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Predictors and Prognostic Implications of Incident Heart Failure in Patients With Prevalent Atrial Fibrillation

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ABSTRACT

OBJECTIVES The purpose of this study was to determine the significant clinical predictors of incident heart failure (HF) and its prognostic effect on long-term outcomes among community-based patients with established atrial fibrillation (AF).

BACKGROUND AF is associated with an increased risk of HF. However, in this population, little focus is placed on risk stratification for and the prevention of HF.

METHODS Patients with AF but without HF at baseline enrolled in the ORBIT-AF (Outcomes Registry for Informed Treatment of Atrial Fibrillation) registry were included. Separate multivariable-adjusted Cox frailty regression models were used to identify significant predictors of HF incidence and determine the associated risk of adverse clinical events.

RESULTS The study included 6,545 participants with AF from 173 participating sites. Incident HF developed in 236 participants (3.6%) over the 2-year follow-up period; ejection fraction was preserved (>40%) in 64%, reduced (≤40%) in 13.5%, and missing in 22.5%. In multivariable analysis, traditional HF risk factors (age, coronary artery disease, renal dysfunction, and valvular disease), presence of permanent AF (hazard ratio [HR]: 1.60 [95% confidence interval (CI): 1.18 to 2.16]; reference group: paroxysmal AF), and elevated baseline heart rate (HR: 1.07 [95% CI: 1.02 to 1.13] per 5 beats/min higher heart rate) were independently associated with incident HF risk. Incident HF among patients with AF was independently associated with higher risk of mortality, all-cause hospitalization, and bleeding events.

CONCLUSIONS Incident HF among patients with AF is common, is more likely to be HF with preserved ejection fraction, and is associated with poor long-term outcomes. Traditional HF risk factors, AF type, and baseline heart rate are independent clinical predictors of incident HF. (J Am Coll Cardiol HF 2017;5:44-52) © 2017 by the American College of Cardiology Foundation.

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Atrial fibrillation (AF), the most common cardiac rhythm disorder among developed countries, is associated with increased morbidity, mortality, and health care costs (1-4). Along with stroke, incident heart failure (HF) is a significant complication of AF, with some studies reporting 3 to 4× higher incidence of HF among patients with versus without AF (5-8). However, little focus is placed on risk stratification for and prevention of HF. This is particularly relevant considering the growing burden of these 2 cardiovascular diseases.

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AF and HF share several risk factors as well as underlying pathophysiological mechanisms, and often coexist. Previous studies have reported that the epidemiological relationship between AF and HF is bidirectional, such that prevalent AF is associated with an increased risk of incident HF and vice versa (6,9). An important first step toward HF prevention among patients with AF is to identify those patients who are at highest risk for the disease. Previous studies evaluating the predictors of incident HF in this patient population have been limited by small sample size, few HF events, and lack of focus on AF-specific clinical characteristics (7,10). Furthermore, although previous studies have demonstrated that prevalent HF among patients with coexisting AF is associated with poor outcomes (8), the prognostic implications of incident HF for subsequent outcomes in a contemporary AF population are not well studied. In this study, we evaluated the significant clinical predictors of incident HF and its prognostic effect on long-term outcomes among community-based patients with established AF.

METHODS

The present study utilized data from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), a community-based registry of outpatients with AF that enrolled patients from 176 U.S. practices, including internal medicine-, cardiology-, or electrophysiology-based practices, between June 2010 and August 2011. The details about the rationale and design of the registry have been published previously (11). Briefly, patients ≥18 years of age with electrocardiographic evidence of AF that was not attributable to a reversible cause and with life expectancy >6 months at the time of enrollment were included in the registry after written informed consent. An interactive, web-based data collection form was used to abstract baseline patient data from the clinical chart on demographics, insurance status, medical history, date of diagnosis, type of AF, pharmacological treatment strategy (rate vs. rhythm control), invasive therapies (ablation, cardioversion), provider characteristics, vital signs, electrocardiographic and echocardiographic findings, arrhythmia-related symptoms, medical therapies/procedures, and quality of life. As reported previously in other studies from the ORBIT-AF cohort, participating centers were instructed to record patient's heart rate at baseline after a 5-min resting period on the basis of electrocardiogram or average pulse rate (beats/min) on physical examination (12,13). AF type at baseline was determined using well-established definitions: paroxysmal AF was defined as episodes of recurrent AF that terminate within 1 week; persistent AF was defined as recurrent AF episodes lasting longer than 1 week; and permanent AF was identified if the presence of AF was sustained and accepted by the patient and the physician (12,14). Follow-up data were collected at approximately 6-month intervals for up to 24 months after initial enrollment. Major clinical outcomes assessed at follow-up were AF progress; adverse events including death, HF, myocardial infraction, stroke, or systemic embolism; major bleeding as defined by the International Society of Thrombosis and Haemostasis criteria; and cardiovascular as well as all-cause hospitalization. The Duke Clinical Research Institute managed study coordination. The Duke Institutional Review Board approved the ORBIT-AF registry, and all participating sites obtained institutional review board approval as per local requirements.

STUDY POPULATION. The starting population for the present study included all participants with available

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CAD = coronary artery disease
CI = confidence Interval
EF = ejection fraction
HR = hazard ratio
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction

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baseline data (n = 10,137; 176 U.S. practices) who were enrolled from June 29, 2010, through August 9, 2011. Patients without any follow-up data (n = 388) and those with prevalent HF at the time of enrollment (n = 3,204) were excluded. The final study population included 6,545 study participants from 173 participating sites.

STUDY OUTCOMES. The primary outcome of interest was HF incidence on follow-up. Incident HF was defined as the occurrence of new diagnosis of clinical HF observed on follow-up visits. The HF diagnosis was on the basis of clinical signs and symptoms of congestion, such as dyspnea, fluid retention, rales on lung auscultation, jugular venous distention, and other radiographic evidence of pulmonary edema. Among patients with incident HF, ejection fraction (EF) reported on the visit of incident HF diagnosis or subsequent follow-up was used to identify HF subtypes: heart failure with preserved ejection fraction (HFpEF) (EF >40%) and heart failure with reduced ejection fraction (HFrEF) (EF ≤40%). Secondary outcomes that were compared between patients with versus without incident HF were all-cause death, all-cause hospitalization, stroke/thromboembolism, and bleeding events.

STATISTICAL ANALYSIS. The study population was stratified by incidence of HF on follow-up: patients with versus without HF incidence. Baseline characteristics of study participants in the 2 groups were described as median (interquartile range) for continuous variables and count (proportion) for categorical variables. Differences between study groups were assessed using the Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. Proportional use of different AF management strategies across the 2 study groups was also compared using the chi-square test.

Significant predictors of incident HF were determined by constructing a multivariable-adjusted Cox frailty regression model using all of the clinical and demographic characteristics as detailed in Online Table 1. The Cox frailty model accounts for the variability in incident HF between sites. Backward selection was used for the model with a retention p value criterion of <0.05 for the final multivariable model. All continuous variables were evaluated for nonlinearity with the outcome and linear splines were used if they did not meet the linear relationship criteria. Mortality was considered as competing risk for incident HF in the final model, and patients were censored at the time of mortality. Multiple imputations from the overall ORBIT-AF cohort were used to handle missing data on the covariates used in the multivariable-adjusted models. Missingness of baseline covariates was <7% for most covariates except left atrial size (13.8%), hematocrit (10.2%), and left ventricular EF (10%). The final risk estimates (hazard ratio [HR] and 95% confidence interval [CI]) were calculated by combining estimates from 5 imputed datasets. Sensitivity analysis was performed to identify significant predictors of HFpEF and HFrEF by constructing a cause-specific hazard model for each HF type outcome using a similar approach as described in the previous text and treating the other HF type as an additional competing risk.

Multivariable-adjusted Cox frailty regression models were also used to determine the risk of adverse clinical events (all-cause mortality, stroke/thromboembolism, all-cause hospitalization, and bleeding) associated with time-dependent incident HF in the study population. Separate models were constructed for each clinical outcome and adjusted for covariables as previously identified and detailed in Online Table 2.

SENSITIVITY ANALYSIS. Sensitivity analysis was performed to determine the predictors of incident HF among subgroups of patients without evidence of subclinical stage B HF at baseline. For this, patients with asymptomatic systolic dysfunction (left ventricular EF <50%), asymptomatic diastolic dysfunction (left atrial size >95% percentile), or moderate to severe left ventricular hypertrophy (posterior wall thickness ≥14 mm) at baseline were excluded. We also performed sensitivity analysis among patients who were not on diuretic agents at baseline and among those with paroxysmal AF and normal sinus rhythm at baseline.

All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina). All p values were on the basis of 2-sided tests, and alpha = 0.05 was used to establish the significance of the tests.

RESULTS

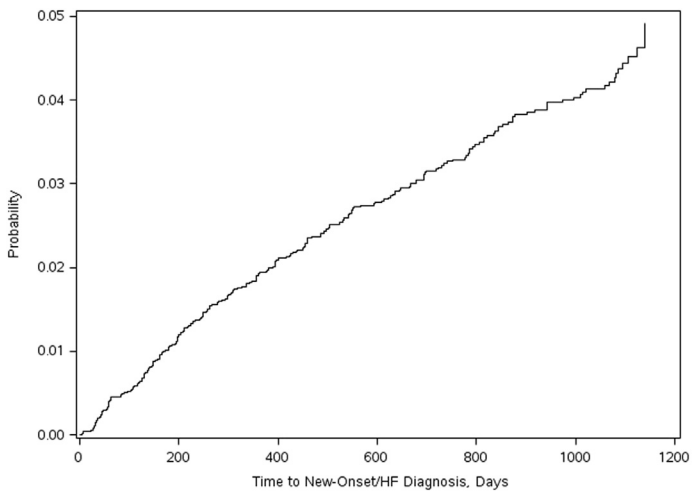
PATIENT CHARACTERISTICS. We included 6,545 participants without prevalent HF who were enrolled from 173 ORBIT-AF participating sites. Incident HF developed in 236 participants (3.6%) at the rate of 1.58 (95% CI: 1.39 to 1.79) per 100 person-years over the 2-year follow-up period (**Figure 1**). Of these, 64% (n = 151) developed HFpEF, 13.5% (n = 32) developed HFrEF, and 22.5% (n = 53) developed HF that could not be further classified due to missing EF information. The baseline characteristics of study participants with and without incident HF are compared in **Table 1**. Patients who developed HF were older, less

commonly on private insurance, and more likely to be current or former smokers. They also had a significantly higher prevalence of coronary artery disease (CAD), including prior myocardial infarction and revascularization, COPD, and anemia. Among other clinical characteristics, patients with incident HF on follow-up were more likely to have a higher heart rate, lower creatinine clearance, and higher stroke as well as bleeding risk at baseline. Left atrial enlargement (64% vs. 57%) and prevalence of permanent AF were also more common at baseline among patients with versus without HF development on follow-up. In contrast, the prevalence of subclinical systolic dysfunction on echocardiography was not different between the 2 groups. The AF symptom burden and quality of life were not significantly different at baseline between the 2 groups.

AF MANAGEMENT STRATEGIES. Proportional use of rhythm control strategies was significantly lower at baseline among patients with versus without subsequent incident HF (25.4% vs. 34.6%; p = 0.003). This was largely reflective of a lower use of invasive rhythm control strategies, such as cardioversion and catheter ablation (Table 2). Use of antiarrhythmic agents and anticoagulants at baseline was not significantly different between the 2 groups. In contrast, baseline use of antihypertensive medications, such as angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, and diuretic agents, were significantly higher among patients who developed HF on follow-up (Table 2).

BASELINE PREDICTORS OF HF RISK. In multivariable-adjusted analysis, presence of permanent AF was strongly associated with a higher risk of incident HF (Table 3). Similarly, the presence of CAD and significant valvular abnormalities at baseline were each associated with up to 50% higher risk of HF. Among other risk factors, older age, renal dysfunction, and higher heart rate at baseline were also independently associated with increased HF risk on follow-up. Differences in cumulative incidence of HF across low versus high levels of these risk factors are shown in Figure 2. Finally, a nonlinear relationship was observed between blood pressure and HF risk such that a higher diastolic blood pressure above the normal limit (80 mm Hg) was associated with an increased risk of HF, with a trend toward significance (Table 3). For outcomes of different HF subtypes (HFpEF and HFrEF), baseline risk factors that independently predicted HFpEF incidence were not different from those identified for overall HF (Online Table 3). Due to relatively few HFrEF events in our cohort (n = 32), we could not perform an adjusted analysis to determine the significant clinical predictors of HFrEF.

FIGURE 1 Cumulative Incidence of HF Events Over Time Among Patients With Atrial Fibrillation



HF = heart failure.

SENSITIVITY ANALYSIS. Among subgroups of patients without baseline stage B HF and patients without diuretic agent use at baseline, predictors of HF risk were not very different for the overall population (Online Tables 4 and 5). Higher than normal body mass index, systolic blood pressure, and insurance status were additional significant predictors of HF risk in the subgroup of patients who were free of stage B HF at baseline. Among patients with paroxysmal AF and normal sinus rhythm at baseline (n = 2,095), 49 HF events were observed on follow-up. In this subgroup, the magnitude of the hazard estimate for incident HF-associated baseline heart rate was similar to the overall study population, but was not statistically significant (HR: 1.05 [95% CI: 0.93 to 1.18]).

OUTCOMES EVENTS IN PATIENTS WITH AF AND WITH INCIDENT HF. The incidence of major adverse clinical events, such as all-cause mortality, all-cause hospitalization, stroke/thromboembolism, and bleeding, were significantly higher in patients with AF with subsequent incident HF compared with those without HF during follow-up (Table 4). In multivariable analysis, incident HF during follow-up among patients with AF was independently associated with a higher risk of mortality, all-cause hospitalization, and bleeding events (Table 4). The association between incident HF and risk of stroke/thromboembolism attenuated and was not significant after adjustment for potential confounders.

TABLE 1 Baseline Characteristics of Study Participants

	Without Incident HF (n = 6,309)	With Incident HF (n = 236)	p Value
Age, yrs	74.0 (66.0-81.0)	80.0 (72.0-84.0)	<0.0001
Race/ethnicity			0.7090
White	90.1	91.1	
Black or African American	4.1	3.0	
Hispanic	4.2	3.8	
Other	1.5	2.1	
Payer/insurance			<0.0001
Medicaid or Medicare	67.5	83.1	
Private	27.8	15.7	
Others	4.7	1.3	
Female	43.4	47.9	
Smoking			0.0065
Nonsmoker	54.2	45.8	
Recent or former smoker	40.2	50.4	
Current smoker	5.5	3.8	
Hypertension	80.9	83.9	0.2538
Diabetes	24.9	28.8	0.1732
Obstructive sleep apnea	16.2	14.8	0.5663
Anemia	13.5	25.0	<0.0001
History of CAD	27.7	39.4	<0.0001
Heart rate, beats/min	70.0 (62.0-79.0)	72.0 (64.0-80.0)	0.0197
LVEF			
≥50%	79.7	79.2	0.4318
>40% to <50%	4.1	5.1	
≥30% to <40%	3.7	5.1	
<30%	0.7	0.0	
EGFR	69.9 (56.6-84.7)	61.4 (49.6-74.0)	<0.0001
Type of AF			
First detected /new onset	5.4	3.8	<0.0001
Paroxysmal atrial fibrillation	55.4	43.2	
Persistent atrial fibrillation	15.4	12.3	
Permanent atrial fibrillation	23.7	40.7	
EHRA score			0.3928
No symptoms	40.4	35.2	
Mild	45.4	48.7	
Severe	12.4	14.4	
Disabling	1.6	1.3	
CHA_2DS_2-VASc risk score	3.0 (2.0-4.0)	4.0 (3.0-5.0)	<0.0001
ATRIA score	3.0 (1.0-4.0)	3.0 (2.0-6.0)	<0.0001
AFEQT overall score (QOL)	83.3 (68.6-94.4)	81.5 (66.7-91.7)	0.3283

Values are median (interquartile range) or %.

AF = atrial fibrillation; AFEQT = atrial fibrillation effect on quality of life; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; CAD = coronary artery disease; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 yrs, female; EGFR = estimated glomerular filtration rate; EHRA = European Heart Rhythm Association; HF = heart failure; LVEF = left ventricular ejection fraction; QOL = quality of life.

DISCUSSION

Among patients with AF, subsequent development of HF was common. A majority of incident cases were HFpEF. Along with traditional HF risk factors, clinical characteristics such as presence of permanent AF and higher baseline heart rate were independent predictors of incident HF in patients with AF. Finally, incident HF was significantly associated with adverse clinical outcomes, including higher rates of mortality, hospitalization, and bleeding events in this patient population.

HF INCIDENCE AMONG PATIENTS WITH AF. The incidence of HF in our study cohort of patients with prevalent AF (1.58 per 100 patient-years) was higher than that reported in the general population (0.2 to 1 per 100 patient-years) (15,16). Among patients with AF, investigators from the FHS (Framingham Heart Study) and Olmsted County have demonstrated a higher incidence rate of 3 to 4 per 100 patient-years (5,7,8). Both of these cohorts included patients from the 1980s to 1990s who may not be representative of the contemporary AF population (Online Table 6). The lower incidence of HF in our study cohort of patients with AF from 2010 to 2011 could be related to the previously reported decline in HF incidence in the past decade, both in the general population as well as in patients with AF (5,16). Potpara et al. (10) reported lower incidence of HF (0.97%) in a European cohort of patients with AF compared with our study population. This low rate of HF in the European cohort could be related to younger age and lower burden of traditional risk factors (Online Table 6).

INDEPENDENT CLINICAL PREDICTORS OF HF IN AF. Few studies have evaluated the significant predictors of incident HF among patients with AF (7,10,17). In the FHS, Schnabel et al. (7) demonstrated that well-established risk factors that are associated with HF risk in the general population were also independent predictors of HF development in patients with AF. Potpara et al. (10) identified left atrial size as an independent predictor of clinical HF along with other established HF risk factors (Online Table 6).

Similar to observations from previous studies, we confirmed well-established HF risk factors such as old age, CAD, renal dysfunction, and valvular heart disease as independent predictors of HF among patients with AF. These findings provide internal validity to the clinical diagnosis of HF used in our study. These risk factors are also associated with increased risk of incident AF, and the observed association highlights the overlap in the pathophysiological mechanisms underlying both diseases (6,7,18–23). Certain unique determinants of HF development were also observed in our study population. Among these, the presence of permanent AF was identified as the strongest predictor of HF development. Permanent AF is associated with a higher burden of cardiovascular risk factors and worse cardiac substrate, which may explain the observed association (24,25). Although AF progression has been associated with higher risk of stroke and mortality (25),

most previous studies evaluating the predictors of incident HF have failed to account for AF progression in adjusted analysis (Online Table 6) (7,10). Our study findings add significantly to the existing published data and highlight the importance of AF progression in long-term outcomes.

Higher heart rate at baseline was also identified as an independent predictor of HF in our study population. This finding is particularly significant in the context of the current guideline recommendations against strict heart rate control among patients with AF (26). These recommendations are on the basis of neutral results from the RACE-2 (The Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II) trial that compared strict versus lenient rate control among patients with AF (27). However, the RACE-2 trial was underpowered to evaluate HF outcomes, with only 11 events in each arm. Furthermore, consistent with our results, previous observations from this cohort have also demonstrated that increasing heart rate is associated with greater symptom burden and higher mortality rates (13). It is noteworthy that the association between baseline heart rate and risk of HF among patients with paroxysmal AF and normal sinus rhythm was not statistically significant. However, this lack of association was likely related to the small number of HF events in this patient population. Future randomized controlled studies with adequate power are needed to determine the optimal rate control strategy and heart rate target in this patient population for HF prevention and to improve long-term outcomes.

INCIDENT HF PHENOTYPE ASSOCIATED WITH AF. Up to two-thirds of the incident HF events observed in the present study were classified as HFpEF. Previous studies have examined the risk of different HF subtypes, HFpEF versus HFrEF, among patients with prevalent AF. Potpara et al. (10) observed a 1.5-fold higher incidence of HFpEF compared with HFrEF (60% vs. 40% of all HF events; n = 83). In contrast, studies from the FHS database have reported that prevalent AF was strongly associated with development of both HF subtypes, with similar incidence rates of HFpEF and HFrEF (6,7). The present study, with a much larger and more contemporary AF population, provides further evidence demonstrating an increased predisposition for HFpEF among patients with AF.

The mechanism underlying the differential risk of HFpEF versus HFrEF among patients with AF is not well understood. HFpEF and AF share several risk factors, such as diabetes, hypertension, age, and obesity.

TABLE 2 Utilization of Care at Baseline Among Patients With AF With and Without Incident HF on Longitudinal Follow-Up

	Without Incident HF (n = 6,309)	With Incident HF (n = 236)	p Value
Current AF management strategy			
Rate control	65.2	74.6	0.0034
Rhythm control	34.6	25.4	
Prior cardioversion	29.1	25.8	0.28
Catheter ablation of AF	6.0	3.4	0.094
Antihypertensive therapies			
Angiotensin-receptor blocker	17.8	20.8	0.244
Aldosterone antagonist	2.4	5.5	0.0023
ACE-I	31.4	42.4	0.0004
Dihydropyridine CCB	15.4	18.2	0.24
Diuretic	37.2	54.2	<0.0001
Rate-control agents			
Beta-blockers	58.7	64.0	0.11
Digoxin	18.1	21.2	0.22
Non-dihydropyridine CCB	18.1	19.9	0.48
Antiarrhythmic therapies			
Amiodarone	8.4	8.5	0.97
Dronedarone	5.4	4.7	0.61
Flecainide	4.1	3.4	0.58
Propafenone	3.1	2.1	0.39
Sotalol	6.9	7.6	0.67
Antiplatelet agents	45.9	44.1	0.58
Novel anticoagulants	5.4	7.6	0.14
Warfarin	68.7	72.5	0.22

Values are %.

ACE-I = angiotensin-converting enzyme inhibitor; CCB = calcium-channel blocker; other abbreviations as in Table 1.

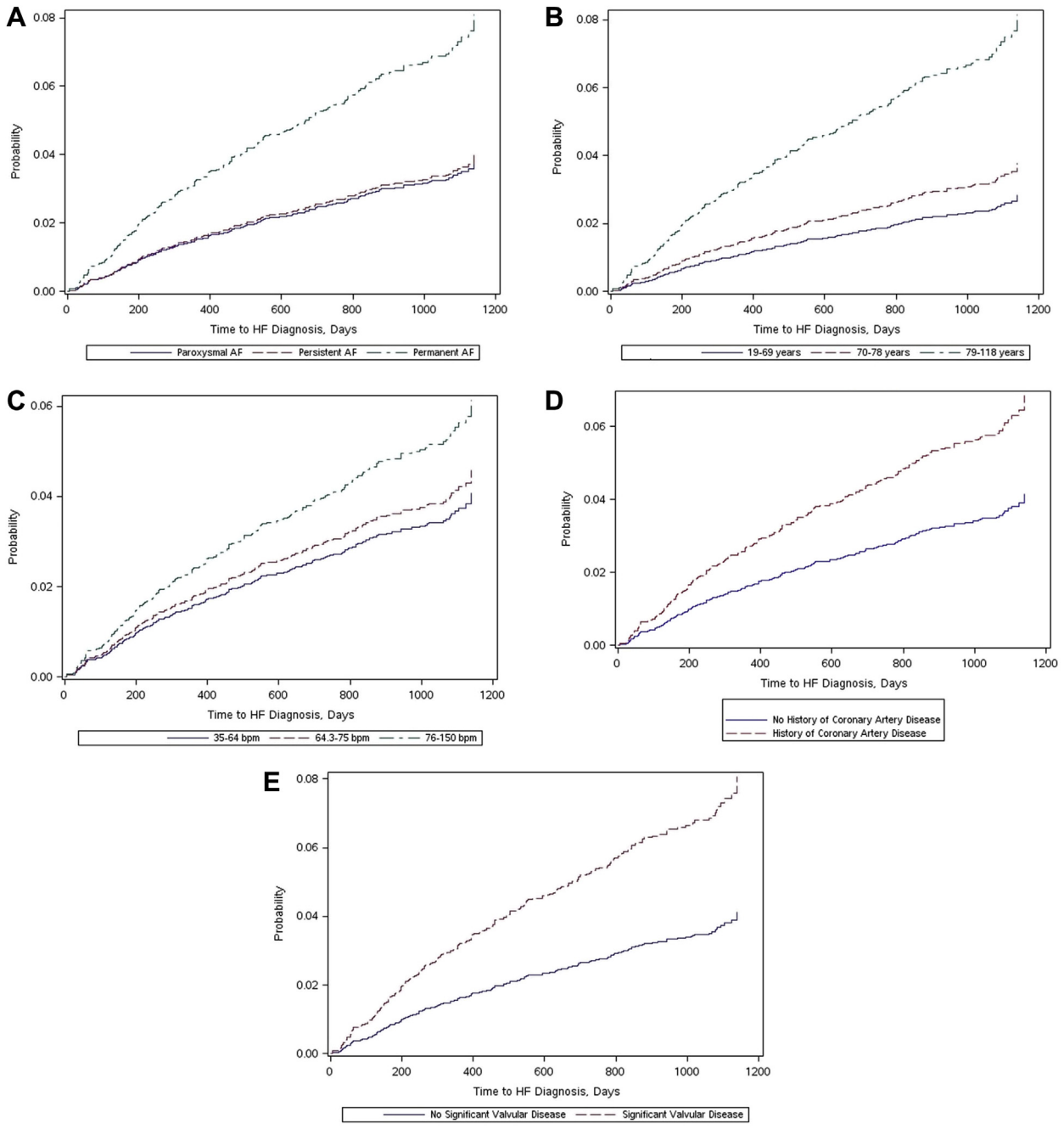
TABLE 3 Significant Clinical Predictors of Incident HF Among AF Patients

Risk Factor	Adjusted HR (95% CI)*	p Value
Type of AF (reference group: paroxysmal AF)		
First detected or new onset	1.01 (0.50–2.04)	0.99
Persistent AF	0.98 (0.64–1.51)	0.94
Permanent AF	1.60 (1.18–2.16)	0.002
Age, yrs	1.17 (1.08–1.26)	0.0001
History of CAD	1.52 (1.16–1.99)	0.0025
Diastolic blood pressure, mm Hg		
>80	1.16 (0.99–1.36)	0.066
≤80	0.89 (0.81–0.96)	0.0047
EGFR, mg/dl	0.95 (0.91–0.98)	0.0033
Significant valvular disease	1.50 (1.12–2.01)	0.0063
Heart rate, beats/min	1.07 (1.02–1.13)	0.0048
Sinus node dysfunction/sick sinus syndrome	1.37 (1.00–1.88)	0.05

Variables included in the adjusted model are detailed in Online Table 1. Adjusted HR for continuous variables are estimated per 5-unit increase. *Risk estimates were estimated by combining estimates from 5 imputed datasets.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

FIGURE 2 Cumulative Incidence of HF Over Time Among Patients With AF Stratified According to Risk Factor Levels



Incidence of heart failure (HF) **(A)** across subgroups of atrial fibrillation (AF) type; **(B)** across age subgroups; **(C)** across subgroups of baseline heart rate; **(D)** among patients with vs. without baseline coronary artery disease; and **(E)** among patients with vs. without significant valve disease.

Similarly, previous studies have also identified intermediate cardiac phenotypes, such as diastolic dysfunction, myocardial fibrosis, and left atrial enlargement, that are common to development of both HFpEF and AF (6,18-23,28). This overlap in the risk factor and disease progression stages may explain the observed predisposition for HFpEF among patients with AF.

CLINICAL OUTCOMES AMONG PATIENTS WITH AF WITH INCIDENT HF. We observed a significantly higher risk of adverse clinical events, such as mortality, all-cause hospitalization, and bleeding, among patients with AF with versus without subsequent incident HF. These findings are consistent with previous observations among patients with coexisting HF and AF and support the validity of the clinical diagnosis of HF in our study population (29). It remains unclear if prevalent AF at baseline adds to the risk of adverse clinical outcomes associated with the development of HF. In a recent study, Santhanakrishnan et al. (6) demonstrated that prevalent AF was not significantly associated with mortality among patients with incident HF. Future studies are needed to characterize the independent contribution of prevalent AF on incident HF-related adverse outcomes. Nonetheless, our study findings highlight the need for HF prevention in patients with AF to improve long-term outcomes. The independent predictors of HF risk identified in the present study may help identify and target high-risk patients with effective preventive therapies at an early stage.

STUDY LIMITATIONS. First, due to the observational nature of our analysis, residual confounding affects our study findings. Second, although ORBIT-AF participating sites were selected to be potentially representative of the national AF population, the study population was not diverse, with ~90% white participants, and the results may therefore not be generalizable to patients of other ethnic groups or those who are managed in different clinical settings than the ORBIT-AF participants. Third, there may be some degree of misclassification in the clinical diagnosis of HF that was used to ascertain the primary study diagnosis of incident HF. Furthermore, we did not have data on levels of HF-specific biomarkers such as N-terminal pro-B-type natriuretic peptide in our study population. Fourth, the incidence of certain adverse events such as stroke among patients who developed HF was low, and there may be a potential for type 2 error. Fifth, heart rate estimation among participants at baseline may have had a potential for measurement error. However, measurement error in an exposure variable would lead to a bias toward null. In the present study, we observed a significant association between baseline heart rate and risk of HF. Furthermore, the association between baseline heart rate and other clinical outcomes has been reported previously from this cohort (13,14). Finally, EF data was missing in a significant proportion of incident HF patients, which may have limited our ability to evaluate significant predictors of the 2 HF subtypes: HFpEF and HFrEF. However, the proportional missingness in EF data is not different from that reported in other large cohort studies (30,31).

TABLE 4 Incidence Rates and Adjusted Risk of Outcomes Among AF Patients With and Without Time-Varying Incident HF on Longitudinal Follow-Up

Outcome	No HF (Per 100 Patient-Yrs)	HF (Per 100 Patient-Yrs)	Adjusted HR (95% CI)	p Value
All-cause death	3.35	8.24	1.84 (1.07-3.17)	0.023
Stroke/TIA or systemic embolism	1.32	3.09	1.53 (0.56-4.16)	0.40
All-cause hospitalization	26.46	90.18	3.35 (2.19-5.15)	<0.0001
Bleeding hospitalization	2.45	8.07	2.25 (1.22-4.15)	0.0094

Variables included in the adjusted model for each outcome are detailed in Online Table 2.
TIA = transient ischemic attack; other abbreviations as in Tables 1 and 3.

CONCLUSIONS

Incident HF observed among stable outpatients with AF is more commonly HFpEF and is associated with poor long-term outcomes. Apart from traditional HF risk factors, AF-specific clinical characteristics, including AF type and baseline heart rate, are independent clinical predictors of incident HF. These findings may help in early-stage risk stratification of patients with AF for future HF development. Additional studies are needed to determine if selective targeting of these high-risk patients with AF with preventive strategies such as risk factor modification may improve long-term clinical outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Incident HF observed in patients with established AF is more commonly HFpEF. Apart from traditional HF risk factors, AF-specific characteristics, including AF type and baseline heart rate, are independent predictors of incident HF risk.

TRANSLATIONAL OUTLOOK: Future research is needed to determine if aggressive risk factor modification in patients with AF may modify the downstream risk of HF.

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KEY WORDS atrial fibrillation, heart failure, heart failure with preserved ejection fraction, outcomes

APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this article.