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Type of Atrial Fibrillation and Outcomes in Patients With Heart Failure and Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) is common in heart failure (HF), but the outcome by type of AF is largely unknown.

OBJECTIVES This study investigated outcomes related to type of AF (paroxysmal, persistent or permanent, or new onset) in 2 recent large trials in patients with HF with reduced ejection fraction.

METHODS The study analyzed patients in the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) and ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) trials. Multivariable Cox regression models were used to estimate hazard ratios (HRs) for outcomes related to AF type.

RESULTS Of 15,415 patients, 5,481 (35.6%) had a history of AF at randomization, and of these, 1,645 (30.0%) had paroxysmal AF. Compared with patients without AF, patients with paroxysmal AF at randomization had a higher risk of the primary composite endpoint of cardiovascular death or HF hospitalization (HR: 1.20; 95% confidence interval [CI]: 1.09 to 1.32; $p < 0.001$), HF hospitalization (HR: 1.34; 95% CI: 1.19 to 1.51; $p < 0.001$), and stroke (HR: 1.34; 95% CI: 1.02 to 1.76; $p = 0.037$), whereas the corresponding risks in patients with persistent or permanent AF were not elevated. Neither type of AF was associated with higher mortality. New onset AF was associated with the greatest risk of adverse outcomes: primary endpoint (HR: 2.21; 95% CI: 1.80 to 2.71), HF hospitalization (HR: 2.11; 95% CI: 1.58 to 2.81), stroke (HR: 2.20; 95% CI: 1.25 to 3.88), and all-cause mortality (HR: 2.26; 95% CI: 1.86 to 2.74), all p values < 0.001, compared with patients without AF. Anticoagulants were used less often in patients with paroxysmal (53%) and new onset (16%) AF than in patients with persistent or permanent AF (71%).

CONCLUSIONS Among HF patients with a history of AF, those with paroxysmal AF were at greater risk of HF hospitalization and stroke than were patients with persistent or permanent AF, underlining the importance of anticoagulant therapy. New onset AF was associated with increased risk of all outcomes. (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF]; NCT01035255) (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure [ATMOSPHERE]; NCT00853658) (J Am Coll Cardiol 2017;70:2490–500)

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Atrial fibrillation (AF) is the most common arrhythmia in patients with heart failure with reduced ejection fraction (HFrEF), with a prevalence that increases with severity of heart failure (HF), reaching up to 50% in patients in New York Heart Association (NYHA) functional class IV (1,2). In some studies, AF has been associated with a poorer prognosis in HFrEF but this has not been a consistent finding after adjustment for other variables associated with worse outcomes. As a result, there is controversy about whether AF is an independent prognostic factor in HFrEF (3-5). The different findings reported may reflect the completeness of clinical data available for adjustment, including information related to medical history, comorbidity, and physiological and laboratory measurements. Notably, no study in chronic HFrEF included measurement of natriuretic peptides, the most powerful independent predictor of outcome in this condition. AF was also inconsistently defined in existing studies with some using medical history and others using the baseline electrocardiogram (ECG) to identify AF (4,6). Consequently, existing analyses have not examined whether type of AF (paroxysmal vs. persistent or permanent) is related to outcome. Similarly, the relationship between incident AF and outcomes has rarely been examined in previous studies.

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To address these outstanding questions, we have examined the association between AF and outcomes in the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) trials, the 2 most recent and largest global multicenter randomized trials in patients with HFrEF (7,8). The trials had an almost identical design and detailed clinical data, including history of AF, were collected at baseline. B-type natriuretic peptides were measured, and an ECG was also recorded, at baseline, in all patients in both trials. Cardiovascular events during follow-up, including new onset AF, were adjudicated by the same endpoint committee.

The main aim of the present study was to investigate the association between type of AF at baseline (paroxysmal vs. persistent or permanent) and outcomes in HFrEF, after fully adjusting for other prognostic variables, including natriuretic peptides. We also examined the association between incident AF during follow-up and outcomes.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

ECG = electrocardiogram

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

LVEF = left ventricular ejection fraction

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

NYHA = New York Heart Association

METHODS

A complete list of the PARADIGM-HF trial and ATMOSPHERE trial investigators and committees can be found in the Online Appendix.

STUDY POPULATION AND PROCEDURES. The study design and main results of both PARADIGM-HF and ATMOSPHERE trials have been published (7-11). The inclusion and exclusion criteria of the 2 trials were almost identical. Briefly, patients were eligible at screening if they were ≥18 years of age, had NYHA functional class II to IV, had left ventricular ejection fraction (LVEF) ≤35% (changed from ≤40% initially in the PARADIGM-HF trial by amendment), had elevated natriuretic peptides (cutoff level independent of AF), and took an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, along with a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist, if indicated. Exclusion criteria at screening included symptomatic hypotension or systolic blood pressure <95 mm Hg (<90 mm Hg in the ATMOSPHERE trial), estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (<35 ml/min/1.73 m^2 in the ATMOSPHERE trial), and potassium >5.4 mmol/l (>5.2 mmol/l in the ATMOSPHERE trial). The trial was approved by ethics committees at all 1,043 participating centers in 47 countries in the

Novartis had no role in this analysis. Except for Dr. Mogensen, all authors or their institutions have received payments from Novartis for their involvement in PARADIGM-HF and/or ATMOSPHERE trials. Dr. Mogensen has received a speaker fee from Novo Nordisk and Merck Sharp & Dohme. Dr. Jhund has received consulting and speaker fees from Novartis. Dr. Desai has received research grant support from Novartis; and has served as a consultant for Novartis, Abbott, Relypsa, AstraZeneca, Janssen, and DalCor. Dr. Dickstein has served as a member of the Executive Steering Committee for Atmosphere. Dr. Packer has served as a consultant for Bayer, Amgen, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi-Sankyo, Celyad, Relypsa, Novartis, Sanofi, Admittance, Takeda, and ZS Pharma. Dr. Rouleau has served as a consultant for Novartis, AstraZeneca, and Bayer. Drs. Solomon and Zile have received research grant support from and served as a consultant for Novartis. Dr. Swedberg has served as a consultant for and received honoraria from Novartis. Dr. Køber has received a speaker honorarium from Novartis. Dr. McMurray's employer, Glasgow University, was paid by Novartis for his role in the PARADIGM-HF and ATMOSPHERE trials. Novartis has paid for open access to this paper.

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PARADIGM-HF trial and 789 centers in 43 countries in the ATMOSPHERE trial, and all patients provided written informed consent.

On trial entry, ongoing therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was stopped and patients entered a sequential run-in, first receiving enalapril followed by sacubitril/valsartan in the PARADIGM-HF trial and enalapril followed by the combination of enalapril plus aliskiren in the ATMOSPHERE trial. Patients tolerating both run-in periods were randomly assigned to double-blind therapy with sacubitril/valsartan or enalapril in a 1:1 ratio in the PARADIGM-HF trial or enalapril, aliskiren, or both drugs in a 1:1:1 ratio in the ATMOSPHERE trial.

Information on AF at the randomization visit was based on the medical history (investigators were asked to state whether there was a history of AF and if yes, whether the AF was paroxysmal or persistent or permanent) and analysis of the baseline ECG (investigators were asked to report whether this showed AF). The few patients with a history of atrial flutter or atrial flutter on their baseline ECG were classified as unspecified AF. In a sensitivity analysis, AF was defined according to the presence or absence of AF or atrial flutter on the ECG at randomization alone.

Among patients without AF (no history of AF and no AF in the ECG) at baseline, new onset AF was identified as a clinical endpoint using a specific case report form in both studies. The CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years; diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category) score, reflecting the risk of thromboembolic events, was calculated using patient characteristics at randomization. The HAS-BLED score was similarly used to calculate bleeding risk (with a point for alcohol consumption given if patients reported >1 drinks/day).

OUTCOMES. The primary outcome of both trials was a composite of cardiovascular death or HF hospitalization. In the present study, we investigated the association between AF and risk of the primary outcome, each of its components, death due to worsening HF, sudden death, all-cause mortality, and stroke. All endpoints were adjudicated by the same clinical endpoint committee according to pre-specified criteria.

STATISTICAL ANALYSES. Baseline characteristics are presented as mean ± SD or median (interquartile range) for continuous variables and frequency and percentage for categorical variables. Differences in baseline characteristics according to type of AF at baseline were assessed using the chi-square test for categorical variables and either 2-sided Student's *t*-test or the Kruskal-Wallis test for continuous variables.

Incidence rates for the outcomes of interest are presented per 100 person-years. Cumulative incidence functions for outcomes of interest with death as a competing risk were compared according to AF status at randomization. Gray's test was used to compare the cumulative incidence functions. Relative hazard ratios (HRs) with 95% confidence intervals (CIs) of outcomes according to type of AF were calculated using cause-specific Cox proportional hazard models using no AF as reference. To assess the prognostic significance of new onset AF during follow-up, AF was included as a time-dependent variable. Thereby, the patients who developed new onset AF were removed from the no-AF subgroup and instead classified as new onset AF from the date of new onset AF and onward.

Final models included adjustment for randomized treatment (enalapril, sacubitril/valsartan, aliskiren, or combination of enalapril and aliskiren), and the following baseline characteristics: age, sex, region, race, NYHA functional class, LVEF, heart rate, systolic blood pressure, eGFR, diabetes, body mass index, time since HF diagnosis, history of HF hospitalization, history of stroke, prior myocardial infarction, and log N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Analyses were performed using Stata version 13 (StataCorp, College Station, Texas). Two-sided p values < 0.05 were considered significant.

RESULTS

BASELINE CHARACTERISTICS. Of the 15,415 patients randomized in both trials, 5,481 (35.6%) patients had a history of AF. Of these, 3,770 (68.8%) patients were categorized as having persistent or permanent AF and 1,645 (30.0%) patients were categorized as having paroxysmal AF (66 patients had undefined AF). A total of 3,654 (23.7%) patients had AF on their baseline ECG and 369 patients developed new onset AF during follow-up.

PATIENTS WITH PERSISTENT OR PERMANENT VERSUS PAROXYSMAL AF VERSUS PATIENTS WITHOUT AF. Baseline patient characteristics according to AF status are presented in Table 1. Patients with both types of AF were older, more often men, had longer duration HF, worse NYHA functional class and Kansas City Cardiomyopathy Questionnaire score, lower eGFR, and more often had a history of prior HF hospitalization, hypertension, stroke, and chronic obstructive pulmonary disease compared with patients without a history of AF. LVEF was higher in patients with both types of AF compared with those without, as was median NT-proBNP.

Patients with persistent or permanent AF less often had an ischemic etiology (50.6%) than either patients with paroxysmal AF (63.6%) or patients without AF (60.2%) did. There was a similar difference in history of myocardial infarction (30.0%, 49.2%, and 45.5% in each group, respectively).

The frequency of use of a beta-blocker was similar according to baseline AF status but the use of diuretics was more frequent in patients with either type of AF compared with those without AF. The use of digoxin was much more common in patients with persistent or permanent AF (50.8%) than in those with paroxysmal AF (28.7%) and in patients without AF (23.8%). The pattern of use of amiodarone also differed considerably (used in 8.7%, 24.9%, and 7.1% of each group, respectively).

The average CHA_2DS_2-VASc score was lowest in patients without AF (3.5 ± 1.7) but higher in patients with paroxysmal AF (4.1 ± 1.8) than in patients with persistent or permanent AF (3.9 ± 1.8; $p = 0.005$). More than 90% of patients in each AF category had a CHA_2DS_2-VASc score of 2 or more (Online Appendix, Online Table 1, Online Figure 1). Oral anticoagulants were used most commonly in patients with persistent or permanent AF (71.2%), at an intermediate level in those with paroxysmal AF (53.1%), and least frequently in individuals with no history of AF (16.0%). The opposite was true for antiplatelet therapy (used in 31.4%, 50.8%, and 67.8% of each group, respectively).

PATIENTS WITH NEW ONSET (INCIDENT) AF. Patients with new onset (incident) AF had characteristics intermediate between those without AF and patients with paroxysmal AF (**Table 1**). The more striking differences were in duration of HF (longer than in those without a history of AF) and NT-proBNP, which was as high as in those with persistent or permanent AF. Baseline pharmacological treatment was similar to that in patients without a history of AF.

ASSOCIATION BETWEEN AF AND OUTCOMES. Incidence rates and hazard ratios for the risk of each outcome of interest, according to presence of AF at baseline or during follow-up, are presented in **Table 2, Figure 1**, and the **Central Illustration**.

PATIENTS WITH PAROXYSMAL VERSUS PERSISTENT OR PERMANENT VERSUS NO AF. In unadjusted analyses, rates of each of the primary composite endpoints, cardiovascular death, HF hospitalization, all-cause mortality, and stroke were higher in patients with both types of AF compared with individuals without a history of AF (**Table 2, Figure 1**). However, in adjusted analyses, the risk of the primary endpoint was only higher in patients with paroxysmal AF (HR: 1.20; 95% CI: 1.09 to 1.32; $p < 0.001$), compared with patients without AF. This was not the case for patients with persistent or permanent AF (HR: 0.94; 95% CI: 0.87 to 1.02; $p = 0.138$). This higher risk of the primary composite endpoint among patients with paroxysmal AF was primarily due to a higher risk of HF hospitalization (HR: 1.34; 95% CI: 1.19 to 1.51; $p < 0.001$) compared with patients with no history of AF, and compared with patients with persistent or permanent AF (HR: 1.42; 95% CI: 1.25 to 1.63; $p < 0.001$) rather than cardiovascular death (HR: 1.09; 95% CI: 0.97 to 1.24; $p = 0.156$; HR: 1.12; 95% CI: 0.98 to 1.28; $p = 0.088$, respectively).

Patients with paroxysmal AF also had a higher risk of stroke compared with patients with no AF (HR: 1.34; 95% CI: 1.02 to 1.76; $p = 0.037$), although this was not apparent when compared with patients with persistent or permanent AF (HR: 1.04; 95% CI: 0.83 to 1.32; $p = 0.72$) (**Table 2, Central Illustration**).

Finally, patients with paroxysmal AF had a higher risk of pump-failure death when compared with patients with no AF (HR: 1.53; 95% CI: 1.22 to 1.91; $p < 0.001$) and when compared with patients with persistent or permanent AF (HR: 1.35; 95% CI: 1.06 to 1.71; $p = 0.014$). However, neither type of AF was associated with higher overall mortality (**Table 2, Central Illustration**).

Sensitivity analysis: patients with AF on their baseline ECG. Patients with AF or atrial flutter on their baseline ECG ($n = 3,760$) did not have an elevated risk of the primary endpoint (adjusted HR: 0.91; 95% CI: 0.84 to 0.98; $p = 0.014$), CV death (adjusted HR: 0.94; 95% CI: 0.86 to 1.03; $p = 0.18$), HF hospitalization (adjusted HR: 0.90; 95% CI: 0.81 to 0.99; $p = 0.036$), or all-cause mortality (adjusted HR: 0.92; 95% CI: 0.85 to 1.00; $p = 0.06$), compared with patients without AF on their baseline ECG.

Patients with incident (new onset) AF. Patients who developed new onset AF during follow-up were at higher risk of the primary endpoint, each of its components, all-cause mortality, and stroke compared with patients without AF at baseline and during follow-up (**Table 2, Central Illustration,** Online Appendix, Online Figure 2). Patients with new onset AF also had a higher adjusted risk of the primary endpoint compared with patients with a history of AF at baseline: (HR: 2.13; 95% CI: 1.73 to 2.62), CV death (HR: 2.37; 95% CI: 1.92 to 2.91), HF hospitalization (HR: 1.91; 95% CI: 1.46 to 2.60), all-cause mortality (HR: 2.24; 95% CI: 1.85 to 2.73), all p values <0.001,

TABLE 1 Baseline Characteristics by AF Type

	AF Type at Randomization				
	No AF (n = 9,828)	Paroxysmal (I) (n = 1,645)	Persistent/Permanent (II) (n = 3,770)	p Value (I vs. II)	New Onset AF (n = 369)
Age at screening, yrs	61.6 ± 11.8	66.9 ± 10.1*	67.2 ± 10.3*	0.292	64.3 ± 11.6*
Female	2,245 (22.8)	329 (20.0)†	755 (20.0)†	0.982	56 (15.2)†
Region				<0.001	
North America	478 (4.9)	178 (10.8)*	116 (3.1)*		29 (7.9)*
Latin America	1,910 (19.4)	143 (8.7)*	468 (12.4)*		47 (12.7)*
Western Europe	2,267 (23.1)	533 (32.4)*	1,055 (28.0)*		114 (30.9)*
Central Europe	2,357 (24.0)	581 (35.3)*	1,774 (47.1)*		112 (30.4)*
Asia/Pacific and other	2,816 (28.7)	210 (12.8)*	357 (9.5)*		67 (18.2)*
Race				<0.001	
White	5,580 (56.8)	1,307 (79.5)*	3,133 (83.1)*		269 (72.9)*
Black	419 (4.3)	52 (3.2)*	59 (1.6)*		10 (2.7)*
Asian	2,726 (27.7)	194 (11.8)*	327 (8.7)*		61 (16.5)*
Other	1,103 (11.2)	92 (5.6)*	251 (6.7)*		29 (7.9)*
Systolic blood pressure, mm Hg	121.9 ± 16.8	123.0 ± 17.4†	123.5 ± 16.3*	0.307	124.0 ± 17.7†
Heart rate, beats/min	71.1 ± 11.3	69.8 ± 12.5*	75.4 ± 13.6*	<0.001	69.5 ± 12.0†
eGFR, ml/min/1.73 m^2	72.7 ± 22.1	64.2 ± 18.5*	67.7 ± 23.0*	<0.001	70.5 ± 23.1†
Ischemic HF etiology	5,915 (60.2)	1,046 (63.6)†	1,907 (50.6)*	<0.001	225 (61.0)
Ejection fraction, %	28.5 ± 6.0	29.1 ± 6.1*	30.3 ± 5.6*	<0.001	29.2 ± 6.1†
BMI, kg/m^2	27.2 ± 5.4	28.4 ± 5.3*	29.1 ± 5.4*	<0.001	28.5 ± 5.2*
BMI category				<0.001	
<18.5 kg/m^2	266 (2.7)	15 (0.9)*	23 (0.6)*		4 (1.1)*
18.5–24.9 kg/m^2	3,293 (33.6)	435 (26.5)*	802 (21.3)*		79 (21.4)*
25–29.9 kg/m^2	3,688 (37.6)	644 (39.2)*	1,460 (38.8)*		167 (45.3)*
≥30 kg/m^2	2,565 (26.1)	549 (33.4)*	1,475 (39.2)*		119 (32.2)*
NYHA functional class				<0.001	
I	446 (4.5)	42 (2.6)*	72 (1.9)*		14 (3.8)
II	7,207 (73.4)	1,133 (69.0)*	2,298 (61.0)*		260 (70.5)
III	2,108 (21.5)	455 (27.7)*	1,352 (35.9)*		91 (24.7)
IV	61 (0.6)	12 (0.7)*	44 (1.2)*		4 (1.1)
Duration of HF				0.861	
≤1 yr	3,517 (35.8)	399 (24.3)	925 (24.5)*		80 (21.7)*
1–5 yrs	3,675 (37.4)	624 (37.9)*	1,449 (38.4)*		144 (39.1)*
>5 yrs	2,632 (26.8)	622 (37.8)*	1,396 (37.0)*		144 (39.1)*
Current smoking	1,516 (15.4)	195 (11.9)†	377 (10.0)*	0.041	46 (12.5)

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and stroke (HR: 1.91; 95% CI: 1.08 to 3.38; p = 0.026). The median time from new onset AF to HF hospitalization in those experiencing this event was 131 (interquartile range [IQR]: 43 to 454) days.

Sensitivity analysis: reclassifying patients with persistent AF but no AF in the baseline ECG. Among patients with persistent AF, 543 (14.4%) did not have AF on the baseline ECG. If these patients were reclassified as patients with paroxysmal AF, paroxysmal AF remained associated with an increased risk of HF hospitalization compared with patients with no AF (HR: 1.28; 95% CI: 1.15 to 1.43; p < 0.001), and compared with patients with persistent or permanent AF (HR: 1.42; 95% CI: 1.25 to 1.62; p < 0.001). However, the higher risk of stroke in patients with paroxysmal AF versus those with no AF was no longer statistically significant (HR: 1.21; 95% CI: 0.94 to 1.57; p = 0.15). Associations between type of AF and outcomes otherwise remained generally unchanged (Online Table 2).

DISCUSSION

We investigated the association between AF and outcomes in HFrEF. We found that, after adjustment for other prognostic variables, including natriuretic peptides, paroxysmal, but not persistent or permanent AF, was associated with a higher risk of the composite outcome of HF hospitalization or death from cardiovascular causes (**Central Illustration**). The higher risk was primarily related to an elevated risk of hospital admission for worsening HF. Paroxysmal AF was also

TABLE 1 Continued

	AF Type at Randomization				
	No AF (n = 9,828)	Paroxysmal (I) (n = 1,645)	Persistent/Permanent (II) (n = 3,770)	p Value (I vs. II)	New Onset AF (n = 369)
History of					
Hypertension	6,120 (62.3)	1,190 (72.3)*	2,848 (75.5)*	0.013	241 (65.3)
Diabetes	3,108 (31.6)	532 (32.3)	1,160 (30.8)	0.251	97 (26.3)†
Myocardial infarction	4,469 (45.5)	809 (49.2)†	1,130 (30.0)*	<0.001	184 (49.9)
Heart failure hospitalization	5,767 (58.7)	1,090 (66.3)*	2,480 (65.8)*	0.732	217 (58.8)
Stroke	635 (6.5)	180 (10.9)*	388 (10.3)*	0.473	20 (5.4)
COPD	1,050 (10.7)	265 (16.1)*	525 (13.9)*	0.036	43 (11.7)
Cancer	366 (3.7)	96 (5.8)*	190 (5.0)†	0.228	19 (5.1)
Renal disease	1,032 (10.5)	359 (21.8)*	651 (17.3)*	<0.001	49 (13.3)
Medications at baseline					
Beta-blocker	9,094 (92.5)	1,508 (91.7)	3,484 (92.4)	0.349	350 (94.9)
Aldosterone antagonist	4,597 (46.8)	768 (46.7)	1,825 (48.4)	0.244	159 (43.1)
Diuretic	7,642 (77.8)	1,319 (80.2)†	3,228 (85.6)*	<0.001	291 (78.9)
Digoxin	2,337 (23.8)	472 (28.7)*	1,916 (50.8)*	<0.001	88 (23.8)
Amiodarone	693 (7.1)	410 (24.9)*	328 (8.7)†	<0.001	19 (5.1)
Statins	5,623 (57.2)	997 (60.6)†	1,683 (44.6)*	<0.001	213 (57.7)
Anticoagulative therapy	1,172 (11.9)	874 (53.1)*	2,685 (71.2)*	<0.001	59 (16.0)†
Aspirin	6,032 (61.4)	769 (46.7)*	1,066 (28.3)*	<0.001	230 (62.3)
Other antiplatelet	1,689 (17.2)	192 (11.7)*	226 (6.0)*	<0.001	45 (12.2)†
Any antiplatelet	6,491 (66.0)	836 (50.8)*	1,185 (31.4)*	<0.001	250 (67.8)
ICD	1,132 (11.5)	324 (19.7)*	339 (9.0)*	<0.001	64 (17.3)†
CRT	546 (5.6)	200 (12.2)*	207 (5.5)	<0.001	26 (7.0)
NT-proBNP, pg/ml	1,244 (694–2,521)	1,474 (774–2,876)*	1,801 (1,096–3,200)*	<0.001	1,694 (819–3,154)*
KCCQ clinical summary score‡	82.3 (65.6–92.7)	77.1 (60.4–89.6)*	74.0 (56.3–87.5)*		79.2 (63.5–91.7)*
CHA_2DS_2-VASc	3.5 ± 1.7	4.1 ± 1.8*	3.9 ± 1.8*	0.005	3.6 ± 1.8
CHA_2DS_2-VASc score ≥2	8,816 (89.7)	1,561 (94.9)*	3,507 (93.0)*	0.01	331 (89.7)

Values are mean ± SD, n (%), or median (interquartile range). A total of 66 patients had unspecified type of atrial fibrillation (AF) and an additional 106 had a history of atrial flutter or atrial flutter on their electrocardiogram at randomization and are not included in the table. Patients with new onset AF were compared with patients with no AF at randomization and during follow-up (n = 9,459). *p < 0.001 for comparison with no AF. †p < 0.05 for comparison with no AF. ‡Missing in 1,862 patients.

BMI = body mass index; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years; diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

associated with a higher risk of stroke but persistent or permanent AF was not; however, approximately three-quarters of patients with persistent AF were treated with an oral anticoagulant, whereas only around one-half of patients with paroxysmal AF were. Last, new onset (incident) AF conferred the greatest risk of all, being associated with a higher risk both of hospitalization and death, as well as of stroke.

Prior studies have reported conflicting findings as to whether AF is an independent predictor of adverse outcomes (3–5,12–19). This conflict has been thought to reflect the varying level of adjustment for other prognostic variables as patients with AF have generally been older, had more severe HF, and more comorbidity than did those without AF. This has led to debate about whether AF is just a marker of more advanced disease in sicker patients, rather than an independent prognostic risk factor. When we examined all patients with a history of AF we found a similar picture to that described previously, although LVEF was slightly higher in patients with AF compared to those without. However, when we compared patients with paroxysmal AF to those with persistent or permanent AF, important differences emerged. Patients with paroxysmal AF generally had less evidence of advanced HF and less comorbidity, with a risk profile intermediate between individuals without AF and those with persistent or permanent AF (although patients with paroxysmal AF had the highest prevalence of coronary artery disease of all groups examined). Despite this, patients with paroxysmal AF exhibited a higher crude and adjusted rate of HF hospitalization.

A unique aspect of the present study was the measurement of NT-proBNP at baseline. This is important because natriuretic peptides are the single

TABLE 2 Risk of Different Endpoints According to AF Type at Randomization

	Events	Crude Rate per 100 PY (95% CI)	Unadjusted HR (95% CI)	p Value	Model 1 HR (95% CI)	p Value	Model 2 HR (95% CI)	p Value
Primary composite								
No AF	2,572	11.0 (10.6–11.4)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Persistent/permanent AF	1,110	12.5 (11.7–13.2)	1.14 (1.06–1.22)	<0.001	1.04 (0.97–1.13)	0.273	0.94 (0.87–1.02)	0.138
Paroxysmal AF	544	14.4 (13.2–15.6)	1.31 (1.19–1.43)	<0.001	1.23 (1.11–1.35)	<0.001	1.20 (1.09–1.32)	<0.001
New onset AF	97	25.6 (21.0–31.3)	2.64 (2.15–3.24)	<0.001	2.53 (2.06–3.10)	<0.001	2.21 (1.80–2.71)	<0.001
HF hospitalization								
No AF	1,415	6.0 (5.7–6.4)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Persistent/permanent AF	639	7.2 (6.6–7.7)	1.19 (1.08–1.31)	<0.001	1.04 (0.94–1.16)	0.411	0.94 (0.85–1.04)	0.239
Paroxysmal AF	364	9.6 (8.7–10.7)	1.59 (1.42–1.78)	<0.001	1.37 (1.22–1.55)	<0.001	1.34 (1.19–1.51)	<0.001
New onset AF	50	13.2 (10–17.4)	2.67 (2.01–3.54)	<0.001	2.42 (1.82–3.23)	<0.001	2.11 (1.58–2.81)	<0.001
CV death								
No AF	1,665	6.6 (6.3–6.9)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Persistent/permanent AF	737	7.5 (7.0–8.1)	1.14 (1.05–1.24)	0.003	1.08 (0.98–1.19)	0.11	0.97 (0.88–1.07)	0.555
Paroxysmal AF	319	7.5 (6.7–8.4)	1.14 (1.01–1.28)	0.037	1.11 (0.98–1.26)	0.088	1.09 (0.97–1.24)	0.156
New onset AF	100	19.0 (15.6–23.1)	2.77 (2.26–3.39)	<0.001	2.77 (2.26–3.41)	<0.001	2.43 (1.97–2.98)	<0.001
Pump failure death								
No AF	353	1.4 (1.3–1.6)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Persistent/permanent AF	209	2.1 (1.9–2.5)	1.52 (1.28–1.81)	<0.001	1.31 (1.09–1.59)	0.005	1.13 (0.94–1.37)	0.193
Paroxysmal AF	112	2.6 (2.2–3.2)	1.88 (1.52–2.32)	<0.001	1.58 (1.27–1.97)	<0.001	1.53 (1.22–1.91)	<0.001
New onset AF	39	7.4 (5.4–10.1)	4.84 (3.46–6.77)	<0.001	4.42 (3.15–6.20)	<0.001	3.70 (2.63–5.21)	<0.001
Sudden death								
No AF	783	3.1 (2.9–3.3)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Persistent/permanent AF	279	2.9 (2.5–3.2)	0.92 (0.80–1.05)	0.229	0.98 (0.84–1.14)	0.797	0.89 (0.76–1.04)	0.142
Paroxysmal AF	107	2.5 (2.1–3.0)	0.81 (0.66–0.99)	0.043	0.92 (0.74–1.13)	0.405	0.90 (0.73–1.11)	0.319
New onset AF	29	5.5 (3.8–7.9)	2.05 (1.41–2.98)	<0.001	2.20 (1.51–3.20)	<0.001	1.95 (1.34–2.84)	0.001
All-cause mortality								
No AF	1,979	7.9 (7.5–8.2)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Persistent/permanent AF	898	9.2 (8.6–9.8)	1.17 (1.08–1.26)	<0.001	1.06 (0.97–1.15)	0.216	0.95 (0.87–1.04)	0.302
Paroxysmal AF	391	9.2 (8.3–10.2)	1.17 (1.05–1.31)	0.004	1.10 (0.98–1.23)	0.092	1.08 (0.96–1.21)	0.186
New onset AF	114	21.6 (18–26)	2.62 (2.17–3.18)	<0.001	2.56 (2.11–3.10)	<0.001	2.26 (1.86–2.74)	<0.001
Stroke								
No AF	278	1.1 (1.0–1.3)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Persistent/permanent AF	135	1.4 (1.2–1.7)	1.25 (1.02–1.54)	0.031	1.11 (0.88–1.40)	0.373	1.04 (0.83–1.32)	0.715
Paroxysmal AF	68	1.6 (1.3–2.1)	1.46 (1.12–1.91)	0.005	1.36 (1.03–1.79)	0.029	1.34 (1.02–1.76)	0.037
New onset AF	13	2.6 (1.5–4.4)	2.27 (1.30–3.98)	0.004	2.36 (1.34–4.16)	0.003	2.20 (1.25–3.88)	0.006

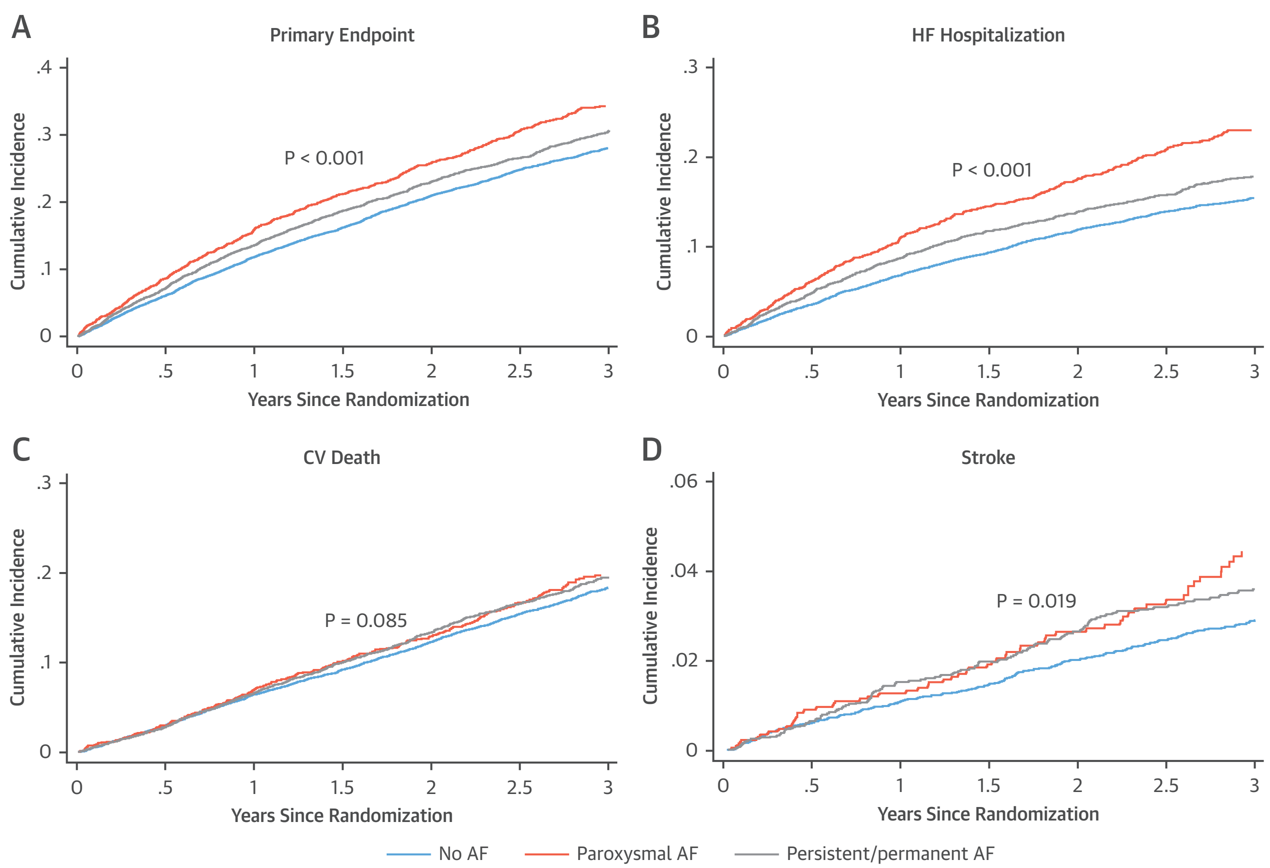
Model 1: age, sex, region, race, NYHA functional class, ejection fraction, heart rate, systolic blood pressure, eGFR, diabetes, BMI, time since HF diagnosis, history of HF hospitalization, history of myocardial infarction, history of stroke, and randomized treatment (enalapril, sacubitril/valsartan, aliskiren, or combination). Model 2: Model 1 + log NT-proBNP. A total of 172 patients had AF of unspecified type or atrial flutter at randomization and are not included above.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; PY = person-years; other abbreviations as in Table 1.

most powerful predictor of outcomes in HF, but no prior study in patients with chronic HFrEF has been able to adjust for natriuretic peptide concentration when examining the prognostic impact of AF. Even after incorporating NT-proBNP in our multivariable risk models, paroxysmal (but not persistent or permanent AF) remained an independent predictor of HF hospitalization as well as pump-failure death. We are not aware of any robust prior analysis of the risk associated with these 2 different types of AF in chronic HFrEF. In 1 small study of hospitalized HF patients in Japan, HF rehospitalization was more common among the 28 individuals with paroxysmal AF, compared with 103 patients with chronic AF and 239 patients in sinus rhythm (20). However, these findings were not confirmed in a later similarly small study from the same investigators (21).

Why paroxysmal (as opposed to persistent or permanent) AF is associated with this increased risk is uncertain. It is possible that paroxysms of AF are a reflection of HF instability more generally (e.g., rises in atrial pressure precipitating both episodes of AF and decompensation leading to hospital admission). In addition, or alternatively, patients with paroxysmal AF (as opposed to persistent or permanent AF) may receive less treatment to control the ventricular rate.

FIGURE 1 **Cumulative Incidence of Outcomes According to Type of AF at Randomization**



The cumulative incidence of **(A)** the primary composite endpoint (cardiovascular [CV] death or heart failure [HF] hospitalization), **(B)** HF hospitalization, **(C)** CV death, and **(D)** stroke accounting for death as a competing risk. The p values for comparison of the cumulative incidence functions according to type of atrial fibrillation (AF) (AF at randomization no AF, paroxysmal AF, or persistent or permanent AF) are based on Gray's test. As illustrated, patients with paroxysmal AF had the highest incidence of the primary endpoint, primarily driven by a higher rate of HF hospitalization. Patients with both types of AF versus no AF had higher incidence of stroke.

Although the rate of use of beta-blocker was similar, the rate of use of digoxin in patients with paroxysmal AF was just over one-half of that in patients with persistent or permanent AF. Digoxin added to a beta-blocker does provide better control of the ventricular rate in AF (22). Although a trial comparing more to less strict rate control in AF did not show an advantage to the former, it really asked a different question (i.e., it asked about modest differences in ventricular rate in patients with persistent or permanent AF as opposed to prophylactic treatment in patients at risk of paroxysms of potentially very rapid ventricular rate and associated detrimental hemodynamic changes) (23). Moreover, only 287 patients in that trial had HF and most had preserved rather than reduced ejection fraction. Likewise, in the 1 large trial in HF comparing a strategy of rhythm control with one of rate control, only one-third of patients (~430) had paroxysmal AF (24). Therefore, it remains possible that prevention of paroxysms of AF by catheter ablation might reduce the risk of decompensation in patients with HFrEF and the value of this treatment is presently being evaluated in a number of clinical trials (25).

Of note, new onset AF carried the greatest risk of all, including a heightened risk of death. Although the number of patients and events in this category was relatively small, we believe that it is real and has been reported previously (4,6,26). Again the reasons for this are uncertain, although the same considerations discussed in relation to paroxysmal AF may apply.

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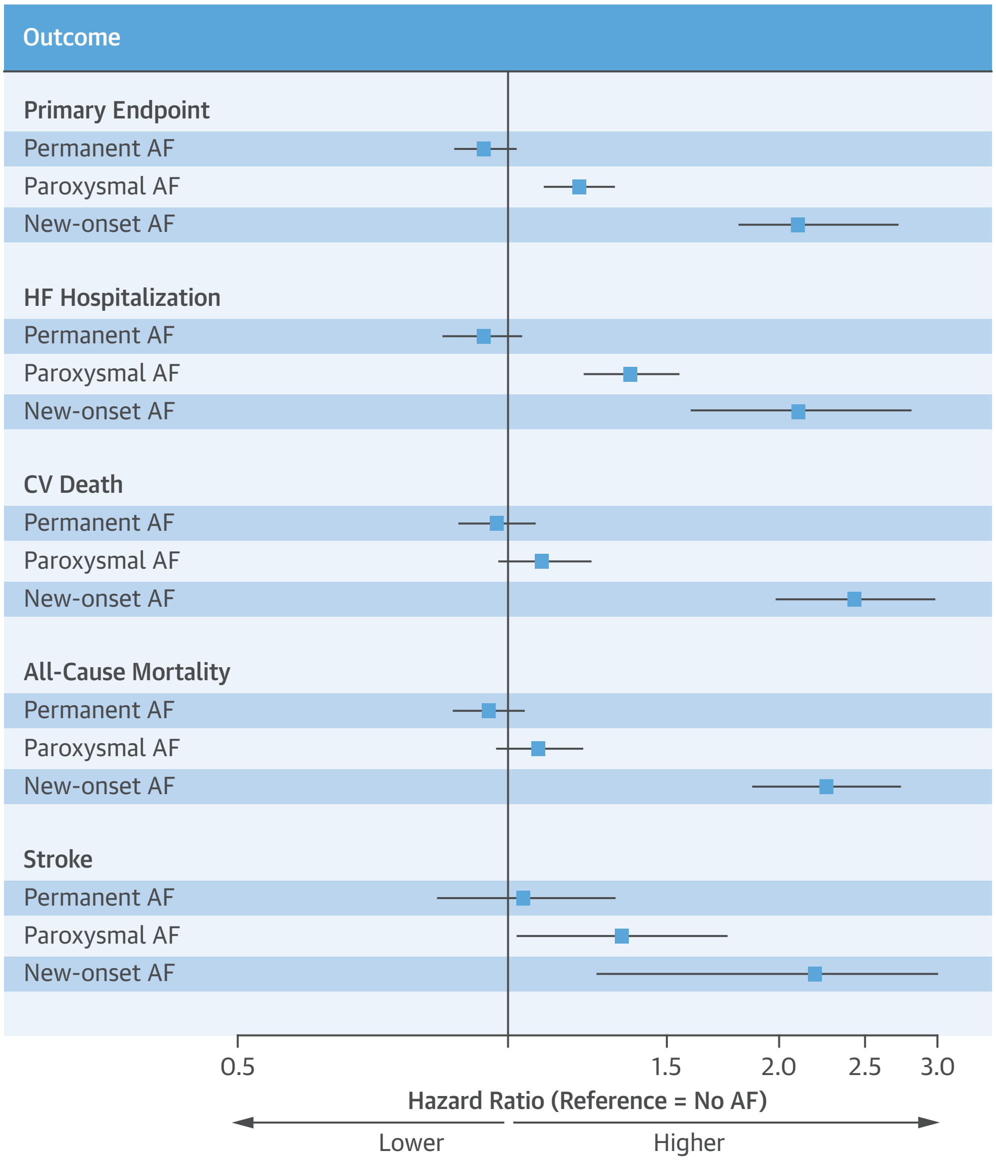
CENTRAL ILLUSTRATION Type of AF at Randomization Compared With Patients Without AF: HRs of Outcomes



Mogensen, U.M. et al. J Am Coll Cardiol. 2017;70(20):2490-500.

Hazard ratios (HRs) of outcomes according to type of atrial fibrillation (AF) using no AF as reference. HRs with 95% confidence intervals were calculated using cause-specific Cox models, adjusted for age, sex, region, race, New York Heart Association functional class, ejection fraction, heart rate, systolic blood pressure, estimated glomerular filtration rate, diabetes, body mass index, time since HF diagnosis, history of HF hospitalization, history of myocardial infarction, history of stroke, log N-terminal pro-B-type natriuretic peptide, and randomized treatment (enalapril, sacubitril/valsartan, aliskiren, or combination). The p values are for difference between paroxysmal and persistent or permanent AF. CV = cardiovascular.

Our findings reinforce the value of using HF treatments that also reduce the risk of new onset AF, specifically renin-angiotensin system antagonists, mineralocorticoid receptor antagonists, and beta-blockers (27-29).

Both new onset AF and paroxysmal AF were also associated with an increased risk of stroke compared with no AF and persistent or permanent AF. The greater risk associated with new onset AF and paroxysmal AF presumably, at least in part, reflects the much lower use of oral anticoagulants in these patients. Although low use of oral anticoagulants is understandable in the patients with incident AF, it is less so in patients with paroxysmal AF. The latter patients had at least as high an average CHA_2DS_2-VASc score as did individuals with persistent or permanent AF, and guidelines recommend use of oral anticoagulants in both types of AF to reduce the risk of thromboembolism (30). Although more than 90% of patients with each type of AF had a CHA_2DS_2-VASc score ≥2 (i.e., an indication for anticoagulation), only 71% of those with persistent or permanent AF and 53% of those with paroxysmal AF were actually treated with an anticoagulant. This large gap between the ideal and reality clearly demonstrates the considerable potential benefit of greater use of anticoagulant therapy in patients with HF and paroxysmal AF.

STUDY LIMITATIONS. The analyses of paroxysmal versus persistent or permanent AF were not planned prospectively. The trial inclusion and exclusion criteria limit the generalizability of our findings results, for example, to patients with severe renal impairment or HF with preserved ejection fraction. Patient history of AF was investigator reported and it is possible that some patients said not to have AF may have had undiagnosed paroxysmal AF and AF type might have been misclassified in some patients. Similarly, serial ECG monitoring might have identified more incident AF than was reported by investigators. Information on duration of AF at randomization was not available. Finally, the number of patients with new onset AF was relatively small, and these patients also had relatively few events during follow-up.

CONCLUSIONS

Among HF patients with a history of AF, we found those with paroxysmal AF were at greater risk of HF hospitalization. Paroxysmal AF was also associated with a greater risk of stroke than in patients with persistent or permanent AF, underlining the importance of anticoagulant therapy in these patients. New onset AF was associated with the greatest risk of all and should prompt immediate consideration of anticoagulant therapy as well as close surveillance for evidence of decompensation and treatment as appropriate.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with HFrEF, those with newly identified AF and paroxysmal AF, rather than persistent or permanent AF, are at higher risk of adverse outcomes, including hospitalization for worsening HF and stroke, but not mortality.

TRANSLATIONAL OUTLOOK: Further studies are needed to explore strategies to prevent adverse outcomes, including stroke, in patients with HFrEF by identifying those most likely to develop AF.

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KEY WORDS atrial fibrillation, heart failure, mortality, paroxysmal, stroke

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