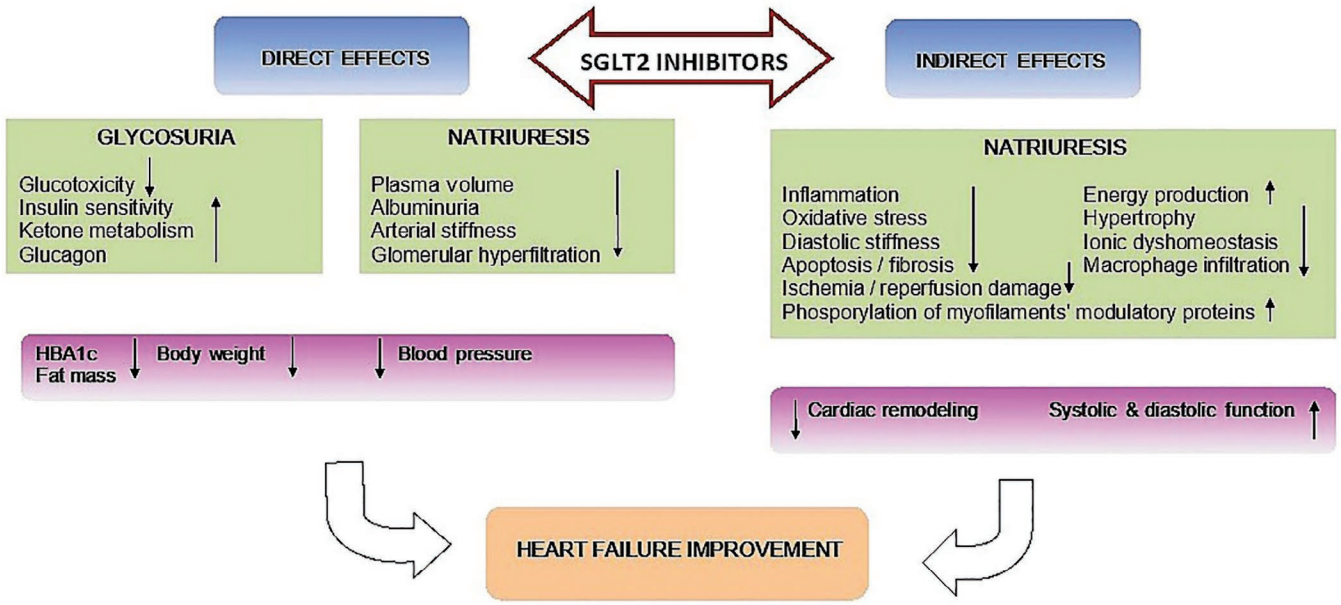
poration of SGLT2i into the standard treatment of HFrEF based on two transcendental studies: DAPA-HF and EMPEROR-Reduced.[1]

The DAPA-HF study was the first placebo-controlled clinical trial investigating the role of an SGLT2i (dapagliflozin) in patients with HFrEF (diabetic or non-diabetic). A total of 4744 individuals were included with the criteria of NYHA functional class II–IV, LVEF ≤40%, NT-proBNP level of ≥600 pg/mL (≥400 if HFH in the previous year, and ≥900 if in atrial fibrillation or flutter) and eGFR >30 mL/min/1.73 m^2 (Table 2).[6]

Enrolled individuals were randomized to dapagliflozin 10 mg once daily or placebo (added to GDMT) and, during a median of 18.2 months, the primary endpoint (a combination of worsening HF (hospitalization or an urgent visit requiring intravenous therapy) or CV death) was significantly decreased in the dapagliflozin group (16.3% *versus* 21.2%; HR 0.74, 95% CI 0.65–0.85; $p<0.001$). This result was largely based on a reduction of HFH/urgent HF visits (9.7% *versus* 13.4%; HR 0.70, 95% CI 0.59–0.83; $p<0.001$) and of death from CV causes (9.6% *versus* 11.5%; HR 0.82; 95% CI 0.69–0.98). During the trial period, HFH occurred in less patients in the active arm (9.7% *versus* 13.4%; HR 0.70, 95% CI 0.59–0.83; $p<0.001$) and both first and recurrent HFH were significantly reduced (Table 3). The secondary combined outcome of HFH or CV death followed the trend (567 *versus* 742 events, HR 0.74, 95% CI 0.65–0.85; $p<0.001$) with a 17% reduction in all-cause death (HR 0.83; 95% CI 0.71–0.97) and a non-significant 29% decrease in renal function aggravation. No excess in any serious adverse event was documented in the dapagliflozin group.[6]

The EMPEROR-Reduced study (n=3730) was conceived to assess the effects of empagliflozin (given 10 mg once daily *versus* placebo) in patients with HFrEF (already receiving an appropriate treatment) with or without T2DM.[5] Patients were required to have an NYHA functional class II–IV, LVEF ≤40%, eGFR >20 mL/min/1.73 m^2 and NT-proBNP levels entry criteria dependent on the baseline LVEF. These admission levels were ≥600 pg/mL if LVEF ≤30%, ≥1000 pg/mL if LVEF 31–35% and ≥2500 pg/mL if LVEF >35%. In cases of concomitant atrial fibrillation, these levels were required to be doubled[7] (Table 2). The primary outcome was the combination of CV death or HFH and, after a median of 16 months, it significantly occurred in less patients of the empagliflozin arm (19.4% *versus* 24.7%; HR 0.75, 95% CI 0.65–0.86; $p<0.001$). This result was primarily based on a HFH reduction (13.2% *versus* 18.3%; HR 0.70, 95% CI 0.58–0.85; $p<0.001$) without a significant impact over CV death (10.0% *versus* 10.8%; HR 0.92, 95% CI 0.75–1.12); in addition, empagliflozin did not significantly reduce overall mortality (13.4% *versus* 14.2%; HR 0.92, 95% CI 0.77–1.10; $p>0.05$). Total hospitalizations were significantly reduced (388 *versus* 553; $p<0.001$) and negative renal outcomes affected less patients in the active group (n=30) than in the placebo group (n=58) (HR 0.50, 95% CI 0.32–0.77; $p<0.01$) (Table 3). The annual rate of eGFR deterioration was attenuated with empagliflozin (-0.55

Figure 4. Proposed cardioprotective direct and indirect effects of SGLT2 inhibitors.



Possible mechanisms of action of SGLT2 inhibitors in heart failure.[7,8]

Table 3. Contemporary heart failure studies: comparative of main outcomes.

Outcome	PARADIGM	DAPA HF	EMPEROR-Reduced	SOLOIST-WHF
Population (*n*)	8842	4744	3770	1222
Follow-up (months)	27.0	18.2	16.0	9.0
Primary outcomes rate: active/placebo (%)				
Combined (CV death + HFH)	21.8/26.5	16.3/21.2	19.4/24.7	40.3/57.8
HFH	12.8/15.6	10.0/13.7	10.7/15.5	40.4/63.9
CV death	13.3/16.5	9.6/11.5	7.6/8.1	8.4/9.5
All-cause death	17.0/19.8	11.6/13.9	13.4/13.2	10.7/12.4
HR (95% CI)				
Combined (CV death + HFH)	0.80 (0.73–0.87)	0.74 (0.65–0.85)	0.75 (0.65–0.86)	0.67 (0.52–0.85)
HFH	0.79 (0.71–0.89)	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.64 (0.49–0.83)
CV death	0.80 (0.71–0.89)	0.82 (0.69–0.98)	0.92 (0.75–1.12)	0.84 (0.58–1.22)
All-cause death	0.84 (0.76–0.93)	0.83 (0.71–0.97)	0.91 (0.77–1.10)	0.82 (0.59–1.14)

CV, cardiovascular; HFH, heart failure hospitalization.
Table adapted from PARADIGM-HF, DAPA-HF, EMPEROR-Reduced and SOLOIST-WHF trials.[6,7,10,32]

versus -2.28 mL/min/1.73 m^2 per year, $p<0.001$) and non-severe genital tract infections were more often associated with empagliflozin.[7]

The SOLOIST-WHF study (n=1222) was the first large randomized controlled trial to show the efficacy of an SGLT2i (sotagliflozin) in patients with T2DM recently hospitalized for an AHF episode. Patients were stabilized prior to the administration of sotagliflozin 200 mg once daily (up-titrated to 400 mg, dependent on side effects) or placebo. To be included, eligible patients with T2DM should have been admitted for HF decompensation and required intravenous diuretics, have eGFR >30 mL/min/1.73 m^2 and an NT-proBNP level of at least ≥600 pg/mL (1800 pg/mL if atrial fibrillation). Median LVEF of the study was 35% and 21% of included patients had HFpEF (Table 2); the initial dose (sotagliflozin or placebo) was given prior to discharge in 48.8% and at a median of 2 days once discharged in 51.2%.[32] The primary outcome was the total number of CV deaths and hospitalizations or urgent visits for HF (first and subsequent episodes) and, at a median of 9.0 months, there were less events with sotagliflozin than with placebo (51% *versus* 76%; HR 0.67, 95% CI 0.52–0.85; $p<0.001$). However, no major disparities in risk of death (10.6% *versus* 12.5%; HR 0.84, 95% CI 0.58–1.22) or overall death (13.5% *versus* 16.3%; HR 0.82, 95% CI 0.59–1.14) were found (Table 3) and patients in the sotagliflozin arm had more (*versus* placebo) episodes of diarrhoea (6.1% *versus* 3.4%) or hypoglycaemia considered as severe (1.5% *versus* 0.3%). This was an event-driven trial (originally estimated in 947 adjudicated primary endpoint events) that ended prematurely due to funding issues but, nevertheless, demonstrated that sotagliflozin therapy initiation right before or shortly after discharge was safe and effective. Furthermore, these benefits were constant in all predefined subgroups of patients stratified according to when the first dose was administered.[32]

The initiation of empagliflozin in patients admitted for an episode of AHF (*de novo* or chronic decompensated HF) was evaluated in the double-blind EMPULSE trial (n=530) in which hospitalized but clinically stable patients (regardless of their LVEF) were randomized to empagliflozin 10 mg once daily (n=265) or placebo (n=265).[33] Its primary endpoint was a pre-established concept of clinical benefit, defined as the composite of death from any cause, number of HF events and time to first HF event, or a difference of five points or more in change from baseline in the Kansas City Cardiomyopathy Total questionnaire Symptom Score (KCCQ-TSS) at 90 days, assessed by a stratified win ratio.[33] The median time from hospital admission to randomization was 3 days whilst the median age of patients was 71 years (34% women). In the empagliflozin arm, 88 patients had *de novo* HF (87 with placebo) and 177 had chronic decompensated HF (178 with placebo) whilst 182 patients had LVEF ≤40% (172 with placebo) and 76 had LVEF ≥40% (93 with placebo). Other items, such as levels of NT-proBNP or percentage of patients with T2DM, were also balanced. Compared with the placebo arm, fewer patients treated with empagliflozin died (4.2% *versus* 8.3%) or had at least one episode of HF (10.6% *versus*

14.7%) whilst the mean change on the KCCQ-TSS was greater in the empagliflozin group (36.2 *versus* 31.7 points). The win ratio of clinical benefit was 53.9% in the empagliflozin arm and 39.7% in the placebo arm, implying a win ratio of 1.36 in favour of empagliflozin (95% CI 1.09–1.68; p=0.0054). This clinical benefit was seen in both types of randomized AHF and was independent of LVEF or the presence or not of T2DM. The safety profile was satisfactory and serious adverse events were documented in 32.3% of patients treated with empagliflozin (43.6% with placebo). In any case, the EMPULSE study indicated that the initiation of empagliflozin in patients hospitalized for AHF was well tolerated and was associated with a significant clinical benefit within 90 days after initiation of treatment.[33]

The phase III DELIVER trial was a multicentre, event-driven, double-blind, randomized controlled trial in which patients with chronic HF (≥40 years old) with a LVEF >40%, structural heart disease and elevated natriuretic peptides were assigned to dapagliflozin 10 mg/daily (n=3131) or placebo (n=3132) in addition to their usual therapy.[34] After a median of 2.3 years, the primary outcome (composite of worsening HF or CV death) occurred in 16.4% of patients in the dapagliflozin group *versus* 19.5% in the placebo group (HR 0.82, 95% CI 0.73–0.92; p<0.001). Worsening HF was reported in 11.8% in the dapagliflozin group and in 14.5% in the placebo group (HR 0.79, 95% CI 0.69–0.91) whilst CV death was documented in 7.4% and 8.3%, respectively (HR 0.88, 95% CI 0.74–1.05).[34] The incidence of adverse events was comparable in both groups and the clinical benefits were similar between patients with T2DM and those without, with LVEF above or below 60%, and in other prespecified subgroups. One of these subgroups was defined time of enrolment on/or within 30 days of HFH or did not occur on/or within 30 days of HFH and this information may be relevant in deciding when to start an SGLT2i. In this case, an earlier introduction of dapagliflozin after a decompensation episode was more favourable (HR 0.78, 95% CI 0.60–1.03 *versus* HR 0.82, 95% CI 0.72–0.94).[34]

Discussion

This review focused on assessing the effects of three of the current four therapeutic families instituted by the latest ESC guideline update as the basis of HFrEF treatment.[1] In our opinion, there are three main topics that should be analysed: the value of adding an MRA (still underutilized), the value of changing an ACEi/ERB for an ARNi and the value of incorporating an SGLT2i.

In the case of MRAs, RALES (1999) fixed its indication in moderate-to-severe HFrEF (NYHA class III–IV),[9] EPHESUS (2003) expanded it to postmyocardial infarction HFrEF[12] and, finally, EMPHASIS-HF (2011) included patients with mild HFrEF (NYHA II).[13]

Clinical introduction of this type of agent in both clinical trials and in real-world settings has been limited by fear of side effects (possibly overestimated)[17,18] and, in this context, the concomitant use of SGLT2i could be a useful resource to protect against the development of hyperkalaemia.[19,20] Of note, in this same scenario, the introduction of the relatively new potassium binders (patiromer or sodium zirconium cyclosilicate) should be considered to facilitate the administration of an MRA to patients with HF and prevent the onset of hyperkalaemia given that these agents increase faecal potassium elimination.[35]

In 2014, the PARADIGM-HF trial showed that S/V was superior to an ACEi in preventing CV deaths or HFH (reduced by 20%) and all-cause mortality (reduced by 16%) in HFrEF (mostly NYHA II–III).[10] Subsequently, the safety of starting an ARNi in stabilized patients after an AHF episode was demonstrated, in 2019, in the TRANSITION and PIONEER-HF trials.[28,29] In addition, ARNi therapy provides incremental benefit with respect to reductions in NT-proBNP levels and anti-remodelling effects, including functional mitral regurgitation as was detected in the PROVE-HF, PRIME-HF and EVALUATE-HF studies in 2019.[25–27]

On the other hand, the efficacy of SGLT2i in addition to standard therapies for patients with HFrEF was confirmed by the use of dapagliflozin in the DAPA-HF study (2019) and of empagliflozin in the EMPEROR-Reduced study (2020), reaching, in both cases, a steady and near similar 25% risk reduction of the combined primary outcome of CV death or HFH and even slowing down the deterioration of renal function.[6,7] These benefits were also observed in HFpEF (EMPEROR-Preserved, 2021, and DELIVER trial, 2022),[8,34] making this type of agent unique and outstanding.

Vaduganathan et al. estimated, based on a cross-trial analysis, the lifetime benefits of a comprehensive disease-modifying pharmacological therapy in HFrEF based only on ACEi/ARB and a BB. In this setting, switching to an ARNi (instead of ACEi/ARB) and the addition of an MRA and an SGLT2i (four therapeutic pillars) could extend the life of a typical patient with HFrEF by an additional 5 years because it implies the following aggregate risk reductions: 62% (53–70%) of the combined CV death/HFH endpoint; 50% (33–63%) of CV death; 68% (57–76%) of HFH and, finally, 47% (30–60%) of all-cause mortality.[36]

In another systematic review and network meta-analysis of pharmacological treatment of HFrEF, Tromp et al. showed that the combination ARNi+BB+MRA+SGLT2i was

the most effective in comparison with other types of double, triple and quadruple combinations. In this case, this therapeutic scheme was able to extend the life of a 70-year-old patient by five additional years (2.5–7.5) and showed to be the most valuable in reducing all-cause death (HR 0.39, 95% CI 0.31–0.49), the composite outcome of CV death or HFH (HR 0.36, 95% CI 0.29–0.46), and CV mortality (HR 0.33, 95% CI 0.26–0.43).[37]

It is important, in our opinion, to underline that, as previously described, the LVEF value phenotypically divides symptomatic patients with HF into having HFrEF (≤40%), HFmrEF (41–49%) or HFpEF (≥50%).[1] It is clear that patients with HFrEF are the most represented individuals in clinical trials and those that offer the least controversies regarding their clinical management and are therefore the greatest beneficiaries of a quadruple therapeutic scheme.[1] On the other hand, there are certain doubts about the real clinical identity of patients with HFmrEF, considering that HF in these (intermediate) patients can present as both HFpEF and HFrEF because their diagnosis is only conditioned by a narrow range of LVEF. In this context, the weakness of the phenotypic determination of HF must be highlighted given its limitations and its capacity to change over time or with the evolution of HF.[38]

Conclusion

The current GDMT for HFrEF is based on the simultaneous use of four different drug families as the most effective scheme in terms of reducing morbidity and mortality. Additionally, the effects of each therapeutic class are complementary. Therefore, and considering the widespread use of ACEi/ARBs and BBs, the change to ARNi and the introduction of MRAs and SGLT2i should be clearly promoted.

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References

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726. http://doi.org/10.1093/eurheartj/ehab368
2. 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 J Heart Fail*. 2016;18(8):891–975. http://doi.org/10.1002/ejhf.592
3. Zaccardi F, Webb DR, Htike ZZ, et al. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab*. 2016;18(8):783–794. http://doi.org/10.1111/dom.12670
4. Williams DM, Nawaz A, Evans M. Sodium-glucose co-transporter 2 (SGLT2) inhibitors: are they all the same? A narrative review of cardiovascular outcome trials. *Diabetes Ther*. 2021;12:55–70. https://doi.org/10.1007/s13300-020-00951-6
5. Lahnwong S, Chattipakorn SC, Chattipakorn N. Potential mechanisms responsible for cardioprotective effects of sodium-glucose co-transporter 2 inhibitors. *Cardiovasc Diabetol*. 2018;17(1):101. https://doi.org/10.1186/s12933-018-0745-5
6. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995–2008. http://doi.org/10.1056/NEJMoa1911303
7. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413–1424. http://doi.org/10.1056/NEJMoa2022190
8. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451–1461. http://doi.org/10.1056/NEJMoa2107038
9. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709–717. https://doi.org/10.1056/NEJM199909023411001
10. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993–1004. https://doi.org/10.1056/NEJMoa1409077
11. Bauersachs J. Heart failure drug treatment: the fantastic four. *Eur Heart J*. 2021;42(6):681–683. https://doi.org/10.1093/eurheartj/ehaa1012
12. 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(14):1309–1321. https://doi.org/10.1056/NEJMoa030207
13. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11–21. https://doi.org/10.1056/NEJMoa1009492
14. Maggioni AP, Orso F, Calabria S, et al. The real-world evidence of heart failure: findings from 41413 patients of the ARNO database. *Eur J Heart Fail*. 2016;18(4):402–410. https://doi.org/10.1002/ejhf.471
15. Maggioni AP, Anker SD, Dahlström U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2013;15(10):1173–1784. https://doi.org/10.1093/eurjhf/hft134
16. Tsigkas G, Apostolos A, Aznaouridis K, et al. Real-world implementation of guidelines for heart failure management: a systematic review and meta-analysis. *Hellenic J Cardiol*. 2022;66:72–79. https://doi.org/10.1016/j.hjc.2022.04.006
17. Jonsson A, Norberg H, Bergdahl E, Lindmark K. Obstacles to mineralocorticoid receptor antagonists in a community-based heart failure population. *Cardiovasc Ther*. 2018;36(5):e12459. https://doi.org/10.1111/1755-5922.12459

18. Savarese G, Carrero JJ, Pitt B, et al. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2018;20(9):1326–1334. https://doi.org/10.1002/ejhf.1182
19. Shen L, Kristensen SL, Bengtsson O, et al. Dapagliflozin in HfrEF patients treated with mineralocorticoid receptor antagonists: an analysis of DAPA-HF. *JACC Heart Fail*. 2021;9(4):254–264. https://doi.org/10.1016/j.jchf.2020.11.009
20. Ferreira JP, Zannad F, Pocock SJ, et al. Interplay of mineralocorticoid receptor antagonists and empagliflozin in heart failure: EMPEROR-reduced. *J Am Coll Cardiol*. 2021;77(11):1397–1407. https://doi.org/10.1016/j.jacc.2021.01.044
21. Maric C, Zheng W, Walther T. Interactions between angiotensin II and atrial natriuretic peptide in renomedullary interstitial cells: the role of neutral endopeptidase. *Nephron Physiol*. 2006;103(3):149–156. https://doi.org/10.1159/000092457
22. Volpe M, Rubattu S, Burnett J Jr. Natriuretic peptides in cardiovascular diseases: current use and perspectives. *Eur Heart J*. 2014;35(7):419–425. https://doi.org/10.1093/eurheartj/eht466
23. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *JACC Heart Fail*. 2014;2(6):663–670. https://doi.org/10.1016/j.jchf.2014.09.001
24. Gu J, Noe A, Chandra P, et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol*. 2010;50(4):401–414. https://doi.org/10.1177/0091270009343932
25. Januzzi JL, Prescott MF, Butler J, et al. Association of change in N-terminal pro–B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA*. 2019;322(11):1085–1095. https://doi.org/10.1001/jama.2019.12821
26. Kang DH, Park SJ, Shin SH, et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation*. 2019;139(11):1354–1365. https://doi.org/10.1161/CIRCULATIONAHA.118.037077
27. Desai AS, Solomon SD, Shah AM, et al. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2019;322(11):1077–1084. https://doi.org/10.1001/jama.2019.12843
28. Wachter R, Senni M, Belohlavek J, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur J Heart Fail*. 2019;21(8):998–1007. https://doi.org/10.1002/ejhf.1498
29. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-Neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380(6):539–548. https://doi.org/10.1056/NEJMoa1812851
30. Mann DL, Givertz MM, Vader JM, et al. Effect of treatment with Sacubitril/Valsartan in patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA Cardiol*. 2022;7(1):17–25. https://doi.org/10.1001/jamacardio.2021.4567
31. Jering KS, Claggett B, Pfeffer MA, et al. Prospective ARNI *vs* ACE inhibitor trial to DetermIne Superiority in reducing heart failure events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics. *Eur J Heart Fail*. 2021;23(6):1040–1048. https://doi.org/10.1002/ejhf.2191
32. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384(2):117–128. https://doi.org/10.1056/NEJMoa2030183
33. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28:568–74. https://doi.org/10.1038/s41591-021-01659-1
34. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387:1089–1098. https://doi.org/10.1056/NEJMoa2206286
35. Zannad F, Ferreira JP, Pitt B. Potassium binders for the prevention of hyperkalaemia in heart failure patients: implementation issues and future developments. *Eur Heart J Suppl*. 2019;21(Suppl. A):A55–A60. https://doi.org/10.1093/eurheartj/suy034
36. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020;396(10244):121–128. https://doi.org/10.1016/S0140-6736(20)30748-0
37. Tromp J, Ouwerkerk W, van Veldhuisen DJ, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *JACC Heart Fail*. 2022;10(2):73–84. https://doi.org/10.1016/j.jchf.2021.09.004
38. Palazzuoli A, Beltrami M. Are HfpEF and HfmrEF so different? The need to understand distinct phenotypes. *Front Cardiovasc Med*. 2021;8:676658. https://doi.org/10.3389/fcvm.2021.676658