ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITORS

RESEARCH REVIEW

The Impact of Angiotensin Receptor–Neprilysin Inhibitors on Arrhythmias in Patients with Heart Failure: A Systematic Review and Meta-analysis

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ABSTRACT. Angiotensin receptor–neprilysin inhibitor (ARNI) use has become increasingly popular. Current guidelines recommend using ARNI therapy for heart failure with reduced (HFrEF) and preserved ejection fraction (HFpEF). As therapies become more widely available, heart failure-associated burdens such as ventricular arrhythmias and sudden cardiac death (SCD) will become increasingly prevalent. We conducted a systematic review and meta-analysis to assess the impact of ARNI therapy on HFrEF and HFpEF pertaining to arrhythmogenesis and SCD. We performed a search of MEDLINE (PubMed), the Cochrane Library, and ClinicalTrials.gov for relevant studies. The odds ratios (ORs) of SCD, ventricular tachycardia (VT), ventricular fibrillation (VF), atrial fibrillation/flutter (AF), supraventricular tachycardia (SVT), and implantable cardioverter-defibrillator (ICD) shocks were calculated. A total of 10 studies, including 6 randomized controlled trials and 4 observational studies, were included in the analysis. A total of 18,548 patients from all studies were included, with 9,328 patients in the ARNI arm and 9,220 patients in the angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) arm, with a median follow-up time of 15 months. There was a significant reduction in the composite outcomes of SCD and ventricular arrhythmias in patients treated with ARNIs compared to those treated with ACEIs/ARBs (OR, 0.71; 95% confidence interval, 0.54–0.93; P = .01; I² = 17%; P = .29). ARNI therapy was also associated with a significant reduction in ICD shocks. There was no significant reduction in the VT, VF, AF, or SVT incidence rate in the ARNI group compared to the ACEI/ARB group. In conclusion, the use of ARNIs confers a reduction in composite outcomes of SCD and ventricular arrhythmias among patients with heart failure. These outcomes were mainly driven by SCD reduction in patients treated with ARNIs.

KEYWORDS. Angiotensin receptor–neprilysin inhibitor, arrhythmia, sudden cardiac death, ventricular tachycardia.

Introduction

Heart failure (HF) remains a crucial contributor to recurrent hospitalization and death among individuals aged 50–89 years, with an exponential rise in prevalence over time.¹ The American Heart Association estimates that >6 million people in the United States have a diagnosis of...
The impact of ARNIs on arrhythmias in patients with HF

Impact of ARNIs on Arrhythmias in Patients with HF

Arrhythmias are one of the significant burdens to those with HF diagnoses. The pathophysiology, as it relates to arrhythmogenesis, is complex but includes multifactorial manifestations of fibrosis, neurohormonal imbalance, and variability of ion channels including under- and overexpression, in addition to electrolyte abnormalities. One pharmacologic therapy gaining much popularity and enthusiasm is angiotensin receptor-neprilysin inhibitors (ARNIs) due to their ability to reduce the adverse manifestations of HF diagnoses. Proposed theories regarding the effect ARNIs have on the reduction of mortality and sudden death from an arrhythmia perspective are not well understood; however, circulating natriuretic peptides reduce the harmful effects of the sympathetic and renin-angiotensin systems by decreasing myocyte death, hypertrophy, fibrosis, and inflammation, which have all been implicated in arrhythmogenesis.

Regarding HF with reduced ejection fraction (HFrEF), ARNIs have demonstrated a clear survival benefit as demonstrated in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF (PARADIGM-HF) trial and is now further used in the treatment of HF with preserved ejection fraction (HFrEF) due to results from the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial. The effect of ARNIs on sudden cardiac death (SCD) has been widely reported, and while meta-analyses on outcomes such as primary total mortality and HF endpoints have been reported, little data exist regarding their effect on arrhythmia. Given such a positive effect on reducing morbidity and mortality in HF patients, we aimed to emphasize the additional importance of reducing the arrhythmia in this patient population using ARNI therapy.

Methods

Data sources and search strategies

We conducted a systematic review using MEDLINE (PubMed), the Cochrane Library, and ClinicalTrials.gov from inception to January 10, 2022. We used the terms “LCZ696” or “LCZ-696” or “entresto” or “sacubitril” or “sacubitril valsartan” or “sacubitril–valsartan” or “angiotensin receptor–neprilysin inhibitor” and “heart failure” for the search strategy. The meta-analysis was conducted and performed using the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. We included studies that incorporated the following characteristics: (1) enrolled adult patients >18 years of age with a diagnosis of HFrEF or HFrEF, (2) compared ARNI therapy to an active control group or placebo, (3) were randomized controlled trials (RCTs) or observational cohort studies, and (4) included arrhythmia endpoints. We excluded studies with duplicate data or no data of interest from an arrhythmia perspective.

Data extraction and quality assessment

Two reviewers independently performed data extraction and quality assessments of the included studies. The data reported include the type of study, baseline characteristics of the patients, intervention, control, randomization, follow-up duration, and sample size. The outcomes of interest included SCD, ventricular tachycardia (VT), ventricular fibrillation (VF), atrial fibrillation/flutter (AF), supraventricular tachycardia (SVT), and implantable cardioverter-defibrillator (ICD) shocks. All the studies considered appropriate for the meta-analysis had their full text analyzed by 2 reviewers. In addition, data from ClinicalTrials.gov and supplemental sections were reviewed if they included the arrhythmia endpoints of our interest.

Risk of bias assessment

All included RCTs were graded for bias using the Cochrane Handbook for Systematic Reviews of Interventions. The observational studies were graded for bias using the Newcastle–Ottawa scale. Two reviewers assessed the risk of bias for each included study.

Statistical analysis

Summary odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a random-effects model. The random-effects model incorporates heterogeneity between trials and usually gives wider and more conservative CIs. The 95% CIs were estimated using a binomial distribution. Heterogeneity across all studies was assessed using the chi-squared and I² tests. According to published guidelines, it is accepted that an I² value of 25%–49% indicates low heterogeneity, 50%–74% indicates moderate heterogeneity, and >75% indicates high heterogeneity. A P value of <.10 was used as an indicator for significance regarding heterogeneity, and P < .05 was used to indicate significance for the arrhythmia outcomes. A subgroup analysis was performed for studies with at least moderate or significant heterogeneity. The analysis was performed using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Baseline characteristics

A total of 6 RCTs and 4 observational studies published between 2014–2021 met the inclusion criteria for this meta-analysis (Figure 1 and Table 1). All 6
RCTs were double-blinded, while observational studies included 3 prospective cohort studies and 1 retrospective cohort study. The follow-up period in all studies ranged from 3–36 months, with mean and median follow-up times of 18.2 and 15 months, respectively. A total of 18,548 patients from all the studies were included, of whom 9,328 (50.3%) patients were on ARNIs and 9,220 (49.7%) were on angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs). The mean age of the studied population was 66.7 ± 9.27 years, with the majority of patients (72.7%) being men. All studies except 2 RCTs included HFrEF patients. The PARAGON-HF and Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients (PARALLAX) trials involved HFpEF patients. The mean left ventricular ejection fraction among all studied groups was 33.3% ± 8.01%. The majority of patients (60.2%) had ischemic cardiomyopathy. Most patients had New York Heart Association functional class II symptoms (67.3%). In addition to ACEIs/ARBs and ARNIs, most participants reported taking ≥1 additional guideline-directed medical therapy, including β-blockers (87.6% of patients) and mineralocorticoid antagonists (60.7% of patients) (Table 2). Quality and bias assessments of the RCTs and observational studies are included in Tables 3 and 4, respectively.

Outcomes

The composite endpoint of sudden cardiac death and ventricular arrhythmias. There were a total of 312 events in the ARNI group and 414 events in ACEI/ARB groups of SCD events and ventricular arrhythmias including VT and VF, which was statistically significant (OR, 0.71; 95% CI, 0.54–0.93; P = .01; F = 17%; P = .29) (Figure 2A). The PARADIGM-HF trial included a 49.7% weight of the sample size. A sensitivity analysis was performed by excluding the observational studies, resulting
Table 1: Characteristics of Included Studies Enrolling Patients with Heart Failure with Reduced Ejection Fraction or Preserved Ejection Fraction Treated with Angiotensin Receptor–Neprilysin Inhibitors Versus Angiotensin-converting Enzyme Inhibitors/Angiotensin II Receptor Blockers

| Study (year)      | Study Population | Randomization | Intervention/Control | Data Source |
|-------------------|------------------|---------------|----------------------|-------------|
| PARADIGM-HF (2014) | Age ≥18 years, NYHA ≥ II, EF ≤ 35% | 1:1           | Control              | NA          |
| OUTSTEP-HF (2018)  | Age ≥18 years, NYHA ≥ II, EF ≤ 40% | 1:1           | Control              | NA          |
| PARAGON-HF (2019)  | Age ≥50 years, NYHA ≥ II, EF ≤ 45% | 1:1           | Control              | NA          |
| PIONEER-HF (2019)  | Age ≥18 years, NYHA ≥ II, EF ≤ 40% | 1:1           | Control              | NA          |
| EVALUATE-HF (2019) | Age ≥50 years, NYHA I–III, EF ≤ 40% | 1:1           | Control              | NA          |
| PARALLAX (2021)    | Age ≥45 years, NYHA ≥ II, EF ≥ 40% | 1:1           | ACEI/ARB             | NA          |
| Martens et al. (2019) | ≥18 years, NYHA ≥ II, EF ≥ 40% | 1:1           | ACEI/ARB             | NA          |
| Gonçalves et al. (2019) | ≥18 years, EF ≤ 40% | 1:1           | ACEI/ARB             | NA          |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; EF, ejection fraction; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; NA, not applicable; NYHA, New York Heart Association.

SCD and ventricular arrhythmias were also analyzed in patients with HFrEF only, which revealed a total of 280 events in the ARNI group compared to 374 events in the ACEI/ARB group (OR, 0.63; 95% CI, 0.40–0.98; P = .04; F = 35%; P = .15) (Figure 3A). A sensitivity analysis was performed, excluding the observational studies, which continued to show a significant reduction in the endpoints of SCD and ventricular arrhythmias without any heterogeneity between the groups. A significant reduction in the composite of SCD and ventricular arrhythmia events was observed in the ARNI group compared to the ACEI/ARB group in the 4 RCTs with only HFrEF patients (OR, 0.80; 95% CI, 0.68–0.95; P = .009; F = 0%; P = .65) (Figure 3B).

**Sudden cardiac death.** SCD outcomes were only available from the 6 RCTs. Most of the events reported were from only 1 trial (PARADIGM-HF with 87.8% weight). A total of 181 SCD, cardiac arrest, or sudden death events were reported in the ARNI group versus 237 events reported in the ACEI/ARB group. SCD was significantly reduced in patients treated with ARNIs compared to ACEIs/ARBs (OR, 0.76; 95% CI, 0.63–0.93; P = .007; F = 0%; P = .69) (Figure 4).

**Ventricular tachycardia.** There were 103 VT events reported in the ARNI group versus 143 events reported in the ACEI/ARB group. There was no statistically significant difference between the 2 groups (OR, 0.72; 95% CI, 0.42–1.21; P = .21; F = 47%; P = .06) (Figure 5A). A sensitivity analysis was performed by excluding the observational studies from the analysis, which showed resolution of the 47% heterogeneity between the groups. However, ARNIs did not lead to a significant reduction in VT compared to ACEIs/ARBs in the 5 RCTs (OR, 1.15; 95% CI, 0.66–2.00; P = .61; F = 25%; P = .26) (Figure 5B).

**Ventricular fibrillation.** VF outcomes were only available from 3 RCTs. Most of the events reported were from only 1 trial (PARADIGM-HF with 81.3% weight). There were 28 VF events reported in the ARNI group versus 34 events reported in the ACEI/ARB group. There was no significant reduction in the incidence of VF in the ARNI group compared to the ACEI/ARB group (OR, 0.82; 95% CI, 0.50–1.36; P = .45; F = 0%; P = .67) (Figure 6).

**Implantable cardioverter-defibrillator shocks.** Data on appropriate ICD shocks were available only from the 3 observational studies. There were 10 appropriate ICD shocks in the ARNI group versus 41 in the ACEI/ARB group. The number of ICD shocks was significantly reduced in patients treated with ARNIs compared to
### Table 2: Baseline Characteristics of the Study Population

| NYHA Functional Class, no. (%) | Ischemic Cardiomyopathy, no. (%) | CRT, no. (%) | Atrial Fibrillation, no. (%) | ACEI or ARB, no. (%) | Mineralocorticoid Antagonist, no. (%) | β-Blocker, no. (%) | Mean EF (± SD) | White, no. (%) | Male, no. (%) | Mean Age ± SD (years) | Study |
|-------------------------------|----------------------------------|-------------|----------------------------|---------------------|---------------------------------------|------------------|---------------|---------------|--------------|----------------|--------------------|
| IV 33 (0.8)                  | 2,998 (23.1)                    | 180 (4.3)   | 2,509 (59.9)               | 292 (7.0)           | 1,517 (36.2)                         | 3,266 (78)      | 2,271 (54.2) | 1,223 (29.2) | 3,363 (80.3) | 3,899 (92.2) | 29.6 ± 6.1          | PARADIGM-HF |
| III 2 (0.65)                 | 146 (47.25)                     | 161 (52.10) | 0                           | 177 (57.28)         | NA                                    | 147 (47.57)     | 309 (97.7)   | 199 (77.7)   | 240 (90.6)   | NA              | 298 (96.4) | 238 (77.02)     | OUTSTEP-HF |
| II 8 (0.3)                   | 458 (19.0)                      | 73 (3.0)    | 899 (37.4)                  | N/A                 | N/A                                   | 775 (32.2)      | 2,074 (86.2) | 592 (79.9)   | 2,294 (95.3) | 1,922 (96.3) | 57.6 ± 7.8          | PARAGON-HF |
| I N/A                        | N/A                             | N/A         | N/A                         | N/A                 | N/A                                   | 208 (47.3)      | 48 (10.9)    | 41 (9.3)     | 292 (66.3)   | 262 (59.5)   | 24                 | PIONEER-HF |
| N/A                          | N/A                             | N/A         | N/A                         | N/A                 | N/A                                   | N/A             | N/A           | N/A           | 1,112 (96)   | 1,271 (49.3) | 72.6 ± 8.5          | PARALLAX |
| N/A                          | N/A                             | N/A         | N/A                         | N/A                 | N/A                                   | N/A             | N/A           | N/A           | 1,112 (86)   | 1,271 (49.3) | 72.6 ± 8.5          | PARALLAX |
| 0 100 (21.5)                 | 313 (67.3)                      | 61 (13.1)   | 283 (60.9)                  | N/A                 | N/A                                   | N/A             | 391 (84)     | 115 (24.7)   | 258 (55.4)   | 400 (86)     | 33.5 ± 10          | EVALUATE-HF |
| N/A                          | N/A                             | N/A         | N/A                         | 98 (82)             | 52.8 (44)                            | 57.2 (56)       | 17 (14)       | 116 (75)     | 90 (75)      | 117 (98)     | 30.4 ± 4           | de Diego et al. |
| 3 46 (1.3)                   | 102 (68)                        | 0           | 69                          | 105 (69.6)          | 63 (41)                              | 63 (30.4)       | 130 (86)     | 13 (9)       | 73 (48)      | 143 (95)     | 29 ± 9            | Martens et al. |
| N/A                          | N/A                             | N/A         | N/A                         | 15 (42.9)           | 7 (20)                                | 30 (85.6)       | 33 (94.3)    | 9 (25.7)     | 35 (100)     | N/A           | 35 (100)          | Gonçalves et al. |
| 0 55 (33)                    | 112 (67)                        | 0           | 86.8 (52.1)                 | N/A                 | N/A                                   | 34 (20)         | 167 (100)    | 150 (90)     | 167 (100)    | 164 (98)     | 28.1 ± 3.2         | Russo et al. |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CRT, cardiac resynchronization therapy; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; N/A, not applicable; no., number; NYHA, New York Heart Association; SD, standard deviation.
Table 3: Quality Assessment of Bias for Included Randomized Controlled Trials

| Study             | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Reporting |
|-------------------|-----------------------------|------------------------|----------------------------------------|-------------------------------|------------------------|---------------------|
| PARADIGM-HF       | Low risk                    | Low risk               | Low risk                               | Low risk                     | Low risk               | Low risk            |
| OUTSTEP-HF        | Low risk                    | Low risk               | Low risk                               | Low risk                     | Low risk               | Low risk            |
| PARAGON-HF        | Low risk                    | Low risk               | Low risk                               | Low risk                     | Low risk               | Low risk            |
| PIONEER-HF        | Low risk                    | Low risk               | Low risk                               | Low risk                     | Low risk               | Low risk            |
| PARALLAX-EVALUATE-HF | Low risk                | Low risk               | Low risk                               | Low risk                     | Low risk               | Low risk            |

Table 4: Quality Assessment of Bias for Included Observational Studies

| Study             | Type of Study | Selection | Comparability | Outcome |
|-------------------|---------------|-----------|---------------|---------|
| de Diego et al.²⁰ | Prospective cohort | ⭐⭐⭐⭐⭐ | ⭐⭐⭐⭐⭐ | ⭐⭐⭐⭐⭐ |
| Martens et al.²¹  | Retrospective cohort | ⭐⭐⭐⭐⭐ | N/A           | ⭐⭐⭐⭐⭐ |
| Russo et al.²¹    | Prospective cohort | ⭐⭐⭐⭐⭐ | ⭐⭐⭐⭐⭐ | ⭐⭐⭐⭐⭐ |
| Gonçalves et al.²² | Prospective cohort | ⭐⭐⭐⭐⭐ | ⭐⭐⭐⭐⭐ | ⭐⭐⭐⭐⭐ |

Abbreviation: N/A, not applicable. Possible maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for outcome, respectively.

Figure 2: Composite outcome of sudden cardiac death and ventricular arrhythmias among heart failure patients treated with angiotensin receptor–neprilysin inhibitors versus angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers in all included studies (A) and in only randomized controlled trials (B). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; M–H, Mantel–Haenszel.
ACEIs/ARBs (OR, 0.23; 95% CI, 0.11–0.47; \(P < .0001; I^2 = 0\%\)) (Figure 7).

Atrial fibrillation/flutter and supraventricular tachycardia. There was no significant difference in the incidence of AF events between the ARNI group and the ACEI/ARB group (OR, 0.87; 95% CI, 0.65–1.17; \(P = .37; I^2 = 51\%\); \(P = .05\)) (Figure 8A). A subgroup analysis was performed between the RCTs and observational studies due to a moderate heterogeneity of 51%. The observational studies showed a significant reduction in AF in the ARNI group (OR, 0.56; 95% CI, 0.38–0.83; \(P = .004; I^2 = 0\%\)) (Figure 8B), which was not evident among the RCTs (OR, 1.05; 95% CI, 0.88–1.26; \(P = .57; I^2 = 5\%\); \(P = .38\)) (Figure 8C). The RCTs also included data on the incidence of SVT. There were a total of 49 events reported in the ARNI group and 59 events in the ACEI/ARB group. There was no significant difference between the groups in terms of SVT events (OR, 0.82; 95% CI, 0.56–1.20; \(P = .31; I^2 = 0\%\); \(P = .73\)) (Figure 8D).
**Figure 5:** Ventricular tachycardia among heart failure patients treated with angiotensin receptor–neprilysin inhibitors versus angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers in all included studies (A) and in only randomized controlled trials (B). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; M–H, Mantel–Haenszel.

| Study or Subgroup | ARNI Events | ARNI Total | ACEIs/ARBs Events | ACEIs/ARBs Total | Weight | Odds Ratio M–H, Random, 95% CI | Odds Ratio M–H, Random, 95% CI |
|-------------------|-------------|------------|-------------------|------------------|--------|-------------------------------|-------------------------------|
| de Diego et al., 2018 | 1 | 120 | 8 | 120 | 5.2% | 0.12 [0.01, 0.96] | 0.01 [0.01, 0.96] |
| EVALUATE-HF, 2019 | 1 | 231 | 0 | 233 | 2.5% | 3.04 [0.12, 74.99] | 0.01 [0.01, 0.96] |
| Goncalves et al., 2019 | 2 | 35 | 6 | 42 | 7.5% | 0.36 [0.07, 1.93] | 0.01 [0.01, 0.96] |
| Mavromatis et al., 2016 | 10 | 151 | 19 | 151 | 17.4% | 0.49 [0.22, 1.10] | 0.01 [0.01, 0.96] |
| OUTSTEP-HF, 2018 | 3 | 309 | 1 | 310 | 4.8% | 3.03 [0.31, 29.28] | 0.01 [0.01, 0.96] |
| PARADIGM-HF, 2014 | 66 | 4203 | 85 | 4298 | 26.2% | 0.78 [0.56, 1.08] | 0.01 [0.01, 0.96] |
| PARAGON-HF, 2019 | 9 | 2419 | 4 | 2462 | 11.9% | 2.24 [0.69, 7.20] | 0.01 [0.01, 0.96] |
| PIONEER-HF, 2020 | 7 | 436 | 5 | 438 | 12.2% | 1.42 [0.45, 4.50] | 0.01 [0.01, 0.96] |
| Russo et al., 2020 | 4 | 167 | 15 | 182 | 12.5% | 0.25 [0.08, 0.77] | 0.01 [0.01, 0.96] |
| Total (95% CI) | 8071 | 8093 | 100.0% | 0.72 [0.42, 1.21] | 0.01 [0.01, 0.96] |

| Study or Subgroup | ARNI Events | ARNI Total | ACEIs/ARBs Events | ACEIs/ARBs Total | Weight | Odds Ratio M–H, Random, 95% CI | Odds Ratio M–H, Random, 95% CI |
|-------------------|-------------|------------|-------------------|------------------|--------|-------------------------------|-------------------------------|
| EVALUATE-HF, 2019 | 1 | 231 | 0 | 233 | 2.8% | 3.04 [0.12, 74.99] | 0.01 [0.01, 0.96] |
| OUTSTEP-HF, 2018 | 3 | 309 | 1 | 310 | 5.5% | 3.03 [0.31, 29.28] | 0.01 [0.01, 0.96] |
| PARADIGM-HF, 2014 | 66 | 4203 | 85 | 4298 | 57.7% | 0.78 [0.56, 1.08] | 0.01 [0.01, 0.96] |
| PARAGON-HF, 2019 | 9 | 2419 | 4 | 2462 | 16.8% | 2.24 [0.69, 7.20] | 0.01 [0.01, 0.96] |
| PIONEER-HF, 2020 | 7 | 436 | 5 | 438 | 17.3% | 1.42 [0.45, 4.50] | 0.01 [0.01, 0.96] |
| Total (95% CI) | 7598 | 7613 | 100.0% | 1.15 [0.66, 2.00] | 0.01 [0.01, 0.96] |

**Figure 6:** Ventricular fibrillation among heart failure patients treated with angiotensin receptor–neprilysin inhibitors versus angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; M–H, Mantel–Haenszel.

| Study or Subgroup | ARNI Events | ARNI Total | ACEIs/ARBs Events | ACEIs/ARBs Total | Weight | Odds Ratio M–H, Random, 95% CI | Odds Ratio M–H, Random, 95% CI |
|-------------------|-------------|------------|-------------------|------------------|--------|-------------------------------|-------------------------------|
| OUTSTEP-HF, 2018 | 1 | 309 | 0 | 310 | 2.4% | 3.02 [0.12, 74.41] | 0.01 [0.01, 0.96] |
| PARADIGM-HF, 2014 | 22 | 4203 | 28 | 4229 | 81.3% | 0.78 [0.44, 1.33] | 0.01 [0.01, 0.96] |
| PARAGON-HF, 2019 | 5 | 2419 | 5 | 2424 | 16.3% | 0.99 [0.29, 3.43] | 0.01 [0.01, 0.96] |
| Total (95% CI) | 6931 | 6941 | 100.0% | 0.52 [0.30, 0.91] | 0.01 [0.01, 0.96] |

**Figure 7:** Appropriate implantable cardioverter-defibrillator shocks among heart failure patients treated with angiotensin receptor–neprilysin inhibitors versus angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; M–H, Mantel–Haenszel.

| Study or Subgroup | ARNI Events | ARNI Total | ACEIs/ARBs Events | ACEIs/ARBs Total | Weight | Odds Ratio M–H, Random, 95% CI | Odds Ratio M–H, Random, 95% CI |
|-------------------|-------------|------------|-------------------|------------------|--------|-------------------------------|-------------------------------|
| de Diego et al., 2018 | 1 | 120 | 8 | 120 | 11.6% | 0.12 [0.01, 0.96] | 0.01 [0.01, 0.96] |
| Mavromatis et al., 2016 | 0 | 151 | 20 | 161 | 57.2% | 0.37 [0.11, 0.70] | 0.01 [0.01, 0.96] |
| Russo et al., 2020 | 3 | 167 | 13 | 180 | 31.3% | 0.22 [0.08, 0.78] | 0.01 [0.01, 0.96] |
| Total (95% CI) | 438 | 438 | 100.0% | 0.23 [0.11, 0.47] | 0.01 [0.01, 0.96] |

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Figure 8: Atrial fibrillation among heart failure patients treated with angiotensin receptor–neprilysin inhibitors (ARNIs) versus angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) in all included studies (A), observational studies (B), and randomized controlled trials (C). Supraventricular tachycardia among patients treated with ARNIs versus ACEIs/ARBs in randomized controlled trials (D). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; M–H, Mantel–Haenszel.
The inhibition of angiotensin receptors and neprilysin results in the inactivation of RAAS and the natriuretic peptide system, which are overactivated in patients with HF. Neprilysin, a membrane metalloendopeptidase enzyme, is responsible for the degradation of multiple vasoactive peptides and reduces preload and ventricular remodeling. Additionally, ARB blocks the receptor type-1 and decreases the effects of angiotensin II, which prevents vasoconstriction, water retention, and myocardial hypertrophy.

Additionally, ARB blocks the receptor type-1 and decreases the effects of angiotensin II, which prevents vasoconstriction, water retention, and myocardial hypertrophy.

Clinical manifestations of HF are vast, with arrhythmias being one of the most common. Ventricular remodeling resulting in clinical pump failure has been implicated in SCD and strongly correlates with arrhythmia. ARNI therapy has been shown to improve cardiovascular outcomes in patients with HF. Neprilysin, a membrane metalloendopeptidase enzyme, is responsible for the degradation of multiple vasoactive peptides and reduces preload and ventricular remodeling. Additionally, ARB blocks the receptor type-1 and decreases the effects of angiotensin II, which prevents vasoconstriction, water retention, and myocardial hypertrophy.

To the best of our knowledge, we are the first to conduct a meta-analysis on the outcomes of arrhythmia and SCD in patients with both HFrEF and HFP EF treated with ARNI therapy. This study included an analysis of the composite incidence of ventricular arrhythmias and SCD from RCTs and observational studies. While composite outcomes of ventricular arrhythmia and SCD were statistically significant, the interpretation of VT and VF separately showed no statistically significant differences. The under-reporting or inaccurate identification of ventricular arrhythmic events may be responsible for the lack of significant statistical outcomes, which is one of the limitations of this study. All studies demonstrated adverse outcomes of tachycardia; however, specification as to whether it was explicitly ventricular was lacking. This inconsistent terminology may be responsible for outcomes favoring a reduction in SCD, but not demonstrating a statistically significant reduction in individual arrhythmias. Additionally, studies did not separate the events in terms of sustained or non-sustained VT, which could be helpful in subgroup analysis. Another limitation of this study includes observational studies with the possible presence of ascertainment bias. Regarding the use of guideline-directed medical therapy, nearly 80% of patients enrolled were on β-blocker therapy, and the use of anti-arrhythmic therapy was not reported in all studies, which could have influenced the results. Thus, further studies are needed to fully understand the impact of ARNIs on ventricular arrhythmias and SCD.
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