Acute Heart Failure and Atrial Fibrillation: Insights From the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) Trial

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Background—Patients with acute heart failure (AHF) frequently have atrial fibrillation (AF), but how this affects patient-reported outcomes has not been well characterized.

Methods and Results—We examined dyspnea improvement and clinical outcomes in 7007 patients in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial. At baseline, 2677 (38.2%) patients had current or a history of AF and 4330 (61.8%) did not. Patients with a history of AF were older than those without (72 vs. 63 years) and had more comorbidities and a higher median left ventricular ejection fraction (31% vs. 27%; \( P < 0.001 \)). Compared to those without AF, patients with AF had a similar mean ventricular rate on admission (81 vs. 83 beats per minute [bpm]; \( P = 0.138 \)) but a lower rate at discharge (75 vs. 78 bpm; \( P = 0.001 \)). There was no difference in dyspnea improvement between patients with and without AF at 6 hours (\( P = 0.087 \)), but patients with AF had less dyspnea improvement at 24 hours (\( P < 0.001 \)). Compared to patients without AF, patients with AF had a higher 30-day all-cause mortality rate (4.7% vs. 3.3%; \( P = 0.005 \)), a higher 30-day HF rehospitalisation rate (7.2% vs. 5.3%; \( P = 0.001 \)), and a higher coprimary composite outcome of 30-day death or readmission (11.6% vs. 8.6%; \( P < 0.001 \)). This difference persisted after adjustment for prognostic variables (adjusted odds ratio = 1.19; 95% confidence interval, 1.02 to 1.38; \( P = 0.029 \)).

Conclusions—Among patients admitted to the hospital with AHF, current or a history of AF is associated with less dyspnea improvement and higher morbidity and mortality at 30-days, compared to those not in AF.

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Key Words: acute heart failure • atrial fibrillation • clinical trials • outcome

Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia associated with acute or chronic heart failure (HF) with a prevalence of 30% to 45%. In the setting of acute heart failure (AHF), AF is associated with significant morbidity and an increased mortality rate. AF is also associated with worsening in-hospital outcomes among patients hospitalized for AHF; however, its association with dyspnea relief is unknown, and this has not been well characterized in a contemporary, large international trial.

Despite the importance of heart rate as a predictor of clinical outcomes for patients with sinus rhythm, limited information about the relationship of heart rate (or the change in heart rate) to postdischarge outcomes is known in patients with AF and AHF. Furthermore, quality of care, such as anticoagulation for patients with AF, is important given that it is linked to clinical outcomes and subject to geographical variation, patient characteristics, and system-related features.

Accordingly, we evaluated the baseline clinical characteristics, dyspnea improvement, and readmission and death in patients with and without AF in the ASCEND-HF trial. We also

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Patients were classified as having AF if it was identified on the case report form in the baseline medical history section (ie, a history of or current AF). Where appropriate and possible, this has been referred to as “patients with AF.” No core lab reading of electrocardiogram (ECG) was performed, but patients in ASCEND-HF were recommended to have appropriate standard of care, which includes an ECG when presenting with AHF. A total of 5378 (77%) patients had information from a baseline ECG entered on the case report form; however, this did not include reporting of sinus rhythm or atrial fibrillation from the ECG as a specific variable.

Clinical Outcomes
For this analysis, we examined the ASCEND-HF coprimary endpoint of 6- and 24-hour dyspnea relief (measured using a 7-point Likert scale) and the coprimary composite of 30-day all-cause mortality or HF rehospitalisation, its individual components and 180-day all-cause mortality.

Quality-of-Care Outcome
We measured adherence rates to quality-of-care measures (QCM) based on the Class I American College of Cardiology/American Heart Association (ACC/AHA) recommendations for care of patients with HF, as used in the Get With The Guidelines (GWTG)-HF program. Specifically, we examined the use of oral anticoagulation for patients with atrial fibrillation at hospital discharge, barring documented contraindications, intolerances or specific reasons for nonuse, or documented plan for initiation at a later date. The use of antithrombotic medication (ie, an antiplatelet or an anticoagulant) was also evaluated according to the CHADS2 score. Because patients in ASCEND-HF were admitted with AHF, all had a CHADS2 score ≥1. We also examined control of the ventricular (“heart”) rate in patients with AF over the course of their admission.

Statistical Analysis
Baseline patient characteristics and clinical outcomes are reported according to whether or not patients had a history of AF at baseline. Data for continuous variables are presented as medians with 25th and 75th percentiles, and categorical variables are presented as frequencies and percentages. Wilcoxon’s rank-sum tests were used to measure differences for continuous variables, and the chi-square or Fisher’s exact tests were used for categorical variables. Statistical significance was determined at the 2-sided $\alpha=0.05$ level.

Multivariable models, which were previously developed in the ASCEND-HF trial, were used to adjust the associations of AF with 30-day outcomes (all-cause death and HF rehospitalization), and with 31- to 180-day outcomes (all-cause death). These models included the following characteristics at the time of randomization for 30-day outcomes: age; blood urea nitrogen (BUN); serum sodium; dyspnea severity; and systolic blood pressure (SBP). Resultant odds ratios (ORs) are presented with 95% confidence intervals (CIs) comparing patients with AF to patients without AF (reference group). The studies conducted, with ethical approval, beginning May 18, 2007 through August 2010 at 398 centers globally. All patients gave written informed consent. Patients were included in ASCEND-HF if they were hospitalized for ADHF occurring within 24 hours before they received their first intravenous treatment for HF or if they had received a diagnosis of ADHF <48 hours after hospitalization for another cause and underwent randomization <24 hours after intravenous treatment for HF. Other criteria for inclusion included: dyspnea at rest or with minimal activity; 1 or more accompanying signs (respiratory rate ≥20 breaths per minute or pulmonary congestion or edema with rales one third of the way or more up the lung fields); and 1 or more additional measures of HF (evidence of congestion or edema on chest radiography, a B-type natriuretic peptide [BNP] level ≥400 pg/mL or an N-terminal pro-BNP [NT-pro-BNP] level ≥1000 pg/mL, pulmonary capillary wedge pressure >20 mm Hg, or left ventricular (LV) ejection fraction [LVEF] <40% in the previous 12 months). Complete eligibility and exclusion criteria are described elsewhere. Patient with or without AF were allowed into the study, and there was no inclusion or exclusion criteria related to heart rate. Given that no treatment effect on mortality or rehospitalization with the study drug nesiritide was demonstrated, the treatment arms were pooled in this analysis. Patients who did not receive study drug were excluded from this analysis (n=134; 1.9%).

Demographic, clinical, laboratory, and diagnostic data were collected at randomization. In addition to this, further blood pressure (BP), laboratory, and medication data, as well as subsequent diagnostic testing, were collected up to, and including, hospital discharge. Patients were followed by a clinical visit at 30 and 180 days after discharge.

AF Definition
Patients were classified as having AF if it was identified on the case report form in the baseline medical history section (ie, a history of or current AF). Where appropriate and possible, this has been referred to as “patients with AF.” No core lab reading of electrocardiogram (ECG) was performed, but patients in ASCEND-HF were recommended to have appropriate standard of care, which includes an ECG when...
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Results

Baseline Characteristics

Of the 7007 patients in the ASCEND-HF trial, 2677 (38.2%) had a history of AF at baseline and 4330 (61.8%) did not have a history of AF at baseline. Patients with AF were older, more likely to be white, have a higher BMI, and had more comorbidities, including diabetes, coronary artery disease, previous, and COPD (Tables 1 and 2). There was no difference in gender or vital signs (heart rate, SBP, and respiratory rate) between those with and without AF. Patients with AF had a higher ejection fraction (31% vs. 27%; P<0.001), compared to those without AF; NT-proBNP levels were not, however, different (AF: 4496 pg/mL; no AF: 4238 pg/mL; P=0.406).

Heart rate at baseline was similar between groups (83 bpm in patients without AF vs. 81 bpm with AF; P=0.138). Patients with current or a history of AF had a lower heart rate at 24 hours (78 vs. 80 bpm; P=0.012) and at discharge (75 vs. 80 bpm; P<0.001; Figure 1).

Dyspnea Improvement, Hospital Course, and Clinical Outcomes

There was no difference in dyspnea improvement between patients with or without AF at 6 hours (P=0.087). However, patients with AF had less improvement in dyspnea during the first 24 hours (P<0.001; Figure 2).

Patients with AF had a longer median in-hospital length of stay (7 vs. 6 days; P<0.001). Compared to patients without AF, patients with AF had a higher in-hospital all-cause mortality rate (2.6% vs. 1.7%; P=0.015), a higher 30-day all-cause mortality rate (4.7% vs. 3.3%; P=0.005), a higher 31- to 180-day mortality rate (11.1% vs. 8%; P=0.001), and a higher 180-day mortality rate (15.3% vs. 11.1%; P<0.001). Patients with AF also had a higher 30-day HF rehospitalisation rate (7.2% vs. 5.3%; P=0.001). Hence, more patients in the AF group experienced the coprimary composite outcome of death or readmission at 30 days than in the group without AF (8.6% vs. 11.6%; P<0.001). This difference persisted after adjustment for the predefined prognostic variables (adjusted OR=1.19; 95% CI, 1.02 to 1.38; adjusted P=0.029; Table 3). However, after adjustment, neither the difference in 30-day mortality (adjusted OR=1.20; 95% CI, 0.91 to 1.58), or in 31- to 180-day mortality was significant (adjusted HR, 1.15; 95% CI, 0.93 to 1.43).

Quality-of-Care Outcomes

In patients with current or a history of AF, anti-coagulation rates according to CHADS2 score at discharge were 61.5%, 59.1%, 58.7%, and 57.5% for scores of 1, 2, 3 or 4, and ≥5, respectively (trend, P=0.782; Table 2; Figure 3). Antiplatelet use in patients with current or a history of AF according to CHADS2 score was 36.1%, 51.6%, 58.3%, and 61.1% for scores of 1, 2, 3 or 4, and ≥5 respectively (trend, P<0.001). Patients with current or a history of AF had a higher use of anticoagulants and a lower use of antiplatelet agents across all CHADS2 scores (all comparisons, P<0.001). Patients without AF had higher use of antiplatelet across all CHADS2 scores (all comparisons, P<0.001), but anticoagulants use was only higher in CHADS2 (≥5). The percentage of patients with current or a history of AF discharged on neither an antiplatelet nor anticoagulant was 17.6%, 14.2%, 12.3%, and 11.1% for CHADS2 scores of 1, 2, 3 or 4, and ≥5 respectively. The percentage of patients with or without AF discharged on any antiplatelet/anticoagulant was 86.7% and 76.9%, respectively.

Discussion

In this retrospective analysis of patients with AHF enrolled in the ASCEND-HF study, patients with current or a history of AF had a 19% higher rate of the coprimary endpoint at 30 days, and a lower rate of dyspnea improvement at 24 hours. Second, we found that patients with current or a history of AF had a lower heart rate on admission as well as discharge, when compared to patients without AF. Third, the overall anticoagulation or antiplatelet therapy rate was lower than expected given the evidence base for the use of these agents in patients with AF and provides an opportunity for improvement.

Dyspnea is a key symptom in acute cardiovascular disease and has been the focus as a primary endpoint for AHF clinical trials.4,5 Interestingly, patients with current or a history of AF in the ASCEND-HF trial had a trend to less dyspnea improvement by 24 hours, when compared to patients without AF. This occurred on the background of greater baseline dyspnea at rest than patients without AF, and with
Table 1. Baseline Patient Characteristics

|                          | Total (N=7007) | HF Without AF (n=4330) | HF With Current or a History of AF (n=2677) | P Value |
|--------------------------|----------------|------------------------|---------------------------------------------|---------|
| Age, y                   | 67.0 (56.0, 76.0) | 63.0 (53.0, 73.0) | 72.0 (63.0, 79.0) | <0.001 |
| Female, n (%)            | 2391 (34.1) | 1479 (34.2) | 912 (34.1) | 0.9391 |
| Race, n (%)              |               |                        |                                            | <0.001 |
| Asian                    | 1747 (24.9) | 1450 (33.5) | 297 (11.1) |       |
| White                    | 3916 (55.9) | 1874 (43.3) | 2042 (76.3) |       |
| Black or African American| 1040 (14.8) | 784 (18.1) | 256 (9.6) |       |
| Other                    | 303 (4.3) | 222 (5.1) | 81 (3.0) |       |
| Vital signs              |               |                        |                                            |         |
| Weight, kg               | 78.0 (64.1, 95.0) | 75.3 (62.0, 92.0) | 82.0 (69.0, 98.0) | <0.001 |
| Body mass index          | 27.5 (23.8, 32.6) | 27.0 (23.2, 32.2) | 28.3 (24.6, 33.1) | <0.001 |
| Heart rate, beats per minute | 82 (72, 95)  | 83 (72, 94) | 81 (70, 96) | 0.138 |
| Respiratory rate, breaths per minute | 23 (21, 26) | 24 (21, 26) | 23 (21, 25) | 0.023 |
| Systolic BP, mm Hg       | 123 (110, 140) | 124 (110, 140) | 122 (110, 138) | 0.012 |
| Diastolic BP, mm Hg      | 74 (67, 83) | 75.0 (68, 85) | 73.0 (65, 81) | <0.001 |
| Presenting signs and symptoms, n (%) |          |                        |                                            |         |
| Dyspnea at rest          | 4339 (61.9) | 2628 (60.7) | 1711 (63.9) | 0.007 |
| Dyspnea with minimal activity | 2667 (38.1) | 1702 (39.3) | 965 (36.1) |       |
| Orthopnea                | 5388 (77.0) | 3322 (76.8) | 2066 (77.2) | 0.749 |
| Pulmonary congestion     | 6088 (86.9) | 3768 (87.1) | 2320 (86.7) | 0.689 |
| JVP elevated             | 3934 (56.2) | 2446 (56.5) | 1488 (55.6) | 0.449 |
| S3                       | 1642 (23.4) | 1227 (28.4) | 415 (15.5) | <0.001 |
| Peripheral edema         | 5234 (74.7) | 3077 (71.1) | 2157 (80.6) | <0.001 |
| Medical history, n (%)   |               |                        |                                            |         |
| Diabetes                 | 2987 (42.6) | 1952 (45.1) | 1035 (38.7) | <0.001 |
| Smoking                  | 2493 (35.6) | 1437 (33.2) | 1056 (39.5) | <0.001 |
| Hyperlipidemia           | 2914 (41.6) | 1650 (38.1) | 1264 (47.2) | <0.001 |
| CAD                      | 3523 (50.3) | 2044 (47.2) | 1479 (55.2) | <0.001 |
| Previous PCI             | 1143 (16.3) | 707 (16.3) | 436 (16.3) | 0.981 |
| Previous CABG            | 1278 (18.2) | 689 (15.9) | 589 (22.0) | <0.001 |
| ICD only                 | 597 (8.5) | 355 (8.2) | 242 (9.0) | 0.220 |
| Pacemaker only           | 433 (6.2) | 151 (3.5) | 282 (10.5) | <0.001 |
| CRT-D                    | 535 (7.6) | 256 (5.9) | 279 (10.4) | <0.001 |
| PVD                      | 725 (10.3) | 392 (9.0) | 333 (12.4) | <0.001 |
| CVA                      | 823 (11.8) | 399 (9.2) | 424 (15.8) | <0.001 |
| COPD/asthma              | 1150 (16.4) | 591 (13.6) | 559 (20.9) | <0.001 |
| Laboratory investigations|               |                        |                                            |         |
| Sodium, mmol/L           | 139 (136, 141) | 138 (136, 141) | 139 (137, 142) | <0.001 |
| Creatinine, µmol/mL      | 108.0 (88.4, 140.6) | 106.1 (88.4, 134.4) | 114.9 (89.3, 141.4) | <0.001 |
| Blood urea nitrogen, mmol/L | 9.1 (6.4, 13.9) | 8.8 (6.1, 13.6) | 9.6 (6.8, 14.5) | <0.001 |
| BNP, pg/mL               | 990 (543, 1867) | 1040 (536, 1974) | 945 (561, 1644) | 0.018 |

Continued
60% of both groups (AF and not AF) having a moderate or marked improvement in dyspnea. Whether or not therapies targeted at the underlying pathophysiology of AF would provide greater dyspnea relief than diuretics or vasodilators is uncertain, as is the underlying mechanism of dyspnea for many patients. Given that dyspnea is a patient-reported

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Table 1. Continued

|               | Total (N=7007) | HF Without AF (n=4330) | HF With Current or a History of AF (n=2677) | P Value |
|---------------|----------------|------------------------|---------------------------------------------|---------|
| NT-proBNP, pg/mL | 4312 (2140, 9048) | 4238 (2087, 9266) | 4496 (2369, 8842) | 0.406 |
| Troponin I, ng/mL | 0.05 (0.03, 0.10) | 0.06 (0.03, 0.11) | 0.05 (0.03, 0.10) | 0.003 |
| Troponin T, ng/mL | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.05) | 0.02 (0.01, 0.04) | 0.131 |
| Ejection fraction, % | 30.0 (20.0, 37.0) | 27.0 (20.0, 35.0) | 31.0 (24.0, 43.0) | <0.001 |

Continuous variables are reported as median with 25th and 75th percentiles. AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization-defibrillator; CVA, cerebrovascular disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; JVP, jugular venous pulse; NT-proBNP, N-terminal pro-BNP; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; S3, third heart sound.

Table 2. Baseline and Discharge Medications

| Baseline medications | Total (N=7007) | HF Without AF (n=4330) | HF With Current or a History of AF (n=2677) | P Value |
|----------------------|----------------|------------------------|---------------------------------------------|---------|
| ACE/ARB inhibitors, n (%) | 4256 (60.7) | 2582 (59.6) | 1674 (62.5) | 0.016 |
| Beta-blockers, n (%) | 4074 (58.1) | 2335 (53.9) | 1739 (65.0) | <0.001 |
| MRA, n (%) | 1950 (27.8) | 1175 (27.1) | 775 (29.0) | 0.100 |
| CCB, n (%) | 901 (12.9) | 505 (11.7) | 396 (14.8) | <0.001 |
| Digoxin, n (%) | 562 (8.0) | 279 (6.4) | 283 (10.6) | <0.001 |
| Antiarrhythmic agents, n (%) | 819 (11.7) | 291 (6.7) | 528 (19.7) | <0.001 |
| Clopidogrel, n (%) | 1123 (16.0) | 851 (19.7) | 272 (10.2) | <0.001 |
| Aspirin, n (%) | 3435 (49.0) | 2203 (50.9) | 1232 (46.0) | <0.001 |
| Any antiplatelet agent, n (%) | 3743 (53.4) | 2436 (56.3) | 1307 (48.8) | <0.001 |
| Anticoagulation agents, n (%) | 1687 (24.1) | 392 (9.0) | 1295 (48.4) | <0.001 |
| No antiagulant or antiplatelet agent, n (%) | 2270 (32.4) | 1679 (38.8) | 591 (22.1) | <0.001 |

Discharge medications

| Discharge medications | Total (N=7007) | HF Without AF (n=4330) | HF With Current or a History of AF (n=2677) | P Value |
|----------------------|----------------|------------------------|---------------------------------------------|---------|
| ACE/ARB inhibitors, n (%) | 5210 (74.3) | 3285 (75.9) | 1925 (71.9) | <0.001 |
| Beta-blockers, n (%) | 5102 (72.8) | 3127 (72.2) | 1975 (73.8) | 0.154 |
| MRA, n (%) | 3238 (46.2) | 2021 (46.7) | 1217 (45.5) | 0.322 |
| CCB, n (%) | 826 (11.8) | 507 (11.7) | 319 (11.9) | 0.794 |
| Digoxin, n (%) | 2462 (35.1) | 1336 (30.9) | 1126 (42.1) | <0.001 |
| Antiarrhythmic agents, n (%) | 967 (13.8) | 396 (9.2) | 571 (21.3) | <0.001 |
| Clopidogrel, n (%) | 1317 (18.8) | 1045 (24.1) | 272 (10.2) | <0.001 |
| Aspirin, n (%) | 4219 (60.2) | 2833 (65.4) | 1386 (51.8) | <0.001 |
| Any antiplatelet agent, n (%) | 4540 (64.8) | 3087 (71.3) | 1453 (54.3) | <0.001 |
| Anticoagulation agents, n (%) | 2067 (29.5) | 488 (11.3) | 1579 (59.0) | <0.001 |
| No anticoagulant or antiplatelet agent, n (%) | 1354 (19.3) | 999 (23.1) | 355 (13.3) | <0.001 |
| Either of anticoagulant or antiplatelet, n (%) | 5633 (80.7) | 3331 (76.9) | 2322 (86.7) | <0.001 |

Antiarrhythmic agents included amiodarone, dronedarone, or sotalol. ACE/ARB indicates angiotensin-converting enzyme/angiotensin receptor blocker; AF, atrial fibrillation; CCB, calcium-channel blocker; HF, heart failure; MRA, mineralocorticoid antagonist.

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symptom, as opposed to an objective measure, such as peak expiratory flow rate, it remains uncertain whether other patient features, other than heart rate, may be feeding into their perception of breathlessness.

Figure 1. HR at different time points comparing patients with and without AF. AF indicates atrial fibrillation; HF, heart failure; HR, heart rate.

Figure 2. Dyspnea improvement comparing patients with and without AF. AF indicates atrial fibrillation.

Table 3. Clinical Event Rates of Patients With or Without AF

| Event Type                              | Total (N=7007) | Without AF (n=4330) | With Current or a History of AF (n=2677) | P Value | Unadjusted Association* | P Value | Adjusted Association* | Adjusted P Value |
|-----------------------------------------|----------------|---------------------|----------------------------------------|--------|------------------------|--------|----------------------|-----------------|
| 30-day all-cause mortality, n (%)      | 267 (3.8)      | 143 (3.3)           | 124 (4.6)                              | 0.005  | 1.41 (1.10 to 1.81)   | 0.006  | 1.20 (0.91 to 1.58)  | 0.193           |
| 30-day HF-related rehospitalization, n (%) | 412 (6.0)    | 223 (5.3)           | 189 (7.2)                              | 0.001  | 1.40 (1.14 to 1.70)   | 0.001  | 1.46 (1.17 to 1.82)  | 0.001           |
| 30-day mortality or HF-related rehospitalization, n (%) | 666 (9.7)    | 362 (8.6)           | 304 (11.6)                             | <0.001 | 1.46 (1.28 to 1.67)   | <0.001 | 1.19 (1.02 to 1.38)  | 0.029           |
| 31- to 180-day all-cause mortality, n (%) | 609 (9.2)     | 329 (8.0)           | 280 (11.1)                             | <0.001 | 1.36 (1.15 to 1.61)   | <0.001 | 1.15 (0.93 to 1.43)  | 0.194           |

AF indicates atrial fibrillation; HF, heart failure.

*For 30-day outcomes, associations are presented as an odds ratio (95% confidence interval). For 31- to 180-day mortality, hazard ratios (95% confidence interval) are reported. The reference group is patients without atrial fibrillation. Adjusted for age, systolic blood pressure, blood urea nitrogen, sodium, and dyspnea severity.
however, other studies of patients with AF and concomitant HF or LV dysfunction have identified this as a risk factor for stroke (and thus a target for anticoagulation).\textsuperscript{18,22} Though there are geographical differences in the HF or AF guidelines during the years of conduct of the ASCEND-HF trial, in patients with a CHADS\textsubscript{2} score \(\geq 2\), guidelines universally recommend oral anticoagulation with or without concomitant antiplatelet agents. Hospitalization provides an ideal time for patients and clinicians to assess risks and benefits of choices for oral anticoagulation or antiplatelet strategy.

**Conclusion**

We found that patients with current or a history of AF differed from those not in AF in their age, LVEF, comorbidity burden, and other clinical features. Patients with current or a history of AF had greater heart rate reduction by the day of discharge, but less dyspnea relief and higher rates of readmission and mortality. Finally, we also identified that many patients with current or a history of AF do not receive appropriate stroke prevention strategies despite the opportunity while in the hospital to assess the risks and benefits of oral anticoagulants or antiplatelet agents.

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