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Review Article

Renin-angiotensin-aldosterone system inhibition in patients affected by heart failure: efficacy, mechanistic effects and practical use of sacubitril/valsartan. Position Paper of the Italian Society of Cardiology

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ABSTRACT

Renin-angiotensin-aldosterone system (RAAS) inhibition is a mainstay of the pharmacological treatment of heart failure with reduced ejection fraction (HFrEF). In the last years RAAS blockade has been improved by the introduction of the Angiotensin Receptor-Neprilysin Inhibitor (ARNI) sacubitril/valsartan, that combines RAAS inhibition with the block of neprilysin, boosting the positive effects of natriuretic peptides. The PARADIGM-HF trial demonstrated a significant advantage of sacubitril/valsartan over enalapril on the reduction of cardiovascular (CV) mortality and heart failure hospitalizations rates. Then, several randomized clinical trials and observational studies investigated its role in different clinical settings and its efficacy has been fully recognized in the most recent HFrEF European and USA guidelines. The effects of sacubitril/valsartan on major CV outcomes are associated with reduction of NT-proBNP levels and reverse cardiac remodeling and mitral regurgitation, recognized as one of the mechanistic effects of the drug explaining the favorable prognostic effects. A careful evaluation of patients' clinical profile is relevant to implement the use of ARNI in the clinical practice and to obtain the maximal treatment efficacy. The present Position Paper reports the opinion of the Italian Society of Cardiology on the optimal blockade of the RAAS system in HF patients with the aim of fostering widespread implementation of scientific evidence and practice guidelines in the medical community.

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Renin-angiotensin-aldosterone system (RAAS) activation is one the main pathophysiological mechanisms involved in the development and progression of heart failure (HF) and its inhibition is a mainstay of the pharmacological treatment of HF with reduced ejection fraction (HFrEF) [1]. In the last years several trials investigated the role of RAAS modulation in HF and, recently, RAAS blockade has been further developed by the introduction of the Angiotensin Receptor-Neprilysin Inhibitor (ARNI) sacubitril/valsartan, that combines RAAS inhibition with the antagonism of neprilysin (NEP), boosting the positive effects of natriuretic peptides [2]. In parallel, novel pharmacological approaches, namely SGLT2 inhibition, have demonstrated to favorably modify the course of HFrEF, and were introduced among recommended disease modifying therapies in recent European Guidelines [3]. The current Position Paper of the Italian Society of Cardiology focalizes on RAAS modulation with sacubitril/valsartan, providing a practical approach to optimized RAAS inhibition in the context of new evidence for pharmacological treatment of HFrEF.

1. RAAS modulation in HFrEF

Several and consistent data, from randomized controlled studies, have demonstrated the efficacy of RAAS blockade in HFrEF (Fig. 1). In 1998 the CONSENSUS study [4] firstly reported a 31% mortality risk reduction with enalapril in patients with advanced symptomatic HF; similarly, in the SOLVD trial [5] enalapril reduced by 16% all-cause mortality and by 26% the composite outcome of hospitalization due to HF (HHF) and death in patients with EF ≤35% and stable clinical conditions (NYHA class II/III). Subsequently, the trials SAVE [6], TRACE [7] and AIRE [8] confirmed the efficacy of captopril, trandolapril, and ramipril in post-myocardial infarction HF. Moreover, the ATLAS trial [9] reported a greater beneficial effect of high-dose lisinopril compared to low-dose, in particular patients in the high-dose group had a non-significant 8% lower risk of death ($p = 0.128$) but a significant 12% lower risk of death or hospitalization for any reason ($P = 0.002$) and 24% fewer HHF ($P = 0.002$). Thus, in the context of RAAS inhibition also the dose matters. Then, at the beginning of '90 the pharmacological research focused on the development of AT1R antagonists, generating the angiotensin receptor blockers (ARBs), that antagonize the effects of Angiotensin II independently from the mechanisms involved in its synthesis, as the chymase pathway activated as an escape mechanism in patients treated with ACE inhibitors (ACEi). In the Val-HeFT trial [10], enrolling patients with EF <40% and in NYHA class II-IV, valsartan reduced by 13% cardiovascular (CV) mortality and by 27% HHF. The CHARM-Reduced study, derived from a joint analysis of CHARM-Added and CHARM-Alternative, [11] enrolled patients with EF <40% demonstrating that candesartan reduced by around 20% the composite of CV mortality and HHF. Later, the role of mineralocorticoid receptor antagonists (MRA) was investigated. The RALES trial [12] enrolled patients in NYHA class III/IV with EF ≤35% and reported a 30% reduction of all-cause mortality and a 35% reduction of HHF in patients treated with spironolactone on top of an ACEi. The EMPHASIS-HF trial [13] reported, in patients with EF ≤35%, a 23% reduction of the risk of CV mortality and a 39% reduction of the risk of HHF in patients receiving eplerenone compared to placebo. Finally, the EPHESUS trial [14], the first major trial of eplerenone in post-myocardial infarction HFrEF, demonstrated that the addition of eplerenone to optimal medical therapy reduced morbidity and mortality in this setting (Table 1).

2. RAAS modulation in HF with preserved EF (HFpEF)

In patients with HFpEF modulation of RAAS led to non-significant effects. The CHARM-Preserved trial [15], conducted on patients with EF >40%, reported no significant differences between candesartan and placebo in the composite outcome of CV mortality and HHF. However, a lower number of hospitalizations was observed in the candesartan group ($p = 0.017$). The I-Preserved trial [16], conducted on patients with EF of at least 45%, showed no significant differences between irbesartan and placebo on the primary outcome of death from any causes or hospitalization for a CV cause. The TOPCAT study [17], enrolling patients with EF ≥45%, reported a significant reduction of HHF in spironolactone-treated patients, however no differences vs. placebo in the primary composite outcome of CV mortality, HHF, resuscitated cardiac arrest and total hospitalizations. Similarly, the PEP-CHF trial [18] reported with perindopril a reduction of HHF with no effects on the primary outcome of non-planned HHF and CV mortality.

3. Beyond RAAS inhibition: sacubitril/valsartan

Sacubitril/valsartan is the prototype of a new class of drugs known as ARNI [19], developed to deal with two main pathophysiological HF mechanisms: RAAS activation, inhibited by valsartan, and reduced sensitivity to the system of natriuretic peptides (NP), boosted by the inhibition of NEP with sacubitril [20].

3.1. Natriuretic peptides/neprilysin system

ANP and BNP are the main NP, together with their amino-terminal fragments (NT) and the prohormone from which they derive. ANP and BNP levels in HF increase proportionally to the severity of left ventricular (LV) dysfunction, and the long-lasting half-life of BNP and NT-proBNP (20 and 120 min, respectively) allow their use as clinical and prognostic indicators [21]. ANP and BNP act both as hormones and autacoids, increasing natriuresis, inhibiting renin and aldosterone release, reducing blood pressure by vasodilation and by increasing

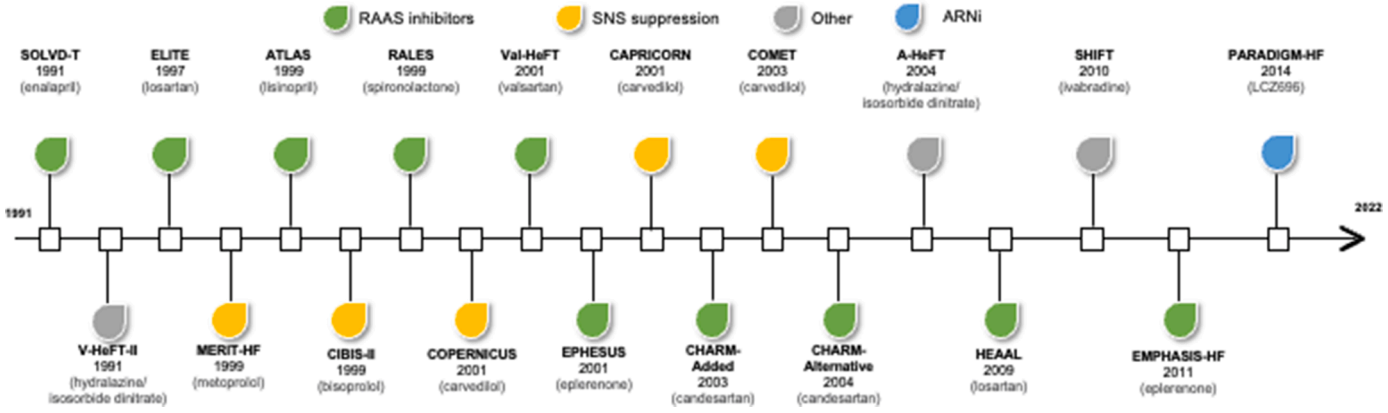

Fig. 1. Clinical trials on HFrEF patients.
RAAS = Renin-angiotensin-aldosterone system; SNS = Sympathetic nervous system.

vascular permeability. Moreover, in a paracrine way, they favorably affect fibrosis and LV hypertrophy, counterbalancing RAAS and sympathetic nervous system activation. ANP and BNP are cleaved and inactivated by a membrane bound endopeptidase, NEP. With the progression of HF, a state of resistance to the beneficial effect of NP occurs, thus providing the rationale for NEP inhibition. In the OVERTURE trial [22], omapatrilat, a combined NEP and ACEi, did not reduce CV outcome while increasing the incidence of angioedema due to the elevation of bradykinin levels caused by the inhibition of both ACE and NEP. Thereafter, pharmacological research concentrated on the combination of NEP inhibition with ARBs, that do not interfere with bradykinin metabolism. Sacubitril/valsartan is a single pill drug combination of sacubitril, a NEP inhibitor, and valsartan, an AT1R antagonist, and represent the successful completion of this efforts.

3.2. Sacubitril/valsartan clinical trials: PARADIGM-HF, PARAGON-HF, PARADISE-MI

3.2.1. PARADIGM-HF

The PARADIGM-HF [23] has been the first double blind head-to head trial investigating the effects of ARNI vs enalapril on top of beta blockers and MRA (Fig. 2) in 8442 stable HFrEF patients (NYHA class II-IV, EF <40%). The study was prematurely stopped, after a median follow-up of 27 months, due to an evident excess of benefit of sacubitril/valsartan over enalapril, with a risk reduction of 20% for the primary endpoint of CV mortality or HHF (HR 0.80, 95% CI 0.73-0.87, $p < 0.001$) (Fig. 3), that was also observed for the single components (-21% HHF; -20% CV mortality). Notably, the reduction of CV mortality was equally due to reduction of HF progression and of sudden death (HR 0.79, 95% CI 0.64–0.98, $p = 0.034$ vs. HR 0.80, 95% CI 0.68–0.94, $p = 0.008$, respectively) [24]. Sacubitril/valsartan significantly increased BNP levels, reducing NT-proBNP concentrations on which is inactive [25]. The study also reported good drug tolerability with a lower incidence of worsening renal function and hyperkalemia vs enalapril, however causing a greater tendency to hypotension.

The study design (head-to head comparison of two active treatments) and results of the PARADIGM-HF trial led to a Class I Recommendation for switching from ACEi to sacubitril/valsartan in HFrEF in the recent European Guidelines [3], with a preferential use of ARNI over RAAS inhibitors. In the Paradigm HF trial only NT-proBNP peptides changes were reported, and, therefore, the correlation between clinical effects and peptides changes could be only partially elucidated [26]. In particular, effects of ARNI-induced ANP changes would have contributed to clarify the role of this peptide, sharing natriuretic, insulin-sensitizing and sympathetic nervous system modulating properties, that might concur to the favorable effects of ARNI.

3.2.2. PARAGON-HF

The PARAGON-HF trial [27] investigated the effects of sacubitril/valsartan in HFpEF patients (EF ≥45%) on a primary endpoint of CV mortality and total HHF. The study enrolled 4822 patients and 894 primary events occurred in the sacubitril/valsartan group vs 1009 in the valsartan group, yet missing statistical significance (HR 0.87, 95% CI 0.75–1.01, $p = 0.06$) (Fig. 3). The prespecified subgroup analysis showed a significant interaction with sex and EF with an evident benefit of sacubitril/valsartan in patients with EF ≤57%, in women and in patients treated with MRA.

A combined analysis of PARADIGM-HF and PARAGON-HF trials, aiming to assess the efficacy of sacubitril/valsartan along the EF spectrum, observed a significant reduction (16%) of the composite outcome of CV mortality and first HHF, a 12% reduction of all-cause mortality, and a 18% reduction of total hospitalizations and HF mortality, suggesting that the effects of sacubitril/valsartan also extend to patients with mildly reduced EF (HFmrEF) [28]. Thus, in 2021 the FDA approved

Table 1
RAAS inhibitors trials in HFrEF.

ACEi						
Study name	**N. pts**	**NYHA class**	**EF as inclusion criteria**	**Primary endpoint**	**Mean FU duration**	**Results**
CONSENSUS [4]	253	IV	Not measured	All-causes mortality	6 months	HR 0,69 (p=0,001)
SOLVD [5]	2569	I-IV	≤35%	All-causes mortality	41,4 months	HR 0,84 (p=0,0036)
SAVE [6]	2231	Not evaluated	≤40%	All-causes mortality	42 months	HR 0,81 (p=0,019)
TRACE [7]	1749	I	≤35%	All-causes mortality	36 months	RR 0,78 (95% CI 0,67-0,91; p=0,001)
AIRE [8]	2006	II-III	≤40%	All-causes mortality	15 months	HR 0,63 (p=0,002)
ARBs						
Study name	**N. pts**	**NYHA class**	**EF as inclusion criteria**	**Primary endpoint**	**Mean FU duration**	**Results**
Val-HeFT [10]	5010	II-IV	<40%	Time to death and time to first morbid event, defined as death, sudden death with resuscitation, requirement of intravenous therapy for HF or HHF	23 months	RR 0,87 (97,5% CI 0,77-0,97; p=0,009)
CHARM [11]	4576	II-IV	≤40%	CV death or HHF	40 months	HR 0,82 (95% CI 0,74-0,90; p<0,001)
MRA						
Study name	**N. pts**	**NYHA class**	**EF as inclusion criteria**	**Primary endpoint**	**Mean FU duration**	**Results**
RALES [12]	1663	III-IV	≤35%	All-causes mortality	24 months	RR 0,70 (95% CI 0,60-0,82; p<0,001)
EMPHASIS-HF [13]	2737	II	≤35%	CV death or HHF	21 months	HR 0,63 (95% CI 0,54-0,74; p < 0,001)
EPHESUS [14]	6642	Not evaluated	≤40%	All-causes mortality	16 months	RR 0,85 (95% CI 0,75-0.96; p=0.008)

ACEi = ACE inhibitors; ARBs = Angiotensin receptor blockers; CV = Cardiovascular; EF = Ejection Fraction; FU = Follow-up; HF = Heart failure; HHF = Hospitalization for heart failure; HR = Hazard ratio; MRA = mineralocorticoid receptor antagonists; RR = Risk reduction.

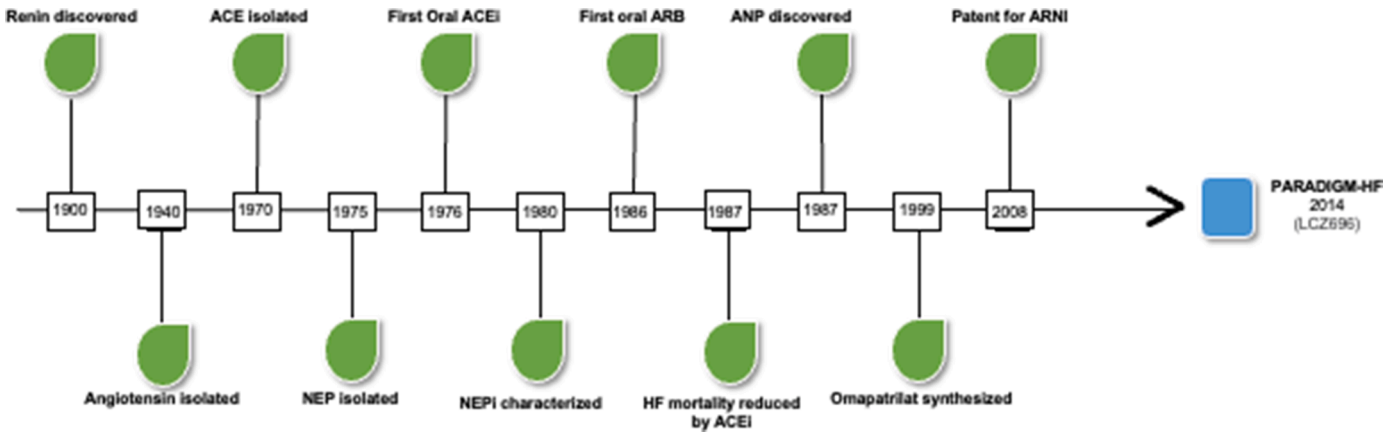

Fig. 2. Pathway leading to the PARADIGM-HF trial.
Modified from ref#22 ACE = Angiotensin converting enzyme; ACEi = ACE inhibitors; ANP = Atrial natriuretic peptide; ARB = Angiotensin receptor blockers; ARNI = Angiotensin receptor-neprilysin inhibitor; HF = Heart failure; NEP = Neprilysin; NEPi = NEP inhibitors

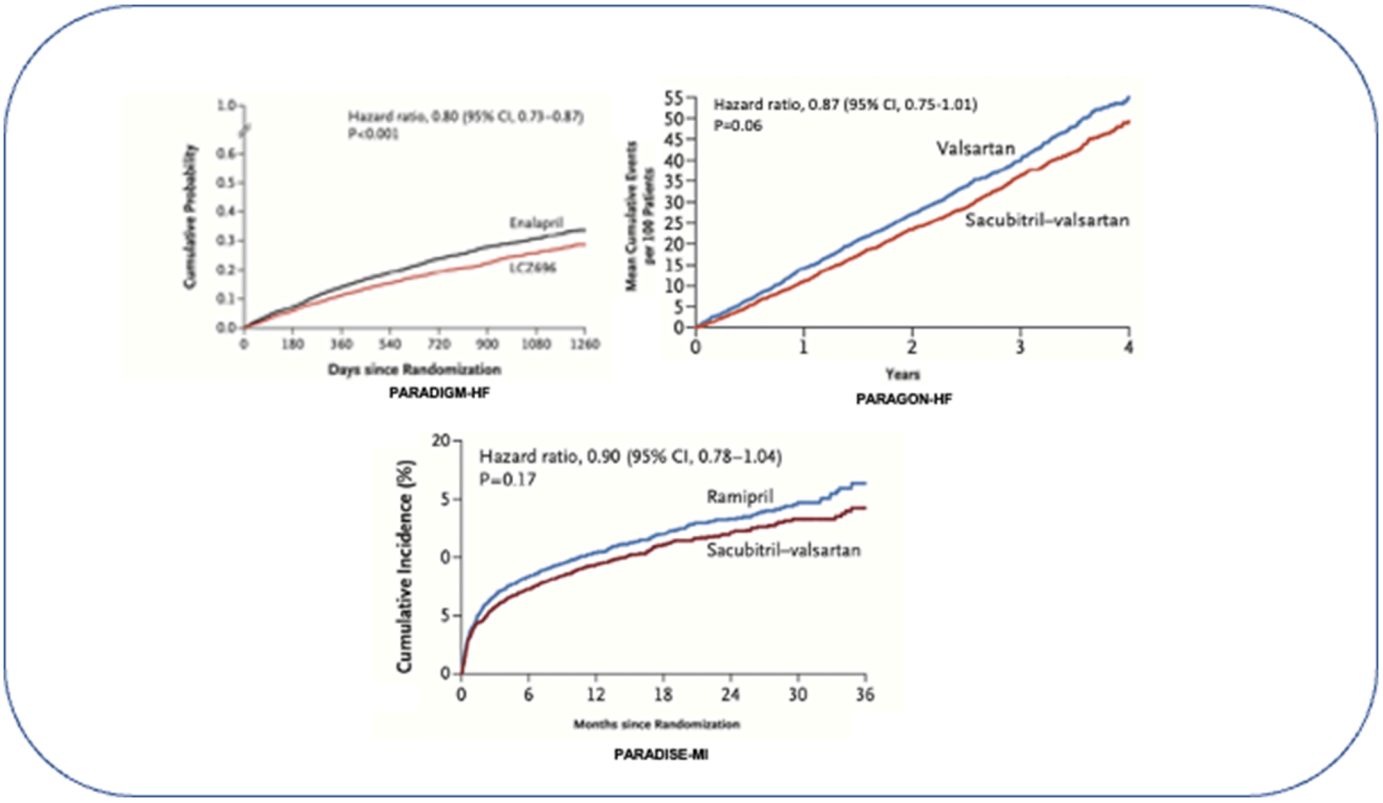

Fig. 3. Primary endpoint of the PARADIGM-HF, PARAGON-HF and PARADISE-MI trials.

the use of sacubitril/valsartan in HF patients with an EF below the normal value, considering the variability of EF measurement and leaving the choice to clinical judgment. Notably, at variance with the Paradigm HF trial, the Paragon Study compared sacubitril-valsartan to valsartan, thus normalizing the effects of the combination for the presence of valsartan, that might have diluted the favorable effects of ARNI.

3.2.3. *PARADISE-MI*

The PARADISE-MI [29] investigated the effects of sacubitril/valsartan vs ramipril on a combined endpoint of HF and CV mortality in patients with a recent (12 hours to 7 days) acute myocardial infarction (AMI) and EF ≤40%. No significant differences were observed between the two treatment strategies (Fig. 3); in a subgroup analysis a lower number of events with sacubitril/valsartan was reported in patients aged ≥65 years or treated with PCI.

3.3. *Sacubitril/valsartan use in clinical practice: TITRATION, PIONEER and TRANSITION studies*

The TITRATION study aimed at evaluating the tolerability of initiating/uptitrating sacubitril/valsartan in daily clinical practice, using a 'condensed' (3 weeks) vs a 'conservative' (6 weeks) regimen [30]. A similar proportion of patients in the two groups reached the maximal dose of 97/103 mg bid (77.8% and 84.3%, respectively; ($p = 0.078$)); more gradual initiation/uptitration maximized attainment of target dose in *de novo* patients, in patients with a systolic blood pressure <110

mmHg, in those naïve to RAAS inhibitors, and in patients coming from low-dose ACEi/ARBs [31].

The PIONEER trial [32] investigated whether the initiation of sacubitril/valsartan is safe and effective in patients hospitalized for acutely decompensated HF. The study enrolled 881 hospitalized patients randomly assigned to sacubitril/valsartan or enalapril after hemodynamic stabilization that were followed up for 8 weeks. A significant (within one week) more pronounced reduction of NT-proBNP was observed (primary endpoint) with sacubitril/valsartan vs enalapril (percent change -47% vs. -25%); rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not significantly differ between the two groups.

Similarly, the TRANSITION study [33] assessed safety and tolerability of sacubitril/valsartan in 1002 patients stabilized after an episode of HHF; the drug was administered in-hospital or within two weeks from discharge. The proportion of patients reaching the maximal dose of 97/103 mg bid at 10 weeks (primary endpoint of the study) was similar between the two groups (45% vs. 50.4%, respectively; RR 0.89, 95% CI 0.78–1.01), including 29% of patients with *de novo* HFrEF and 24% not treated with RAAS inhibitors [34].

Thus, TRANSITION and PIONEER trials established the safety and tolerability of sacubitril/valsartan also in post-acute HF patients, extending these data to *de novo* HF patients in whom treatment can be initiated without the need of a pre-treatment with ACEi/ARBs (Class IIb recommendation in European Guidelines).

3.4. Mechanisms of sacubitril/valsartan benefit on clinical outcomes

Cardiac remodeling is a main step in the progression of HFrEF and is characterized by changes in LV geometry and in myocardial function; it is associated with an increased risk of adverse events and represents an important therapeutic target. In HFrEF, the beneficial effect of beta-blockers [35,36], ACEi, ARBs, and MRA on cardiac remodeling has been related to reduced levels of natriuretic peptides and to reduced mortality rates [3].

The PROVE-HF [37] was an open-label study conducted in 794 HFrEF patients initiating sacubitril/valsartan and followed for 12 months, aimed to assess a correlation between NP reduction and cardiac remodeling. The trial reported a significant reduction of LV volumes and an improvement of EF, already observed at 6 months, and continued up to 12 months of follow-up, together with a reduction of left atrial volume and an improvement of diastolic function. Over time NT-proBNP changes were significantly correlated with parameters of inverse cardiac remodeling, including LV end-diastolic and end-systolic volume, EF, left atrial volume and diastolic function; results were confirmed in all prespecified subgroups, including *de-novo* o RAAS inhibitors naïve patients.

In addition, the PRIME study [38] randomized 118 HFrEF patients to sacubitril/valsartan or valsartan for 12 months investigating the effects on a primary endpoint represented by change in effective regurgitant orifice area of functional mitral regurgitation, reporting a more pronounced decrease in the sacubitril/valsartan group compared to the valsartan group. Altogether, these data bring evidence to the favorable effects of sacubitril/valsartan on LV volumes, thereby leading to reduced mitral regurgitation, that are reflected by proportional changes in the plasma NT-proBNP levels and likely represent a relevant mechanism for reduced progression of HF (and associated CV mortality) observed in treated patients.

The PARADIGM-HF trial reported a 22% reduction of the risk of sudden cardiac death in patients treated with sacubitril/valsartan [23]. This effect was mostly relevant in the subgroup on “non-ischemic cardiomyopathy” and independent from implantable defibrillator that was present in 15% of enrolled patients [39]. Small studies reported a reduced arrhythmic burden with fewer defibrillator interventions in patients on ARNI [40,41], yet there are no definitive explanations for these effects. An effect on the neuro-hormonal pathway has been also proposed as an alternative/complementary explanation of this effect [42].

3.5. Quality of life and functional capacity

A sub-analysis of the PARADIGM-HF trial [43] conducted on 7623 patients that completed the Kansas City Cardiomyopathy Questionnaire (KCCQ), reported a significant improvement in sacubitril/valsartan vs enalapril patients. The PARALLAX trial [44] observed, in 2572 HFpEF patients followed for a median of 24 weeks, a greater reduction of NT-proBNP levels with sacubitril/valsartan vs RAAS inhibitors or placebo. However, no differences were reported for NYHA class, functional capacity at the 6MWT or CPET [45] and quality of life at KCCQ, despite a decline in the progression of renal dysfunction and reduced rates of HHF.

The effects of sacubitril/valsartan on functional capacity are more controversial. A first pilot study [46] in 58 HFrEF patients initiating sacubitril/valsartan, reported an improvement in 6MWT distance after 30 days of treatment (+13.9%). However, a more recent study [47] conducted in 52 patients, confirmed the improvement of exercise capacity after initiation of sacubitril/valsartan, but no differences in peak VO_2 or 6MWT distance were observed vs enalapril after 12 and 24 weeks.

3.6. Renal effects of RAAS inhibitors

An impairment of glomerular filtration rate (GFR) is frequent in HF and is associated with higher rates of mortality and CV events [48,49]. Moreover, the presence of renal impairment often hampers the optimization of HFrEF pharmacological treatment [3].

The interaction between the heart and the kidney leads to a condition known as cardiorenal syndrome, a vicious circle between cardiac failure and renal disease. The inadequate renal perfusion due to HF is responsible of RAAS activation, increased post-glomerular resistance and preferential vasoconstriction of the efferent arteriole with increased intra-glomerular pression, finalized to maintain constant filtration rate and GFR. In this context, RAAS inhibition leads to efferent arteriole vasodilation, often causing a reduction in GFR; ARNI, through NP effects, causes pre-glomerular arteriole dilation and increased diuresis, natriuresis, and glomerular permeability [48,50].

In the PARADIGM-HF trial [23] the greater efficacy of sacubitril/valsartan over enalapril was confirmed also in patients with chronic renal disease at baseline; moreover, ARNI treatment was associated with slower progression of renal dysfunction [51], lower rates of hyperkalemia [52], and lower diuretics’ use [53].

4. Recommendations for the use of ARNI in guidelines

4.1. HFrEF

American College of Cardiology/American Heart Association (ACC/AHA) 2016 Guidelines and the 2017 update [54,55] positioned sacubitril/valsartan in Class I of Recommendation (Level of Evidence B-R - Randomized) for HFrEF patients, including patients on RAAS inhibitor treatment and those naïve to treatment. This concept has been further reinforced in the 2021 ACC/AHA update [56] where ARNI is suggested as first therapeutic choice for symptomatic HFrEF (stage C) together with a beta-blocker, using ACEi or ARBs only in patients with a contraindication to ARNI, then considering the introduction of other drugs depending on the phenotype of single patient.

2021 European Society of Cardiology (ESC) Guidelines [3], compared to previous 2016 recommendations [57], reported relevant changes on the optimization of pharmacological therapy for HFrEF, including:

1. The presence of a central therapeutic algorithm for all HFrEF patients, that includes ACEi/ARNI, beta-blockers, MRA and SGLT2

inhibitors, considered "disease modifier" drugs, with the recommendation of a fast (within weeks) introduction and uptitration of all classes;

2. An upgrade of sacubitril/valsartan and MRA as first line treatments with a Class I (Level of Evidence B) Recommendation for sacubitril/valsartan to replace ACEi in HFrEF, and a Class IIb (Level of Evidence B) Recommendation in naïve or *de novo* patients;

3. Introduction of SGLT2 inhibitors as new class of drugs with a Class I (Level of Evidence A) Recommendation in HFrEF;

Thus, a key point of these Guidelines is the remodulation of the therapeutic algorithm, with the introduction of the concept of "disease modifier" drugs that positively interfere with CV mortality and HHF (beta-blockers, RAAS inhibitors or preferentially ARNI, MRA and SGLT2 inhibitors) and the removal of a stepwise drug introduction guided by persistence of symptoms. In this new approach, the four classes of "disease modifier" drugs are considered to provide synergistic effects and need to be introduced in a short-time period (4-6 weeks), then gradually titrated up to the maximal tolerated dose [58,59].

4.2. HFmrEF

In recent ESC Guidelines diuretics are the only drugs with Class I Recommendation to alleviate symptoms due to congestion. Pharmacological treatment for HFrEF, including ARNI, have a Class IIb recommendation, reflecting the lack of definitive evidence of benefit at the time of ESC Guidelines publication in 2021.

4.3. HFpEF

These patients, compared to those with HFrEF are more frequently women and older; comorbidities as atrial fibrillation and renal dysfunction are more common in HFpEF than in HFrEF. When ESC 2021 Guidelines [3] were published, no treatment had demonstrated significant benefit in this setting. Thus, the recommended therapeutic approach is an optimal comorbidities management according to the phenotype of patients. However, at the time of Guidelines publication, results of the EMPEROR-Preserved trial [60] were published, reporting a significant effect of empagliflozin on the combined endpoint of CV mortality and HHF, independent from the presence of diabetes mellitus at baseline and mainly due to a reduction in HHF. Moreover, from a combined analysis of PARADIGM-HF and PARAGON-HF trial [28], the efficacy of sacubitril/valsartan was evident up to EF value of 55%, thus including a subgroup of HFpEF patients, with a beneficial effect in women also seen at higher EF.

5. The position of the Italian Society of Cardiology

ESC Guidelines recommend in patients with HErEF, without contraindications and whenever possible, the use of ARNI to be preferred as one of the RAAS inhibitors, then adding SGLT2 inhibitors on top of RAAS inhibition and beta-blocking; nevertheless, a wide debate in the scientific community have ensued due to the lack of clear indications for sequencing of drug implementation, especially in *de novo* patients, and to the consideration that SGLT2 inhibitors have more neutral effects on hemodynamics, mainly heart rate and blood pressure, making them quite well tolerated, in addition to the lack of uptitration. In fact, the introduction and increase of ARNI dose may be hampered by systolic blood pressure below 100 mmHg, the limit adopted in the PARADIGM-HF [23], and by severely reduced glomerular filtration rate (<30 ml/min). Yet, it is the opinion of this panel that, due to the consideration that all evidence of benefit from SGLT2 trials was derived from patients treated with beta-blockers and RAAS blockers (including ARNI), all efforts should be pursued to include RAAS blockers, preferably ARNI as first line therapy (together with beta-blockers) in the treatment of HFrEF patients. Implementation and uptitration of ARNI may be facilitated by reducing non-modifier therapies that reduce blood pressure, like calcium channel blockers, nitrates and diuretics, in favor of disease modifying agents. The use of ambulatory blood pressure measurement could be relevant in those patients with a pressure profile borderline for ARNI introduction and to evaluate ARNI therapy pressure effect after drug initiation. Notably, analysis from the PARADIGM-HF clearly indicate the benefit of ARNI vs. enalapril in patients not reaching the highest dose or in whom a downtitration was needed, reporting that any dose reduction was associated with a higher subsequent risk of the primary event (HR 2.5, 95% CI 2.2–2.7) [61]. The introduction of ARNI in patients already on RAAS inhibitors should follow a washout time of at least 36 hours if on ACEi in order to reduce the risk of angioedema, while no washout time is necessary if the RAAS inhibitor is an ARB.

The panel identified the following **phenotypes** (Fig. 4) for treatment:

5.1. De novo HFrEF (acute or chronic)

ESC Guidelines consider the possibility that patients with de novo HFrEF may start sacubitril/valsartan, with a IIb Class of Recommendation, Level of Evidence B [3]. In fact, some studies reported the safety and efficacy of sacubitril/valsartan when started early in hospitalized patients with newly diagnosed HF. In the PIONEER-HF trial, 303 (34%) patients had *de novo* HF and 459 (52%) were not receiving ACEi [25]. In the TRANSITION trial, 286 (29%) patients had *de novo* HF and 241 (24%) had never been treated with an ACEi [32]. The effect of an early introduction of sacubitril/valsartan was assessed in a post-hoc analysis of the PIONEER-HF trial reporting a 42% decrease in CV death and HHF compared to patients treated with enalapril [62]. Additionally, a subgroup analysis from the TRANSITION trial reported that the risk-benefit profile of sacubitril/valsartan as first-line treatment was superior in patients with acute *de novo* HF compared to those with known HF [34]. This panel agrees that sacubitril/valsartan should be considered as first line therapy for RAAS inhibition in *de novo* patients.

5.2. Acute HFrEF patients already on RAAS inhibitors

Sacubitril/valsartan has been demonstrated to be safe and efficacious when started in-hospital or within few days after discharge in patients stabilized after acute deterioration of HF [32,33]. The early separation of the curves and the magnitude of the benefit in terms of event reduction (CV mortality and HHF) match the benefits reported in the PARADIGM-HF trial in patients with chronic HF, that was also evident and more robust in patients with recent hospitalization [63].

This panel agrees that the same ESC Guidelines recommendation for chronic patients be applied in this clinical context, that is replacement of ACEi in acute stabilized patients, following a washout time of at least 36 hours.

5.3. Chronic HF patients on RAAS inhibitors

Evidence from PARADIGM-HF trial [23], that compared two active treatments in a head-to-head study design, prompted ESC Guidelines to recommend replacement of ACEi with ARNI in chronic patients with HFrEF independently of symptoms (Class I, Level of Evidence B). Prospective registries confirmed treatment's effectiveness and tolerability in clinical practice, with a higher risk of death from any cause in patients who stopped sacubitril/valsartan [64]. However, there is a gap between the patients included in the trials and the "real-world" population suitable for treatment, which is expected to range from 34 to 76% of patients with HFrEF. This Panel strongly supports adoption of this recommendation in clinical practice [65].

5.4. Post-acute myocardial infarction patients with reduced EF

In a small trial enrolling 200 patients with ST segment elevation MI within 24 hours from onset, sacubitril/valsartan was compared to ramipril for the occurrence of MACE (CV death, AMI or stroke) at 30

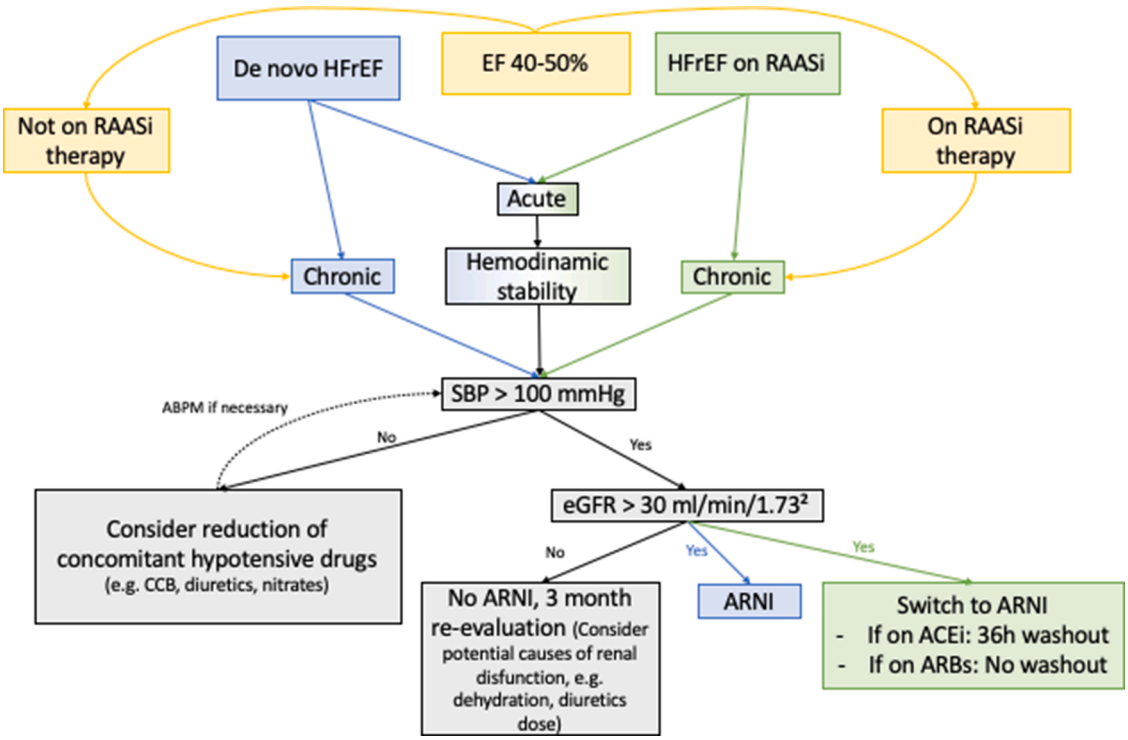

Fig. 4. Suggested therapeutic algorithm for ARNI introduction.
ABPM = Ambulatory blood pressure measurement; ACEi = ACE inhibitors; ARB = Angiotensin receptor blockers; ARNI = Angiotensin receptor-neprilysin inhibitor;; CCB = Calcium channel blockers; EF = Ejection fraction; eGFR = Estimated glomerular filtration rate; HFrEF = Heart failure with reduced ejection fraction; RAASi = Renin-angiotensin-aldosterone system inhibitors; SBP = Systolic blood pressure.

days and 6 months of follow up. Sacubitril/valsartan did not reduce MACE at 1 month, whereas a significant reduction occurred at 6 months and that was accompanied by improvement of EF and LV volumes compared to ramipril [66]. However, the PARADISE-MI trial [28] failed to demonstrate that sacubitril/valsartan was more effective than ramipril in reducing CV death and development of HF in 5669 patients with acute MI and evidence of LV systolic dysfunction (EF<40%) or pulmonary congestion, most of them treated with percutaneous revascularization. When all hospitalizations for HF were included in the composite outcome, patients treated with ARNI showed a significant benefit compared to those treated with ramipril. Finally, McMurray's et al. reported that in asymptomatic patients with LV systolic dysfunction secondary to prior MI, sacubitril/valsartan did not improve remodeling compared to ARBs alone [67]. Thus, this panel acknowledge the lack of benefit evidence regarding the use of ARNI in patients developing post—MI LV systolic disfunction and the need of further investigations in this setting. Yet, patients with chronic ischemic HFrEF are to be considered as belonging to phenotype 3 (see above).

5.5. Patient with mildly reduced or preserved EF

ESC Guidelines recommendations consider sacubitril/valsartan in patients with HF and mildly reduced EF (Class of Recommendation IIb, Level of Evidence C) [3]. This indication comes from the combined analysis of PARADIGM-HF and PARAGON-HF trials, that reported a benefit of treatment up to ejection fraction of 55% [63]. This Panel agrees that sacubitril/valsartan should be considered for treatment of patients with mildly reduced EF whereas no definitive evidence support the use in patients with preserved EF.

6. Conclusion

From earliest observations to date, RAAS inhibitors demonstrated to substantially improve mortality and mobility in HF patients with reduced EF, thereby representing a disease modifier therapy in this clinical setting. More recently combined RAAS-NEP inhibition with sacubitril/valsartan provide strong evidence of more effective antagonism of RAAS activation compared to ACE inhibition in patients with HFrEF, leading to recent recommendation for replacement of ACEi in patients with chronic HFrEF in ESC Guidelines [3]. Yet, despite the majority of patients with HFrEF would be eligible for treatment, a large number of them remain untreated [68], thus limiting the full benefits of optimized therapy for patients with HFrEF. This document represents the position of the Italian Society of Cardiology on the use of ARNI in clinical practice, with the aim to support implementation of scientific evidence and Guidelines recommendations across the clinical community.

Declaration of Competing Interest

None.

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