Atrial fibrillation is an independent risk factor for heart failure hospitalization in heart failure with preserved ejection fraction

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Abstract

Aim: Atrial fibrillation (AF) is a common comorbid condition in heart failure with preserved ejection fraction (HFrEF). The effect of AF on heart failure (HF) exacerbation in HFrEF has not been well described. This study investigated how AF modifies the clinical trajectory of HFrEF patients after hospitalization for decompensated HF.

Methods and results: We stratified HFrEF subjects by AF diagnosis and performed longitudinal analysis to compare risk for HF hospitalization after index hospitalization for decompensated HF. All-cause mortality, 30 day all-cause readmissions, and response to inpatient diuresis were also evaluated. Of 90 subjects enrolled, 35.6% (n = 32) had AF. Subjects with AF were older (72.5 vs. 60.5 years; P < 0.01), more often male (46.9% vs. 24.1%; P = 0.03), and had greater left atrial diameter (4.9 vs. 3.8 cm; P < 0.01) compared with those without AF. Subjects with AF had a higher risk for HF hospitalization than their counterparts without AF (P = 0.02); this relationship remained significant following multivariable competing risk regression with propensity score weighting (hazard ratio 2.53, P = 0.04 and hazard ratio 2.91, P = 0.04, with overlap and inverse probability weighting, respectively). Although having AF appeared to increase the risk of all-cause hospital readmission within 30 days of discharge (37.5% vs. 17.5%; P = 0.036), this relationship failed to remain significant following propensity score adjustment for clinical covariates.

Conclusions: Atrial fibrillation is an independent risk factor for HF rehospitalization in HFrEF. Further understanding of the interplay between AF and HFrEF will be critical to guide the selection of appropriate rhythm management strategies in this population.

Keywords: Atrial fibrillation; Heart failure with preserved ejection fraction; Heart failure hospitalization; Survival analysis; All-cause hospital readmissions; All-cause mortality

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Background

An estimated 6 million Americans will have heart failure with preserved ejection fraction (HFrEF) by 2030, representing at least half of all individuals in the USA carrying the diagnosis of congestive heart failure (HF). Although HFrEF is one of the fastest growing epidemics within cardiology, it is also one of the most poorly understood. Indeed, despite concerted efforts by our medical scientific community to develop our understanding of this pathology, there remain exceedingly limited therapies with proven benefit. As these efforts continue, the median survival rate for HFrEF patients following first HF hospitalization, remains poor. Intrinsic to HFrEF are numerous medical comorbidities, many of which affect the clinical trajectory of these patients.
At least one-third of all HFpEF patients have atrial fibrillation (AF), which has been associated with significantly reduced exercise tolerance and poorer survival in retrospective review.1–3 The presence of AF has been associated with increased right-sided and left-sided pressures on right heart catheterization.10 However, understanding the effect of AF on HF exacerbation in HFpEF patients has been limited by the many potential confounders associated with carrying a concomitant diagnosis of AF. We posit that the higher right-sided and left-sided pressures seen in HFpEF patients with concomitant AF may lead to increased risk for HF exacerbation requiring hospitalization.

To address this hypothesis, we evaluated the impact of AF on response to therapy during index HF hospitalization and subsequent risk for rehospitalization due to HF exacerbation. Our primary outcome was time from discharge from index HF hospitalization to readmission for HF exacerbation. Secondary outcomes included response to intravenous diuretic therapy, and length of stay during the index hospitalization, all-cause hospitalizations within 30 days of discharge, and death. Improving our understanding of the effect of AF as a risk factor for adverse outcomes in the HFpEF population is crucial to guiding selection of appropriate AF treatment strategies and carries the potential to improve the clinical trajectory of a significant subset of the HFpEF population.

Materials and methods

Study population

We performed secondary analysis of the ROPA-DOP study, which was a prospective, randomized, single-blinded trial conducted at Johns Hopkins Hospital. HFpEF patients (n = 90) hospitalized for treatment of acute HF were enrolled within 24 h of admission. The diagnosis of acute HF was based on the presence of at least one symptom (dyspnoea, orthopnoea, or oedema) and one sign of HF (rales, jugular venous distension, positive hepatogenous reflex, peripheral oedema, ascites, or pulmonary vascular congestion on chest radiography). Patients were included if they had an established left ventricular ejection fraction (EF) ≥ 50% within 12 months of admission without interval history, electrocardiography changes, or cardiac biomarkers to suggest a cardiac event (myocardial infarction, myocarditis, pericarditis) that may have resulted in a decline in cardiac function. Further detailed inclusion and exclusion criteria have been described previously.11 All participants provided informed consent, and the study was approved by the Johns Hopkins Institutional Review Board. Laboratory studies including N-terminal pro-B type natriuretic peptide (NT-proBNP), renal function, and exercise capacity were monitored and collected at baseline, 72 h into enrolment, and upon discharge. Clinical information for follow-up was ascertained during active and passive surveillance following discharge from index hospitalization.

ROPA-DOP participants were stratified by whether they carried a diagnosis of AF at the time of study enrolment: an AF diagnosis was defined as previously documented AF leading up to their index admission electrocardiogram. The primary endpoint under investigation was the time to the first hospitalization for acute HF exacerbation following discharge from index hospitalization. Secondary endpoints included all-cause hospitalizations within 30 days of discharge from index hospitalization, all-cause mortality, and length of stay of index hospitalization.

Statistical analysis

Simple summary statistics were used to tabulate demographic and clinical parameters stratified by AF history. Continuous data from each subgroup were analysed using the Student’s t-test or Wilcoxon rank sum test and reported as means with standard deviation. All results demonstrating non-linearity in distribution were described using median and interquartile range. Categorical data were analysed using the χ² test and reported as a number (%). Univariable logistic regression was performed to assess the effect of AF on diuresis volume and on 30 day readmission risk. Potential predictor variables were categorized into the following groups: demographic parameters (i.e. age), clinically comorbid conditions (i.e. glomerular filtration rate [GFR]), and biomarkers indicating effective decongestion using intravenous diuretics (total urine output). A two-sided P-value < 0.05 was considered significant.

Time-to-event analysis for heart failure exacerbation

Time to hospitalization for HF exacerbation was estimated by taking the difference between the day of hospital admission for acute HF and the day of discharge from index hospitalization. Administrative censoring was set on 30 May 2020. Kaplan–Meier methods were used to assess unadjusted differences between study subgroups, which were compared using the log-rank test. Factors associated with the primary endpoint were identified using Cox proportional hazard analysis. Variables with P < 0.05 in the univariable model were included in the multivariable model. In addition, history of prior hospitalizations for HF exacerbation as well as left atrial diameter were both included in the multivariable model as indirect measures of duration of AF and HF diagnoses, in order to account for lead-time bias.12–14 Interaction terms were used to assess whether there was difference between diuretic dosing strategies (continuous infusion vs. intermittent bolus) and, separately, to assess whether any differences arose from use of dopamine during inpatient decongestion.

To account for confounders associated with AF, our covariate of interest, two separate propensity score weighting...
techniques, overlap weighting and inverse probability treatment weighting (IPTW), were used to conduct weighted multivariable competing risk regression with robust standard errors.15–18 Both of these propensity score weighting methods balance covariates based on the probability of the individual having the covariates of interest (AF), using multivariable logistic regression to adjust for covariates of age, sex, race, prior HF admissions, beta-blocker, aldosterone, dose of loop diuretic, hypertension, hyperlipidaemia, diabetes mellitus, obstructive sleep apnoea, history of coronary artery disease, active tobacco use, 6 min walk distance upon admission for acute decompensated HF, estimated glomerular filtration rate on admission (eGFR), initial NT-proBNP, New York Heart Association (NYHA) class, and body mass index (BMI).

To reduce the variability of IPTW weights and give individuals with extreme weights less influence, a stabilization technique was implemented by multiplying the treatment and comparison weights by a constant, equal to the expected value of being in the treatment or comparison groups.19,20 Model discrimination index (c-statistics 0.91) and Hosmer–Lemeshow goodness-of-fit test (P = 0.47) were used to confirm appropriate predictive power of the propensity score model prior to implementation in these doubly robust multivariable longitudinal regression models.

**Odds for all-cause hospital readmission within 30 days of index hospitalization discharge**

To compare risk for all-cause readmission to the hospital within 30 days, multivariable logistic regression was performed with sequential addition of demographic parameters to start given small sample size to avoid over-adjustment. Interaction terms were used to assess whether there was any interaction between continuous dopamine infusion and AF status, and whether there was any interaction between diuresis-dosing strategy (continuous vs. intermittent) and AF status. Doubly robust logistic regression was then performed alternately with overlap weighting and IPTW models as described above to adjust for clinical covariates associated with AF.

All statistical analyses were performed with STATA (STATACORP, Austin, TX, USA, Version 15.2) and R software 3.1.3 [R Foundation for Statistical Computing (http://www.r-project.org)].

**Results**

**Demographics and comorbidities**

Out of a total of 90 HFrEF subjects enrolled, 35.6% (n = 32) had documented history of AF: 56% of these subjects had paroxysmal AF (18/32), and 44% had persistent AF (14/32); 81% (26/32) were in AF at the time of study enrolment. Subjects with AF were significantly older (72.5 vs. 60.5 years; P < 0.01), more often male (46.9% vs. 24.1%; P = 0.03), had greater left atrial diameter by echocardiography (4.9 cm [4.5, 5.3] vs. 3.8 cm [3.4, 4.3]; P < 0.01), and trended towards higher NT-proBNP levels on admission (1918 pg/mL [991, 3900] vs. 961.5 pg/mL [169, 2417]; P = 0.10) compared with those without AF (Table 1). Unadjusted univariable analysis of study subgroups suggested that AF was not associated with a significantly higher prevalence of other common clinical comorbidities, such as hypertension and diabetes mellitus. Biomarkers of comorbid disease severity, including haemoglobin A1c and eGFR, were also not significantly different between HFrEF subjects with and without AF. The mean follow-up for study subjects was 870 days until the subjects were censored, from reaching the primary endpoint of HF rehospitalization, death, or administrative censoring.

**Response to decongestion with intravenous diuretic therapy during index hospitalization**

In general, NT-proBNP on admission was higher in subjects with AF; however, there was no significant difference in length of stay, volume of decongestion, renal function, nor change in NT-proBNP from admission to discharge following intravenous diuresis (Figure 1). HFrEF subjects with AF had comparable exercise capacity to their counterparts without AF; however, there was no significant improvement in exercise capacity between admission and discharge, as measured by 6 min walk test distance. Subjects with AF endorsed similar symptoms as their counterparts without AF upon admission and also had comparable improvement in their overall symptomatology, as measured by interval changes in global well-being and dyspnoea scores taken on admission and discharge from index hospitalization.

**Time to heart failure hospitalization**

Following discharge from index hospitalization, the subgroup of HFrEF patients with AF had a significantly higher hazard for HF hospitalization than their counterparts without AF, with a total of 18 out of 32 individuals with AF and 43 out of 58 individuals without AF requiring inpatient admission for HF exacerbation (Figures 2B and 3B, P = 0.02). The univariable associations of clinical comorbidities with AF were assessed. Using a stepwise forward Cox regression model, AF remained significantly associated with higher hazard for HF decompensation after adjusting for AF, age, sex, prior history of HF hospitalization, GFR, and left atrial diameter (hazard ratio = 2.18 [1.09, 4.33]; P = 0.03; Table 2A).
Diagnosis in HFpEF was associated with higher rates of adverse events. Univariable analysis showed that carrying a concomitant AF diagnosis in HFpEF was associated with higher rates of hospital readmission and all-cause mortality.

**Table 1 Baseline demographics and clinical findings stratified by history of atrial fibrillation**

| Demographics and clinical comorbidities | HfPfEf with AF (n = 32) | HfPfEf without AF (n = 58) | P-value<sup>a</sup> |
|-----------------------------------------|--------------------------|----------------------------|---------------------|
| Age (years)                             | 72.5 [66, 82]            | 60.5 [52, 70]              | <0.01               |
| Gender (% female)                       | 53.1 (17/32)             | 75.9 (44/58)              | 0.03                |
| Race (% African American)               | 62.5 (20/32)             | 62.1 (36/58)              | 0.97                |
| NYHA class (I–IV)                       | 3                        | 3                          | 0.33                |
| Hypertension (%)                        | 96.9 [89.8, 103.4]       | 93 [86.1, 99.8]           | 0.46                |
| Diabetes mellitus (%)                   | 53.3 (17/32)             | 60.4% (35/58)             | 0.71                |
| Former smoking (%)                      | 12.5 (4/32)              | 15.7 (9/58)               | 0.56                |
| Obstructive sleep apnoea (%)            | 40.6 [21.4, 58.6]        | 32.7 [19.1, 44.0]         | 0.46                |
| Body mass index (kg/m<sup>2</sup>)      | 35.5 [27.7, 45.9]        | 41.6 [34.1, 49.1]         | 0.19                |
| Systolic blood pressure (mmHg)          | 123.5 [113.5, 141.5]     | 137.5 [115, 160]          | 0.22                |
| Heart rate (b.p.m.)                     | 71 [62.5, 78]            | 80 [70, 90]               | 0.03                |
| 6MWT at enrolment (feet)                | 83.8 [16.2, 142.6]       | 85 [15.2, 155.07]         | 0.86                |
| Global well-being assessment score (1–100) | 25 [10, 76]          | 40 [26, 59]               | 0.42                |
| Left atrial diameter (cm)               | 4.9 [4.5, 5.3]           | 3.8 [3.4, 4.3]            | <0.01               |
| LVEF (%)                                | 60 [55, 65]              | 65 [60, 70]               | 0.17                |
| LVESD (cm)                              | 4.75 [4.2, 5.3]          | 4.7 [4.3, 5.1]            | 0.89                |
| LVMI (kg/m<sup>2</sup>)                 | 97.9 [74.2, 125.7]       | 91 [73.4, 114.28]         | 0.37                |
| NT-proBNP (pg/mL)                       | 1918 [991, 3900]         | 961.5 [169, 2417]         | 0.10                |
| GFR (mL/min per 1.73 m<sup>2</sup>)     | 45.95 [33.9, 80.6]       | 62.5 [42.5, 88.4]         | 0.38                |
| Beta-blocker (%)                        | 72 (23/32)               | 58 [34/58]                | 0.18                |
| Aldosterone (%)                         | 25 (8/32)                | 14 (8/58)                 | 0.17                |
| ACE inhibitors (%)                      | 28 (9/32)                | 34 (20/58)                | 0.57                |
| Insulin (%)                             | 25 (8/32)                | 36 (21/58)                | 0.28                |

Clinical treatment outcomes

| Change in weight at discharge (kg)      | 4.35 [1.5, 10]           | 2.70 [1.0, 5.40]          | 0.06                |
| Change in NT-proBNP at discharge (pg/mL)| 620 [204, 1095]         | 563 [68, 1314]           | 0.93                |
| Length of inpatient hospitalization (days) | 8 [6, 11]              | 6 [4, 8]                 | 0.67                |

All-cause mortality was also noted during longitudinal follow-up, affecting a total of 3 out of 32 individuals with AF and 8 out of 58 individuals without AF (Figure 3A and 3C, P = 0.98). Multivariable competing risk regression was subsequently performed to account for mortality events that preceded HF hospitalizations, which demonstrated that AF remained a significant risk factor for HF hospitalization (hazard ratio = 1.77 [1.04, 3.02]; P = 0.04; Table 2B). Further covariate balance was achieved with overlap weighting and alternately with IPTW. Multivariable competing risk regression using either of the two propensity score weighting strategies revealed AF to be a strongly significant risk factor for HF hospitalization. In sum, carrying a diagnosis of AF was associated with at least a 2.5-fold greater hazard for HF hospitalization, even after doubly robust regression strategies to balance contribution from clinical confounders.

**Thirty-day all-cause hospital readmissions**

Univariable analysis showed that carrying a concomitant AF diagnosis in HFpEF was associated with higher rates of 30 day hospital readmission (Figure 2A, 37.5% vs. 17.5%, n = 89; P = 0.04), with 7 out of 32 participants with AF and 7 out of 58 participants without AF requiring rehospitalization. The presence of AF remained an independent predictor of 30 day hospital readmission (odds ratio 4.13 [1.23, 13.55]; P = 0.02) after adjusting for age, gender, and race in multivariable logistic regression analysis. However, unlike the sustained risk AF posed for HF readmissions, this relationship failed to remain significant after further covariate balance was sought using propensity score weighting, suggesting that this increased risk was likely attributable to clinical covariates associated with carrying an AF diagnosis (Table 3).

**Discussion**

Atrial fibrillation has previously been identified as a risk factor for decreased exercise capacity,7 stroke,21 and mortality in HFpEF.8,22–24 However, little is known regarding the impact of AF on response to inpatient therapies for decompensated HF and the risk for subsequent HF hospitalization. We
Figure 1  Response to inpatient decongestion with intravenous diuretic therapy, stratified by AF status. No significant difference was seen in either AF subgroup in response to intravenous diuretic therapy during index hospitalization for decompensated heart failure, with regard to (A) total length of stay, (B) change in weight from admission to discharge, (C) change in NT-proBNP from admission to discharge, (D) percent change in NT-proBNP from admission to discharge, (E) creatinine over the course of hospitalization, and (F) prescribed loop diuretic dose over 24 h. AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide.
assessed the impact of AF as a risk factor for HF and all-cause readmission in hospitalized HfPpEF patients, using doubly robust regression techniques to isolate the contribution of AF from associated clinical comorbidities. We found that HfPpEF patients with AF are at significantly higher risk for HF readmission and showed that this risk was in spite of adjustment for other clinical risk factors. Our findings add to the growing investigation surrounding the interplay between AF and HfPpEF. Previous studies on risk for HF hospitalization in AF were largely focused on outcomes in HF with reduced EF, with very few studies reporting effects on risk for decompensation in HfPpEF.24—26

Atrial fibrillation did not significantly impact diuretic response in HfPpEF patients admitted for HF exacerbation. HfPpEF subjects with and without AF had comparable hospitalization days, urine output, change in body weight, and similar decreases in NT-proBNP over the course of their hospitalization. We postulate that the similarities in response to inpatient therapy arise from two possible sources. First, inpatients are subject to frequent dose adjustments and titrations of decongestive therapies in response to serially checked parameters for kidney function and urine output. These frequent adjustments may mask underlying differences in response to fluid fluctuations and decongestion that may exist between HfPpEF patients with and without AF on the inpatient front and lends further credence to our explanation for their divergent clinical courses following hospital discharge. Second, while we know that over 85% of the patients who had a history of AF presented with this arrhythmia on the day of admission for their index hospitalization, we do not have information on their AF burden—the proportion of time they were in AF—over the course of their hospitalization. As the interquartile ranges shown for various decongestion parameters are consistently wider for HfPpEF
patients with AF, it may be that responsiveness to deconges-
tion is related to overall AF burden. Understanding the rela-
tionship between AF burden as a continuous variable and
its impact on clinical risk factors in the HFpEF population will
be critical in guiding selection of AF therapies and requires
additional investigation.

Following discharge from index hospitalization, HFpEF pa-
tients with AF were at significantly higher risk for redevel-
oping decompensated HF requiring hospitalization. This may be because HFpEF patients with AF have a narrower euvo-
lemic window, with higher baseline right-sided filling
pressures that place them at higher risk for HF decompensa-
tion in the setting of natural outpatient fluctuations in fluid
status. Previous publications have highlighted baseline hae-
modynamic differences in left-sided and right-sided filling
pressures for HFpEF patients with AF. From a physiologic
perspective, elimination of atrial filling in end-diastole de-
creases cardiac output and simultaneously leads to increases
in pulmonary pressures. These effects may lead to greater in-
tolerance to fluid fluctuations, decreased exercise capacity,
and increased susceptibility to developing volume overload
and decompensated HF.

While clinical comorbidities associated with AF may cer-
tainly contribute to risk for HF exacerbation, we demonstrate
a sustained significant association between AF and risk for
decompensated HF. These findings suggest that HFpEF pa-
tients with AF may benefit from closer outpatient follow-up.
As such, further investigation on the frequency of follow-up
for HFpEF patients with AF should be performed to try to pre-
vent readmissions.

We found that AF was associated with significantly higher
rates of all-cause readmission within 30 days and remained
an independent predictor of 30 day readmission after
adjusting for age, gender, and race in multivariable logistic re-
gression analysis. However, AF did not remain a significant
risk factor after propensity score weighting adjustments. This
suggests that all-cause readmissions in HFpEF, unlike HF read-
misions, are driven largely by the multiple comorbidities
common to many HFpEF patients, rather than AF alone. How-
ever, unlike many other clinical risk factors associated with
poor outcomes in HFpEF, there are many different therapies
readily available for managing this arrhythmia. Demonstrat-
ing that AF serves as an independent risk factor for HF exac-
erbation, even after balancing for other clinical comorbidities,
raises the important question of whether we are able to
modify AF to abrogate risk for HF decompensation in the
HFpEF population.

Given recent randomized control studies assessing rhythm
control strategies in HF with reduced EF (i.e. CASTLE-AF and
CAMERA-MRI), further studies on rhythm control in AF for
HFpEF patients need to be conducted and carry the potential
for great clinical impact. While none of the study subjects
underwent catheter ablation for AF management, other ob-
servational retrospective studies and post hoc analyses have
suggested promising initial results, which will need to be
verified with prospective randomized control studies ded-
icated to investigating the impact of AF ablation in the HFpEF
population. In preparation for these randomized control
studies, additional research should be done to enhance our
understanding of the relationship between continuous AF

Figure 3 Kaplan–Meier curves showing time-to-event analysis following
index hospitalization for (A) composite outcome of heart failure hospital-
ization or all-cause mortality, (B) heart failure exacerbation requiring hos-
pitalization, and (C) all-cause mortality. Groups are stratified by concomitant diagnosis of AF, with number of subjects in each subgroup
at risk listed in the tables. AF, atrial fibrillation.
burden and risk for HF hospitalization, which will be critical in identifying which subgroup of HFpEF patients with AF may benefit most from rhythm control therapies.

This study should be taken in the context of several limitations. First, this was a relatively small, single-centre data study, and therefore limited the power necessitating use of propensity score methods to balance the potential confounders, and external generalizability. Although the study design attempted to mitigate potential confounding diagnoses leading to the inclusion of individuals with diastolic dysfunction arising from valvular and infiltrative aetiologies, there is intrinsic heterogeneity that underlies the HFpEF pop-

Table 2 Unadjusted and adjusted longitudinal data analysis showing both (A) Cox proportional regression and (B) competing risk regression for heart failure hospitalization following index hospitalization

(A)

| Treatment group | Cox regression | Unweighted | Inverse probability weighting | Overlap weighting |
|-----------------|----------------|------------|-------------------------------|------------------|
| AF vs. no AF    |                |            |                               |                  |
| Covariates      |                |            |                               |                  |
| Age             | 1.01           | [0.99, 1.03] | 0.44                          | 1.01             | [0.98, 1.04] | 0.46 |
| GFR             | 0.99           | [0.98, 1.00] | 0.1                           | 0.99             | [0.98, 1.00] | 0.06 |
| Prior HF admission | 1.75     | [0.99, 3.10] | 0.05                          | 2.28             | [1.07, 4.87] | 0.033 |
| Left atrial diameter | 0.76     | [0.52, 1.10] | 0.15                          | 0.63             | [0.37, 1.07] | 0.09 |

(B)

| Treatment group | Competing risk regression | Unweighted | Inverse probability weighting | Overlap weighting |
|-----------------|---------------------------|------------|-------------------------------|------------------|
| AF vs. no AF    |                           |            |                               |                  |
| Covariates      |                           |            |                               |                  |
| Age             | 1                         | [0.98, 1.02] | 0.99                          | 1                | [0.97, 1.03] | 0.96 |
| GFR             | 0.99                      | [0.98, 1.00] | 0.1                           | 0.99             | [0.98, 1.00] | 0.08 |
| Prior HF admission | 1.77          | [1.00, 3.12] | 0.05                          | 2.02             | [0.98, 4.19] | 0.06 |
| Left atrial diameter | 0.74     | [0.54, 1.03] | 0.08                          | 0.69             | [0.42, 1.14] | 0.15 |

AF, atrial fibrillation; CI, confidence interval; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio.

Competing risk regression was analysed against risk for death, with and without propensity score weighting, adjusted for AF status, age, GFR, prior history of HF, and echocardiographic proxy measure for duration of AF/HF with preserved ejection fraction. Adjusted HRs were performed serially with only propensity score weighting and AF as the other multivariable covariate, given limited sample size. Adjusted AF hazard is listed after adjusting for all listed covariates. From this table, it is evident that both assessed with history of AF and evidence of AF on admission EKG remained statistically significant after doubly robust multivariable regression.

Table 3 Crude and adjusted logistic regression of 30 day readmission on atrial fibrillation status, demographics, and biomarkers of effective inpatient diuresis

|                | Crude       | Multivariable logistic regression | Overlap weighting + Multivariable logistic regression |
|----------------|-------------|----------------------------------|-----------------------------------------------------|
|                | OR 95% CI   | P-value                          | OR 95% CI                                           | P-value                          |
| AF vs. no AF   |             |                                  |                                                     |                                  |
| Demographics   |             |                                  |                                                     |                                  |
| Age (years)    | 1.02        | 1.06                             | 0.82                                                | 0.99–1.05                        |
| Male vs. female | 1.16        | 3.44                             | 0.785                                               | 1.50                             |
| Race/ethnicity |             |                                  |                                                     |                                  |
| Black vs. other | 0.86        | 0.34                             | 2.12                                                | 0.91                             |
| Biomarkers of effective diuresis | | | | |
| Urine output from admission to discharge | 1.00        | 0.99                             | 1.00                                                | 0.99                             |
| Glomerular filtration rate | 0.99        | 1.02                             | 0.801                                               | 1.00                             |
| (mL/min per 1.73 m²) | | | | |
| Change in pro-BNP between admission and discharge | 1.00        | 0.99                             | 0.652                                               | 1.00                             |

AF, atrial fibrillation; CI, confidence interval; OR, odds ratio.

*Adjusted: The adjusted odds for biomarkers of effective diuresis was performed serially with only AF status as the other multivariable covariate, given limited sample size. Adjusted AF odds remained significantly higher after correcting for each biomarker of effective diuresis.

*AF is adjusted for all demographic parameters along with change in pro-BNP.

AF, atrial fibrillation; CI, confidence interval; OR, odds ratio.
ulation. As such, one major limitation of this study arises from the residual confounding present within the many contributing entities leading to diastolic dysfunction that is inherent to any research done on this HF subpopulation. Second, lead-time bias was not able to be completely addressed: the index hospitalization was not confirmed to be the first HF hospitalization for each patient, nor was the duration since diagnosis of HFpEF or AF available for analysis. As time since diagnosis of HFpEF, of AF, and the time since first acute HF hospitalization were not available for analysis, we attempted to adjust for these factors using indirect covariates that have been previously correlated with duration with HF and AF, such as left atrial size. Finally, our study is limited by potential residual confounding from risk factors that may not have been fully addressed by multivariable regression and propensity score weighting techniques. Despite the limitations inherent to the data source available, we felt that the robust longitudinal clinical data with relatively little patient drop-out allowed for more granular adjustment of confounders known to be predictive of clinical outcomes. Finally, 6% of individuals who did not carry an AF diagnosis upon index hospitalization were noted to have developed AF during longitudinal follow-up; the development of new onset AF may be one of the explanations to why the initially significant differences noted in short-term follow-up became less pronounced over time.

Conclusions

In a hospitalized HFpEF cohort with acute decompensated HF, we demonstrated that a concomitant diagnosis of AF was associated with increased risk for recurrent HF exacerbation. While the increased risk for readmission within 30 days may largely be attributable to other comorbid clinical risk factors that are associated with AF, AF serves as a strong, independent risk factor for HF exacerbation. Our data suggest that HFpEF patients with AF may benefit from closer outpatient follow-up given significantly higher risk for redeveloping decompensated HF. These findings also underscore the need to determine whether AF is a modifiable risk factor in HFpEF—light of recent randomized control studies showing benefit in rhythm control in HF with reduced EF. Further studies investigating the potential benefit of reducing AF burden in HFpEF patients will be imperative to guiding treatment of individuals with both of these cardiovascular conditions.

Conflict of interest

J.V. declared no relevant disclosures or conflicts of interest. E.S. declared no relevant disclosures or conflicts of interest. J.L. declared no relevant disclosures or conflicts of interest. S.S. declared no relevant disclosures or conflicts of interest. H.C. declared no relevant disclosures or conflicts of interest. R.B. declared no relevant disclosures or conflicts of interest. S.R. declared no relevant disclosures or conflicts of interest. K.S. is an advisory board member and consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Novartis and NovoNordisk and receives honoraria. She receives research funding support from the American Heart Association and Amgen.

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