

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

Seraj Abualnaja, MD; Mohua Podder, PhD; Adrian F. Hernandez, MD, MHS; John J. V. McMurray, MD; Randall C. Starling, MD, MPH; Christopher M. O'Connor, MD; Robert M. Califf, MD; Paul W. Armstrong, MD; Justin A. Ezekowitz, MBCh, MSc

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.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00475852. (*J Am Heart Assoc.* 2015;4:e002092 doi: 10.1161/JAHA.115.002092)

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%.^{1–6} In the setting of acute heart failure (AHF), AF is associated with significant

morbidity and an increased mortality rate.^{7,8} AF is also associated with worsening in-hospital outcomes among patients hospitalized for AHF⁹; 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,¹⁰ 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.¹¹ 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.^{7,12}

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

From the University of Alberta, Edmonton, Canada (S.A., P.W.A., J.A.E.); University of Dammam, Saudi Arabia (S.A.); Canadian VIGOUR Center, Edmonton, Alberta, Canada (M.P., P.W.A., J.A.E.); Duke Clinical Research Institute, Durham, NC (A.F.H., C.M.O., R.M.C.); BHF Cardiovascular Research Center, University of Glasgow, Scotland (J.J.V.M.); Cleveland Clinic, Cleveland, OH (R.C.S.).

Correspondence to: Justin A. Ezekowitz, MBCh, MSc, 2C2 WMC- 8440-112 St, Edmonton, Alberta, Canada T6G 2B7. E-mail: jae2@ualberta.ca

Received April 14, 2015; accepted July 20, 2015.

© 2015 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley Blackwell. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

explored adequacy of ventricular rate control and use of anticoagulation as measures of quality of care in patients with AF and AHF.

Methods

Study Design

The study design and the primary results of the ASCEND-HF trial have been published.^{5,13} In brief, the trial was 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.^{13,14} 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

presenting with AHF.¹⁵ 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,¹⁶ as used in the Get With The Guidelines (GWTG)-HF program.¹⁷ 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.¹⁸ 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

adjustment model for 31- to 180-day mortality included age, weight, BUN, SBP, sodium, dyspnea severity, and elevated jugular venous pressure; previous history of cerebrovascular disease, chronic obstructive pulmonary disease (COPD)/chronic respiratory disease; and HF rehospitalization 1 year before admission. Resultant hazard ratios (HRs) are presented with 95% CIs comparing patients with AF to patients without AF (reference group). Clinically meaningful 2-way interactions between age, dyspnea severity, and CHADS₂ score and AF status were also evaluated; none were significant.

All tests were 2-sided with a 5% level of significance. All analyses were performed using SAS statistical analysis software (version 9.2; SAS Institute Inc, Cary, NC).

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%; $P<0.001$) and lower BNP level (945 vs. 1051 pg/mL; $P=0.005$), 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, anticoagulation 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, μ mol/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

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.

>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

Table 2. Baseline and Discharge Medications

	Total (N=7007)	HF Without AF (n=4330)	HF With Current or a History of AF (n=2677)	P Value
Baseline medications				
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 anticoagulant or antiplatelet agent, n (%)	2270 (32.4)	1679 (38.8)	591 (22.1)	<0.001
Discharge medications				
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 antiplatelet or anticoagulant, n (%)	5653 (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.

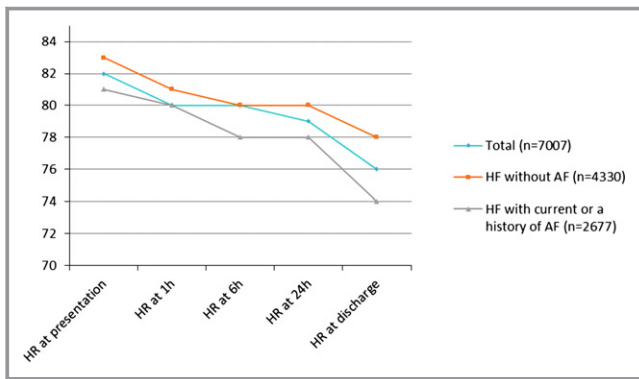


Figure 1. HR at different time points comparing patients with and without AF. AF indicates atrial fibrillation; HF, heart failure; HR, heart rate.

symptom, as opposed to an objective measure, such as peak expiratory flow rate,¹⁹ it remains uncertain whether other patient features, other than heart rate, may be feeding into their perception of breathlessness.

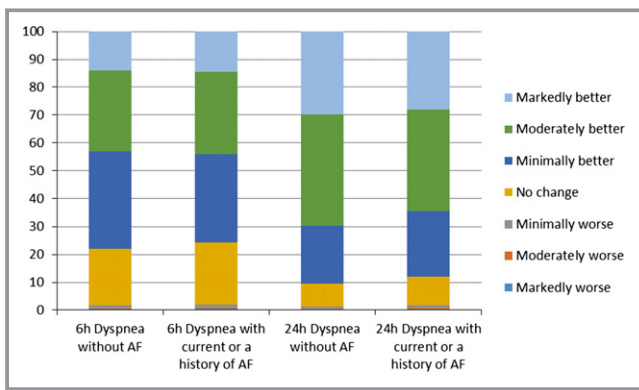


Figure 2. Dyspnea improvement comparing patients with and without AF. AF indicates atrial fibrillation.

Although there was no difference in heart rate at presentation between patients with or without AF, heart rate was significantly lower at 6 and 24 hours and at discharge in patients with AF and less dyspnea relief at 24 hours for patients with current or a history of AF. There are likely multiple plausible explanations for this finding, including choices for therapy, aggressiveness of heart rate as a clinical target for therapy, underlying differences in patient characteristics, activation of the sympathetic nervous system, and features related to the conduct of a clinical trial. Patients with current or a history of AF in ASCEND-HF had high rates of digoxin use as well as antiarrhythmic medications, which may reflect local variation in practice in a global trial, or clinicians using these medications to actively lower the heart rate or improve symptoms (noting the rate of beta-blocker use was similar in patients with or without a current or a history of AF). Additionally, we noted that BNP levels (but not NT-proBNP levels) were lower in patients with AF, in contradistinction to other studies. This may be explained, in part, by trial entry criteria, which allowed for patients with an elevated BNP to be enrolled without distinction of AF, as is now done in other trials.⁴ This may be further compounded by an older age, worse renal function, and higher rates of coronary artery disease burden, which may be related and increase levels of NT-proBNP.^{20,21}

In this study, there was greater usage of anticoagulation therapy among patients with current or a history of AF than those without AF across all CHADS₂ scores; however, there is still undertreatment with anticoagulation. In a previous study from ASCEND-HF, significant global variation was noted when anticoagulation for patients with current or a history of AF was assessed by quality performance metrics, with only 33% of Asia-Pacific and 76% of Western Europe meeting the quality performance metric.¹² Whether this finding impacts longer-term clinical outcomes is not elaborated in the current study;

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

	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.

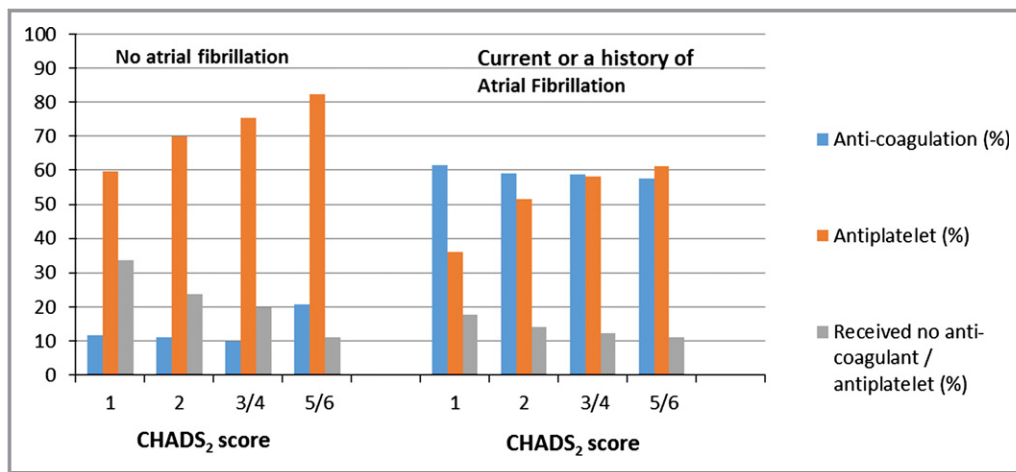


Figure 3. Use of anticoagulation or antiplatelet therapy at discharge among patients with and without atrial fibrillation according to CHADS₂ score.

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).^{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 CHADS₂ score ≥ 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.

Sources of Funding

The ASCEND-HF trial was funded through its sponsor, Johnson & Johnson Inc. The sponsor had no role in this study.

Disclosures

Dr Armstrong reports research support from Johnson & Johnson and Bayer. Dr Ezekowitz reports consulting fees from

Pfizer and research support from Amgen, Bayer, and Johnson & Johnson. Dr Hernandez reports research funding from Johnson & Johnson, Bayer, Amylin, and Portola and honorarium from Corthera and Cytokinetics. Dr Starling is a consultant for Medtronic, Novartis, BioControl, and CardioMEMS and received research funding from Johnson & Johnson. Dr McMurray received research funding from Novartis and Johnson & Johnson. Dr Califf reports research funding from Amylin, Johnson & Johnson-Scios, Merck/Schering Plough, Novartis, and Bristol-Myers Squibb Foundation; consulting from Johnson & Johnson-Scios, Novartis, Bayer, Roche, Pfizer, and Bristol-Myers Squibb Foundation; and equity in NITROX LLC. Dr O'Connor reports consulting fees/honoraria from Amgen and Actelion Pharmaceuticals Ltd; ownership/partnership/principal from Biscardia, LLC; and research grants from Otsuka, Astellas, Gilead, BG Medicine, Roche Diagnostics, Critical Diagnostics, and ResMed. Complete financial disclosures for Armstrong and Ezekowitz can be found at <http://www.vigour.ualberta.ca/About/RelationshipsWithIndustry.aspx>. Full financial disclosures for Hernandez, Califf, and O'Connor can be found at <http://www.dcri.duke.edu/about-us/conflict-of-interest>.

References

1. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J*. 2012;33:1750–1757.
2. Kociol RD, Hammill BG, Fonarow GC, Klaskala W, Mills RM, Hernandez AF, Curtis LH. Generalizability and longitudinal outcomes of a national heart failure clinical registry: comparison of Acute Decompensated Heart Failure National Registry (ADHERE) and non-ADHERE Medicare beneficiaries. *Am Heart J*. 2010;160:885–892.
3. Bui AL, Grau-Sepulveda MV, Hernandez AF, Peterson ED, Yancy CW, Bhatt DL, Fonarow GC. Admission heart rate and in-hospital outcomes in patients hospitalized for heart failure in sinus rhythm and in atrial fibrillation. *Am Heart J*. 2013;165:567–574.e6.

4. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF Jr, Dorobantu MI, Grinfeld LR, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin TM, Metra M. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet*. 2012;381:29–39.
5. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJV, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clauseff N, Corbalán R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Méndez GF, Metra M, Mittal S, Oh B-H, Pereira NL, Ponikowski P, Tang WHW, Wilson WH, Zannad F, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Januzzi F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365:32–43.
6. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozd J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L; on behalf of the Heart Failure Association of the ESC (HFA). EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail*. 2014;12:1076–1084.
7. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of get with the guidelines-heart failure. *Circ Heart Fail*. 2012;5:191–201.
8. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107:2920–2925.
9. McManus DD, Saczynski JS, Lessard D, Kinno M, Pidikiti R, Esa N, Harrington J, Goldberg RJ. Recent trends in the incidence, treatment, and prognosis of patients with heart failure and atrial fibrillation (the Worcester Heart Failure Study). *Am J Cardiol*. 2013;111:1460–1465.
10. Cullington D, Goode KM, Zhang J, Cleland JGF, Clark AL. Is heart rate important for patients with heart failure in atrial fibrillation? *JACC Heart Fail*. 2014;2:213–220.
11. O'Connor CM, Mentz RJ, Cotter G, Metra M, Cleland JG, Davison BA, Givertz MM, Mansoor GA, Ponikowski P, Teerlink JR, Voors AA, Fiuzat M, Wojdyla D, Chiswell K, Massie BM. The PROTECT in-hospital risk model: 7-day outcome in patients hospitalized with acute heart failure and renal dysfunction. *Eur J Heart Fail*. 2012;14:605–612.
12. Howlett JG, Ezekowitz JA, Podder M, Hernandez AF, Diaz R, Dickstein K, Dunlap ME, Corbalán R, Armstrong PW, Starling RC, O'Connor CM, Califf RM, Fonarow GC; ASCEND-HF Investigators. Global variation in quality of care among patients hospitalized with acute heart failure in an international trial: findings from the acute study clinical effectiveness of nesiritide in decompensated heart failure trial (ASCEND-HF). *Circ Cardiovasc Qual Outcomes*. 2013;6:534–542.
13. Hernandez AF, O'Connor CM, Starling RC, Reist CJ, Armstrong PW, Dickstein K, Lorenz TJ, Gibler WB, Hasselblad V, Komajda M, Massie B, McMurray JJV, Nieminen M, Rouleau JL, Swedberg K, Califf RM. Rationale and design of the acute study of clinical effectiveness of nesiritide in decompensated heart failure trial (ASCEND-HF). *Am Heart J*. 2009;157:271–277.
14. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XHT, Deswal A. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol*. 2012;59:998–1005.
15. Ezekowitz JA, Hernandez AF, Starling RC, Yancy CW, Massie B, Hill JA, Krum H, Diaz R, Ponikowski P, Metra M, Howlett JG, Gennevois D, O'Connor CM, Califf RM, Fonarow GC. Standardizing care for acute decompensated heart failure in a large megatrial: the approach for the acute studies of clinical effectiveness of nesiritide in subjects with decompensated heart failure (ASCEND-HF). *Am Heart J*. 2009;157:219–228.
16. Bonow RO, Bennett S, Casey DE Jr, Ganiats TG, Hlatky MA, Konstam MA, Lambrew CT, Normand S-LT, Piña IL, Radford MJ, Smith AL, Stevenson LW, Bonow RO, Bennett SJ, Burke G, Eagle KA, Krumholz HM, Lambrew CT, Linderbaum J, Masoudi FA, Normand S-LT, Ritchie JL, Rumsfeld JS, Spertus JA. ACC/AHA clinical performance measures for adults with chronic heart failure. *J Am Coll Cardiol*. 2005;46:1144–1178.
17. Hernandez AF, Fonarow GC, Liang L, Heidenreich PA, Yancy C, Peterson ED. The need for multiple measures of hospital quality: results from the Get With the Guidelines-Heart Failure Registry of the American Heart Association. *Circulation*. 2011;124:712–719.
18. Gage BF, Waterman AD, Shannon W, Boehler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *J Am Med Assoc*. 2001;285:2864–2870.
19. Ezekowitz JA, Hernandez AF, O'Connor CM, Starling RC, Proulx G, Weiss MH, Bakal JA, Califf RM, McMurray JJV, Armstrong PW. Assessment of dyspnea in acute decompensated heart failure. *J Am Coll Cardiol*. 2012;59:1441–1448.
20. Kim HN, Januzzi JL. Natriuretic peptide testing in heart failure. *Circulation*. 2011;123:2015–2019.
21. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ, Wilkoff BL; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:e240–e327.
22. McMurray JJV, Ezekowitz JA, Lewis BS, Gersh BJ, van Diepen S, Amerena J, Bartunek J, Commerford P, Oh B-H, Harjola VP, Al-Khatib SM, Hanna M, Alexander JH, Lopes RD, Wojdyla DM, Wallentin L, Granger CB; for the ARISTOTLE Committees and Investigators. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Circ Heart Fail*. 2013;6:451–460.

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

Seraj Abualnaja, Mohua Podder, Adrian F. Hernandez, John J. V. McMurray, Randall C. Starling, Christopher M. O'Connor, Robert M. Califf, Paul W. Armstrong and Justin A. Ezekowitz

J Am Heart Assoc. 2015;4:e002092; originally published August 24, 2015;

doi: 10.1161/JAHA.115.002092

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://jaha.ahajournals.org/content/4/8/e002092>

Subscriptions, Permissions, and Reprints: The *Journal of the American Heart Association* is an online only Open Access publication. Visit the Journal at <http://jaha.ahajournals.org/> for more information.