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# Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction

## The PARAGON-HF Trial

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## ABSTRACT

**OBJECTIVES** In this study, the authors sought to assess the relationship between AFF and outcomes, the treatment response to sacubitril/valsartan and first-detected AFF in patients with HFpEF enrolled in the PARAGON-HF trial.

**BACKGROUND** Atrial fibrillation and flutter (AFF) are common in heart failure with preserved ejection fraction (HFpEF) and increase the risk of adverse outcomes.

**METHODS** A total of 4,776 patients formed 3 groups: those with AFF according to electrocardiography (ECG) at enrollment (n = 1,552; 33%), those with history of AFF but without AFF on ECG at enrollment (n = 1,005; 21%), and those without history of AFF or AFF on ECG at enrollment (n = 2,219, 46%). We assessed outcomes, treatment response to sacubitril/valsartan in each group, and the risk associated with first-detected AFF in patients without any known AFF. The primary outcome was a composite of total heart failure hospitalizations and cardiovascular death.

**RESULTS** History of AFF and AFF at enrollment were associated with higher risk of the primary outcome (risk ratio [RR]: 1.36 [95% CI: 1.12-1.65] and RR: 1.31 [1.11-1.54], respectively), than no AFF. Neither history of AFF nor AFF at enrollment modified the treatment effect of sacubitril/valsartan. Post randomization AFF occurred in 12% of patients without previous AFF and was associated with 2.8-fold higher risk of the primary outcome, but it was not influenced by sacubitril/valsartan.

**CONCLUSIONS** History of AFF and AFF on ECG at enrollment were associated with a higher risk of the primary outcome. First-detected AFF was not influenced by sacubitril/valsartan, yet it was associated with increased risk of all subsequent outcomes and may represent a potential target for future HFpEF trials. (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF]; NCT01920711) (J Am Coll Cardiol HF 2022;10:336-346) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Atrial fibrillation and atrial flutter (AFF) are common in heart failure with preserved ejection fraction (HFpEF), with incidences of 5% to 32% (over 3.1-3.7 years),[1,2] and prevalence reported of 15% to 65%.[3,4] Atrial fibrillation in HFpEF contributes to increased risk of adverse outcomes.[5] In a post hoc analysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; NCT00094302), in which 43% of the study population had either a history of AFF or AFF at enrollment, AFF at enrollment was associated with heightened risk for the primary composite outcome of cardiovascular death or hospitalizations for heart failure (HF). Despite this elevated risk, neither of these conditions appeared to modify the treatment effect of spironolactone, nor did spironolactone affect the development of new AFF after randomization, which was a harbinger of increased early risk of adverse outcomes.[6]

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In the PARAMOUNT (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker on Management of Heart Failure With Preserved Ejection Fraction; NCT00887588), sacubitril/valsartan resulted in greater reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) at 12 weeks and greater reduction in left atrial size after 36 weeks compared with valsartan.[7] These hypothesis-generating findings were the rationale for the phase 3 PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; NCT01920711), which was designed to determine whether sacubitril/valsartan improves outcomes in patients with HFpEF.[8] We assessed the relationship between AFF status at baseline and outcomes, whether AFF modified the sacubitril/valsartan treatment effect, and whether sacubitril/valsartan influenced the development of new AFF after randomization in patients without known previous AFF enrolled in the PARAGON-HF trial.

## METHODS

**STUDY POPULATION.** The design and the results of the double-blind, active comparator PARAGON-HF trial were published previously.[8,9] In the trial, 4,822 patients were randomized to receive either sacubitril/valsartan or valsartan after a sequential run-in period designed to ensure tolerability of both drugs at half target doses. The key inclusion criteria were age of 50 years or older, symptomatic heart failure (New York Heart Association [NYHA] functional class II-IV) requiring diuretic therapy, structural heart disease (defined as left atrial enlargement or left ventricular hypertrophy) confirmed by means of echocardiography with preserved ejection fraction of ≥45% in the preceding 6 months, and elevated natriuretic peptide levels. The required natriuretic peptide levels for inclusion in the trial varied in relation to previous heart failure hospitalization and presence of AFF at the time of screening: 3-fold higher NT-proBNP levels were required in patients with AFF on screening-visit electrocardiography compared with those in sinus rhythm. Patients with AFF at screening were limited by protocol to approximately 33% of the study sample.[8] Ethics committee approval was obtained at each of the 848 trial centers in 43 countries before enrollment of the first patient, and every patient signed written informed consent for participation.[8,9]

**OUTCOMES.** The examined outcomes in this post hoc analysis included the PARAGON-HF primary composite end point: a composite of total (first and recurrent) hospitalizations for HF and cardiovascular death and its components. To allow for comparison with previous studies, we also examined the first occurrence of the primary composite end point—first hospitalization for HF and cardiovascular death (time to first outcome)—and its component first hospitalization for HF, as well as all-cause death and nonfatal stroke.

A prespecified exploratory end point of first-detected AFF was assessed in patients that developed incident AFF after randomization. It was assessed in those without history of AFF, without AFF on electrocardiography (ECG) at enrollment and without adjudication-confirmed AFF events between the screening and randomization visit. All events reported by the site investigators were independently adjudicated by a Clinical End Points Committee, including potential new-onset AFF events, which were adjudicated based on the received ECG tracings and other supporting material.[8]

**CLASSIFICATION OF AFF.** The data on known history of AFF were collected by enrolling physicians during the screening visit. An ECG was performed during the same visit and interpreted by the enrolling physician. Presence of AFF at screening was noted as the underlying rhythm in the electronic case report forms. According to those data, the patients were classified into the 3 groups: 1) patients without known history of AFF or AFF on the ECG at enrollment ("no

**ABBREVIATIONS AND ACRONYMS**

**AFF** = atrial fibrillation and flutter

**BMI** = body mass index

**ECG** = electrocardiography

**eGFR** = estimated glomerular filtration rate

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**NYHA** = New York Heart Association

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**TABLE 1 Baseline Characteristics by Atrial Fibrillation and Flutter Group at Enrollment**

| | No AFF (n = 2,219) | History of AFF Only (n = 1,005) | AFF on ECG at Enrollment (n = 1,552) | Group *P* Value |
|---|---|---|---|---|
| Age, y | 71.1 ± 8.8 | 73.9 ± 8.0 | 74.3 ± 7.7 | <0.001 |
| Female | 1,178 (53.1%) | 564 (56.1%) | 725 (46.7%) | <0.001 |
| Race | | | | <0.001 |
| Asian | 335 (15.1%) | 63 (6.3%) | 208 (13.4%) | |
| Black or African American | 68 (3.1%) | 14 (1.4%) | 19 (1.2%) | |
| Other | 116 (5.2%) | 16 (1.6%) | 47 (3.0%) | |
| White | 1,700 (76.6%) | 912 (90.7%) | 1,278 (82.3%) | |
| Geographic region | | | | <0.001 |
| Asia/Pacific and other | 403 (18.2%) | 98 (9.8%) | 258 (16.6%) | |
| Central Europe | 816 (36.8%) | 371 (36.9%) | 527 (34.0%) | |
| Latin America | 224 (10.1%) | 31 (3.1%) | 112 (7.2%) | |
| North America | 222 (10.0%) | 171 (17.0%) | 164 (10.6%) | |
| Western Europe | 554 (25.0%) | 334 (33.2%) | 491 (31.6%) | |
| Systolic blood pressure, mm Hg | 133 ± 15 | 131 ± 16 | 127 ± 15 | <0.001 |
| Heart rate, beats/min | 69 ± 11 | 67 ± 11 | 75 ± 13 | <0.001 |
| Body mass index, kg/m$^2$ | 30.1 ± 5.0 | 30.7 ± 5.0 | 30.1 ± 5.0 | <0.001 |
| Serum creatinine (mg/dL) | 93 ± 28 | 99 ± 26 | 99 ± 27 | <0.001 |
| eGFR, mL/min/1.73 m$^2$ | 67 ± 21 | 61 ± 18 | 62 ± 18 | <0.001 |
| Ischemic etiology | 957 (43.1%) | 335 (33.3%) | 426 (27.4%) | <0.001 |
| Ejection fraction, % | 57.5 ± 8.2 | 58.3 ± 7.7 | 57.0 ± 7.5 | <0.001 |
| LA volume, mL | 65.2 ± 20.6 | 73.6 ± 24.2 | 86.9 ± 33.5 | <0.001 |
| NT-proBNP, pg/mL | 574 (368-1,020) | 642 (408-1,139) | 1,589 (1,168-2,281) | <0.001 |
| NYHA functional class | | | | 0.001 |
| I | 78 (3.5%) | 24 (2.4%) | 35 (2.3%) | |
| II | 1750 (78.9%) | 774 (77.0%) | 1166 (75.2%) | |
| III | 384 (17.3%) | 204 (20.3%) | 340 (21.9%) | |
| IV | 6 (0.3%) | 3 (0.3%) | 10 (0.6%) | |
| History of hypertension | 2,128 (95.9%) | 961 (95.6%) | 1,477 (95.2%) | 0.56 |
| History of diabetes | 1,040 (46.9%) | 402 (40.0%) | 610 (39.3%) | <0.001 |
| History of stroke | 196 (8.8%) | 110 (11.0%) | 201 (13.0%) | <0.001 |
| History of hospitalization for heart failure | 972 (43.8%) | 529 (52.6%) | 799 (51.5%) | <0.001 |
| History of myocardial infarction | 673 (30.3%) | 198 (19.7%) | 207 (13.3%) | <0.001 |
| Implanted ICD | 4 (0.2%) | 7 (0.7%) | 7 (0.5%) | 0.07 |
| Implanted pacemaker | 113 (5.1%) | 167 (16.6%) | 176 (11.3%) | <0.001 |
| Diuretic at randomization | 2,094 (94.4%) | 969 (96.4%) | 1,502 (96.8%) | <0.001 |
| ACEi/ARB at screening | 1,964 (88.5%) | 853 (84.9%) | 1,306 (84.1%) | <0.001 |
| MRA at randomization | 532 (24.0%) | 243 (24.2%) | 460 (29.6%) | <0.001 |
| Beta-blocker at randomization | 1,735 (78.2%) | 806 (80.2%) | 1,270 (81.8%) | 0.022 |
| Oral anticoagulant at randomization | 117 (5.3%) | 734 (73.0%) | 1,374 (88.5%) | <0.001 |
| $CHA_2DS_2$-VASc score | 4.7 ± 1.4 | 4.9 ± 1.4 | 4.8 ± 1.4 | 0.001 |

Values are mean ± SD, n (%), or median (IQR).

ACEi = angiotensin-converting enzyme inhibitor; AFF = atrial fibrillation and flutter; ARB = angiotensin receptor blocker; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LA = left atrial; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

AFF"); 2) patients with history of AFF, but without AFF on the ECG at enrollment; and 3) patients with AFF on the ECG at enrollment.

A 12-lead ECG was performed during each on-site visit, including the randomization visit and those following randomization, and interpreted by the site physicians. The occurrence of AFF on any of these ECGs was required to be noted in the 12-lead ECG evaluation case report form. In patients in whom AFF was detected but who did not have a history of AFF or AFF present on ECG at enrollment, reporting the end point of "new onset of atrial fibrillation" was prespecified by the study protocol.

**STATISTICAL ANALYSIS.** Baseline characteristics were expressed as n (%) for categoric variables and as mean ± SD or median (IQR) for continuous variables. Differences among the 3 groups were evaluated by means of the chi-square test for categoric variables or

analysis of variance for continuous variables, and Kruskal-Wallis tests for nonnormally distributed continuous variables.

The primary composite outcome and total (first and recurrent) hospitalizations for HF were assessed with the use of the semiparametric method of Lin, Wei, Yang, and Ying.[10] Incidence rates for each of the examined end points were estimated for the 3 AFF groups, and Kaplan-Meier curves were used to depict the time to first outcome. HRs were estimated with the use of Cox proportional hazards models using the group of patients without known AFF as the reference group. Multivariable models were adjusted for the following covariates: age, sex, race, region, body mass index (BMI), estimated glomerular filtration rate (eGFR), ischemic heart disease, left ventricular ejection fraction, NYHA functional class, history of hypertension, history of diabetes, history of stroke, previous HF hospitalization, history of myocardial infarction, previous angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker, use of diuretics, mineralocorticoid receptor antagonist, beta-blocker at randomization, and treatment assignment. We tested for interaction between randomized treatment and AFF groups at screening for each outcome except incident AFF (stratified according to geographic region for the primary composite outcome).

To determine the predictors of incident AFF after randomization in patients without known previous AFF and without adjudication-confirmed AFF events between the screening and randomization visit, we used multivariable models adjusted for the covariates mentioned above. In those patients, we explored whether treatment assignment influenced the incidence of AFF after randomization in an intention-to-treat and on-treatment analysis (with time to discontinuation of study drug as end of follow-up in the latter). In a time-varying analysis with new AFF after randomization as the time-varying covariate (the analysis being initiated at the occurrence of new AFF after randomization, where applicable), we assessed the association between new AFF after randomization and the occurrence of the clinical outcomes, also adjusted for the mentioned variables.

A $P$ value of $<0.05$ was considered to be statistically significant. The statistical analyses were performed in Stata version 16 (StataCorp).

**TABLE 2 Outcomes by AFF Group at Enrollment**

| Outcome | No AFF | History of AFF Only | AFF on ECG at Enrollment |
|---|---|---|---|
| Primary outcome: total (first and recurrent) HF hospitalizations and CV death | | | |
| IR (95% CI) | 11.7 (10.9-12.5) | 15.9 (14.5-17.5) | 15.3 (14.2-16.5) |
| RR (95% CI) | REF | 1.36 (1.12-1.65) $P = 0.002$ | 1.31 (1.11-1.54) $P = 0.002$ |
| Adjusted RR (95% CI) | REF | 1.15 (0.94-1.40) $P = 0.19$ | 1.14 (0.96-1.37) $P = 0.14$ |
| Total (first and recurrent) HF hospitalizations | | | |
| IR (95% CI) | 8.7 (8.0-9.5) | 13.5 (12.2-14.9) | 11.8 (10.9-12.9) |
| RR (95% CI) | REF | 1.54 (1.24-1.92) $P < 0.001$ | 1.35 (1.11-1.64) $P = 0.002$ |
| Adjusted RR (95% CI) | REF | 1.27 (1.01-1.59) $P = 0.044$ | 1.19 (0.97-1.47) $P = 0.10$ |
| First occurrence of the primary outcome (First HF hospitalization and CV death) | | | |
| IR (95% CI) | 7.3 (6.7-8.1) | 9.8 (8.7-11.1) | 9.6 (8.7-10.6) |
| HR (95% CI) | REF | 1.34 (1.15-1.56) $P < 0.001$ | 1.31 (1.14-1.50) $P < 0.001$ |
| Adjusted HR (95% CI) | REF | 1.22 (1.04-1.44) $P = 0.015$ | 1.19 (1.03-1.38) $P = 0.018$ |
| First HF hospitalization | | | |
| IR (95% CI) | 5.3 (4.8-6.0) | 8.4 (7.3-9.6) | 7.4 (6.6-8.3) |
| HR (95% CI) | REF | 1.57 (1.32-1.87) $P < 0.001$ | 1.40 (1.19-1.63) $P < 0.001$ |
| Adjusted HR (95% CI) | REF | 1.35 (1.13-1.61) $P = 0.001$ | 1.23 (1.04-1.46) $P = 0.016$ |
| Cardiovascular death | | | |
| IR (95% CI) | 2.9 (2.5-3.4) | 2.5 (2.0-3.1) | 3.4 (2.9-4.0) |
| HR (95% CI) | REF | 0.84 (0.64-1.10) $P = 0.20$ | 1.17 (0.95-1.45) $P = 0.14$ |
| Adjusted HR (95% CI) | REF | 0.78 (0.58-1.03) $P = 0.08$ | 1.04 (0.83-1.31) $P = 0.73$ |
| All-cause death | | | |
| IR (95% CI) | 4.4 (3.9-4.9) | 4.5 (3.8-5.4) | 6.2 (5.5-6.9) |
| HR (95% CI) | REF | 1.03 (0.84-1.27) $P = 0.77$ | 1.41 (1.19-1.66) $P < 0.001$ |
| Adjusted HR (95% CI) | REF | 0.96 (0.77-1.19) $P = 0.70$ | 1.22 (1.03-1.46) $P = 0.025$ |
| Nonfatal stroke | | | |
| IR (95% CI) | 1.2 (1.0-1.5) | 1.2 (0.8-1.6) | 2.0 (1.6-2.4) |
| HR (95% CI) | REF | 0.95 (0.63-1.43) $P = 0.81$ | 1.63 (1.20-2.22) $P = 0.002$ |
| Adjusted HR (95% CI) | REF | 0.95 (0.62-1.45) $P = 0.82$ | 1.56 (1.12-2.17) $P = 0.008$ |

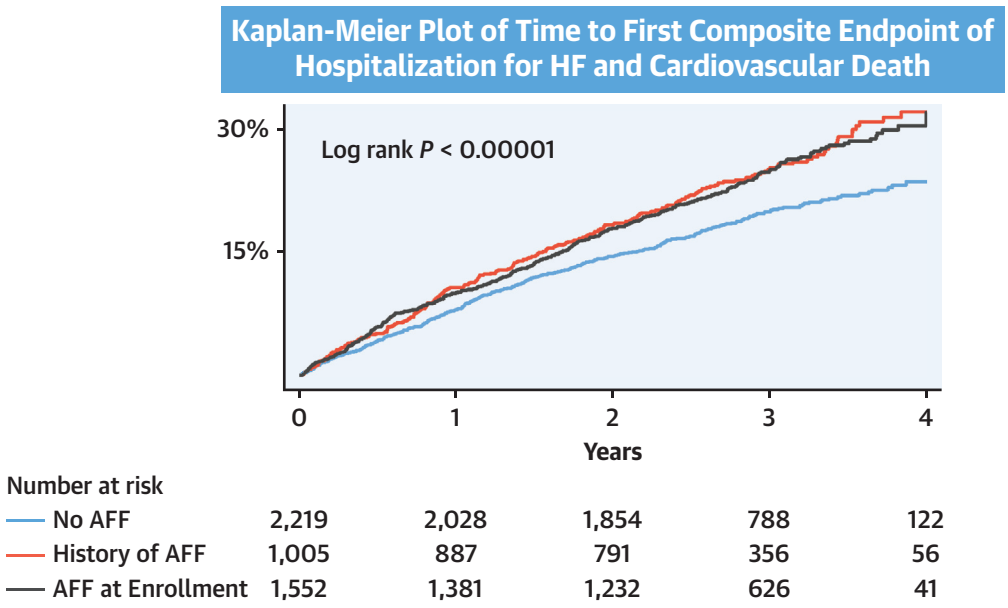
Adjusted for age, sex, race category, region category, body mass index, estimated glomerular filtration rate, ischemic heart disease category, left ventricular ejection fraction, New York Heart Association functional class, history of hypertension, history of diabetes, history of stroke, prior heart failure hospitalization, history of myocardial infarction, use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker at screening, use of diuretics, mineralocorticoid receptor antagonist, beta-blocker at randomization, and treatment assignment.

AFF = atrial fibrillation and flutter; CV = cardiovascular; ECG = electrocardiography; HF = heart failure; IR = incidence rate (per 100 patient-years); REF = reference; RR = risk ratio.

## RESULTS

**BASELINE CHARACTERISTICS.** AFF status was determined in 4,776 patients at enrollment (after exclusion of 24 patients from a site closed for good clinical practice violations and 20 patients because of missing data on AFF status). Totals of 2,219 patients (46%) had no evidence of AFF, 1,005 patients (21%) had only a history of AFF, and 1,552 (33%) had AFF on

**CENTRAL ILLUSTRATION** **Hospitalizations for Heart Failure and Cardiovascular Death, According to Atrial Fibrillation/Flutter Status**

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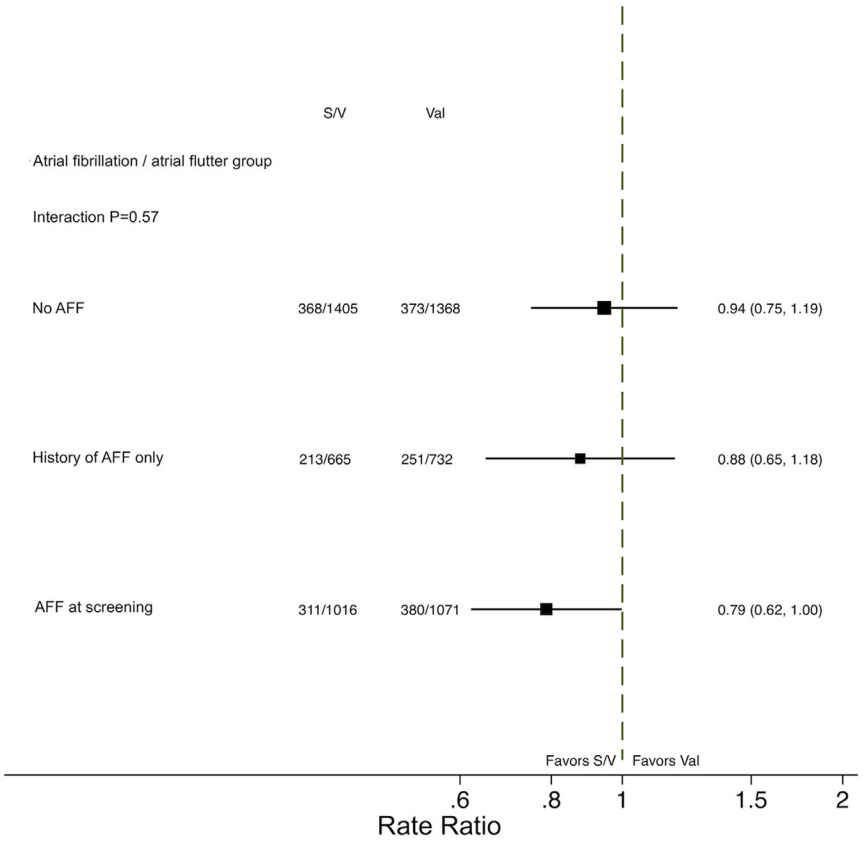
Kaplan-Meier plot of time to first composite end point of hospitalization for heart failure (HF) and cardiovascular death, according to atrial fibrillation and flutter (AFF) status.

the ECG at enrollment. The baseline characteristics of patients according to AFF groups are presented in Table 1. Patients with a history of AFF or AFF at enrollment were older and had significantly lower systolic blood pressure and eGFR values compared with those without any known AFF. They were less likely to have diabetes or a history of myocardial infarction but were more likely to have had previous hospitalizations for HF or stroke, compared with those without any known AFF. Patients with a history of AFF or AFF at enrollment were also more frequently in NYHA functional class III. Patients in these 2 groups were also more likely to have received diuretic agents and beta-blockers, but less likely to have received an ACE inhibitor/angiotensin receptor blocker, than those with no history of AFF. Patients with AFF at enrollment were more frequently male, they had significantly higher heart rates, and their median NT-proBNP values were significantly higher compared with those with only a history of AFF or with AFF at enrollment. The comparison of patients without AFF and those with only a history of AFF is presented in Supplemental Table 1.

**THE INFLUENCE OF ATRIAL FIBRILLATION/FLUTTER ON OUTCOMES.** During a median follow-up of 2.9 years (IQR: 2.5-3.4 years), the primary composite outcome occurred in 1,896 patients and the first occurrence of the primary composite outcome in 1,079 patients. The crude incidence rates (IRs) of the primary outcome, first occurrence of the primary outcome, total HF hospitalizations, and first HF hospitalization were the greatest in patients with history of AFF alone, whereas the patients with AFF at enrollment had the highest IRs of cardiovascular and all-cause death and stroke (Table 2). Patients with a history of AFF or AFF at enrollment had a >30% higher unadjusted risk of the primary outcome (risk ratio [RR]: 1.36 [95% CI: 1.12-1.65; $P = 0.002$] and RR: 1.31 [95% CI: 1.11-1.54; $P = 0.002$], respectively) and first occurrence of the primary outcome (HR: 1.34 [95% CI: 1.15-1.56; $P < 0.0001$] and HR: 1.31 [95% CI: 1.14-1.50; $P < 0.0001$], respectively), compared with those with no known AFF (Central Illustration, Table 2). After adjusting for baseline covariates, history of AFF or AFF at enrollment was not significantly associated with the risk of the primary outcome, but it remained significantly associated with higher risk of the first occurrence of the primary outcome (HR: 1.22 [95% CI: 1.03-1.43; $P = 0.018$] and HR: 1.19 [95% CI: 1.03-1.38; $P = 0.021$] for those with history of AFF and

**FIGURE 1** Treatment Effect of Sacubitril/Valsartan vs Valsartan on Total Hospitalizations for Heart Failure and Cardiovascular Death, According to Atrial Fibrillation and Flutter Status




Treatment effect of sacubitril/valsartan (S/V), compared to valsartan (Val), on the PARAGON-HF primary end point (first and recurrent hospitalizations for heart failure and cardiovascular death), according to atrial fibrillation and atrial flutter (AFF) status at screening and stratified by region.

AFF at enrollment, respectively), which was mainly driven by a higher adjusted risk of first HF hospitalization (HR: 1.34 [95% CI: 1.12-1.61; $P = 0.001$] and HR: 1.23 [95% CI: 1.04-1.46; $P = 0.016$] for those with history of AFF and AFF at enrollment, respectively) (Table 2). The significantly higher adjusted risk for total (first and recurrent) HF hospitalizations was associated with having a history of AFF (HR: 1.26 [95% CI: 1.01-1.59]; $P = 0.044$). However, only 21 patients (2%) with a history of AFF and 25 patients (1%) with no AFF had AFF present as a concomitant reason for hospitalization during an HF hospitalization (first and recurrent). The adjusted risk of all-cause death (HR: 1.21 [95% CI: 1.02-1.45]; $P = 0.032$) and stroke (HR: 1.56 [95% CI: 1.12-2.17]; $P = 0.008$) was significantly higher in patients with AFF at enrollment, compared with those without any known AFF (Table 2). Neither history of AFF nor AFF at enrollment modified the treatment effect of sacubitril/valsartan on the PARAGON-HF primary composite outcome (interaction $P = 0.57$) or other examined end points ($P \geq 0.13$) (Figure 1).

**NEW AFF AFTER RANDOMIZATION.** During follow-up, new AFF occurred after randomization in 258 patients (12%) without known previous AFF (IR: 4.3 [95% CI: 3.8-4.9] per 100 person-years). Predictors of first-detected AFF in those without previous AFF were older age (HR: 1.05 [95% CI: 1.03-1.07] per 1 year; $P < 0.0001$), lower heart rate (HR: 0.88 [95% CI: 0.78-1.00] per 10 beats/min; $P = 0.042$), higher BMI (HR: 1.05 [95% CI: 1.02-1.08] per 1 kg/m$^2$; $P = 0.002$), and higher NT-proBNP (HR: 1.24 [95% CI: 1.11-1.38] per doubling of NT-proBNP; $P < 0.001$) (Table 3).

Randomization to sacubitril/valsartan did not significantly influence the incidence of AFF after

**TABLE 3 Predictors of Incident Atrial Fibrillation and Flutter in Those Without Previous Atrial Fibrillation or Atrial Flutter**

| Predictor | HR | 95% CI | *P* Value |
|---|---|---|---|
| Age | 1.05 | 1.03-1.07 | <0.0001 |
| BMI | 1.05 | 1.02-1.08 | 0.002 |
| Heart rate | 0.88 | 0.78-1.00 | 0.042 |
| Log NT-proBNP | 1.24 | 1.11-1.38 | <0.0001 |

BMI = body mass index; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

randomization in an intention-to-treat (HR: 1.06 [95% CI: 0.83-1.35]; $P = 0.64$) or on-treatment (HR: 1.05 [95% CI: 0.81-1.37]; $P = 0.70$) analysis. Patients who developed AFF after randomization had higher rates and significantly higher risk (more than 2.3-fold for adjusted risks) for all the studied outcomes subsequent to the AFF event (Table 4). The IR of the first occurrence of the primary outcome was the greatest in the first 30 days following incident AFF (IR: 51.7 [95% CI: 26.9-99.4]) and declined between 30 days and 1 year (IR: 18.9 [95% CI: 13.0-27.3]) and after 1 year (IR 8.7 [95% CI: 5.0-14.9]).

## DISCUSSION

**MAIN FINDINGS.** In patients with HFpEF enrolled to the PARAGON-HF trial, history of AFF or AFF at enrollment was associated with a significantly higher risk of hospitalizations for HF or cardiovascular death compared with no known AFF. This finding was mainly driven by a higher risk of HF hospitalization. The crude and adjusted risks of all-cause death and stroke were also significantly higher in patients with AFF at enrollment compared with those without known AFF. Neither history of AFF nor AFF at enrollment modified the treatment effect of sacubitril/valsartan with regard to any of the examined study end points. Randomization to sacubitril/valsartan did not influence the occurrence of new AFF after randomization, but those who developed new AFF after randomization had substantially higher subsequent rates of all study end points, particularly during the first 30 days.

**INCREASING BURDEN OF AFF IN PATIENTS WITH HFpEF.** Despite a protocol-defined cap on the enrollment of patients with AFF on ECG to approximately 33% of the study population, the 54% prevalence of any known AFF in the contemporary PARAGON-HF cohort is consistent with an incremental trend from previous clinical trials: The prevalence of AFF at enrollment was 16% in CHARM-Preserved (Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity; NCT00634712) (478 of 3,023 patients had AFF at baseline), and any known AFF was present in 30% of patients in I-Preserve (Irbesartan in Heart Failure With Preserved Systolic Function; NCT00095238) and 43% in TOPCAT[1,5,6] (Table 5). An analysis of the Framingham Heart Study participants showed that those with first-detected HFpEF had previous or concurrent AFF in 32% and 18% of the cases, respectively.[11] Data from the SwedeHF (Swedish Heart Failure Registry) show an even higher proportion of 65% of patients with any known atrial fibrillation within a large nationwide population of 9,525 patients with HFpEF.[4] These findings are consistent with the increasing burden of AFF in the general population: over the past 50 years: A fourfold increase in the age-adjusted prevalence of AFF has been noted in the Framingham Study population.[12] This phenomenon is likely in part caused by increased monitoring, both in clinical practice and with the use of widely available wearables that offer this option. Furthermore, consistently with the data from TOPCAT and CHARM-Preserved, patients with any known AFF enrolled in PARAGON-HF were older than those with no AFF.[1,6] Another factor that may have influenced the higher rate of AFF in this trial was the requirement for structural heart disease including left atrial enlargement and elevated natriuretic peptides for inclusion; although the latter were higher for patients in AFF at screening, AFF itself can increase natriuretic peptides substantially, which may have enriched for patients with AFF.

**INCREASED RISK OF ADVERSE OUTCOMES IN PATIENTS WITH AFF.** Notwithstanding the increasing prevalence of AFF, the risk of adverse outcomes associated with AFF was lower in this analysis compared with the majority of previous studies. Although the adjusted risk for the primary outcome in PARAGON-HF was not significantly different between those with a history of AFF or AFF and enrollment compared with those without known AFF, the adjusted risks for the composite outcome of first occurrence of hospitalization for HF and cardiovascular death were increased by 19% and 22% in patients with only a history of AFF and patients with AFF and enrollment, respectively. This finding was driven mainly by higher adjusted risks for first hospitalization for HF (23% higher risk in patients with AFF at enrollment and 34% higher risk in those with history of AFF only). Furthermore, a significantly higher adjusted risk (26%) for total hospitalizations for HF was found in those with a history of AFF only. Neither history of AFF or AFF at enrollment portended an increased risk of cardiovascular death,

**TABLE 4 Outcomes Subsequent to Incident AFF vs Outcomes in Patients Without Incident AFF**

| Outcome | No Incident AFF | Incident AFF |
|---|---|---|
| Primary outcome: total (first and recurrent) HF hospitalizations and CV death | | |
| IR (95% CI) | 11.0 (10.2-11.9) | 30.6 (25.6-36.5) |
| RR (95% CI) | REF | 2.82 (2.13-3.74) $P < 0.001$ |
| Adjusted RR (95% CI) | REF | 2.55 (1.88-3.48) $P < 0.001$ |
| Total (first and recurrent) HF hospitalizations | | |
| IR (95% CI) | 8.1 (7.4-8.9) | 24.1 (19.7-29.4) |
| RR (95% CI) | REF | 2.95 (2.17-4.01) $P < 0.001$ |
| Adjusted RR (95% CI) | REF | 2.56 (1.80-3.63) $P < 0.001$ |
| First occurrence of the primary outcome (first HF hospitalization and CV death) | | |
| IR (95% CI) | 6.8 (6.2-7.6) | 15.8 (12.0-20.9) |
| HR (95% CI) | REF | 2.65 (1.96-3.59) $P < 0.001$ |
| Adjusted HR (95% CI) | REF | 2.64 (1.92-3.62) $P < 0.001$ |
| First HF hospitalization | | |
| IR (95% CI) | 4.9 (4.4-5.5) | 12.4 (9.0-16.9) |
| HR (95% CI) | REF | 2.86 (2.02, 4.04] $P < 0.001$ |
| Adjusted HR (95% CI) | REF | 2.79 (1.94-4.02) $P < 0.001$ |
| Cardiovascular death | | |
| IR (95% CI) | 2.7 (2.3-3.2) | 6.5 (4.4-9.6) |
| HR (95% CI) | REF | 2.54 (1.66-3.90) $P < 0.001$ |
| Adjusted HR (95% CI) | REF | 2.57 (1.65-3.99) $P < 0.001$ |
| All-cause death | | |
| IR (95% CI) | 4.0 (3.6-4.6) | 9.5 (6.9-13.1) |
| HR (95% CI) | REF | 2.24 (1.57-3.18) $P < 0.001$ |
| Adjusted HR (95% CI) | REF | 2.18 (1.52-3.13) $P < 0.001$ |
| Nonfatal stroke | | |
| IR (95% CI) | 1.1 (0.9-1.4) | 2.4 (1.2-4.6) |
| HR (95% CI) | REF | 2.09 (1.02-4.29) $P = 0.045$ |
| Adjusted HR (95% CI) | REF | 2.30 (1.10-4.81) $P = 0.027$ |

Only patients without any known AFF at enrollment or adjudication-confirmed AFF events between the screening and randomization visit are included in this time-updated analysis. Adjusted for age, sex, race category, region category, body mass index, estimated glomerular filtration rate, ischemic heart disease category, left ventricular ejection fraction, New York Heart Association functional class, history of hypertension, history of diabetes, history of stroke, prior heart failure hospitalization, history of myocardial infarction, use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker at screening, use of diuretics, mineralocorticoid receptor antagonist, beta-blocker at randomization, and treatment assignment.

Abbreviations as in Table 2.

whereas there was a 21% higher adjusted risk of all-cause death in patients with AFF at enrollment. Whereas in PARAGON-HF a significant increase in the risk for adverse outcomes was noted in both the patients with AFF at enrollment and those with only a history of AFF, in TOPCAT only patients with AFF at enrollment (and not those with history of AFF) were at increased risk of adverse outcomes, with 36% and 43% higher risks of hospitalization for HF and cardiovascular death, respectively.[6] In CHARM-Preserved, those with AFF at enrollment had a 32% higher adjusted risk of cardiovascular death or first hospitalization for HF—also higher than in PARAGON-HF.[1] The results from I-Preserve are more similar to the current analysis: The adjusted risk for cardiovascular death or first hospitalization for HF was increased by 23% in those with only a history of atrial fibrillation, 13% in those with history of AFF on ECG, and 19% in the combined group, ie, any atrial fibrillation[5] (Table 5). In an analysis of the PARAGON-HF trial, it was shown that patients with AFF at enrollment and NT-proBNP values at the enrollment margins (600 and 900 pg/mL for those with and without a hospitalization for HF in the previous 9 months, respectively) had a lower risk of the primary composite outcome compared with patients with sinus rhythm at enrollment (which included patients with a history of AFF but no AFF at enrollment) and similar NT-proBNP values.[13] Although the study required elevated NT-proBNP values at entry for those in AFF, at any given NT-proBNP level patients in AFF were lower risk, which may explain the increased risk in patients with a history of AFF only compared with those with AFF after adjustment for NT-proBNP.

**INCREASED RISK OF NEW AFF AFTER RANDOMIZATION AND SUBSEQUENT OUTCOMES.** We reported that new AFF after randomization occurred in 12% of patients without known previous AFF, translating to an IR of 4.3 per 100 person-years which surpasses the IR of 3.0 per 100 person-years in TOPCAT (Table 5). However, because of mandated evidence of structural heart disease in the enrollment criteria for PARAGON-HF, the background risk was likely higher. Incident AFF portended a greater than 2-fold risk for the occurrence of all subsequent outcomes analyzed in this study, thus exceeding the higher risks of most adverse outcomes associated with incident AFF in other studies.[6,14] These data strongly suggest that atrial fibrillation is a viable and important potential therapeutic target in patients with HFpEF and that

**TABLE 5 Overview of Findings Pertinent to AF as a Comorbidity in Major HFpEF Randomized Controlled Trials**

| | PARAGON-HF (n = 4,776) | TOPCAT[6] (n = 1,765) | CHARM-Preserved[1,15] (n = 3,023) | I-Preserve[5] (n = 4,128) |
|---|---|---|---|---|
| Prevalence of AF at enrollment | 54% (any known AF) | 43% (any known AF) | 16% (AF at enrollment) | 30% (any known AF) |
| Effect of AF on primary outcome (unadjusted analysis) | First and recurrent HFH, CV death:<br>• History of AF: RR: 1.36 (95% CI: 1.12-1.65; $P = 0.002$);<br>• AF at enrollment: RR: 1.31 (95% CI: 1.11-1.54; $P = 0.002$) | CV death, aborted cardiac arrest, HFH:<br>• History of AF: HR: 0.98 (95% CI: 0.78-1.25; $P = 0.90$);<br>• AF at enrollment: HR: 1.21 (95% CI: 0.99-1.48; $P = 0.06$) | CV death, first HFH:<br>• AF at enrollment: HR: 1.72 (95% CI: 1.45-2.06; $P < 0.001$) | CV death, first HFH (secondary outcome):<br>• History of AF only: HR: 1.81 (95% CI: 1.59-2.06; $P < 0.001$);<br>• History of AF and AF at enrollment: HR: 1.55 (95% CI: 1.36-1.76; $P < 0.001$) |
| Occurrence of new AF after randomization | 4.3 per 100 person-years | 3.0 per 100 person-years | 4.9% of patients | n/a |
| Treatment effect on new AF after randomization | HR: 1.06 (95% CI: 0.83-1.35; $P = 0.64$) (sacubitril/valsartan) | HR: 0.98 (95% CI: 0.68-1.42; $P = 0.92$) (spironolactone) | CHARM-P: OR: 0.89 (95% CI: 0.62-1.30); CHARM-Overall: OR: 0.81 (95% CI: 0.66-1.00; $P = 0.48$)[a] (candesartan) | n/a |

[a]No heterogeneity between treatment arms.

AF = atrial fibrillation; HFH = heart failure hospitalization; HFpEF = heart failure with preserved ejection fraction; n/a = not applicable; other abbreviations as in Table 2.

clinical trials of specific therapies designed to minimize AFF in HFpEF patients may be warranted.

**THE EFFECT OF SACUBITRIL/VALSARTAN ON ADVERSE OUTCOMES.** Despite the favorable effects of sacubitril/valsartan on reverse left atrial remodeling in the PARAMOUNT trial,[7] we did not observe that randomization to sacubitril/valsartan significantly influenced the occurrence of new AFF after randomization. However, ascertainment of post-randomization AFF was limited to protocol-solicited reporting of events noted during study visits or reports of AFF episodes documented between study visits. It is likely that some AFF events remained unrecognized, thus limiting the power to assess the treatment effect of sacubitril/valsartan on incident AFF. Moreover, the requirement for either left ventricular hypertrophy or left atrial enlargement at entry, with 92% of patients having evidence of left atrial enlargement, might have selected for a population less likely to benefit from sacubitril/valsartan for this end point. Finally, angiotensin receptor blockers themselves are associated with reduction in AFF,[14,15] and the incremental benefit of the neprilysin inhibitor for this end point may have been minimal.

**STUDY LIMITATIONS.** Inherent to clinical trials, the specific inclusion and exclusion criteria might limit the generalizability of these results, such as the exclusion of patients with a high BMI (>40 kg/m$^2$). In PARAGON-HF, patients with documented AFF at enrollment were limited to one-third of the overall study population, thus limiting the insight to the true prevalence of AFF in patients in the broader HFpEF population. The stratification of patients according to AFF status that we used is not a duplicate of the currently preferred clinical classifications (paroxysmal, persistent, and permanent atrial fibrillation). However, we think that the classification chosen for this analysis is the most accurate given the data collected in PARAGON-HF. In addition, a history of AFF may have been unrecognized in some patients. Similarly, incident AFF may have been underrecognized, particularly if occurring between study visits. The lack of prospective cardiac rhythm monitoring is a limitation, and although we did not observe a reduction in incident AFF in this study, we cannot rule out the possibility that with cardiac rhythm monitoring we might have observed a reduction in AFF. We anticipate that devices and wearables providing continuous ECG monitoring might improve this type of data collection in future clinical trials.

## CONCLUSIONS

We found that both history of AFF and AFF at enrollment were associated with increased risk of cardiovascular death or heart failure hospitalization, death, and stroke. Although first-detected AFF was not influenced by treatment with sacubitril/valsartan compared with valsartan, it portended a markedly increased risk of morbidity and mortality, suggesting that therapeutic trials to reduce atrial fibrillation burden in HFpEF patients may be warranted.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In patients with HFpEF, AFF is associated with a higher risk of hospitalization for heart failure and cardiovascular death, which was not influenced by sacubitril/valsartan.

**TRANSLATIONAL OUTLOOK 1:** Future studies using wearables providing continuous ECG monitoring should enrich the knowledge regarding epidemiology and clinical impact of subclinical AFF in patients with HFpEF.

**TRANSLATIONAL OUTLOOK 2:** First-detected AFF, associated with substantially higher subsequent rates of adverse outcomes, may represent a potential target for future HFpEF trials.

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**KEY WORDS** atrial fibrillation, echocardiography, heart failure outcomes, heart failure with preserved ejection fraction, sacubitril/valsartan

**APPENDIX** For a supplemental table, please see the online version of this paper.