Atrial Fibrillation can adversely impact Heart Failure with Preserved Ejection Fraction by its association with Heart Failure Progression and Mortality : A Post-Hoc Propensity Score-Matched Analysis of the TOPCAT Americas Trial

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CLINICAL RESEARCH

Atrial Fibrillation can adversely impact Heart Failure with Preserved Ejection Fraction by its association with Heart Failure Progression and Mortality: A Post-Hoc Propensity Score–Matched Analysis of the TOPCAT Americas Trial

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Aims Prevalent atrial fibrillation (AF) is associated with excess cardiovascular (CV) death (D) and hospitalizations (H) in heart failure (HF) with preserved ejection fraction (pEF). We evaluated if it had an independent role in excess CVD in HFpEF and studied its impact on cause-specific mortality and HF morbidity.

Methods and results We used propensity score–matched (PSM) cohorts from the TOPCAT Americas trial to account for confounding by other co-morbidities. Two prevalent AF presentations at study entry were compared: (i) subjects with Any AF event by history or on electrocardiogram (ECG) with PSM subjects without an AF event and (ii) subjects in AF on ECG with PSM subjects in sinus rhythm. We analyzed cause-specific modes of death and HF morbidity during a mean follow-up period of 2.9 years. A total of 584 subjects with Any AF event and 418 subjects in AF on ECG were matched. Any AF was associated with increased CVH [hazard ratio (HR) 1.33, 95% confidence interval (CI) 1.11–1.61, $P = 0.003$], HFH (HR 1.44, 95% CI 1.12–1.86, $P = 0.004$), pump failure death (PFD) (HR 1.95, 95% CI 1.05–3.62, $P = 0.035$), and HF progression from New York Heart Association (NYHA) classes I/II to III/IV (HR 1.30, 95% CI 1.04–1.62, $P = 0.02$). Atrial fibrillation on ECG was associated with increased risk of CVD (HR 1.46, 95% CI 1.02–2.09, $P = 0.039$), PFD (HR 2.21, 95% CI 1.11–4.40, $P = 0.024$), and CVH and HFH (HR 1.37, 95% CI 1.09–1.72, $P = 0.006$ and HR 1.65, 95% CI 1.22–2.23, $P = 0.001$, respectively). Atrial fibrillation was not associated with risk of sudden death. Both Any AF and AF on ECG cohorts were associated with PFD in NYHA class III/IV HF.

Conclusion Prevalent AF can be an independent risk factor for adverse CV outcomes by its selective association with worsening HF, HFH, and PFD in HFpEF. Prevalent AF was not associated with excess sudden death risk in HFpEF. Atrial fibrillation was also associated with HF progression in early symptomatic HFpEF and PFD in advanced HFpEF.

Trial registration TOPCAT trial is registered at www.clinicaltrials.gov:identifier NCT00094302.

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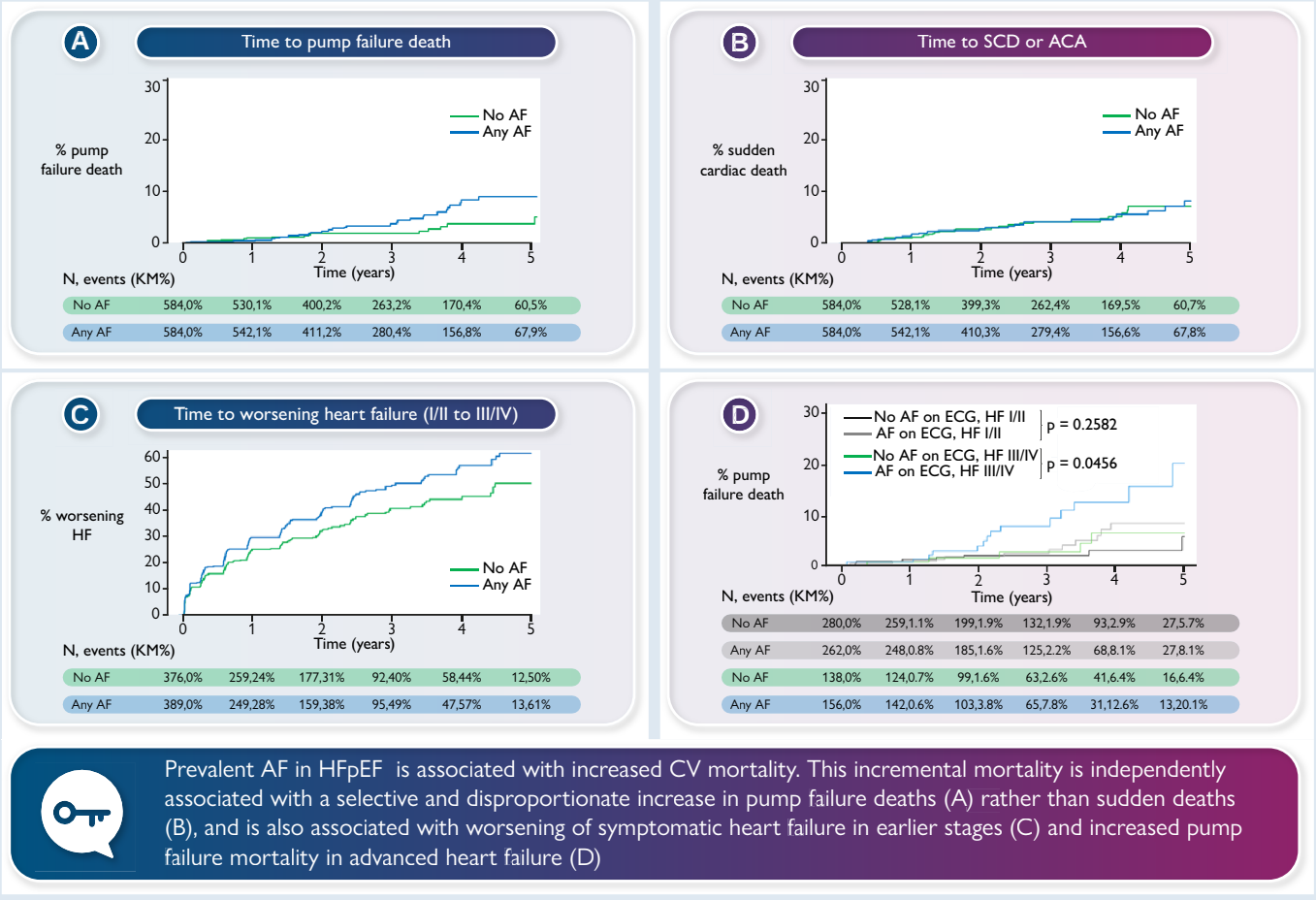
Graphical Abstract



Keywords Atrial fibrillation • Heart failure with preserved ejection fraction • Cardiovascular mortality • Arrhythmias • Sudden death • Antiarrhythmic therapy • Clinical trials • Outcomes research

What's new?

- Atrial fibrillation (AF) in heart failure with preserved ejection fraction (HFpEF) has not been critically analyzed to determine if it has independent impact on cause-specific cardiovascular (CV) mortality in clinical trials, especially with different AF presentations that have varying AF burden. This post-hoc analysis of the TOPCAT Americas trial uses propensity score matching to address confounding from disease state variables. It delineates AF as having an independent association with, rather than just a marker for, increased CV mortality and morbidity.
- Atrial fibrillation presentations are strongly associated with risk of HF progression, HF and CV hospitalization, and increased death due to pump failure. Atrial fibrillation was not independently associated with incremental sudden death in HFpEF.
- Atrial fibrillation was associated with symptomatic HF progression in early stages of HFpEF and increased pump mortality in advanced symptomatic HFpEF.
- In HFpEF, AF and its burden may be associated with observed adverse CV outcomes that are related to advancing HF.

Introduction

Atrial fibrillation (AF) is a frequent concomitant event in heart failure patients with preserved ejection fraction. Several studies have shown that its presence adversely impacts cardiovascular (CV) outcomes.[1,2] While AF with heart failure with preserved ejection fraction (HFpEF) constitutes nearly one-half of the HFpEF population, AF has rarely been examined as to its potential role in HFpEF outcomes. Increased stroke risk has not explained the adverse CV outcomes. Whether prevalent AF reflects only an advanced HFpEF disease state or is an independent CV risk factor associated with additional risk(s) beyond stroke is unknown. Furthermore, its relationship to AF presentation has not been critically studied.

We hypothesized that examining cause-specific modes of death and HF progression with AF would provide insights into its adverse impact in HFpEF. We analyzed The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone antagonist (TOPCAT) Americas study population with and without AF to study the role of prevalent AF and the impact of different AF presentations. Two sets of analyses

were performed, viz., from subjects enrolled in the study *in toto* and after propensity score matching to obtained matched cohorts with and without AF.

Methods

Patient population

The TOPCAT trial recruited consenting subjects who met clinical and/or biomarker criteria for HFpEF. The study design, institutional approval, and primary outcomes have been reported.[3,4] These current analyses were covered by the original consent and review by the New England Institutional Review Board. Eligible subjects included men and women at least 50 years old with symptomatic [New York Heart Association (NYHA) classes II–IV] HF, left ventricular ejection fraction (LVEF) ≥ 45%, and either a hospitalization for HF within the year prior or an elevated natriuretic peptide level [B-type natriuretic peptide (BNP) ≥ 100 pg/mL or N-terminal pro-BNP ≥360 pg/mL] within the 60 days before randomization. There were significant regional differences, and this study examined subjects from the Americas in order to minimize them.[5,6] A medical history, physical examination, electrocardiogram (ECG), and review of prior medical records were performed. Arrhythmias on history, examination, and ECG were reported by the investigator. In addition, a detailed medication record was obtained and anticoagulant use patterns noted. During follow-up, clinic visits with NYHA assessment occurred at 2 and 4 months and thereafter every 4 months. Subjects were censored at the last follow-up visit. The TOPCAT primary outcome was a composite of CV mortality, aborted cardiac arrest, and hospitalization for heart failure.

Prevalent atrial fibrillation presentation-based cohorts

Heart failure with preserved ejection fraction subjects included in this analysis had either a history of AF prior to enrollment or AF on ECG at baseline evaluation.

(1) Subjects manifesting AF *prior to or at* study entry referred to as the 'Any AF' group.
(2) In subjects with an ongoing AF: This subgroup manifested AF on the enrollment ECG referred to hereafter as the 'AF on ECG' group.

These AF cohorts initially were identified in the entire study population and compared with the remaining HFpEF subjects. These cohorts are referred to as the full cohorts. Subsequently, propensity score–matched (PSM) cohorts for each AF presentation and matched subjects were developed. The 'Any AF' group was compared with matched subjects without AF on history or enrollment ECG. The 'AF on ECG' group was compared with matched subjects without AF on enrollment ECG only.

Definitions

Time to CV death, CV hospitalization, HF hospitalization, and pump failure death (PFD) were defined using the original TOPCAT definitions.[4] Pump failure death was defined as death occurring within the context of clinically worsening symptoms and/or signs of HF without evidence of another cause of death. Sudden death (SD) was defined as death that occurred unexpectedly in an otherwise stable subject (i.e. occurring instantaneously or within ≤ 24 h). The type of SD was further subclassified as being either witnessed or subject last seen ≥1 and <24 h. Aborted cardiac arrest was deemed a sudden mortal event and included. The data set collapses NYHA classes into I or II vs. III or IV, so additional granularity in HF changes was not possible. Worsening HF was defined *only* for subjects with baseline NYHA class I or II HF at enrollment as previously indicated. Event time for worsening HF was defined as the time from randomization to the first visit at which NYHA class III or IV HF was reported. The two HF strata were also analyzed for these outcome measures. Any SD was defined as a composite of SD and aborted cardiac arrest.

Study outcomes

The principal outcome in this report was CV mortality. We specifically also analyzed components of CV mortality using adjudicated modes of death as well as non-CV mortality. Modes of death were tabulated based on adjudication of all events by a blinded independent Clinical Events Committee.[5,6] Death due to CV causes (D), CV hospitalization (CVH), and HF hospitalizations (HFH) were analyzed. Cardiovascular deaths were categorized as PFD, SD, or other CV causes and were examined in early and advanced HF strata and with the two different AF presentations. Components of CV morbidity in HFpEF, such as CVH and HFH and HF progression are reported. All CV outcomes analyzed were compared in the matched and full cohorts.

Propensity score matching for post hoc analysis

The goal of development of PSM cohorts was to account for possible confounding, because the subjects in AF were fundamentally different from the subjects in sinus rhythm at baseline. Covariates that might be individually related to baseline rhythm included demographics, co-morbidities, medical history, and heart failure characteristics. Baseline rate and rhythm control drugs, as well as anticoagulants, were not included, as these were strongly associated with the presence of AF. Propensity score–matched study cohorts were matched for 23 clinical, demographic, and ECG variables. They are summarized in *Tables 1* and *2* column 1.

A propensity score model was developed for Any AF vs. No AF beginning with the 23 baseline covariates displayed in *Tables 1* and *2*. A manual forward selection algorithm was used to fit the propensity score model. First, a logistic regression model was run using SAS version 9.4 (Carry, NC) to obtain propensity scores for all Any AF and No AF subjects. Then, a greedy matching algorithm will be used to identify patients in the No AF subjects who had similar propensity scores to Any AF subjects. Using this algorithm, the No AF patient *j* with the smallest difference in propensity scores was selected as the match for Any AF patient *i*. Operationally, this matching was performed using the GMATCH algorithm. Matching was 1:1 between the Any AF and No AF cohort.

The model acceptance criteria were (i) no standardized mean difference (SMD) values larger than 0.1 and (ii) no *P*-values smaller than 0.2. SMDs were calculated for continuous and binary variables using standard methods. SMD for categorical variables was calculated using the method described by Dalton, which is essentially considering a single multinomial variable to be multiple non-redundant dichotomous variables and using the Mahalanobis distance to calculate the SMD. Operationally, this calculation was performed using the Table One, version 0.13.2. *P*-values were calculated using Fisher's exact test or the χ^2 test for categorical variables and *t*-tests for continuous variables. If the largest SMD exceeded the threshold of 0.1, or the smallest *P*-value was less than 0.2, then the covariate with the smallest *F*-statistic was removed from the model and the process was repeated until the acceptance criteria were met. The same algorithm was followed to generate a PSM cohort for the AF on ECG and No AF on ECG groups.

Statistical methods

Once the PSM cohorts were established, baseline demographic and clinical characteristics were tabulated along with the full cohorts in the entire study population. Tests for differences across matched and full cohorts were conducted as described above for comparison of the PSM cohorts.

Unadjusted Kaplan–Meier survival curves were examined for each PSM cohort pair. Proportional hazards models were used to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). All *P*-values and CIs are two sided. No adjustments were made to account for multiple endpoints. As this was a post hoc analysis, values should be considered descriptive and not used for statistical inference. SAS version 9.4 and R version 3.6.2 were used for analysis.

Results

Patient population

A total of 1767 subjects were enrolled in the TOPCAT Americas study and were followed for a mean of 2.9 years. A total of 1765 subjects had baseline ECGs and LVEF measurements and were included in this analysis for the full cohorts. *Table 1* shows the baseline characteristics included in the propensity score model for the 'Any AF' cohort

Table 1 Baseline demographic, clinical, and electrocardiographic characteristics included in propensity score model: full (unmatched) and propensity score–matched cohorts—'Any AF' vs. 'No AF'

Baseline characteristic		Full cohort			PSM cohort		
		Any AF ($n = 760$)	No AF ($n = 1005$)	*P*-value	Any AF ($n = 584$)	No AF ($n = 584$)	*P*-value
Age (years)	Mean ± SD	74.0 ± 8.60	69.7 ± 10.0	**<0.001**	72.7 ± 8.58	73.1 ± 9.54	0.411
Female		345 (46.1%)	517 (52.8%)	**0.007**	272 (46.6%)	273 (46.7%)	1.000
Minority race		103 (13.8%)	270 (27.6%)	**<0.001**	97 (16.6%)	99 (17.0%)	0.938
Baseline NYHA class	I/II	487 (65.1%)	633 (64.7%)	0.879	392 (67.1%)	386 (66.1%)	0.756
	III/IV	261 (34.9%)	346 (35.3%)		192 (32.9%)	198 (33.9%)	
Heart failure hospitalization		378 (49.7%)	579 (57.6%)	**<0.001**	301 (51.5%)	305 (52.2%)	0.861
Met BNP/NT-pro-BNP elevation criteria		532 (71.1%)	573 (58.5%)	**<0.001**	414 (70.9%)	362 (62.0%)	**0.002**
History of MI		137 (18.3%)	215 (22.0%)	0.070	116 (19.9%)	117 (20.0%)	1.000
History of stroke		74 (9.9%)	84 (8.6%)	0.355	54 (9.2%)	50 (8.6%)	0.758
Coronary artery bypass graft		132 (17.6%)	198 (20.2%)	0.195	110 (18.8%)	112 (19.2%)	0.941
Percutaneous coronary intervention		119 (15.9%)	216 (22.1%)	**0.001**	102 (17.5%)	106 (18.2%)	0.819
Chronic obstructive pulmonary disease		125 (16.7%)	159 (16.2%)	0.794	92 (15.8%)	99 (17.0%)	0.635
Hypertension		663 (88.6%)	891 (91.0%)	0.106	518 (88.7%)	524 (89.7%)	0.637
Diabetes		272 (36.4%)	498 (50.9%)	**<0.001**	244 (41.8%)	242 (41.4%)	0.953
Peripheral arterial disease		72 (9.6%)	130 (13.3%)	**0.019**	62 (10.6%)	64 (11.0%)	0.925
Implantable cardioverter defibrillator		22 (2.9%)	19 (1.9%)	0.203	17 (2.9%)	14 (2.4%)	0.716
Pacemaker implantation		159 (21.3%)	78 (8.0%)	**<0.001**	83 (14.2%)	72 (12.3%)	0.388
Body mass index	Mean ± SD	33.01 ± 7.52	34.37 ± 8.42	**<0.001**	33.60 ± 7.55	33.62 ± 8.32	0.962
Systolic blood pressure (mmHg)	Mean ± SD	124.9 ± 14.69	129.6 ± 16.49	**<0.001**	126.1 ± 14.58	126.3 ± 16.07	0.900
Diastolic blood pressure (mmHg)	Mean ± SD	70.93 ± 10.96	71.71 ± 11.87	0.163	71.40 ± 10.95	70.84 ± 11.62	0.401
Heart rate (b.p.m.)	Mean ± SD	68.95 ± 10.86	69.12 ± 11.58	0.745	68.91 ± 10.75	68.24 ± 11.45	0.303
eGFR	Mean ± SD	62.38 ± 18.83	66.06 ± 23.17	**<0.001**	63.70 ± 19.37	63.04 ± 20.22	0.572
Bundle branch block		146 (19.5%)	185 (18.9%)	0.758	121 (20.7%)	122 (20.9%)	1.000
LV hypertrophy		54 (7.2%)	111 (11.3%)	**0.004**	49 (8.4%)	48 (8.2%)	1.000

AF, atrial fibrillation; NYHA, New York Heart Association; MI, myocardial infarction; LV, left ventriclular; eGFR, glomerular filtration rate; BNP, B type natriuretic peptide; SD, standard deviation. $P<0.05$ was considered significant.

compared with the 'No AF' cohort. Before matching (full cohorts), 760 subjects were classified as having 'Any AF,' with remaining 1005 subjects classified as having 'No AF.' Imbalances were seen in the full cohorts for age, minority status, HFH, percutaneous coronary interventions, diabetes, pacemaker implantation, body mass index (BMI), peripheral arterial disease and estimated glomerular filtration rate (eGFR), systolic blood pressure, and LV hypertrophy. Most of these imbalances indicated more advanced co-morbidities in the 'No AF' cohort. After propensity score matching (PSM), 584 'Any AF' subjects were matched (PSM) with 584 subjects from the 'No AF' cohort. All imbalances were eliminated by matching.

Table 2 shows the analogous summary for the full cohort of 446 subjects who had 'AF on ECG' compared with the 1319 subjects who did not. Imbalances seen in the full cohorts for age, minority status, HFH, myocardial infarction (MI), coronary bypass surgery, percutaneous coronary interventions, diabetes, BMI, peripheral arterial disease, systolic blood pressure, and heart rate also indicated more advanced co-morbidities in the 'No AF on ECG' cohort. After PSM, 418 subjects in 'AF on ECG group' were matched with 418 subjects from the 'No AF on ECG' group, and imbalances were eliminated by matching. Importantly, all comparisons for matched and full cohorts in this analysis were balanced for randomization to spironolactone therapy.

Table 3 shows the usage of CV drugs in the full and PSM 'Any AF' vs. 'No AF' cohorts, and *Table 4* shows the results for the 'AF on ECG' vs. 'No AF on ECG' cohorts. Atrial fibrillation ablation for rhythm control was not employed, and novel oral anticoagulant use was limited in this trial as it was conducted from 2006 to 2012. The use of cardiac drugs such as angiotensin-converting enzyme (ACE)/angiotensin receptor blockers (ARBs), diuretics, statins, and nitrates was highly prevalent in all groups, both before and after PSM. Though the magnitudes of the differences in diuretic and antihypertensive agents were small, they remained significantly higher in the AF PSM cohorts. Anticoagulation was employed in 72.7% of the 'Any AF' cohort and 80.5% of the 'AF on ECG' cohort. In comparison, it was significantly lower (6.2%) in those with 'No AF' ($P = 0.007$) and 19.4% in those with 'No AF on ECG' ($P < 0.001$) possibly reflecting a prior AF event in the latter.

Treatment of AF consisted predominantly of rate control in both AF presentations, with only a small minority of subjects receiving a Class 1 or 3 AAD. Rhythm control AAD therapy was employed in a small minority of subjects with 'Any AF' (15.4%) and even less often in AF on ECG (6.3%). The 9% use of rhythm control AADs in the 'No AF on ECG' group was higher than in those with 'No AF.' Simultaneous use of two or more drugs with rate and rhythm control properties was

Table 2 Baseline demographic, clinical, and electrocardiographic characteristics included in propensity score model: full (unmatched) and propensity score–matched cohorts—'AF on ECG' vs. 'No AF on ECG'

Baseline characteristic		Full cohort			PSM cohort		
		AF on ECG ($n = 446$)	No AF on ECG ($n = 1319$)	*P*-value	AF on ECG ($n = 418$)	No AF on ECG ($n = 418$)	*P*-value
Age (years)	Mean ± SD	74.4 ± 8.31	70.6 ± 9.90	**<0.001**	74.0 ± 8.30	74.1 ± 9.51	0.960
Female		195 (43.8%)	667 (52.0%)	**0.003**	185 (44.3%)	188 (45.0%)	0.889
Minority race		58 (13.0%)	315 (24.6%)	**<0.001**	57 (13.6%)	57 (13.6%)	1.000
Baseline NYHA class	I/II	276 (62.0%)	844 (65.8%)	0.150	262 (62.7%)	280 (67.0%)	0.218
	III/IV	169 (38.0%)	438 (34.2%)		156 (37.3%)	138 (33.0%)	
Heart failure hospitalization		212 (47.5%)	745 (56.5%)	**<0.001**	201 (48.1%)	210 (50.2%)	0.580
Met BNP/NT-pro-BNP elevation criteria		316 (71.0%)	789 (61.5%)	**<0.001**	292 (69.9%)	272 (65.1%)	0.161
History of MI		57 (12.8%)	295 (23.0%)	**<0.001**	56 (13.4%)	59 (14.1%)	0.841
History of stroke		43 (9.7%)	115 (9.0%)	0.703	39 (9.3%)	35 (8.4%)	0.715
Coronary artery bypass graft		59 (13.3%)	271 (21.1%)	**<0.001**	58 (13.9%)	54 (12.9%)	0.761
Percutaneous coronary intervention		54 (12.1%)	281 (21.9%)	**<0.001**	52 (12.4%)	47 (11.2%)	0.669
Chronic obstructive pulmonary disease		68 (15.3%)	216 (16.8%)	0.459	61 (14.6%)	71 (17.0%)	0.393
Hypertension		395 (88.8%)	1159 (90.4%)	0.315	371 (88.8%)	360 (86.1%)	0.297
Diabetes		155 (34.8%)	615 (48.0%)	**<0.001**	151 (36.1%)	155 (37.1%)	0.829
Peripheral arterial disease		34 (7.6%)	168 (13.1%)	**0.002**	33 (7.9%)	32 (7.7%)	1.000
Implantable cardioverter defibrillator		13 (2.9%)	28 (2.2%)	0.370	12 (2.9%)	13 (3.1%)	1.000
Pacemaker implantation		67 (15.1%)	170 (13.3%)	0.338	66 (15.8%)	58 (13.9%)	0.496
Body mass index	Mean ± SD	32.61 ± 7.00	34.18 ± 8.37	**<0.001**	32.61 ± 7.01	33.00 ± 7.82	0.456
Systolic blood pressure (mmHg)	Mean ± SD	123.1 ± 14.24	129.1 ± 16.17	**<0.001**	123.6 ± 14.22	122.9 ± 14.99	0.515
Diastolic blood pressure (mmHg)	Mean ± SD	71.68 ± 11.15	71.27 ± 11.61	0.513	71.72 ± 11.26	71.74 ± 11.46	0.978
Heart rate (b.p.m.)	Mean ± SD	70.41 ± 10.42	68.57 ± 11.51	**0.003**	70.13 ± 10.30	70.01 ± 11.64	0.877
eGFR	Mean ± SD	63.31 ± 18.58	64.87 ± 22.37	0.187	63.51 ± 18.53	64.20 ± 20.87	0.613
Bundle branch block		88 (19.8%)	243 (19.0%)	0.727	83 (19.9%)	87 (20.8%)	0.797
LV hypertrophy		36 (8.1%)	129 (10.1%)	0.261	36 (8.6%)	33 (7.9%)	0.802

AF, atrial fibrillation; BNP, B type natriuretic peptide; eGFR, glomerular filtration rate; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association; SD, standard deviation. $P<0.05$ was considered significant.

very infrequent. There was a very small increase in use of Class 1 or 3 antiarrhythmic drugs during the trial.

Cardiovascular outcomes

Table 5 shows the number of endpoint events and follow-up period for the TOPCAT primary outcome and CV death as well as for each component of the outcomes evaluated for both full and PSM cohorts. Both AF presentations in the full cohorts and PSM cohorts adversely impacted the TOPCAT primary outcome as well as CV mortality. Pump failure deaths exceeded SCD as a proportion of CV deaths in both AF cohorts, but not in subjects without AF. Worsening HF events and HFH were both proportionally higher with both AF presentations.

Cardiovascular mortality and hospitalizations in heart failure with preserved ejection fraction with and without atrial fibrillation

Figure 1A shows time to CV mortality for the PSM cohorts of both AF presentations. Propensity score–matched subjects with 'Any AF' had a higher CV mortality risk than those with 'No AF' (25% vs. 19%, respectively, at Year 5). Similarly, CV mortality was higher in PSM subjects with 'AF on ECG' than those in sinus rhythm on this ECG (30% vs. 19%) at Year 5. Comparing instantaneous risk of CV mortality (*Tables 6* and *7*), the risk was higher for 'Any AF' vs. 'No AF' but did not reach statistical significance (HR 1.33, 95% CI 0.97–1.82, $P = 0.079$). The risk was also increased in the 'AF on ECG' group compared with the 'No AF on ECG' group, which was significant (HR 1.46, 95% CI 1.02–2.09, $P = 0.039$). Very similar findings were seen in the full TOPCAT Americas 'Any AF' and 'AF on ECG' cohorts (see Supplementary material online, *Figure S1A* and *B*).

Cardiovascular hospitalizations at 5-year follow-up for these two AF PSM subgroups were significantly higher than in matched cohorts without AF (*Figure 1B*). Cardiovascular hospitalization occurred in 55% of PSM subjects with 'Any AF' compared with 45% of those with 'No AF' at Year 5. Cardiovascular hospitalization occurred in 30% of subjects with 'AF on ECG' compared with 19% of those with 'No AF on ECG.' The comparison of instantaneous risk of CV hospitalization was significantly increased in both AF presentations (*Tables 6* and *7*, 'Any AF' vs. 'No AF': HR 1.33, 95% CI 1.11–1.61, $P = 0.003$, and 'AF on ECG vs. 'No AF on ECG': HR 1.37, 95% CI 1.09–1.72, $P = 0.006$).

Table 3 Cardiovascular drug therapy at study enrollment for full (unmatched) and propensity score–matched cohorts: 'Any AF' vs. 'No AF'

CV medication	Full cohort			PSM cohort		
	Any AF ($n = 760$)	No AF ($n = 1005$)	*P*-value	Any AF ($n = 584$)	No AF ($n = 584$)	*P*-value
Anticoagulation						
Warfarin	533 (70.1%)	59 (5.9%)	**<0.001**	414 (70.9%)	41 (7.0%)	**<0.001**
NOAC	20 (2.6%)	2 (0.2%)	**<0.001**	15 (2.6%)	1 (0.2%)	**<0.001**
Arrhythmia therapy						
Rate control drug[a]	637 (83.8%)	791 (78.7%)	**0.007**	494 (84.6%)	450 (77.1%)	**0.001**
Class I or Ic AAD	10 (1.3%)	2 (0.2%)	**0.006**	8 (1.4%)	2 (0.3%)	0.108
Class III AAD	107 (14.1%)	27 (2.7%)	**<0.001**	85 (14.6%)	16 (2.7%)	**<0.001**
Rate and rhythm drug	81 (10.7%)	17 (1.7%)	**<0.001**	66 (11.3%)	10 (1.7%)	**<0.001**
Other CV medications						
ACE-I or ARB	597 (78.6%)	797 (79.4%)	0.680	467 (80.0%)	446 (76.5%)	0.157
Diuretic	698 (91.8%)	875 (87.2%)	**0.002**	534 (91.4%)	505 (86.6%)	**0.009**
Beta-blocker	602 (79.2%)	784 (78.1%)	0.598	470 (80.5%)	446 (76.5%)	0.102
Other antihypertensive agents	760 (100.0%)	991 (98.7%)	**<0.001**	584 (100.0%)	575 (98.6%)	**0.004**
Statin	484 (63.7%)	663 (66.0%)	0.314	389 (66.6%)	368 (63.1%)	0.220
Lipid lowering	87 (11.4%)	145 (14.4%)	0.075	73 (12.5%)	85 (14.6%)	0.306
Long-acting nitrate	114 (15.0%)	191 (19.0%)	**0.031**	92 (15.8%)	89 (15.3%)	0.872

ACE-1, angiotensin converting enzyme1 blocking agent; ARB, angiotensin II receptor blocking agent; AD, antiarrhythmic drug. $P<0.05$ was considered significant.
[a]Rate control drugs included Vaughan William Class II and Class IV agents, and digoxin.

Table 4 Cardiovascular drug therapy at study enrollment for full (unmatched) and propensity score–matched cohorts: 'AF on ECG' vs. 'No AF on ECG'

CV medication	Full cohort			PSM cohort		
	AF on ECG ($n = 446$)	No AF on ECG ($n = 1005$)	*P*-value	AF on ECG ($n = 418$)	No AF on ECG ($n = 418$)	*P*-value
Anticoagulation						
Warfarin	346 (77.6%)	246 (18.7%)	**<0.001**	328 (78.5%)	86 (20.6%)	**<0.001**
NOAC	13 (2.9%)	9 (0.7%)	**<0.001**	10 (2.4%)	1 (0.2%)	**0.011**
Arrhythmia therapy						
Rate control drug[a]	383 (85.9%)	1045 (79.2%)	**0.002**	361 (86.4%)	307 (73.4%)	**<0.001**
Class I or Ic AAD	3 (0.7%)	9 (0.7%)	1.000	2 (0.5%)	3 (0.7%)	1.000
Class III AAD	25 (5.6%)	109 (8.3%)	0.078	25 (6.0%)	35 (8.4%)	0.228
Rate and rhythm drug	19 (4.3%)	79 (6.0%)	0.189	19 (4.5%)	23 (5.5%)	0.635
Other CV medications						
ACE-I or ARB	352 (78.9%)	1042 (79.1%)	0.946	332 (79.4%)	307 (73.4%)	0.050
Diuretic	418 (93.7%)	1155 (87.6%)	**<0.001**	394 (94.3%)	358 (85.6%)	**<0.001**
Beta-blocker	358 (80.3%)	1028 (78.0%)	0.350	339 (81.1%)	300 (71.8%)	**0.002**
Other antihypertensive agents	446 (100.0%)	1305 (99.0%)	**0.048**	418 (100.0%)	413 (98.8%)	0.062
Statin	267 (59.9%)	880 (66.8%)	**0.010**	254 (60.8%)	258 (61.7%)	0.831
Lipid lowering	42 (9.4%)	190 (14.4%)	**0.007**	39 (9.3%)	53 (12.7%)	0.150
Long-acting nitrate	54 (12.1%)	251 (19.0%)	**<0.001**	52 (12.4%)	63 (15.1%)	0.315

ACE-1, angiotensin converting enzyme1 blocking agent; ARB, angiotensin II receptor blocking agent; AD, antiarrhythmic drug. $P<0.05$ was considered significant.
[a]Rate control drugs included Vaughan William Class II and Class IV agents, and digoxin.

Table 5 TOPCAT primary outcome events, cardiovascular mortality, cause-specific mortality, and other cardiovascular events for full (unmatched) and propensity score–matched cohorts

	Full cohort		PSM cohort		Full cohort		PSM cohort	
	Any AF (*n* = 760)	No AF (*n* = 1005)	Any AF (*n* = 584)	No AF (*n* = 584)	AF on ECG (*n* = 446)	No AF on ECG (*n* = 1005)	AF on ECG (*n* = 418)	No AF on ECG (*n* = 418)
TOPCAT composite primary endpoint	241 (31.7%)	281 (28.0%)	196 (33.6%)	147 (25.2%)	148 (33.2%)	374 (28.4%)	141 (33.7%)	100 (23.9%)
Cardiovascular death	110 (14.5%)	113 (11.2%)	92 (15.8%)	67 (11.5%)	74 (16.6%)	149 (11.3%)	71 (17.0%)	52 (12.4%)
Any sudden cardiac death	29 (3.8%)	48 (4.8%)	27 (4.6%)	25 (4.3%)	20 (4.5%)	57 (4.3%)	19 (4.5%)	20 (4.8%)
Pump failure death	37 (4.9%)	23 (2.3%)	30 (5.1%)	15 (2.6%)	27 (6.1%)	33 (2.5%)	25 (6.0%)	12 (2.9%)
Cardiovascular hospitalization	309 (40.7%)	380 (37.8%)	250 (42.8%)	197 (33.7%)	178 (39.9%)	511 (38.7%)	170 (40.7%)	136 (32.5%)
Worsening HF (HF I/II to III/IV)	225 (45.6%)	233 (36.0%)	178 (45.4%)	140 (36.3%)	123 (44.4%)	335 (38.8%)	115 (43.9%)	115 (41.1%)
Hospitalization for HF	185 (24.3%)	215 (21.4%)	148 (25.3%)	103 (17.6%)	112 (25.1%)	288 (21.8%)	106 (25.4%)	69 (16.5%)
Follow-up (years)—median (25th–75th %)			3.4 (2.09, 4.53)	3.43 (2.34, 4.53)			3.47 (2.06, 4.90)	3.49 (2.44, 4.57)

AF, atrial fibrillation; HF, heart failure.

These findings were not seen in the full cohorts, though the rate of hospitalizations was higher than in the PSM AF cohorts (see Supplementary material online, *Figure S1C* and *D*).

These findings were also analyzed in the two HF strata. The association of AF presentation with CV mortality and hospitalization in the NYHA class III/IV subgroup of the full TOPCAT Americas cohort was a consistent and increased risk of CV death with both presentations and a non-significant increase in CV hospitalization (see Supplementary material online, *Figure S2*).

Cause-specific modes of death in heart failure with preserved ejection fraction with and without atrial fibrillation

Two major cause-specific modes of death in the two PSM AF subgroups were analyzed.

(1) Pump failure death: *Figure 2A* shows that PFD was higher for subjects with 'Any AF' (9%), compared with those with 'No AF' (5%) at 5 years. It was also higher in subjects with 'AF on ECG' (12%) than in those with 'No AF on ECG' (6%) after 5 years of follow-up. The comparison of instantaneous risk of PFD showed significantly increased risk for both AF presentations (*Tables 6* and *7*, 'Any AF' vs. 'No AF': HR 1.95, 95% CI 1.05 −3.62, $P = 0.035$, and 'AF on ECG' vs. 'No AF on ECG': HR 2.21, 95% CI 1.11–4.40, $P = 0.024$). Very similar findings were seen in the full TOPCAT Americas Any AF and AF on ECG cohorts (see Supplementary material online, *Figure S3A* and *B*).

(2) Sudden death: *Figure 2B* shows that for PSM subjects with 'Any AF,' the SD event rate (8%) was comparable to the 7% observed in those with 'No AF' at 5 years. Similarly, in subjects with 'AF on ECG,' the SD event rate (10%) was comparable to those with 'No AF on ECG' (8%) at 5 years. The HRs also showed no difference in risk for SCD (*Tables 6* and *7*, 'Any AF' vs. 'No AF': HR 1.06, 95% CI 0.61–1.82, $P = 0.841$, and 'AF on ECG vs. No AF on ECG': HR 1.01, 95% CI 0.54–1.90, $P = 0.965$). These findings were consistent with the results in the full TOPCAT Americas Any AF and AF on ECG cohorts (see Supplementary material online, *Figure S3C* and *D*).

(3) Other CV etiologies for mortality, e.g. myocardial infarction and vascular events, were identical in the PSM cohorts being 8% at 5 years for both the Any AF and AF on ECG groups. In the unmatched cohorts, it was 7% at 5 years for both Any AF and AF on ECG subgroups.

(4) There was no difference in non-CV death in the PSM Any AF group compared with the No AF group (HR 0.85, 95% CI 0.55–1.31, $P = 0.4483$). There was no difference in non-CV death in the PSM AF on ECG group compared with the No AF on ECG group (HR 0.95, 95% CI 0.58–1.55, $P = 0.8285$).

Symptomatic heart failure progression and hospitalizations in heart failure with preserved ejection fraction with and without atrial fibrillation

Heart failure progression

Subjects in earlier stages of symptomatic HF (NYHA class I/II) were identified for this analysis. Worsening of HF from class I/II to a more advanced symptomatic HF class III/IV is shown in *Figure 3A*. In PSM subjects with 'Any AF,' 61% showed worsening by 5 years which was higher than in those with 'No AF' (50%). The difference in worsening of HF in subjects with 'AF on ECG' (60%) was also higher compared with those with 'No AF on ECG' (56%) at 5 years. The instantaneous risk of HF progression was significantly higher for 'Any AF' compared with 'No AF (*Tables 6* and *7*, HR 1.30, 95% CI 1.04–1.62, $P = 0.02$), but not for the 'AF on ECG' cohort compared with the 'No AF on ECG' cohort (HR 1.08, 95% CI 0.84–1.40, $P = 0.544$). There was a very similar pattern seen in the two AF subgroups in the full cohort (see Supplementary material online, *Figure S4*).

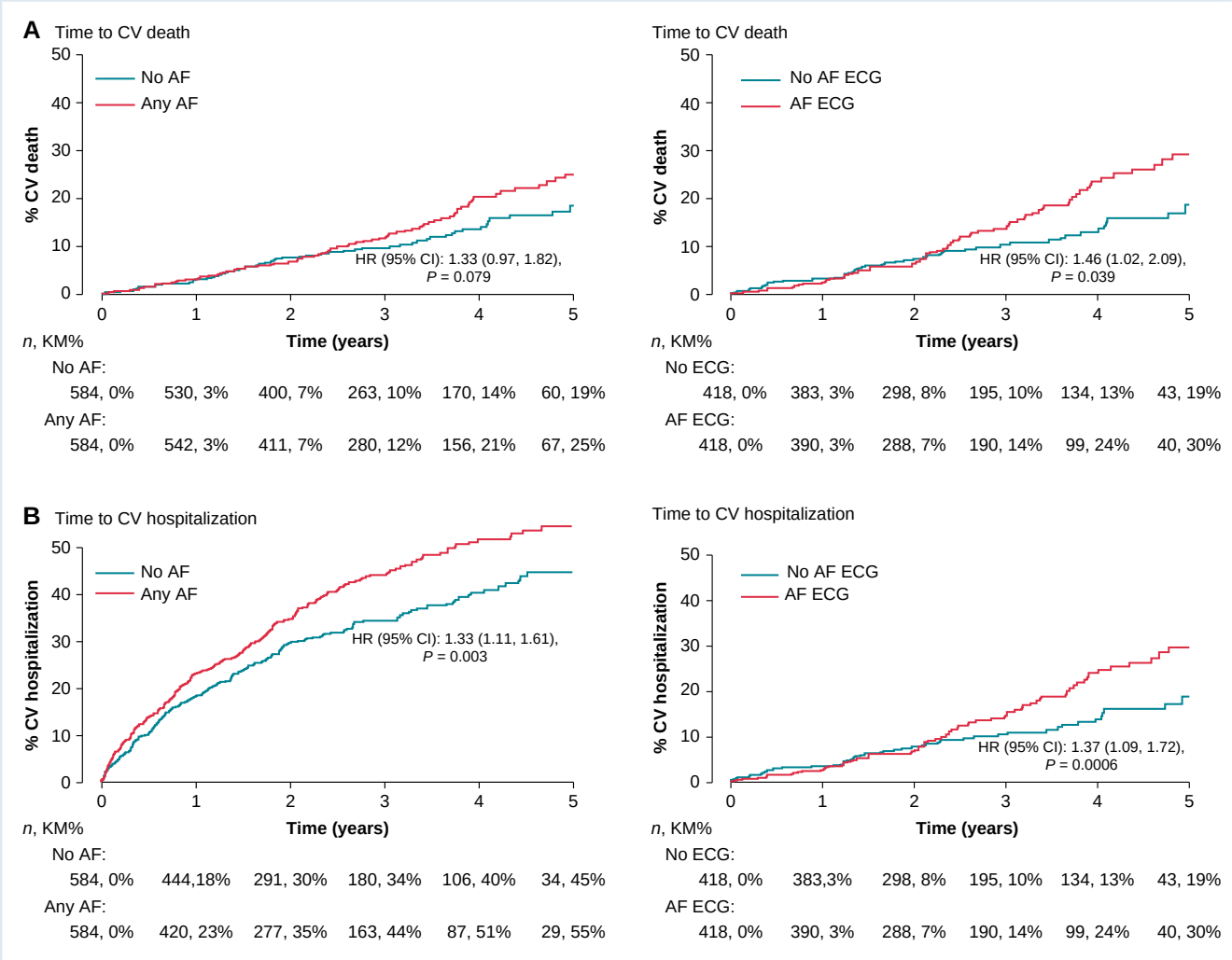


Figure 1 (*A*) Kaplan–Meier survival analysis for risk of cardiovascular (CV) death (percentage: *y*-axis) during follow-up (years: *x*-axis) in propensity score–matched cohorts of subjects with and without Any AF (left panel) and with and without AF on ECG (right panel). Subjects at risk and percentage CV death at yearly intervals are shown below the *x*-axis of the graph at each time period. (*B*) Kaplan–Meier survival analysis for risk of cardiovascular (CV) hospitalization (percentage: *y*-axis) during follow-up (years: *x*-axis) in propensity score–matched cohorts of subjects with and without Any AF (left panel) and with and without AF on ECG (right panel). Subjects at risk and percentage CV hospitalization at yearly intervals are shown below the *x*-axis of the graph at each time period. ACA, aborted cardiac arrest; AF, atrial fibrillation; AF ECG, AF on ECG cohort; No AF ECG, no AF on ECG cohort; SCD, sudden cardiac death.

Table 6 Cox proportional hazard model: hazard ratios for cardiovascular endpoints in the full and propensity score–matched cohorts: Any AF vs. No AF

Endpoint	Full cohort		PSM cohort	
	HR Any AF vs. No AF (95% CI)	*P*-value	HR Any AF vs. No AF (95% CI)	*P*-value
Cardiovascular death	1.17 (0.88, 1.54)	0.276	1.33 (0.97, 1.82)	0.079
Sudden cardiac death/aborted cardiac arrest	0.84 (0.53, 1.34)	0.464	1.06 (0.61, 1.82)	0.841
Pump failure death	1.84 (1.09, 3.10)	**0.022**	1.95 (1.05, 3.62)	**0.035**
Cardiovascular hospitalization	1.06 (0.89, 1.26)	0.551	1.33 (1.11, 1.61)	**0.003**
Hospitalization for heart failure	1.20 (0.98, 1.48)	0.077	1.44 (1.12, 1.86)	**0.004**
Progression and worsening of heart failure	1.25 (1.04, 1.51)	**0.018**	1.30 (1.04, 1.62)	**0.020**

AF, atrial fibrillation; HF, heart failure; HR, Hazard ratio. *P*<0.05 was considered significant.

Table 7 Cox proportional hazard model: hazard ratios for cardiovascular endpoints in the full and propensity score–matched cohorts: AF on ECG vs. No AF on ECG

Endpoint	Full cohort		PSM cohort	
	HR AF on ECG vs. No AF on ECG (95% CI)	*P*-value	HR AF on ECG vs. No AF on ECG (95% CI)	*P*-value
Cardiovascular death	1.46 (1.10, 1.95)	**0.009**	1.46 (1.02, 2.09)	**0.039**
Sudden cardiac death/aborted cardiac arrest	1.12 (0.67, 1.87)	0.676	1.01 (0.54, 1.90)	0.965
Pump failure death	2.23 (1.34, 3.71)	**0.002**	2.21 (1.11, 4.40)	**0.024**
Cardiovascular hospitalization	1.06 (0.88, 1.27)	0.537	1.37 (1.09, 1.72)	**0.006**
Hospitalization for heart failure	1.24 (0.99, 1.55)	0.063	1.65 (1.22, 2.23)	**0.001**
Progression and worsening of heart failure	1.15 (0.94, 1.42)	0.185	1.08 (0.84, 1.40)	0.544

AF, atrial fibrillation; HF, heart failure; HR, Hazard ratio. $P<0.05$ was considered significant.

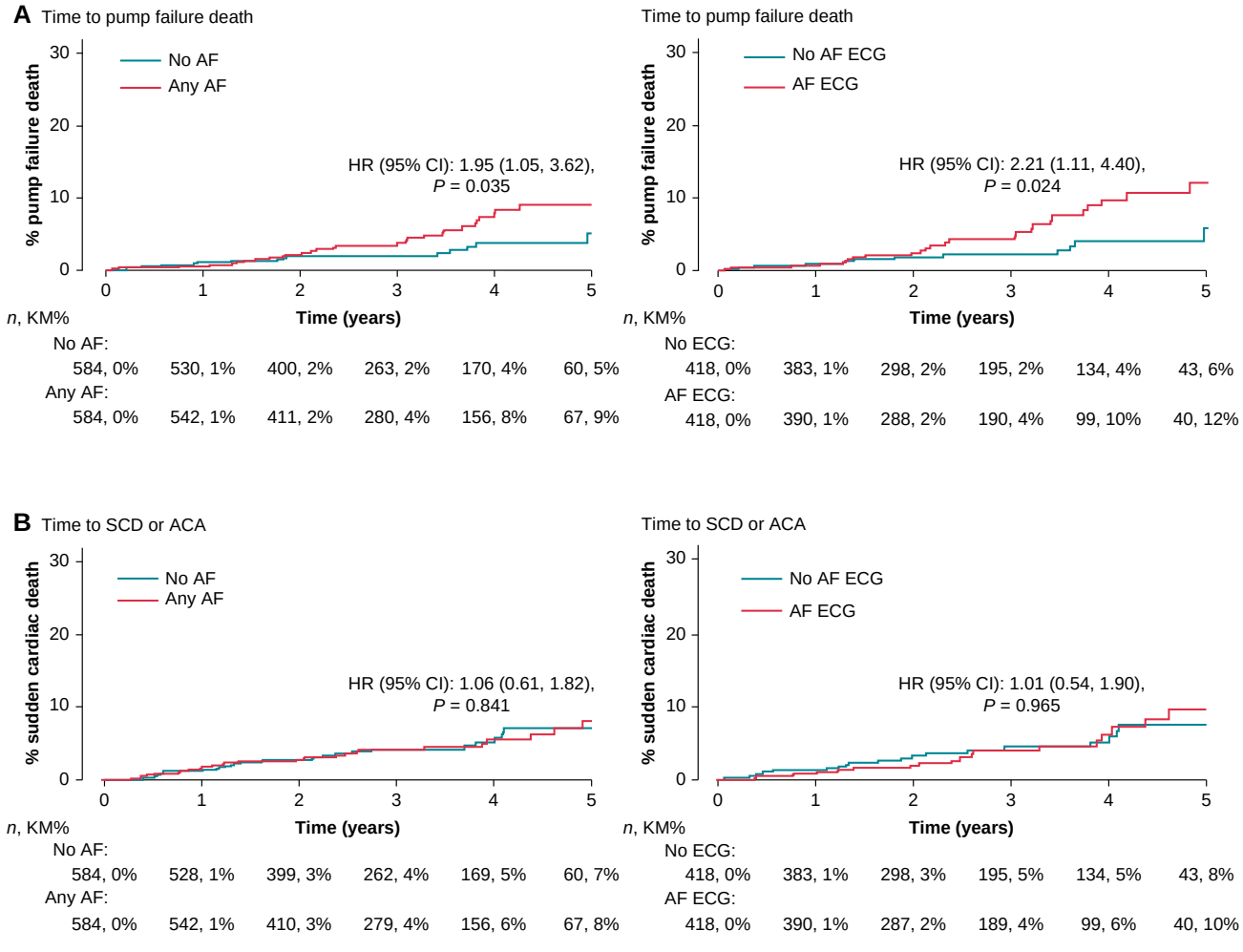


Figure 2 (*A*) Kaplan–Meier survival analysis for risk of death due to pump failure death (percentage: *y*-axis) during follow-up (years: *x*-axis) in propensity score–matched cohorts of subjects with and without Any AF (left panel) and with and without AF on ECG (right panel). Subjects at risk and percentage pump failure death are shown below the *x*-axis of the graph at each time period. (*B*) Kaplan–Meier survival analysis for risk of death due to SCD or ACA (percentage: *y*-axis) during follow-up (years: *x*-axis) in propensity score–matched cohorts of subjects with and without Any AF (left panel) and with and without AF on ECG (right panel). Subjects at risk and percentage SCD or ACA are shown below the *x*-axis of the graph at each time period. ACA, aborted cardiac arrest; AF, atrial fibrillation; AF ECG, AF on ECG cohort; No AF ECG, no AF on ECG cohort; SCD, sudden cardiac death.

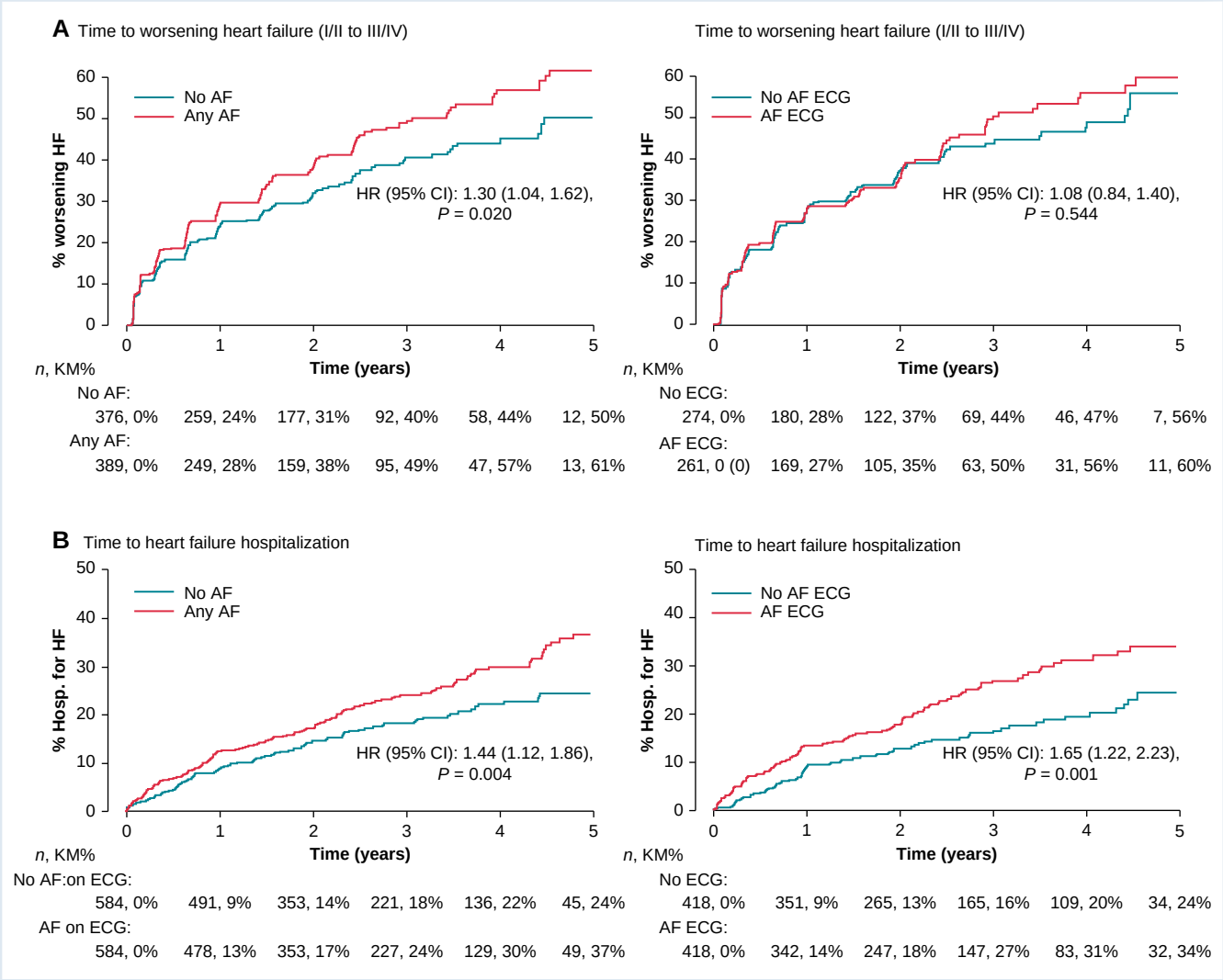


Figure 3 (*A*) Kaplan–Meier survival analysis for risk of worsening heart failure (defined as symptomatic HF progression from NYHA classes I/II to III/IV) (percentage: *y*-axis) during follow-up (years: *x*-axis) in propensity score–matched cohorts of subjects with and without Any AF (left panel) and with and without AF on ECG (right panel). Subjects at risk and percentage with worsening heart failure are shown below the *x*-axis of the graph at each time period. (*B*) Kaplan–Meier survival analysis for risk of hospitalization due to heart failure (percentage: *y*-axis) during follow-up (years: *x*-axis) in propensity score–matched cohorts of subjects with and without Any AF (left panel) and with and without AF on ECG (right panel). Subjects at risk and percentage of hospitalizations due to heart failure are shown below the *x*-axis of the graph at each time period. ACA, aborted cardiac arrest; AF, atrial fibrillation; AF ECG, AF on ECG cohort; No AF ECG, no AF on ECG cohort; SCD, sudden cardiac death.

Heart failure hospitalizations

Figure 3B shows the event rate for HF hospitalization by 5 years was higher in PSM subjects with 'Any AF' (37%) compared with those with 'No AF' (24%). Heart failure hospitalization occurred in 34% of PSM subjects with 'AF on ECG' compared with 24% of those with 'No AF on ECG.' The HRs showed increased risk of HF hospitalization in both groups (*Tables 6* and *7*, 'Any AF' vs. 'No AF': HR 1.44, 95% CI 1.12–1.86, $P = 0.004$, and 'AF on ECG' vs. 'No AF on ECG': HR 1.65, 95% CI 1.22–2.23, $P = 0.001$). The full cohort AF subgroups did not show the differences seen in the PSM cohorts (see Supplementary material online, *Figure S5*).

Impact of baseline heart failure class on cause-specific mode of death in heart failure with preserved ejection fraction with atrial fibrillation

The cause-specific modes of death were analyzed for the two symptomatic HF strata (NYHA class I/II and HF class III/IV) at enrollment in the matched and unmatched cohorts. *Figure 4* shows that presence of Any AF or AF on ECG in the advanced symptomatic HF stratum significantly increased the risk of PFD (panel A)

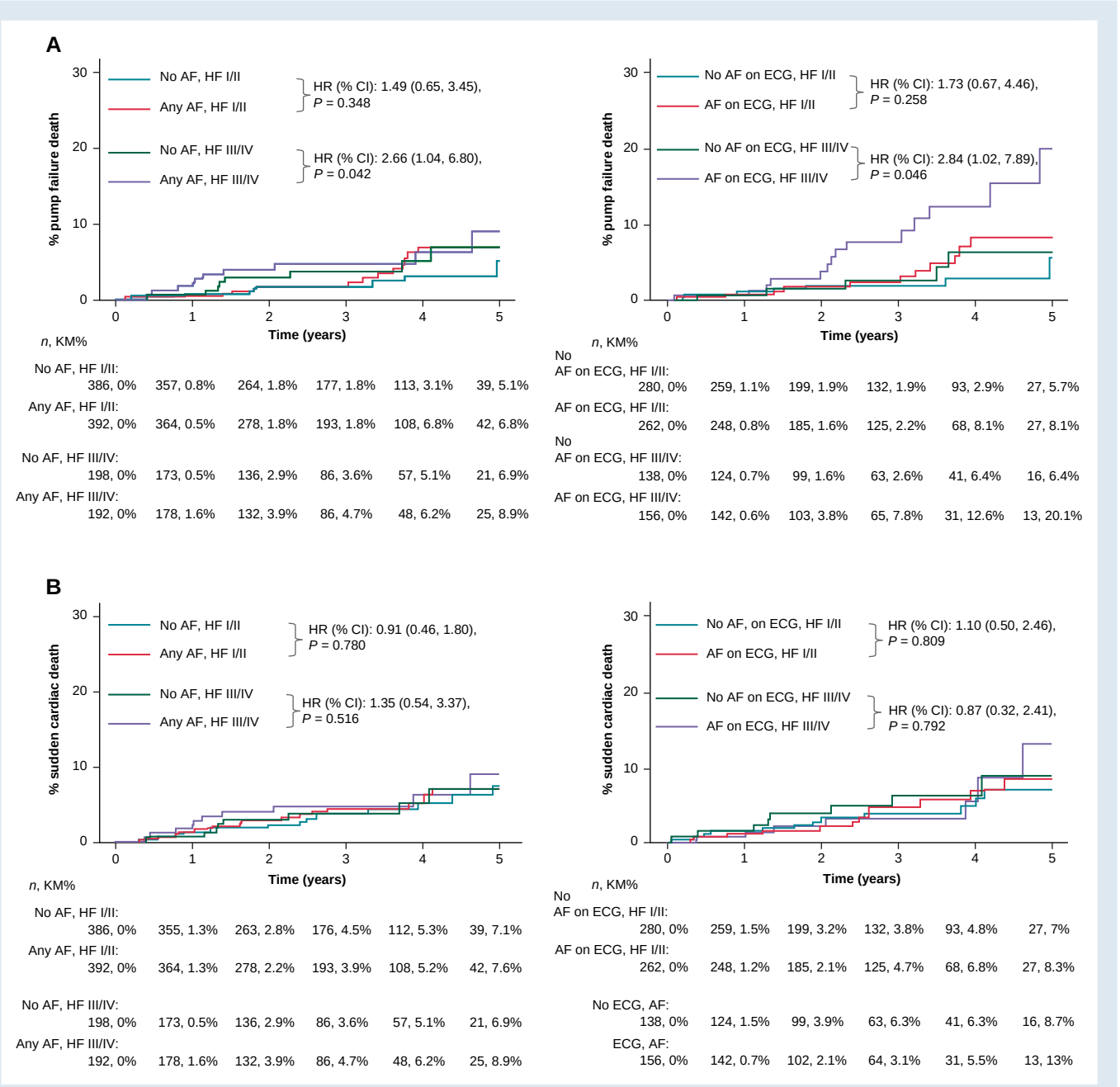


Figure 4 (*A*) Kaplan–Meier survival analysis for risk of pump failure death (percentage: *y*-axis) stratified by baseline symptomatic NYHA heart failure class (I/II vs. III/IV) during follow-up (years: *x*-axis) in propensity score–matched cohorts of subjects with and without Any AF (left panel) and with and without AF on ECG (right panel). Subjects at risk and percentage experiencing pump failure death are shown below the *x*-axis of the graph at each time period. Significance of comparisons is expressed at *P*-values. (*B*) Kaplan–Meier survival analysis for risk of sudden cardiac death (SCD) or aborted cardiac arrest (ACA) (percentage: *y*-axis) stratified by baseline symptomatic NYHA heart failure class (I/II vs. III/IV) during follow-up (years: *x*-axis) in propensity score–matched cohorts of subjects with and without Any AF (left panel) and with and without AF on ECG (right panel). Subjects at risk and percentage experiencing SCD or ACA are shown below the *x*-axis of the graph at each time period. Significance of comparisons is expressed as *P*-values. ACA, aborted cardiac arrest; AF, atrial fibrillation; AF ECG, AF on ECG cohort; No AF ECG, no AF on ECG cohort; SCD, sudden cardiac death.

but not SD (panel B). In the full groups, similar findings were seen with both AF presentations increasing risk of PFD in advanced symptomatic HF (see Supplementary material online, *Figure S6*) but not SD (see Supplementary material online, *Figure S7*), and Any AF also increased risk in earlier stage symptomatic HF.

Discussion

Should atrial fibrillation with heart failure with preserved ejection fraction be better identified as a high-risk cardiovascular disease state?

Heart failure with preserved ejection fraction is now the largest subgroup (~50%) of the HF population in the USA, with an estimated >3 million new cases annually.[7] Over one-half of HFpEF patients have concomitant AF significantly exceeding HFrEF.[2,8–12] Thus, the 'AF–HFpEF' population, by sheer numbers, qualifies as a major public health issue. In addition, the prevalence of AF with HFpEF population may be seriously underestimated. Detailed serial monitoring of heart rhythm for AF detection is rarely done in HFpEF subjects, especially in epidemiologic studies or HFpEF trials, and is not included in current HF guidelines.[2,13] Similarly, AF patients are rarely evaluated for HFpEF, despite overlapping symptoms, and BNP measurements are absent from current AF guidelines.[14] With an increased relative risk of mortality ranging from 43 to 72%%, it is currently also an overlooked, high-risk CV disease state with limited population and evidence-based data.[1,2] To date, prospective HFpEF trials have reported CV and non-CV mortality and cause-specific modes of death in HFpEF populations *in toto*, but not focused on analyzing the excess mortality and morbidity in the AF–HFpEF population as a discrete entity.[2,15–18] Previous data include only all-cause and overall CV mortality without cause-specific mortality or morbidity analysis except a modest risk of stroke in HFpEF, which does not account for the observed increase in mortality. We used PSM analyses and adjusted hazard model makes this analysis more robust in evaluating associations for such analysis.

Atrial fibrillation is often simply considered a marker of advanced CV comorbidity states such as HF. Whether AF is simply a marker for advanced CV disease and a bystander in the development of adverse CV outcomes or has an independent impact in promoting such outcomes has not been definitively addressed. Little is known about different AF presentations, their impact on HF and arrhythmic status, and the mechanism(s) of excess CV mortality and morbidity in this condition. Our PSM data suggest that AF could be an independent risk factor and there may be potentially unique electromechanical mechanisms leading to adverse outcomes.

Atrial fibrillation is an independent risk factor, rather than a marker, in atrial fibrillation–heart failure with preserved ejection fraction subjects

Our analysis of CV outcomes in unmatched and matched AF–HFpEF subjects clearly demonstrates that AF is associated with a similar excess mortality in PSM AF cohorts as in the unmatched AF cohorts. To give emphasis to this finding, we noted that in the unmatched cohorts, the underlying disease state variables were actually more advanced in the sinus rhythm cohort. The PSM analysis shows that AF subjects had increased CV risk, with comparable disease states. The latter is substantiated further by the comparable non-CV mortality. This analysis suggests that AF could be an independent risk factor for several CV outcome measures beyond stroke. Excess CV mortality was significantly greater in subjects presenting with AF on ECG at enrollment, identifying particularly high-risk HFpEF subjects. These subjects are more likely to have continuous AF and high AF burden.[19,20] This novel observation suggests that the degree of loss of sinus rhythm is associated with the magnitude of adverse outcomes observed and is consistent with AF being an independent risk factor.

This analysis of the TOPCAT Americas trial provides important new insights into the 'AF–HFpEF' disease state. Actuarial behavior of PFD and SD, currently unreported, and HF progression with AF, also not previously reported, emerge from this analysis. Heart failure progression was determined by the use of NYHA class which is in part subjective, but is a reliable indicator of HF status in numerous clinical trials and a predictor of major CV outcomes. Finally, the role of different AF presentations raises important questions as to the role of AF burden in HF progression and PFD.

Atrial fibrillation could accelerate a downhill course for 'AF–HFpEF' subjects with a selective and novel impact on symptomatic HF status, viz., HF worsening in earlier HF and pump failure mortality in advanced HF. These data markedly extend and are clearly distinct from our own prior report on the TOPCAT.[2] By analyzing cause-specific mortality with differing presentations, namely, 'Any AF' which is consistent, in most instances, with paroxysmal AF with variable burden and ongoing AF with persistent AF with a high burden, we identified a selective AF association with PFD rather than SD in HFpEF. This finding could explain the excess CV mortality observed with AF. Most importantly, we note a strong association for this selective increase in PFD in the PSM AF cohorts, which is consistent with independent risk conferred by AF. Atrial fibrillation more than doubled the relative risk of the composite endpoint of CV mortality and HF hospitalization (HR 2.32). Olsson *et al.* also noted that patients with AF on baseline ECG had a 72% increase in relative risk for CV death or HF hospitalization in HFpEF compared with 29% for HFrEF subjects. However, the reasons for this observation have remained unclear.[1,17,18] Our data on PFD suggest that it could be related to greater dependence on atrial mechanical function in HFpEF. We also observed that AF was associated with accelerated HF progression. It was associated with HF progression from early to advanced symptomatic HF, HFH, and then, in advanced HFpEF, CV mortality. These novel observations identify specific adverse HF outcomes in the AF–HFpEF population and quantify its morbidity. In our prior report on the AFFIRM trial which was conducted in AF subjects without HF, a similar signal was present.[21] Echocardiographic data identify left atrial dysfunction, which is present in AF, as a predictor of adverse CV outcomes in HFpEF.[22] This is also supported by the analysis of HF hospitalizations and symptomatic HF progression. Both PSM AF cohorts were associated with increased risk of HFH and HF progression to NYHA class III/IV, suggesting this association was potentially independent of disease status. This observation could suggest that AF detection in *advanced* HFpEF may be an inflection point, associated with a sudden increase in CV mortality risk.

Is there a physiologic basis for the association with pump failure deaths in atrial fibrillation with heart failure with preserved ejection fraction?

Atrial fibrillation promotes atrial mechanical dyssynchrony, elevates left atrial (LA) pressures, and produces high ventricular rates with loss of active LV filling due to absence of atrioventricular synchrony. Lower peak LA strain in HFpEF has been associated with both AF and LV systolic dysfunction.[22] Increased heart rate raises pulmonary capillary wedge (PCW) pressures in HFpEF.[23,24] Exertion also increases ventricular rate in AF and shortens LV passive filling. In HFpEF, right ventricular (RV) failure has been correlated with pulmonary vascular hypertension and, secondarily, significantly reduced RV systolic function. This deterioration is less profound with intermittent pulmonary hypertension than persistent pulmonary hypertension. Thus, paroxysmal AF (secondarily, lower AF burden) allows for periods of sinus

rhythm, limiting atrial remodeling and permits intermittent reduction in LA and pulmonary vascular pressures. In contrast, persistent AF would not show such a remission. When present, both could promote pump failure symptoms and mechanical pump failure, but these effects would be more pronounced in the latter situation. Whether AF in HFpEF leads to a cardiomyopathy with impaired LV systolic function or evolution to HFrEF remains to be determined. In the AFFIRM trial, we have previously demonstrated that emergence of new HF is accelerated with increasing frequency of ECG-documented AF in the rhythm control arm.[21]

Analyzing atrial fibrillation presentations in heart failure with preserved ejection fraction with respect to atrial fibrillation burden

Studies monitoring for AF in a systematic fashion in HFpEF populations are sparse. The VIP-HF study done in mid-range and preserved EF subjects detected differing AF presentations in 37% of these subjects during a mean follow-up period of 657 days, with 20% of subjects being hospitalized for HF in the same time.[25] In most HFpEF studies, such detailed AF pattern data are unavailable. Subjects have been segregated at baseline into those with AF on ECG, history of AF and no AF categories, or AF by history has been included in the sinus rhythm group due to its absence on baseline ECG.[1,2] This categorization misses the innate complex patterns of AF from long-term monitoring, the obvious example being those with AF on ECG often have a history of AF as well as a much higher AF burden.[19,20] Thus, it is more relevant to view the categories as reflecting different levels of AF burden. Implantable device data studying the AF evolution into persistent AF show a progressive increase in AF burden in patients with structural heart disease, with a sudden onset of persistent AF.[19,20] In this analysis, the 'Any AF' group is the umbrella group that includes remote or ongoing AF event(s). The 'AF on ECG group' was analyzed as the highest burden subgroup of the entire AF population and represents ongoing AF. Similar parallel strata have been used in HF studies using recent HF hospitalizations or acute HF exacerbations as increasing risk. The 'Any AF' group is populated by paroxysmal and, infrequently, possibly early persistent AF. This can be self-terminating with, on average, a lower individual AF burden due to its intermittent nature.[20] The 'AF on ECG' grouping is more likely to represent established persistent AF subjects with a higher AF burden. This is indirectly supported by the high usage of rate control drug therapy alone and minimal use of rhythm control drugs in AF on ECG subjects. Lastly, assessing AF presentation in HFpEF patients to predict risk is a clinically relevant approach, since these subjects typically lack measurement of AF burden or other prolonged heart rhythm monitoring.

Heart failure and sudden death contributions in 'atrial fibrillation–heart failure with preserved ejection fraction' population

In HFrEF, AF increases SD risk.[17] Sudden death events did outnumber PFD numerically, but SD risk was not associated with either AF presentation or HF stratum in HFpEF. This may be due to a limited substrate for ventricular arrhythmias in HFpEF or other mechanisms of SD. The minimal use of Class 1 or 3 antiarrhythmic drugs is unlikely to impact CV mortality via pro-arrhythmia. The minimal use of amiodarone is also unlikely to have an impact, as seen in our non-CV mortality data.[26]

Future therapeutic considerations in the 'atrial fibrillation–heart failure with preserved ejection fraction' patient

Atrial fibrillation, especially sustained AF in advanced HFpEF, presages a more ominous course with respect to pump failure. The hypothesis that restoring rhythm control in AF with HFpEF with antiarrhythmic drugs or ablation could be beneficial for HF progression or events and perhaps CV mortality is under prospective investigation.[27–31] More aggressive HF management could also potentially ameliorate adverse outcomes and is being evaluated.[27,32,33]

Limitations of the study

This is a post hoc evaluation and results should be interpreted as hypothesis-generating, as the study was powered for the TOPCAT primary composite endpoint and not for the component outcomes, limited recorded events, and the risk of residual confounding. The trial excluded high-risk co-morbidities and required a life expectancy of 3 years, contributing to a survival bias that is not generalizable to the entire HFpEF population. The data set collapses NYHA classes I/II and III/IV and additional granularity in this analysis is not possible. The impact of incident AF on the 'No AF' cohorts could not be assessed due to limited monitoring. Thus, the results are most relevant to HFpEF subjects with prevalent AF at hospitalization or clinic visit. The absence of serial ECGs limits the continuous assessment of cardiac rhythm. No quantitative data on AF burden were obtained. We recognize that since the conduct of the trial, heart failure guidelines recognize an intermediate zone of LVEF which may overlap with the LVEF criterion used in this trial and these analyses.

Supplementary material

Supplementary material is available at *Europace* online.

Author contributions

S.S. and A.S. are responsible for the design and conduct of this study, all study analyses, and drafting the manuscript, and all the authors have contributed to the conception and design, analysis and interpretation of data, and revising it critically for intellectual content and have given final approval to this manuscript. A.S. performed all the statistical analyses from the TOPCAT database in the foundation's possession.

Acknowledgements

The authors gratefully acknowledge the contributions of the TOPCAT study investigators and the leadership of the trial in providing the data for these analyses. The TOPCAT study complied with the Declaration of Helsinki, the institutional review board approved the research protocol, and informed consent has been obtained from all subjects.

Conflict of interest: S.S. was a member of the Steering Committee of the TOPCAT trial. The Electrophysiology Research Foundation received a research grant as an investigational site for the TOPCAT trial. All remaining authors have declared no conflicts of interest with the subject of this manuscript.

Data availability

The database utilized in this study is publicly available at the National Heart Lung Blood Institute, https://biolincc.nhlbi.nih.gov.

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