

Sacubitril/valsartan versus angiotensin inhibitors and arrhythmia endpoints in heart failure with reduced ejection fraction



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BACKGROUND Angiotensin receptor–neprilysin inhibitor (ARNI) therapy has been associated with improved survival for patients with symptomatic heart failure and reduced ejection fraction (HFrEF).

OBJECTIVES We performed a meta-analysis of arrhythmia endpoints from studies comparing ARNI with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for patients with HFrEF to assess for incremental benefit.

METHODS We searched PubMed, Embase, and ClinicalTrials.gov. Baseline study characteristics were collected and outcomes were sustained ventricular arrhythmias, atrial arrhythmias, appropriate implantable cardioverter-defibrillator (ICD) therapy, sudden cardiac death (SCD), and biventricular (BiV) pacing rate.

RESULTS We included 9 studies, 4 randomized trials, and 5 observational studies (5589 patients on ARNI vs 5615 on ACEIs/ARBs). Follow-up ranged from 2 to 51 months. The mean age was 65.4 ± 9.8 years, with 77.3% male patients and a mean ejection fraction of 29.0% ± 7.6%. Ischemic cardiomyopathy was present in 62%

of patients. In the ARNI group, there were less SCD (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.63–0.96; $P = .02$), ventricular arrhythmias (OR 0.45, 95% CI 0.25–0.79; $P = .005$), and appropriate ICD therapy (OR 0.39, 95% CI 0.21–0.74; $P = .004$). Higher rates of BiV pacing were seen (mean difference 3.13, 95% CI 2.58–3.68; $P < .00001$) when compared with ACEIs/ARBs. No difference in atrial arrhythmias was seen.

CONCLUSION ARNI therapy provides incremental benefit with respect to ventricular tachyarrhythmias/SCD, which may, in part, explain improved outcomes in patients with HFrEF compared to ACEIs/ARBs. There was increased BiV pacing and decreased ICD therapy in the ARNI group.

KEYWORDS Angiotensin receptor antagonists; Antiarrhythmia agents; Heart failure; Sacubitril-valsartan; Sudden cardiac death

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Introduction

The underlying pathophysiology for arrhythmogenesis in patients with heart failure with reduced ejection fraction (HFrEF) is complex and multifactorial, including fibrosis, neurohormonal imbalances, dysregulation of calcium homeostasis, endothelial factors, and alterations in the expression of ion channels.^{1,2}

Sacubitril/valsartan, an angiotensin receptor–neprilysin inhibitor (ARNI), has been broadly recommended for patients with HFrEF since the survival benefit

demonstrated in the PARADIGM-HF trial.³ The latest 2021 update to the 2017 American College of Cardiology Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment recommends the use of ARNI rather than angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as a class I recommendation in addition to beta blockers, aldosterone antagonists, and sodium-glucose cotransporter-2 inhibitors in patients with HFrEF, unless contraindicated.⁴ A recent meta-analysis including 20 studies and 10,175 patients demonstrated improvement in cardiac reverse remodeling with ARNI compared with ACEIs/ARBs for both ischemic and nonischemic cardiomyopathy, at 3-month follow-up and with even more pronounced effect at 12 months.⁵

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KEY FINDINGS

- Angiotensin receptor–neprilysin inhibitor (ARNI) use in patients with heart failure and reduced ejection fraction was associated with a lower incidence of sudden cardiac death and ventricular arrhythmias and lower rates of appropriate defibrillator shocks.
- Biventricular (BiV) pacing percentage is inversely proportional to ventricular arrhythmias and a subanalysis of observational studies demonstrated higher BiV pacing rates in the group treated with ARNI.
- The role of ARNI as a potential antiarrhythmic should be further explored and the modulation of the calcium homeostasis might be one of the novel therapeutic targets of heart failure treatment.

Given the impact of remodeling in the pathophysiology of arrhythmia generation, we aimed to study the role of ARNI compared with ACEIs/ARBs in arrhythmia prevention for patients with HFrEF.

Methods

Search strategy

This study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) protocol. MEDLINE (via PubMed), [ClinicalTrials.gov](https://www.clinicaltrials.gov), Embase, and Scopus were systematically searched using the following strategy: (“sacubitril valsartan sodium hydrate” [text word] OR “sacubitril valsartan drug combination” [text word] OR “entresto” [tiab] OR “sacubitril-valsartan” [tiab] OR “LCZ696” [supplementary concept] OR “Angiotensin Receptor-Nepilysin Inhibitor” [text word]) AND (heart failure) NOT “preserved ejection fraction” [tiab]). The search strategy was performed by 2 authors (AF and GCF) on March 22, 2020.

Eligibility criteria and data extraction

Studies with the following characteristics were included: (1) adult patients >18 years old with diagnosed HFrEF; (2) randomized controlled trials (RCTs) or crossover or observational cohort studies; (3) at least 1 arm with use of ARNI; (4) presence of an active control group with use of ACEIs/ARBs; (5) reported incidence of arrhythmic endpoints either in manuscript or at [clinicaltrials.gov](https://www.clinicaltrials.gov). There was no restriction with respect to date of publication, publication status, or language.

Studies with no report of arrhythmic endpoints or duplicate data (published by the same authors or same institution in an overlapping period) were excluded. In cases of duplicate data, only the study with the larger number of patients that contained the variables of interest was selected. All data were reviewed by the senior author (JJG).

All the studies that were deemed appropriate by the eligibility criteria had initially the full text analyzed followed by

their [supplementary material](#) and the results section on [ClinicalTrials.gov](https://www.clinicaltrials.gov) in order to access the arrhythmic endpoints of interest.

Variables of interest

Controlled studies commonly report serious adverse events according to the Medical Dictionary for Drug Regulatory Activities (MedDRA®) terminology, and its list of diagnoses was reviewed to determine prespecified outcomes of interest to be collected from the studies included.

Variables of interest were as follows: (1) study characteristics: study site and period, study design, sample size per group, study population, and length of follow-up; (2) patient characteristics: age, sex, race, mean ejection fraction (EF), etiology of cardiomyopathy, medical therapy (beta blockers, ACEIs/ARBs, mineralocorticoid receptor antagonists, and antiarrhythmic therapy), frequency of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT); and (3) outcomes: incident ventricular arrhythmias (ventricular tachycardia [VT] and/or ventricular fibrillation [VF]), incident atrial arrhythmias (atrial fibrillation and/or atrial flutter), composite of sudden cardiac death (SCD), sudden death or cardiac arrest, appropriate ICD therapy (ICD shocks and/or antitachycardia pacing [ATP] events), percentage of biventricular (BiV) pacing, and annualized rates of arrhythmia events.

Quality assessment and risk of bias

The quality of the included RCTs was assessed using the Cochrane Handbook of Systematic Reviews of Interventions^{6,7} and was presented as a risk of bias summary figure ([Supplemental Figure 1](#)). For the nonrandomized studies, we used the Newcastle-Ottawa scale⁸; the findings are presented in [Supplemental Table 1](#).

Statistical analysis

Dichotomous endpoints were reported as frequencies and continuous variables as mean \pm standard deviation if data were normally distributed or median and interquartile range for nonparametric data. Fixed-effects (FE) or random-effects (RE) models were used to estimate the intervention effects. Outcomes from randomized trials were analyzed using an FE model given the homogeneous inclusion criteria, populations, and methods across studies while RE model was used for observational studies. Heterogeneity was also evaluated with I^2 statistics and $I^2 > 20\%$ was considered as high heterogeneity; RE statistics were also used in those cases. Sensitivity analysis was performed to identify possible outliers, and if an obvious reason for the outlying result could be identified this study was removed from the analysis.^{6,7} Binary endpoint treatment effects were compared using pooled odds ratio (OR) with a 95% confidence interval (CI), and continuous variables were compared using mean difference and a 95% CI. Review Manager 5.3 was used for statistical analysis (The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark, Copenhagen).

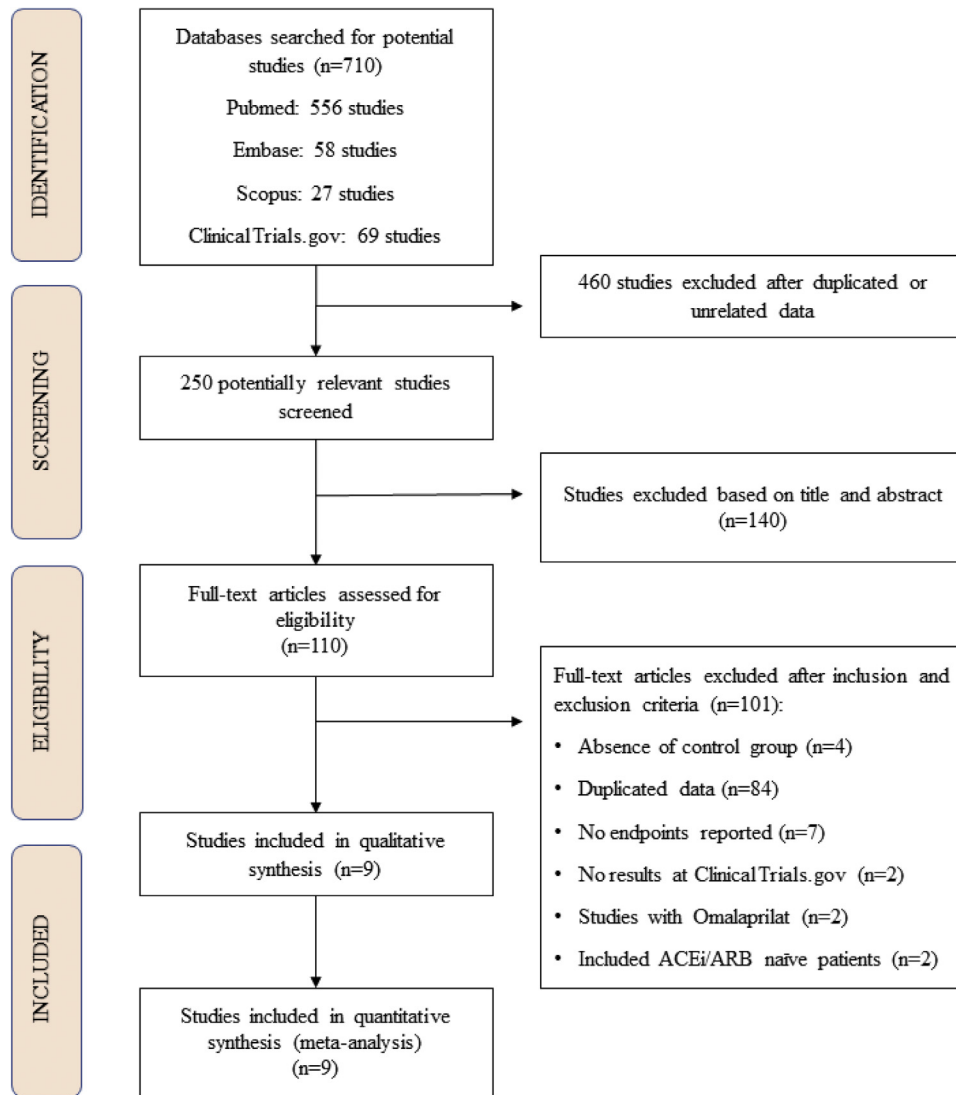


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Cumulative incidence of events was estimated by dividing the total number of events for each variable by the number of patient-years included in the analysis and was presented as events per 1000 patient-years.

Results

Baseline characteristics

A total of 4 RCTs^{3,9-11} and 5 observational studies¹²⁻¹⁶ published between 2018 and 2020 met the inclusion criteria (Figure 1, Table 1), representing a total of 11,204 patients, of whom 5589 were in the ARNI group (49.9%) and 5615 in the ACEi/ARBs group (50.1%). Mean age was 65.4 ± 9.8 years, with a majority male (77.3%). All included patients had an EF $\leq 40\%$, with a mean EF of $29.0\% \pm 7.6\%$. Six studies reported the etiology of the cardiomyopathy,^{10,12-16} which was ischemic in 62%. Follow-up ranged from 2 to 51 months (Table 2). The maximum dose of ARNI was

achieved in 4 out of 5 studies that reported these data and the frequency of guideline-directed medical therapy (GDMT) at the time of recruitment is specified in Supplemental Table 2.

Arrhythmia endpoints

Funnel plot analysis determined that results from El-Battrawy and colleagues¹³ were outliers in the analyses for the variables ventricular arrhythmias and ICD therapy (appropriate ICD shocks and/or ATP therapy), and sensitivity analysis confirmed that the exclusion of this study led to significant reduction in heterogeneity. Furthermore, quality assessment determined high risk of bias for this study owing to the retrospective model associated with a 53% loss of follow-up from the original sample (Supplemental Figure 2 and Supplemental Table 1). Therefore, that study was excluded from these analyses.

Table 1 Characteristics of included studies with patients with heart failure and reduced ejection fraction treated with angiotensin receptor-neprilysin inhibitor vs angiotensin inhibitors (angiotensin-converting enzyme inhibitors / angiotensin receptor blockers)

Study (year)	NCT number	Location	Study design	Population	Randomization	N intervention [†] /control [‡]	Follow-up (months)
<i>Randomized controlled trials</i>							
EVALUATE-HF (2019)	NCT02874794	85 US sites	Randomized, double-blind	EF ≤40%	1:1	231/233	3
OUTSTEP-HF (2018)	NCT02900378	Multicenter (127 sites)	Randomized, double-blind	Chronic HF (EF ≤40%), class ≥II	1:1	309/310	3
PARADIGM-HF (2019)	NCT01035255	Multicenter (1030 sites at US, Latin America, Europe)	Randomized, parallel assignment, double-blind	EF ≤35%	1:1	4209/4233	51
PIONEER-HF (2020)	NCT02554890	Multicenter (127 US sites)	Randomized double-blind, double dummy, parallel group, active-controlled	EF ≤40%, stabilized post hospitalization for acute decompensated HF	1:1	443/444	2
<i>Observational studies</i>							
De Diego (2018)	NA	Spain	Observational prospective cohort	EF ≤40%, class ≥II, and ICD	NA	120/120	18
El-Battrawy (2019)	NA	Germany	Retrospective cohort	EF ≤40%, class ≥II, presence of ICD, CRT, pacemaker and/or loop recorder	NA	127/127	12
Valentim Gonçalves (2019)	NA	Portugal	Prospective cohort	EF ≤40%, class ≥II	NA	35/35	6
Martens (2019)	NA	Belgium	Retrospective cohort	EF <35%, class II–IV, NA presence of ICD or CRT and prior ACEI/ARB treatment	NA	151/151	12
Polymeropoulos (2019)	NA	NA	Observational prospective cohort	EF ≤35% and ICD	NA	42/42	24

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; EF = ejection fraction; HF = heart failure; ICD = implantable cardioverter defibrillator; NA = nonapplicable or nonavailable, NCT = National Clinical Trial.

[†]Intervention: angiotensin receptor-neprilysin inhibitor.

[‡]Control: angiotensin inhibitors (ACEIs/ARBs).

The composite outcome of SCD was available only for the RCTs and it was statistically lower in the group treated with ARNI when compared with ACEIs/ARBs (OR FE 0.78, 95% CI 0.63–0.96; $P = .02$; [Figure 2](#)), although 96.5% of the weight of this analysis was driven by the PARADIGM-HF trial.³ There were 30 SCD events in the ARNI group (1.66/1000 person-years) vs 62 SCD events for the ACEIs/ARBs group (3.41/1000 person-years).

The rate of ventricular arrhythmias (VT and/or VF) in patients receiving ARNI was statistically lower than among those treated with ACEIs/ARBs (1.7% vs 2.4%; OR FE 0.70, 95% CI 0.53–0.91; $P = .008$; [Figure 3A](#)) when considering all studies. A total of 107 ventricular arrhythmias were reported in patients treated with ARNI (5.92/1000 person-years) when compared with 139 events on ACEIs/ARBs (7.65/1000 person-years). If only RCTs were included in this analysis, there was no statistical difference between groups ($P = .15$; [Figure 3B](#)).

Data on BiV pacing were available only for the observational studies, and patients treated with ARNI had a higher percentage of BiV pacing when compared with the ACEIs/ARBs group (mean difference 3.13, 95% CI 2.32–3.95; $P < .00001$; [Figure 4](#)). There was a lower rate of the composite outcome of appropriate ICD therapy (ICD shocks and/or ATP) in the group treated with ARNI instead of ACEIs/ARBs (16/313 vs 36/313, respectively; OR RE 0.41, 95% CI 0.19–0.88; $P = .02$; [Figure 5](#)).

There was no difference in incidence of atrial arrhythmias (atrial fibrillation and/or flutter) between ARNI and ACEIs/ARBs groups (7.25/1000 person-years vs 7.59/1000 person-years; OR FE 1.01, 95% CI 0.78–1.30; $P = .70$; [Supplemental Figure 3](#)).

Discussion

Our analysis demonstrates that patients with heart failure (HF) and EF ≤40% treated with ARNI had a lower incidence

Table 2 Baseline characteristics of included studies

Study (year)	Mean age ± SD	Male (%)	White (%)	Mean EF	Ischemic cardiomyopathy	Outcomes of interest	%ICD intervention [†] /control [‡]	%CRT intervention [†] /control [‡]
<i>Randomized controlled trials</i>								
EVALUATE-HF (2019)	67.8 ± 9.8	170 (74%)	166 (72%)	34 ± 10	137 (59%)	Afib/VF/VT	NA	NA
OUTSTEP-HF (2018)	67.16 ± 11.04	238 (77%)	298 (96.4%)	NA	NA	Afib/Aflutter/VT/VF	NA	NA
PARADIGM-HF (2019)	63.78 ± 11.52	3321 (78.9%)	NA	NA	NA	Afib/Aflutter/VT/VF/SCD	14.9%/14.7%	7%/6.7%
PIONEER_HF (2020)	61 (50.5, 71) [§]	327 (74.3%)	206 (60.2%)	24% (18, 30) [§]	NA	Afib/Aflutter/VT/VF/SCD	NA	NA
<i>Observational studies</i>								
De Diego (2018)	69 ± 8	91 (76%)	NA	30.4% ± 4%	82%	Afib/VF/VT/ICD shocks/BiV pacing	56%/56%	44%/44%
El-Battrawy (2019)	66.8 ± 12.1	NA	NA	25% (5, 45) [§]	53%	VT/VF	57.7%/64.2%	29%/35.5%
Valentim Gonçalves (2019)	58.6 ± 11.1	29 (82.9%)	NA	NA	15 (42.9%)	VT/SCD	85.6%/85.6%	20%/20%
Martens (2019)	67.7 ± 9.9	123 (82%)	NA	29 ± 9	103 (69%)	VT/VF	NA	51%
Polymeropoulos (2019)	67 ± 9	31 (73.8%)	NA	NA	68%	VT/ICD shocks	100%/100%	NA
TOTAL	65.4 ± 9.8	77.3%	—	29 ± 7.6	62%	—	—	—

Afib = atrial fibrillation; Aflutter = atrial flutter; BiV = biventricular; CRT = cardiac resynchronization therapy; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; NA = nonapplicable or nonavailable; SCD = sudden cardiac death; SD = standard deviation; VF = ventricular fibrillation; VT = ventricular tachycardia.

[†]Intervention: angiotensin receptor–neprilysin inhibitor.

[‡]Control: angiotensin inhibitors (angiotensin-converting enzyme inhibitors / angiotensin receptor blockers).

[§]Median (interquartile range).

of SCD, ventricular arrhythmias, and appropriate ICD therapy and presented increased rates of BiV pacing when compared with those on ACEIs/ARBs. There was not enough evidence to support a difference in the incidence of atrial arrhythmias in patients treated with ARNI vs ACEIs/ARBs.

Caution is advised while interpreting the ventricular arrhythmias outcome given the absence of statistical difference when only RCTs were included in the analysis. It is possible that the smaller sample of patients recruited by the trials other than the PARADIGM-HF as well as possible underreporting of ventricular arrhythmia events could have been responsible

for the lack of a statistically significant difference in this outcome, and this should not discourage further research in the field. In addition, the favorable results of ARNI increasing BiV pacing and decreasing appropriate ICD therapy demonstrated by the observational studies need subsequent investigation, given the lower quality of the studies.

A detailed review of the mechanisms of action that are potentially implicated in the antiarrhythmic effects of ARNI points towards its modulatory simultaneous effect on the calcium homeostasis and in 2 of the major neurohormonal regulatory systems: the renin-angiotensin-aldosterone

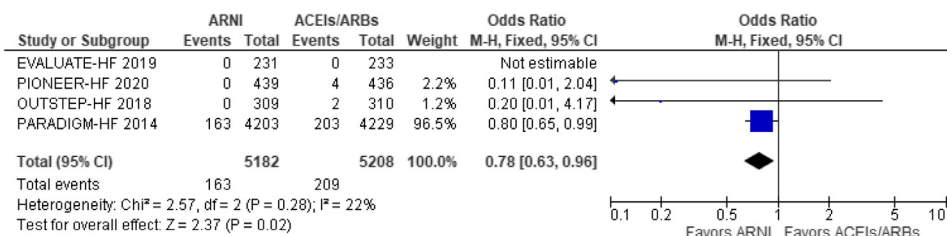


Figure 2 Composite outcome of sudden cardiac death, cardiac arrest, and sudden death among patients treated with angiotensin receptor–neprilysin inhibitor (ARNI) vs angiotensin inhibitors (angiotensin-converting enzyme inhibitors [ACEIs] / angiotensin receptor blockers [ARBs]) in randomized studies.

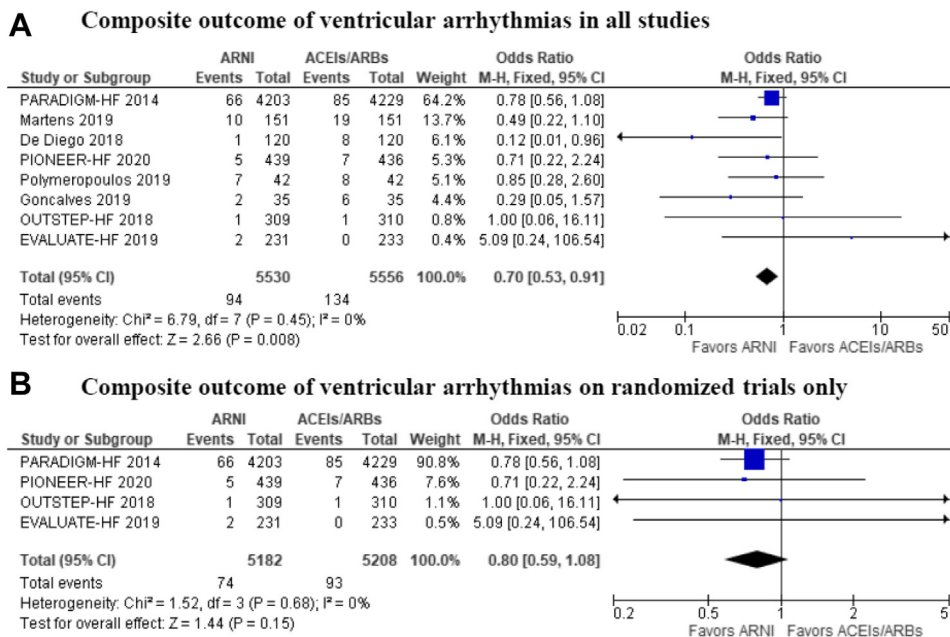


Figure 3 Ventricular arrhythmias among patients treated with angiotensin receptor–neprilysin inhibitor (ARNI) vs angiotensin inhibitors (angiotensin-converting enzyme inhibitors [ACEIs] / angiotensin receptor blockers [ARBs]) including all studies (A) and only on randomized controlled trials (B).

system and the natriuretic peptide system, which are overactivated in patients with advanced HF (graphical abstract).^{1,17,18} The inhibition of the angiotensin receptor and the neprilysin (a zinc metalloprotease present in the endothelial surface of multiple organ systems) results in modulation of the renin-angiotensin-aldosterone system and natriuretic peptide system. Neprilysin inhibition increases the levels of multiple peptides associated with peripheral vasodilation (natriuretic peptides, bradykinin, substance P, adrenomedullin), increasing glomerular filtration rate with subsequent diuresis and natriuresis (atrial natriuretic peptide effect).^{17,19} Neprilysin inhibition also decreases cardiomyocyte hypertrophy by promoting increased levels of atrial natriuretic peptide and brain natriuretic peptide, which inhibit the angiotensin II and endothelin 1 that are responsible for cardiomyocyte and fibroblast growth.²⁰ With HF progression, both mechanical and electrical remodeling are observed in the cardiomyocytes. In a normal heart, the action potential depolarizes the L-type calcium channels at the T-tubules, promoting calcium entrance. The calcium is sensed by the ryanodine receptor type 2 (RyR2) on the surface of the sarcoplasmic reticulum (SR) and causes its opening, resulting in the efflux of accumulated calcium to the intracellular space. Calcium binds to the actin and its conformational change promotes

the myocardial contraction (systole).²¹ Excessive cytosolic calcium either enters back into the SR through the SR Ca²⁺-ATPase-2a or is pumped out the cell in exchange for sodium by the sodium and calcium exchanger during diastole, which results in the cell relaxation. RyR2 malfunction owing to conformational changes secondary to HF progression and oxidative stress causes diastolic calcium leak that is known to cause ventricular arrhythmias by delayed afterdepolarizations.^{1,21,22} ARNI seems to decrease the diastolic calcium leak from the SR.²³ The calcium/calmodulin-dependent protein kinase II plays a crucial role on the sodium and calcium homeostasis and it is also damaged during oxidative stress, resulting in arrhythmias because of early afterdepolarizations, prolongation of action potential, and delayed afterdepolarizations. Hemodynamic improvement promoted by ARNI results in less oxidative stress and fewer translational modifications in the intracellular ion channels involved in calcium homeostasis, which may be the mechanism implicated in the reduction of malignant arrhythmias and sudden cardiac death (graphical abstract).^{1,17,18,21}

Prior studies demonstrated that intracellular diastolic calcium leak secondary to RyR2 malfunction or calcium/calmodulin-dependent protein kinase II overactivation resulting from oxidative stress in failing hearts are associated with

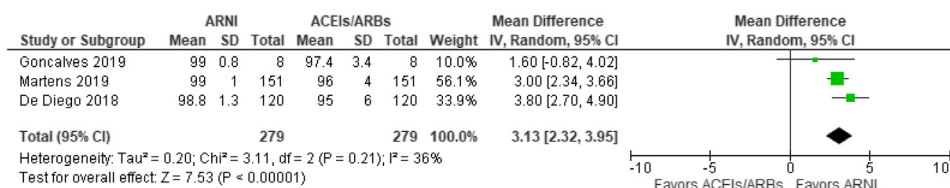


Figure 4 Percentage of biventricular pacing among patients treated with angiotensin receptor–neprilysin inhibitor (ARNI) vs angiotensin inhibitors (angiotensin-converting enzyme inhibitors [ACEIs] / angiotensin receptor blockers [ARBs]) in observational studies.

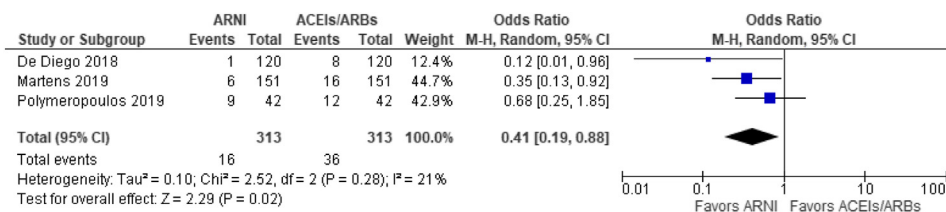


Figure 5 Composite outcome of appropriate implantable cardioverter defibrillator (ICD) shocks and/or antitachycardia pacing in patients treated with angiotensin receptor–neprilysin inhibitor (ARNI) vs angiotensin inhibitors (angiotensin-converting enzyme inhibitors [ACEIs] / angiotensin receptor blockers [ARBs]) in observational studies.

ventricular arrhythmias and SCD.^{24–27} An experimental study with murine and human cardiomyocytes models of end-stage HF aimed to test the effect of ARNI vs valsartan only in calcium homeostasis observed that under normal conditions there was no change in diastolic Ca²⁺-spark frequency or SR Ca²⁺ leak regardless of the therapy given; however, under catecholamine stress, there was a 50% and 74% decrease in those 2 parameters of Ca²⁺ diastolic leak ($P < .01$) on murine and human cardiomyocytes treated with ARNI, respectively, while there was no change in the valsartan group.²³

Additional mechanisms of action of ARNI are related to its effects on vasodilation, natriuresis, decrease in sympathetic activation, decrease in wall stretch and myocardial fibrosis (graphical abstract), and reduced inflammation in human and animal models.^{14,19,28,29} Valentim Gonçalves and colleagues¹⁴ prospectively studied patients with chronic HF (NYHA class \geq III) on optimal GDMT for at least 6 months (100% on beta blockers, 94.3% on mineralocorticoid receptor antagonist, 85.6% with ICD, and 20% with CRT) and recently started on ARNI and found a decrease in QRS duration and QTc interval, decrease in global longitudinal strain, and mechanical dispersion index by echocardiography after 6 months of therapy. Although the ACEIs are known to promote reverse remodeling, they have not been implicated in SCD reduction and the neprilysin inhibition could be a potential key for the observed 20% reduction in cardiovascular death (including sudden death and death due to worsening HF) observed by the PARADIGM-HF trial in patients treated with ARNI when compared with enalapril.^{3,30,31}

Scar and fibrosis are important predictors of VT/VF, SCD, and appropriate ICD therapy.³² The presence of myocardial scar is known to create a reentrant substrate for VT/VF, as the electrophysiologic heterogeneity created by the fibrosis interspersed with normal myocardium promotes slow conduction and dispersion of repolarization/refractoriness.^{1,2} Myocardial fibrosis is commonly observed in patients with chronic HF secondary to an imbalance between production and degradation of extracellular matrix as a result of neuro-hormonal, metabolic and hemodynamic dysregulation.⁵ Zile and colleagues³³ recruited 2067 participants from the PARADIGM-HF trial³ and tested 8 different biomarkers before and after ARNI initiation, observing a decrease in pro-fibrotic markers 8 months after randomization (2 of them associated with change in outcomes), and a decrease in myocardial fibrosis may be one of the factors to explain the

lower rates of SCD and ventricular arrhythmias in patients treated with ARNI compared with ACEIs/ARBs observed in our study.

We decided to include in our outcomes the BiV pacing rates based on a literature review that points towards lower rates of ventricular arrhythmias in patients that experienced improvement in dyssynchrony. Kutuyifa and colleagues,³⁴ in a subanalysis of the MADIT-CRT trial, compared the first episode of VT/VF/death in 764 patients with baseline left bundle branch block and found that an improvement in dyssynchrony of at least 15% promoted by CRT-D was associated with a statistically significant reduction of ventricular arrhythmias at 12 months of follow-up. Hayes and colleagues³⁵ analyzed mortality per quartile of BiV pacing percentage (<95%, 95%–98.5%, 98.5%–99.6%, >99.6%) in a large cohort of 36,935 patients, and reported that a BiV pacing percentage above 99.6% was associated with a 24% reduction in overall mortality when compared with other quartile groups and patients with <95% BiV pacing percentage had a 19% increase in mortality, concluding that even small increases in the % BiV pacing were clinically relevant. Our study showed an increase in the BiV pacing rate and a decrease in appropriate ICD shocks and/or ATP therapy for patients receiving ARNI in a subanalysis composed by observational studies. These findings are in accordance with a recently published expert opinion from the Heart Rhythm and Heart Failure sections of the Polish Cardiac Society,³⁶ which defends that optimization of medical therapy in HF with ARNI might have the additional benefit of decreasing the incidence of appropriate and inappropriate ICD shocks and to increase the rate of BiV pacing. There are no trials reporting BiV pacing rates in patients treated with ARNI and our meta-analysis provides the most updated evidence of this benefit. One of the included studies¹² found that patients with high premature ventricular contraction burden had a lower percentage of BiV pacing rate and patients treated with ARNI achieved reduction of premature ventricular contraction burden and, subsequently, increase in BiV pacing from 95% \pm 6% to 98.8% \pm 1.3% at 9 months, which could represent another potential explanation for the higher rates of BiV pacing in the ARNI group.

Despite the lower risk of SCD in patients with HFrEF who had ICD implantation, ICD shocks have been linked to increased risk of mortality.¹ Proietti and colleagues³⁷ reported an increase in cardiac deaths for patients receiving both appropriate and inappropriate ICD shocks, with a higher

effect size for appropriate therapy (hazard ratio 2.95, 95% CI 2.12, 4.11). There is still debate as to whether the relationship between ICD shocks and mortality is either a result of the HF progression itself or owing to myocardial injury/stunning caused by the electrical current, or both.³⁸ Powell and colleagues³⁹ studied patients with ICD who received therapy (appropriate or inappropriate) in order to determine if the increased mortality after shock was due to the triggering rhythm or secondary to the shock itself, and they concluded that the presenting rhythm was the major factor impacting prognosis, and shocks for VT/VF, atrial fibrillation, or atrial flutter were associated with a higher risk of death when compared with controls without shocks or with inappropriate shocks due to noise, oversensing, or artifact. Lastly, Aktaş and colleagues⁴⁰ in a cohort including 5516 patients enrolled in 5 landmark ICD trials observed that only appropriate ICD shocks were associated with a 38% increased mortality risk at 3 years of follow-up when compared with inappropriate ICD shocks, and mortality was higher in patients who experienced fast VT (≥ 200 beats/min) or VF compared with patients without fast VT or VF (27% vs 10%, respectively). Our analysis of observational studies did show a decrease in appropriate ICD shocks and/or ATP therapy for patients receiving ARNI.

Limitations

The main limitations of our study include the small number of trials and observational studies, the possible presence of ascertainment bias, underreporting of arrhythmic events, and the short and heterogenous length of follow-up in some studies. In terms of ventricular arrhythmias, the studies did not characterize the events in terms of sustained or not sustained, fast or slow events, and this information could potentially be helpful in subgroup analysis. Our analysis supports the need for rigorous collection and adjudication of ventricular arrhythmia endpoints in modern HF trials. The main conclusions of the manuscript are derived from the PARADIGM-HF trial.³ Regarding the use of GDMT, less than 60% of patients enrolled by the PIONEER HF trial¹¹ were on beta-blocker therapy and the presence of antiarrhythmic therapy was variable between the studies selected, which could have influenced our results. Furthermore, no studies reported the use of sodium-glucose cotransporter-2 inhibitors, which has been considered one of the modern cornerstones of GDMT for HFrEF patients, regardless of diabetic status, and has also been associated with decrease in atrial arrhythmic events and SCD.⁴¹ Lastly, we advise caution when interpreting the BiV pacing results, since this variable was reported from device interrogation without analysis of BiV pacing morphology or unipolar electrograms to confirm true BiV pacing.

Conclusion

Our meta-analysis showed a significant reduction in SCD events, ventricular arrhythmias, and appropriate ICD therapy in patients taking ARNI when compared with ACEIs/ARBs,

as well as an increase in BiV pacing rate in patients with HFrEF. We did not find difference in atrial arrhythmic events between groups. Caution is advised when interpreting those results and, importantly, the observed associations do not suggest a causal relationship between ARNI therapy and outcomes.

The neprilysin inhibition component and its effect on calcium homeostasis, decreased remodeling, and scar might be intrinsically responsible for those findings and deserve further investigation in dedicated trials and possibly in large registries.

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Disclosures

The authors have no conflicts to disclose.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement

This study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) protocol.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hroo.2021.09.009>.

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