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REVIEW ARTICLE

Sacubitril/Valsartan: A New Dawn has Begun! A Revisited Review

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Abstract: Heart Failure (HF) is among the major causes of global morbidity as well as mortality. Increased prevalence, frequent and prolonged hospitalization, rehospitalization, long-term consumption of healthcare resources, absenteeism, and death upsurge the economic burden linked to HF. For decades, Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Blockers (ARBs), Beta-Blockers (BBs), and mineralocorticoid receptor antagonists (MRA), have remained the mainstay of the standard of care for HF management. Despite their proven efficacy and cost-effectiveness, HF remains a global pandemic and is still increasing in prevalence. Sacubitril/Valsartan (SAC/VAL) is an Angiotensin Receptor/Neprilysin Inhibitor (ARNI) that proved out to be a game-changer drug in HF treatment. Recent data indicated that SAC/VAL is more efficient and can improve the overall quality of life of HF patients with reduced ejection fraction (HFrEF) with fewer side effects. It is now incorporated in the guidelines as an alternative to ACEIs or ARBs to lower morbidity in addition to mortality in HFrEF patients. This review article will discuss the current guidelines-approved indications and highlight the potential emerging indications, in addition to the currently ongoing clinical trials that will expand the use of SAC/VAL.

Keywords: Sacubitril/valsartan, heart failure with reduced ejection fraction (HFrEF), PARADIGM-HF, heart failure with preserved ejection fraction (HFpEF), ventricular arrhythmias, remodeling.

1. INTRODUCTION

Angiotensin-converting-enzyme inhibitors (ACEIs) are the mainstay of heart failure with reduced ejection fraction (HFrEF) treatment since enalapril had proven to reduce the mortality risk [1]. Meanwhile, Angiotensin-receptor blockers (ARBs) are recommended primarily for intolerable patients with ACEIs. Besides, ARBs were proven to be non-inferior and having fewer adverse effects compared to ACEIs. Later studies revealed that the addition of Beta-Blockers (BBs) as well as Mineralocorticoid-Receptor Antagonists (MRA) to ACEIs resulted in further reduction of mortality in HFrEF patients [2, 3]. Despite the advantages of HF treatment, its mortality remains high (50% at 5 years) [4].

SAC/VAL is the first produced Angiotensin Receptor/Neprilysin Inhibitor (ARNI) containing a Neprilysin Inhibitor (Sacubitril) combined with an ARB (Valsartan). Originally, it was created to reduce the hazards of grave angioedema, and later on, many effects were proven [5].

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2. PATHOPHYSIOLOGY OF HFREF AND THE INVENTION OF ARNI

As the renin-angiotensin-aldosterone system (RAAS) is not the solely activated system in the HF status, but in addition to it, another system is activated, which is the natriuretic peptide system; this system leads to the release of many modulators and signaling peptides, such as adrenomedullin, bradykinin and substance P. These modulators and signaling peptides are regulated by another enzyme called Neprilysin that causes a decrease in sympathetic tone, a decrease in blood pressure, an increase in natriuresis and a decrease in myocardial fibrosis and remodeling. The idea behind the invention of ARNI was to act on the natriuretic peptide system at its final point, which is the Neprilysin enzyme, by making a substance that can inhibit its effects on the modulators and signaling peptides Fig. (**1**) [6].

ARNI in heart failure with reduced ejection fraction (PARADIGM-HF) was a randomized, double-blind study, comparing RAAS inhibitor plus Neprilysin inhibitor (SAC/-VAL) combination versus RAAS inhibitor alone (Enalapril). The study enrolled 8442 patients with New York Heart Association (NYHA) class II, III, IV and left ventricular ejection fraction (LVEF) ≤40%. Participants received either SAC/-VAL (200 mg twice (BID) daily) or enalapril (10 mg BID daily) in addition to a guideline-approved treatment [7].

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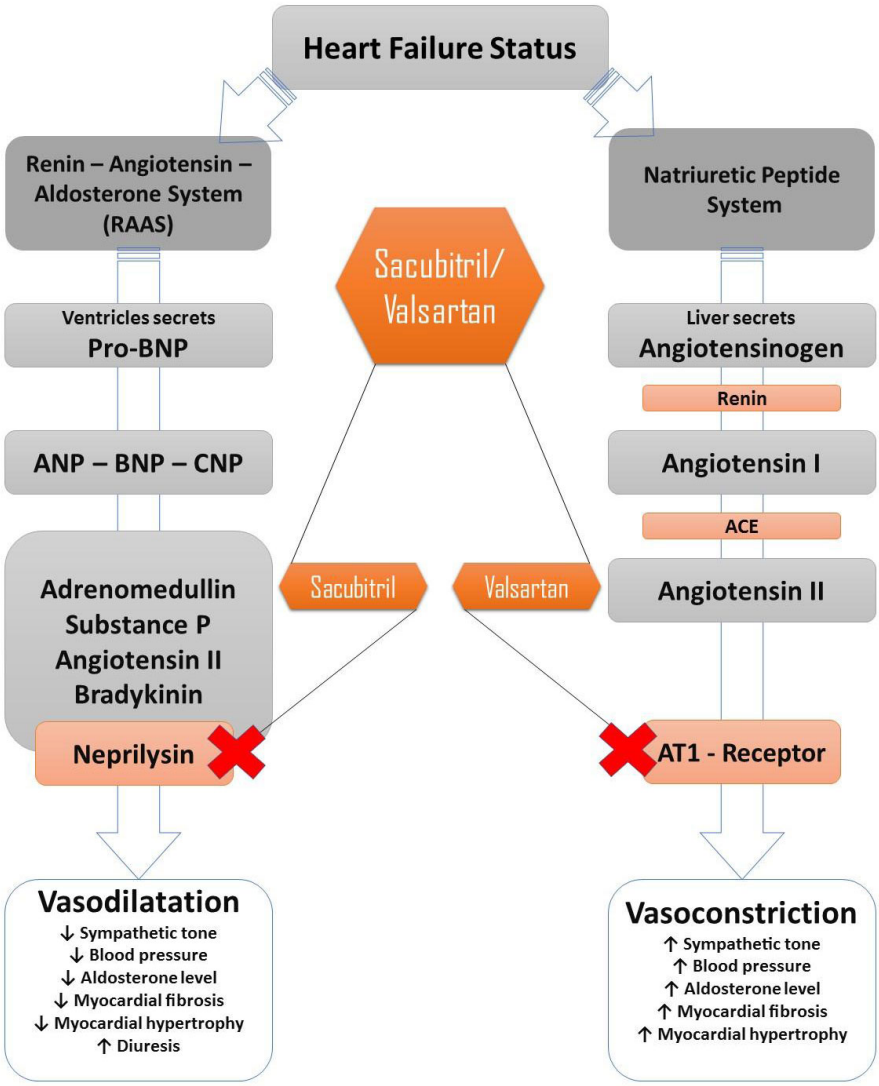

Fig. (1). Mechanism of action of Sacubitril/Valsartan in heart failure. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The primary endpoint was combined with cardiovascular death or first HF hospital admission. Interestingly, it was terminated prematurely because the results showed the superiority of SAC/VAL over enalapril. PARADIGM-HF revealed that cardiovascular mortality and HF hospital admission were less encountered in SAC/VAL arm [n=914, (21.8%)] compared to enalapril arm [n=1117, (26.5%)], hazard ratio (HR) 0.80, 95% confidence interval (CI), 0.73 to 0.87; P<0.001. The risk of HF hospital admission was 21% (P<0.001) less in SAC/VAL arm than enalapril arm (HR 0.79; 95% CI, 0.71 to 0.89), and the number needed to treat to prevent one CV death or HF hospital admission was 21.

In addition, SAC/VAL also significantly decreased HF symptoms and physical limitations (P-value=0.001) based on the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical score, which assesses the quality of life. Moreover, adverse events like cough, renal impairment and hyperkalemia were lower at SAC/VAL arm. However, hypotension and non-serious angioedema were observed with higher frequency in SAC/VAL arm compared to enalapril arm [7].

And because doses of the studied drugs were increased to target levels during the run-in phase, mainly to make sure that patients in the enalapril group received doses that have been shown to reduce mortality, Sunni *et al*. in 2016 started the TITRATION trial, which was a double-blind, randomized controlled trial (RCT) that aimed to provide more information about the initiation, up-titration, tolerability as well as safety of ARNI in the real-life comparing two regimens of up-titration in HFrEF patients [8]. 498 patients with LVEF ≤35% participated and received SAC/VAL for 3 months.

The condensed regimen consisted of 2-week 100 mg SAC/VAL BID followed by 200 mg BID, while in the conservative regimen, a 2-week 50 mg DIB was started, followed by a 3-week 100 mg BID and then 200 mg BID daily. Nearly 75.9% of the enrolled participants completed the course of treatment, a dose of 200 mg BID was reached and maintained for 3 months. Comparing patients who received the condensed regimen to those who received the conservative regimen, the incidence of adverse events (hypotension, renal dysfunction, hyperkalemia, and angioedema) was higher in the condensed regimen group, but that difference was not statistically significant [8]. Also, participants who shifted from the conservative ACEI/ARB regimen to a condensed regimen had a significantly elevated hypertension risk and lower rates to attain treatment success. In most of the patients, up-titration was successful regardless of prior ACEIs/ARBs usage or dosage [8]. Meanwhile, Lower SBP at screening did not impact the success rates [9]. That is why SAC/VAL usage in HFrEF patients with low SBP may be considered with careful monitoring and follow-up of blood pressure.

3. CURRENT GUIDELINE-APPROVED INDICATIONS OF SAC/VAL

After the promising data derived from the PARADIGM-HF trial, SAC/VAL was approved by the European Medicines Agency (EMA) in Europe and the Food and Drug Administration (FDA) in the United States for chronic HFrEF (NYHA class II-IV) treatment, to lower cardiovascular mortality risk and hospitalization [10]. In 2016, the European Society of Cardiology (ESC) guidelines stated that in symptomatic (NYHA Class II-IV) HFrEF patients, SAC/VAL is approved as a substitute for an ACEIs to further reduce HF hospitalization risk as well as mortality in HFrEF patients who were persistently symptomatic despite optimization of medical treatment with an ACEI, BB and an MRA (class of evidence I, level of evidence B) [11-13]. In 2017, the American College of Cardiology (ACC)/American Heart Association Task Force (AHA) guidelines highlighted that we can prescribe ARNI in symptomatic HFrEF NYHA class II or III patients who can withstand the substitution of an ACEI or ARB with an ARNI for additional reduction of morbidity as well Summary of guideline-recommended indications summarized in Table **1**.

It is noteworthy that the combination of oral neprilysin inhibitor and ACEI was studied, but its progress was stopped because of the high incidence of angioedema [14]. This could be explained by the mechanism of action, as ACEI and neprilysin disintegrate to bradykinin, which can induce angioedema directly or indirectly. Hence, SAC is only combined with VAL. Moreover, SAC/VAL must not be commenced in patients with angioedema history because of concerns related to angioedema recurrence. In addition, it is recommended to avoid ARNI use within 36 hours of switching from or to an ACEI [14]. Therefore, when switching from ACEI to SAC/VAL, patients must undergo a washout period of 36 hours to reduce the risk of angioedema.

4. NEW INSIGHTS OF SAC/VAL

Several trials related to SAC/VAL use in several indications have been published (Summarized in Table **2**).

4.1. SAC/VAL Role in Acute Decompensated Heart Failure

PIONEER-HF was a prospective double-blinded study comparing SAC/VAL effects Versus Enalapril on the changes in N-Terminal Pro-Brain Natriuretic Peptide (N-T-proBNP) in 881 stabilized HFrEF patients after admission to the hospital for acute decompensated heart failure (ADHF).

It showed that, among HFrEF patients hospitalized for ADHF, SAC/VAL initiation caused more decrease in NT-proBNP concentration than enalapril therapy (-46.7% *vs*.. -25.3%, hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.63-0.81, $p<0.001$). Additionally, there was a reduction in troponin T levels (-36.6% *vs*.. 25.2%, $p < 0.05$). Moreover, a reduction in rehospitalization for HF was noted over the 8-week follow-up period (8.0% *vs*.. 13.8%, HR 0.56, 95% CI 0.37-0.84). Symptomatic hypotension, angioedema, renal function worsening and increased potassium level revealed no significant differences between the two groups [15]. Later in 2019, Watcher *et al*, published the primary results of the randomized, multicenter, open-label TRANSITION study that addressed the tolerability and optimal timing for the SAC/VAL initiation in hemodynamically stabilized ADHF patients in the hospital or early after discharge [16]. The conclusion favored that SAC/VAL initiation strategy proven practical, with nearly 50% of patients achieving the target dose within 10 weeks. The first few months after ADHF hospitalization are termed the 'vulnerable period' [17]. The estimated risks of mortality and rehospitalization are higher during the initial 3 months [18], with the highest incidence noted in the earliest 30 days after hospital discharge [19-22]. The ESC guidelines stated that admitted HF patients are instructed to commence evidence-based medications through an oral route oral for at least 24 hours before hospital release. [11]

4.2. SAC/VAL Effects on Ejection Fraction and Reverse Remodeling

Iborra-Egea *et al*., [23] suggested that SAC/VAL functions in a synergistic way against cardiomyocyte cell death and extracellular matrix remodeling. Valsartan induced improvement of cardiac remodeling through inhibition of guanine nucleotide-binding protein family members, while Sacubitril reduced cardiomyocyte cell death, hypertrophy, and diminished cardiomyocyte contractility by PTEN inhibition. Therefore, those effects can be the pathophysiological rationale for SAC/VAL to reduce or prevent myocardial infarction-induced remodeling.

Almufleh *et al*., [24] conducted a single-center, retrospective, cohort study on 48 HFrEF patients treated with SAC/VAL for a median duration of 90 days. Clinical and echocardiographic parameters were assessed at 3 different

Table 1. Summary of Guideline-approved indications of SAC/VAL.

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure		
Class of recommendation	Level of evidence	Recommendation
I	B	SAC/VAL is recommended as a replacement for an ACEI to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEI, BB, and MRA.
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure		
Class of recommendation	Level of evidence	Recommendation
I	B-R	ARNI in conjunction with evidence-based BB and MRA in selected patients is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
I	B-R	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.
III	B-R	ARNI should not be administered concomitantly with ACEI or within 36 hours of the last dose of an ACEI.
III	C-EO	ARNI should not be administered to patients with a history of angioedema.
2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure		
Strong Recommendation	High-Quality Evidence	We recommend that an ARNI be used in place of an ACEI or ARB, in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT to decrease cardiovascular death, HF hospitalizations, and symptoms.

Table 2. Summary of published clinical trials on SAC/VAL.

Study/year	patients	Medications used	Enrolment criteria	Primary endpoints	Follow-up	Results	Notes
PARADIGM-HF 2014	8442	SAC/VAL *vs.* Enalapril	-LVEFE≤40% - NYHA class II-IV - Elevated BNP or NT-proBNP	-Death from cardiovascular causes -Hospitalization for HF	Median of 27 months	-Death from cardiovascular causes or hospitalization for HF: SAC/VAL: 21.8%, Enalapril: 26.5%. -Risk of hospitalization for HF was 21% less in SAC/-VAL group than in the Enalapril	Trial was stopped early due to superiority of SAC/VAL.
PIONEER-HF 2019	736	SAC/VAL *vs.* Enalapril	- LVEF≤40% -Admitted ≥24 hrs - Elevated BNP or NT-proBNP -SBP ≥100mmHg -No recent IV vasodilators and/or inotropes	- Change in NT-ProBNP	8 weeks	-Percent of reduction in NT-ProBNP SAC/VAL: 46.7% Enalapril: 25.3% -Reduction in the NT-ProBNP concentration with sacubitril-valsartan than with Enalapril was evident as early as week 1	Rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups.
PARAMOUNT 2012	301	SAC/VAL *vs.* Valsartan	-LVEF ≥ 45% - NYHA class II-III -NT-ProBNP ≥400	-Change in NT-proBNP	12 weeks	NT-proBNP levels SAC/VAL: 783 pg/mL at baseline 605 pg/mL at 12 weeks Valsartan: 862 pg/mL at baseline 835 pg/mL at 12 weeks	GLS was significantly improved at 36 weeks in the ARNI group when compared with the valsartan group, with no significant difference observed in GLS.
Martens *et al*, 2018	125	patients were pretreated with Enalapril for 4 weeks prior to switching to SAC/-VAL	-LVEF≤35% -NYHA class II-IV	-LVEF and volumes by TTE	median of 118 days	-LVEF improved from 29.6 ± 6% to 34.8 ± 6% -LVESV and LVEDV decreased -Reduction in the degree of MR	Metrics of diastolic function improved including a drop in the E/A-wave ratio and diastolic filling time prolonged.
Martens *et al*, 2019	151	Events on ICD/CRT while on ACEI/ARB were compared to events after switching to SAC/VAL	-HFrEF with a class I indication for SAC/VAL -Patient with an implanted ICD or CRT	VT/VF-burden	1 year of incident and antecedent analysis.	Number of Patients developing VT/VF: -on ACEI/ARB: 19 -on VAL/SAC: 10	PVC and non-sustained VT burden dropped significantly after initiating SAC/VAL, however there was no impact on atrial-fibrillation burden.

(Table 2) contd....

TITRATION 2017	498	SAC/VAL for 12 weeks comparing two up-titration regimens in HFrEF patients	Assessment of safety and tolerability of ARNI in the real world, representative to routine practice in patients with an LVEF ≤ 35%	Safety, tolerability, and success of up--titration of SAC/-VAL	12 weeks	Up-titration was successful in most patients regardless of the previous use or dose of ACEIs/ARBs	Results suggested that SAC/VAL use in HFrEF patients with low SBP should be considered with careful monitoring and follow-up of BP.
TRANSITION 2019	1002	Addresses the tolerability and optimal time point for the initiation of SAC/VAL in hemodynamically stabilized AHF patients in hospital or early after discharge	Patients aged ≥ 18 years, hospitalized for AHF were stratified according to pre-admission use of RAAS inhibitors and randomized after stabilization to initiate SAC/VAL either ≥ 12-hrs predischarge or between Days 1-14 post-discharge	Proportion of patients attaining 97/103 mg BID target dose after 10 weeks	10 weeks	Comparable proportions of patients in the pre- and post-discharge initiation groups met the primary endpoint [45.4% *vs*.. 50.7%; risk ratio (RR) 0.90; 95% confidence interval (CI) 0.79-1.02].	Initiation of SAC/VAL in a wide range of HFrEF patients stabilised after an AHF event, either in hospital or shortly after discharge, is feasible with about half of the patients achieving target dose within 10 weeks.
PRIME 2019	118	Either SAC/VAL or VAL, in addition to standard medical therapy for heart failure.	Patients with heart failure with chronic functional MR secondary to left ventricular dysfunction	Change in effective regurgitant orifice area (EROA)	12 months	Change in EROA was significant and showed a decrease by 30% and 9% in the sacubitril/valsartan group and the valsartan Group, respectively with a P value of 0.032	SAC/VAL is more effective in improving functional MR associated with HF than an ARB
EVALUATE-HF 2019	464	SAC/VAL compared with Enalapril	Patients with HF and LVEFE≤40%	Change from baseline to week 12 in aortic characteristic impedance (Zc), a measure of central aortic stiffness	12 weeks	No significant difference in the change in aortic characteristic impedance at 12 weeks among patients treated with SAC/VAL *vs*. Enalapril (-2.9 *vs*. -0.7 dyne × s/cm5).	Failure to show that SAC/VAL was effective at reducing central aortic stiffness
PARAGON-HF 2019	4822	SAC/VAL *vs*. Valsartan	-Chronic HF with an LVEF >45% -Elevated NT-proBNP -Chronic oral diuretic therapy -Structural heart disease supporting HFPEF with TTE	-Cardiovascular death -Total (first and recurrent) HF hospitalizations	Median of 35 months	894 primary events (690 HF hospitalizations and 204 cardiovascular deaths) in 526 patients in SAC/-VAL group and 1009 primary events (797 HF hospitalizations and 212 cardiovascular death) in 557 patients in the Valsartan group (rate ratio, 0.87; 95% CI, 0.75 to 1.01; P=0.06)	-

SAC/VAL: Sacubitril/Valsartan, HF: Heart Failure, LVEF: Left Ventricular Ejection Fraction, NYHA: New York Heart Association, BNP: Brain Natriuretic Peptide, SBP: Systolic Blood Pressure, GCS: Global Longitudinal Strain: GLS, TTE: Transthoracic Echocardiography, LVESV: Left Ventricular Systolic Volume, LVEDV: Left Ventricular Diastolic Volume, MR: Mitral Regurgitation, HFrEF: Heart Failure with Reduced Ejection Fraction, ICD: Intracardiac Defibrillator, CRT: Cardiac Resynchronization Therapy, PVC: Premature Ventricular Contraction, VT: Ventricular Tachycardia, VF: Ventricular Fibrillation, ACEI: Angiotensin Converting Enzyme Inhibitor, ARB: Aldosterone Receptor Antagonist, ARNI: Angiotensin Receptor-Neprilysin Inhibitor, Renin-angiotensin-aldosterone system (RAAS) inhibitors, EROA: Effective Regurgitant Orifice Area.

intervals. (18 months before SAC/VAL initiation (pre-baseline), before SAC/VAL initiation (baseline) and Post SAC/-VAL initiation). The results showed that SAC/VAL treatment for a median duration of 90 days was associated with an increase of LVEF by 5±1.2% from a mean baseline of 25.33%, reaching 30.14% (p<0.001). Also, LV end-diastolic diameter (EDD), LV end-systolic diameter (ESD) and left ventricular mass index were reduced significantly (3.36 mm (p=0.04), 2.64 mm (p=0.02), and 14.4 g/m2 (p<0.01) respectively). The study concluded that SAC/VAL therapy was associated with more LVEF improvement and significant reverse remodeling effects compared to the effects of optimal medical treatment [24]. Despite the promising results, there were several limitations. The observational study design, small sample size, short follow-up period and lack of a placebo group preclude a direct comparison of SAC/VAL patients to those on regular optimal medical therapy.

Martens *et al*., [25] executed a prospective blinded single-center study to establish SAC/VAL reverse remodeling effects in HFrEF patients with a class I indication for SAC/-VAL. The study included 125 HFrEF patients prospectively recruited with a mean age of 66±10 years and a median follow-up period of 118 days after initiation of SAC/VAL. Echocardiographic studies were evaluated by 2 different assessors blinded to the clinical data. The results showed improvement of LVEF (29.6±6% *vs*. 34.8±6%; P<0.001), reduction of LVESV and LVEDV (147±57 ml *vs*. 129±55 ml (P<0.001) and 206 ±71 ml *vs*. 197±72 ml (P=0.027) respectively) and this volumetric remodeling was linked to a reduction of mitral regurgitation degree as well (1.59±1.0 *vs*.

1.11±0.8 (P<0.001)). Also, parameters of diastolic function showed an improvement with a noted drop in the E/A-wave ratio (1.75±1.13 *vs*. 1.38±0.88 (P = 0.002)) and a prolongation of diastolic filling time (48±9% ms *vs*. 52±1% ms (P = 0.005)). Additionally, the percentage of patients who had a restrictive mitral filling pattern was reduced from 47% to 23% (P = 0.004).

Dose-dependent changes were noted in LVEF (P < 0.001) and LVESV (P = 0.031) with higher SAC/VAL doses resulting in more profound reverse remodeling, concluding that switching from RAS-blocker to SAC/VAL therapy in eligible HFrEF patients resulted in beneficial reverse remodeling effects related to both systolic and diastolic function parameters [25].

4.3. SAC/VAL Effects on Ventricular Arrhythmias

De Diego *et al*., [26] investigated the effect of SAC/-VAL on ventricular arrhythmias (VA) as compared to ACEIs or ARBs in HFrEF patients with an implantable cardiac defibrillator (ICD). Device interrogation and remote monitoring showed that SAC/VAL decreased VA and appropriate ICDs shocks in HFrEF patients as compared to ACEIs or ARBs.[26]

Martens *et al*., [27] studied HFrEF patients receiving SAC/VAL for a class-I indication equipped with an ICD or cardiac resynchronization therapy (CRT) with remote telemonitoring; these patients were retrospectively analyzed, concluding that the SAC/VAL initiation was linked to a reduction of ventricular tachycardia or ventricular fibrillation (VT/VF) incidence resulting in lower ICD-interventions. The authors believed that the beneficial effect on VA may be explained by SAC/VAL effect on cardiac reverse remodeling [27].

Zacà *et al*., [28] aimed to evaluate the cost-effectiveness of SAC/VAL as compared with an implantable cardioverter-defibrillator (ICD) on top of optimal medical therapy in HFrEF patients. The results suggested that SAC/VAL can increase survival at fewer costs compared with an ICD in HFrEF patients [28].

4.4. SAC/VAL in Heart Failure with a Preserved Ejection Fraction

The main pathophysiologic mechanisms of HFpEF are related to increased ventricular stiffness, concentric left ventricular hypertrophy (LVH) in response to an increase in ventricular afterload (pressure overload) resulting in elevated diastolic pressures, and impaired relaxation that results in impaired diastolic filling of the LV and elevated filling pressures [29]. Several clinical trials proved the effectiveness of BBs, ACEIs, ARBs, ARNI, sodium-glucose cotransporter-2 inhibitors and CRT in mortality reduction, yet their beneficial effects in HFpEF was not demonstrated, which can be explained by the differences in the pathophysiology of HFpEF and HFrEF. Therefore, HFpEF management is mainly focused on symptomatic treatment of dyspnea and edema with diuretics and associated conditions, such as hypertension, atrial fibrillation [30].

As most of the preceding trials were targeting patients with HFrEF, the PARAMOUNT trial [31] was initiated, it is a double-blind randomzied multicenter trial in 301 NYHA class II-III HF and LVEF ≥45% patients, and NT-proBNP ≥400 pg/ml Patients who were assigned randomly to SAC/-VAL increased to 200 mg BID or VAL increased to 160 mg BID to assess changes in global longitudinal strain (GLS) and global circumferential strain (GCS) from baseline to 36 weeks. GCS was significantly improved at 36 weeks in SAC/VAL arm when compared with the VAL arm (4.42, 95% CI 0.67-8.17, p=0.021), with a non-statistically significant difference observed in GLS (0.25, 95% CI -1.19-1.70, p=0.73). Then it concluded that in HFpEF patients, SAC/-VAL was proved to improve the global circumferential but not longitudinal strain when compared to valsartan during 36-weeks of follow-up [31, 32].

Another trial, PARAGON-HF [33], a randomized, double-blind trial that was initiated to investigate SAC/VAL effects in HFpEF in comparison with VAL alone. The primary endpoint was the reduction of the rate of cardiovascular mortality and complete (first and recurrent) HF hospital admission in HFpEF patients (NYHA Class II-IV; LVEF ≥ 45%). The results revealed that there was no statistically significant difference in primary events (rate ratio, 0.87; 95% CI, 0.75 to 1.01; P=0.06) or cardiovascular death incidence (hazard ratio, 0.95; 95% CI, 0.79 to 1.16) and HF hospitalization between both arms (rate ratio, 0.85; 95% CI, 0.72 to 1.00) concluding that SAC/VAL was not associated with a significant reduction of total HF hospitalizations or cardiovascular death in HFpEF patients.

4.5. SAC/VAL for Functional Mitral Regurgitation "PRIME Study"

The PRIME trial (Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation) had recently demonstrated that SAC/VAL is more effective in improving functional mitral regurgitation (MR) associated with HF than an ARB. In comparison with VAL, SAC/VAL showed a further reduction in the effective regurgitant orifice area (EROA), LV EDV index, left atrial volume index, and the ratio of mitral inflow velocity to mitral annular relaxation velocity (E/E′) [34].

The primary endpoint of EROA change was significant and showed a decrease of 30% and 9% in SAC/VAL group and VAL group, respectively (P=0.032). Even the secondary endpoint, the decrease in regurgitant volume, was also significantly more evident in SAC/VAL arm than in VAL arm (P=0.009). The decrease in EROA was correlated with a decrease in end-systolic volume (P<0.001) or end-diastolic volume (P<0.001) in SAC/VAL group, and VAL group, as well (end-systolic volume P<0.001; and end-diastolic volume: P<0.001) [34]. A strong association between the severity of functional MR and all-cause mortality as well as hospitalization for HF has been described [35-38]. It was concluded that SAC/VAL should be considered part of optimal medical therapy (OMT) for chronic HF and functional MR patients. Current guidelines have already given a class I indication for

switching these patients to an ARNI, assuming that they have reduced LVEF [11].

4.6. SAC/VAL in Reducing Aortic Impedance/stiffness

Desai *et al*. compared the impact of SAC/VAL versus Enalapril on aortic stiffness in HFrEF patients in the randomized clinical trial EVALUATE-HF. In 464 HFrEF patients, no significant difference was detected in the change in aortic characteristic impedance at 3 months among treated patients with SAC/VAL versus enalapril (-2.9 *vs*. -0.7 dyne× s/cm5) [39]. Therefore, the EVALUATE-HF trial failed to show that SAC/VAL was effective at reducing central aortic stiffness.

4.7. SAC/VAL in Post-acute Myocardial Infarction

To date, no published data related to SAC/VAL effects in post-acute myocardial infarction (AMI) is revealed; the only data available is related to animal experimental models that demonstrated SAC/VAL efficacy in the prevention of AMI-induced LV dysfunction in comparison to VAL. Also, SAC/VAL was associated with a significant attenuation of LV scar size following AMI in comparison to placebo [40].

4.8. SAC/VAL in Advanced HF

Given the lack of evidence of SAC/VAL outcomes in advanced heart failure, the LIFE trial (ClinicalTrials.gov Identifier: NCT02816736) was designed to assess SAC/VAL effects in HFrEF patients with severe symptoms. Eligible patients for enrollment were patients with advanced HFrEF (NYHA class IV patients with LVEF≤35% or requiring chronic inotropic therapy). After 6 months of follow-up, neither SAC/VAL combination nor VAL decreased the median NT-proBNP below the baseline level. Also, there was no significant difference between both groups regarding the secondary efficacy endpoint of days alive, non-hospitalization, or HF events free (103.2 *vs*.. 111.2, respectively; p=0.45). Regarding tertiary clinical outcomes, there was no statistically significant improvement with SAC/VAL compared with VAL cardiovascular mortality or HF hospitalization (hazard ratio [HR], 1.32; p=0.20); HF hospitalization (HR, 1.24; p=0.33), and cardiovascular mortality or all-cause mortality. The study concluded that SAC/VAL combination was not superior in comparison to VAL alone in the reduction of NT-proBNP and wasn't associated with improved other clinical outcomes [41].

4.9. Ongoing RCTs and Observational Studies

Currently, there are some ongoing trials related to SAC/VAL use in several indications. (Summarized in Table **3**) PARALLAX trial (ClinicalTrials.gov number, NCT03066804) is another ongoing 24-week, double-blind RCT to study the effects of SAC/VAL on NT-proBNP, symptoms, exercise function, and safety in comparison to separate medical management of comorbidities in HFpEF patients from baseline to 24 weeks [42]. Preliminary results revealed that in 2,572 HFpEF patients randomly assigned to SAC/VAL or RAAS inhibitor or placebo, SAC/VAL had 16.4% more reduction in NT-proBNP levels than optimal individualized medical therapy (P<0.0001) at week 12. While there was no significant difference between both arms in the 6-minute walk test (mean difference -2.5 m; 95% confidence interval -8.5 to 3.5 m; p=0.79).

With an estimated study completion date on March 2022; the PARAGLIDE-HF trial (ClinicalTrials.gov number, NCT03988634), is a double-blind RCT designed to enroll 800 participants to compare SAC/VAL and VAL efficacy in HFpEF patients hospitalized for ADHF. This trial closely mimics the PIONEER-HF trial, yet it will enroll only patients with an LVEF>40% within the last 3 months. The primary endpoint is NT-proBNP level changes after 1 month and 2 months of treatment along with safety and tolerability in stabilized patients during hospital admission, in this study, the treatment was initiated during the hospital stay or within 30 days after discharge [43].

4.10. SAC/VAL in Pediatric HF Group

PANORAMA-HF trial (ClinicalTrials.gov number, NCT02678312) is a prospective trial to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of SAC/-VAL, this study will compare SAC/VAL with enalapril in pediatric HF patients for a 52-week follow-up. The findings of this study will determine if SAC/VAL is more efficient than enalapril in pediatric HFrEF management [44].

4.11. SAC/VAL in HF Patients and Sleep Apnea Syndrome

The ENTRESTO-SAS trial (ClinicalTrials.gov number, NCT02916160.) is a 3-month, multicenter, prospective, open-label cohort study. It will evaluate whether SAC/VAL could improve the outcome of sleep-disordered breathing in chronic HF patients. The findings of these trials may expand SAC/VAL use, and a diverse patient group is likely to be benefited from this drug in the near future [45].

4.12. SAC/VAL Effect on LVEF in HFrEF

The effects of SAC/VAL on the Heart Functions (ClinicalTrials.gov number, NCT03830814) is an ongoing observational case-only trial that ended the recruitment phase of 100 prospective HFrEF patients indicated for SAC/VAL as recommended by recent guidelines with follow-up two dimensional (2D) as well as three dimensional (3D) echocardiography to assess LV volumes, LVEF in a 3-month time frame to evaluate SAC/VAL effects on the functions of the left ventricle utilizing 2D, 3D echocardiography as well as 3D strain parameters [46].

4.13. SAC/VAL in Post-acute Myocardial Infarction

The PARADISE-MI trial (ClinicalTrials.gov number, NCT02924727.) is a multi-center prospective, double-blind phase 3 RCT evaluating ARNI's efficacy and safety compared to ACEI in high-risk patients following an AMI to prove its superiority in the reduction of HF events in these patients [47].

Table 3. Summary of ongoing clinical trials on SAC/VAL.

Study	Patients	Medications used	Enrolment criteria	Endpoints	Follow-up	Results
PARALLAX	2500	SAC/VAL *vs*. Enalapril or Valsartan	- LVEF >40% -NYHA class II-IV requiring treatment with diuretics - left atrial enlargement or left ventricular hypertrophy -Elevated NT-proBNP -KCCQ clinical summary score < 75	-NT-proBNP -6 minute walk distance	-12 weeks -24 weeks	Preliminary results announced
PARAGLIDE-HF	800	SAC/VAL Valsartan	ADHF stabilized during hospitalization and initiated in-hospital or within 30 days post-discharge	-NT-proBNP change from baseline to 4 and 8 weeks. -Composite hierarchical outcome (time to CV death, Total HF hospitalizations, urgent HF visits, NT -ProBNP change from baseline to Weeks 4 and 8 -Cumulative number of recurrent composite overtime (CV death, HF hospitalizations, and urgent HF visits) -Composite RF worsening -NT-proBNP change from baseline to Week 8 -Hs-Troponin (change from baseline to weeks 4 and 8	-4 weeks -8 weeks	March 21, 2022
LIFE	400	SAC/VAL *vs*. Valsartan	-Chronic HF with an LVEF ≤35% -NYHA class IV -3 months of GDMT -Elevated BNP or NT-proBNP	-NT-proBNP change -Composite endpoint consists of: patients are alive and out of hospital, not on transplant list, not implanted or scheduled with an LVAD, not maintained or started on continuous inotropic therapy for ≥ 7 days and not hospitalized twice for HF -Target dose of SAC/VAL -Hypotension, Renal function, hyperkalemia, eGFR and cystatin C level changes. -Inotropic therapy, IV diuretics use	24 weeks	September 21, 2020
PANORAMA-HF	360	SAC/VAL *vs*. enalapril	Pediatric Patients From 1 Month to < 18 Years of Age With Heart Failure Due to LV Systolic Dysfunction	-SAC/ VAL Pharmacokinetics, and Pharmacodynamics -Death, heart transplant list or VAD/ECMO/MV for life support. -Worsening HF, Functional capacity (NYHA/Ross scores)	52 weeks	December 31, 2021
ENTRESTO-SAS	100	SAC/VAL	CHF Patients and SAS	-AHI change compared to baseline -Subject Global Assessment -NYHA class, Heart Rhythm, SBP, DBP -RF compared to baseline -BNP -Quality of life as measured by Minnesota Living with Heart Failure Questionary -Quality of life as measured by EQ-5D-3L Questionary -Epworth Sleepiness Scale -Pichot Fatigue Scale -Type of device used (CPAP/ASV) -CPAP/ASV compliance and settings -Mask type used	3 months	December 15, 2021

(Table 3) contd....

Study	Patients	Medications used	Enrolment criteria	Endpoints	Follow-up	Results
PARADISE-MI	5650	SAC/VAL *vs*. Ramipril	-MI within 12 hours to 7 days of presentation -EF ≤40% or pulmonary congestion requiring IV therapy -Hemodynamic stability	-CV death, HF hospitalization, or outpatient HF -Time to the first confirmed composite of CV death or HF hospitalization -Time to the first confirmed composite of HF hospitalization or outpatient HF -Time to the first occurrence of a confirmed composite of CV death, non-fatal MI or stroke -Total number of recurrent confirmed composite endpoints of CV death, HF hospitalization, non-fatal MI or stroke -Time to all-cause mortality	Up to 43 months	July 9, 2020
RECOVER-LV	93	SAC/VAL *vs*. Valsartan	Asymptomatic LV Systolic Dysfunction After MI	-Change in LVESV index -Change in NT-proBNP, Hs Troponin -Change in LVEDV Index, LAV Index, LVEF, LV Mass Index -Change in patient well being as assessed by Patient global assessment questionnaire	12 months	July 25, 2020
RSV-PAMI	200	SAC/VAL *vs*. Valsartan	In successfully revascularized post-AMI patients with LVEF ≤40%	-1 week MACCE -24 Weeks MACCE - EF change during hospital stay, 3 and 6 months after AMI	6 months	June 1, 2021
nHCM	44	SAC/VAL *vs*. Placebo	nHCM adult patients	-Peak VO2 change from baseline to 50 weeks measured by CPET	50 weeks	May 23, 2022
SILICOFCM	240	SAC/VAL *vs*. Lifestyle	HCM adults patients	-Peak VO2 -LV mass, LVOT obstruction -LVEF (%) -Minnesota Living with Heart Failure questionnaire -SF36 questionnaire -E/A ratio	4 weeks	February 28, 2022

SAC/VAL: Sacubitril/Valsartan, LVEF: Left Ventricualr Ejection Fraction, NYHA, BNP: Brain Naturritic Peptide, CV: Cardiovascular, Hs: High sensitive, Kansas City Cardiomyopathy Questionnaire (KCCQ), ADHF: Acute Decompensated Heart Failure, RF: Renal Function, GDMT: Goal Directed Medical Therapy, LVAD: Left Ventricular Assissed Device, MI: Myocardial Infaction, VAD: Ventricular Assisted Device, ECMO: Extracorporeal Membrane Oxgenation, MV: Mechanical Ventilation, AHI: Apnea Hypoxia Index, CPAP: Continous Positive Airway Pressure, ASV: Adaptive Servo Ventilation, LVESV: Left Ventricular End Systolic Volume, LVEDV: Left Ventricular End Diastolic Volume, LV: Left Ventricular, MACCE: Major Adverse Cardiovascular and Cerebrovascular Events, AMI: Acute Myocardial Infacrtion, NHCM: Non-obstructive Hypertrophic Cardiomyopathy, HCM: Hypertrophic Cardiomyopathy, LVOT: Left Ventricular Outflow Track, CPET: Cardiopulmonary Exercise Test.

The RECOVER-LV trial (ClinicalTrials.gov number, NCT03552575.) will study SAC/VAL effects compared to VAL on LV remodeling in asymptomatic LV systolic dysfunction post-AMI in a double-blinded, Cardiac-MR Based RCT [48].

The RSVP-AMI (The role of Sacubitril-valsartan in post-AMI) (ClinicalTrials.gov number, NCT03893435) will be a randomized open-label interventional clinical trial investigating SAC/VAL effects in post-AMI in patients with reduced LVEF. The primary outcomes will be in-hospital, and 6-month major adverse cardiovascular and cerebrovascular events (MACCE), and LVEF assessed by TTE during the hospital stay, after 3 and 6 months [49].

4.14. SAC/VAL in Pulmonary Hypertension

The PARENT (Pulmonary Artery Pressure Reduction with Entresto) (ClinicalTrials.gov number, NCT02788656.) is a pilot study, which will evaluate SAC/VAL effects versus ACEI/ARB in patients with congestive heart failure having an implanted hemodynamic monitor to assess the pulmonary artery pressure reduction [50].

4.15. SAC/VAL in Non-obstructive Hypertrophic Cardiomyopathy Patients

The ongoing nHCM trial, which is a Multi-center, randomized, placebo-controlled patient and investigator-blinded study, is aimed to explore the efficacy of SAC/VAL in adults with non-obstructive hypertrophic cardiomyopathy (nHCM). It is purposed to discover whether SAC/VAL is safe, tolerable and can results in exercise capacity improvement (*via* increased peak VO2) in non-obstructive HCM patients over a 50-week course of treatment [51].

Another ongoing trial is the SILICOFCM (ClinicalTrials.gov number, NCT03832660) which is an open-label, prospective, multicenter, three-arm randomized control clinical trial recruiting 240 patients with confirmed nonobstructive HCM assigned to SAC/VAL, lifestyle intervention, or optimal standard therapy alone (control group). The primary endpoint will be functional capacity changes (peak oxygen consumption) while secondary endpoints will include: (1) cardiac structure and function changes assessed by TTE and cardiac magnetic resonance (MRI), (2) change in biomarkers changes (CK, CKMB, and NT-proBNP), (3) physical activity and quality of life [52].

CONCLUSION

The introduction of SAC/VAL to the regimen of HF management had a revolutionary effect with its proven superiority over ACE inhibitors in HFrEF patients. Based on the promising results of several newly published and ongoing trials, the expansion of SAC/VAL indications is just a matter of time.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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