Journal of the American Heart Association

ORIGINAL RESEARCH

Atrial Fibrillation, Heart Failure Phenotypes, and Mortality Risk in the Nationwide START Registry: A Propensity Score Matching Analysis

Danilo Menichelli, MD; Emilia Antonucci, PhD; Gianluca Gazzaniga, MD; Daniela Poli, MD; Giuseppe Armentaro, MD; Giordano di Carlo, MD; Rossella Marcucci, MD, PhD; Paolo Calabrò, MD, PhD; Arturo Cesaro, MD, PhD; Gualtiero Palareti, MD; Angela Sciacqua, MD; Pasquale Pignatelli, MD, PhD; Daniele Pastori, MD, PhD; the START 2 Collaborators*

BACKGROUND: Data on atrial fibrillation (AF) and heart failure (HF) with preserved ejection fraction (HFpEF) are scarce. We investigated the association of HFpEF with all-cause mortality in AF.

METHODS: We included 10 369 patients with AF on oral anticoagulants from the nationwide ongoing START (Survey on Anticoagulated Patients Register) registry. Patients were divided into 3 groups: (1) no HF, (2) HF with reduced EF/HF with mildly reduced EF (EF ≤50%), and HFpEF (EF >50%). Patients with HF should have had a clinical diagnosis or a history of HF hospitalization. The association between HF types and all-cause mortality was investigated by Cox proportional hazards regression analysis to estimate hazard ratio (HR) and 95% CI for each factor. The Fine–Gray model and propensity score matching were used.

RESULTS: Mean age was 76.4±9.4 years and 45.8% were women. Overall, 2309 (22.2%) patients had HF, of whom 47.4% had HFpEF. During 720±576 days of follow-up (20 747 patients/year), 727 deaths occurred (3.5 per 100 patient-years). After propensity score matching, both HF with mildly reduced EF/HF with reduced EF and HFpEF were associated with all-cause mortality (HR, 1.33; *P*=0.037 and HR, 1.49; *P*=0.004). HFpEF was associated with mortality in men (HR, 1.654; *P*=0.001) but not in women (HR, 1.243; *P*=0.175). In HFpEF, age≥75 years (HR, 2.247; *P*=0.003), chronic respiratory disease (HR, 2.109; *P*<0.001), anemia (HR, 1.482; *P*=0.035), paroxysmal AF (HR, 0.528; *P*=0.012), creatinine clearance<30 mL/min (HR, 1.791; *P*=0.018), direct oral anticoagulants (HR, 0.575; *P*=0.005), and renin-angiotensin inhibitors (HR, 0.670; *P*=0.033) were associated with all-cause mortality.

CONCLUSIONS: HFpEF is frequent in patients with AF and associated with an increased mortality, especially in men. Comorbidities and treatments associated differently with mortality according to HF phenotype.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02219984.

Key Words: AF ■ atrial fibrillation ■ heart failure ■ HFpEF ■ HFrEF/HFmrEF ■ mortality

Correspondence to: Daniele Pastori, MD, PhD, FESC, Department of Clinical Internal, Anesthesiological, and Cardiovascular Sciences, Sapienza University of Rome, Viale del Policlinico 155, Rome 00161, Italy. Email: daniele.pastori@uniroma1.it

*A complete list of the START 2 Collaborators can be found in the Appendix at the end of the article.

This article was sent to Sula Mazimba, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.125.042586

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Heart failure (HF) with preserved ejection fraction is common in patients with atrial fibrillation and independently associated with increased all-cause mortality.
- The mortality risk linked to HF with preserved ejection fraction is sex specific, being significant in men but not in women.

What Are the Clinical Implications?

- Patients with atrial fibrillation with HF with preserved ejection fraction should not be considered at lower risk—they have significant mortality risk, especially older men with comorbidities.
- Tailored treatment strategies (eg, use of direct oral anticoagulants, renin-angiotensin-aldosterone system inhibitors) may improve outcomes in HF with preserved ejection fraction; recognizing HF phenotype in atrial fibrillation is essential for personalized therapeutic decisions.

Nonstandard Abbreviations and Acronyms

AAD	antiarrhythmic drug
CRF	case report form
DOAC	direct oral anticoagulant
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
OSAS	obstructive sleep apnea syndrome
PSM	propensity score matching
RAASi	renin-angiotensin-aldosterone system inhibitor
VKA	vitamin K antagonist

Atrial fibrillation (AF) and heart failure (HF) often coexist.[1] The reported prevalence of AF in patients with HF ranges between 13% and 27%.[1–4] Notably, this prevalence seems to increase according to HF severity from 5% in mild HF up to 50% in patients with severe HF.[5]

A study performed on Framingham Heart Study participants showed that 37% of 1737 individuals with new-onset AF had concomitant HF and, conversely, 57% of 1166 individuals with new HF had concomitant AF.[6] A further study,[7] performed on 1265 patients with AF showed a prevalence of HF of 34.3%.

The coexistence of these 2 cardiovascular disorders may be partly attributable to the presence of common cardiometabolic risk factors such as arterial hypertension, smoking, diabetes, obesity, and previous myocardial infarction.[1,8] A common pathogenetic mechanism may be represented by systemic inflammation. In particular, the interleukin-6, interleukin-1β, and tumor necrosis factor pathways may activate metalloproteinases and may inhibit the inhibitors of metalloproteinases. Furthermore, these cytokines also induce myocyte hypertrophy and fibrosis.[8] Similarly, the renin-angiotensin pathway, activating the MAP (mitogen-activated protein) kinases pathway, may induce myocyte hypertrophy and fibrosis, increasing the risk of developing both AF and HF.[8]

This coexistence is also linked to a higher risk of worse clinical outcomes, such as mortality. Indeed, a large meta-analysis including 20 studies with 152 306 patients with HF showed a higher risk of death if patients had a coexisting AF.[9] A Polish study[10] including 688 hospitalized patients with AF during 1-year follow-up showed a higher mortality rate in patients with HF, regardless of the phenotype, compared with patients without AF.

A post hoc analysis of the ENGAGE-AF TIMI 48[11] (Effective Anticoagulation With Factor Xa Next Generation in AF-Thrombolysis in Myocardial Infarction 48) trial performed on 21 105 patients with AF (57.4% with HF, of whom 22.1% had unknown EF) showed a higher risk of HF hospitalization and HF death in patients with concomitant AF and HF, without differences in thromboembolic stroke or major bleeding during a median follow-up of 2.8 years.

Thus, the high prevalence and coexistence of these disorders has several clinical implications and represent a challenge for the clinicians. In this context, evidence on the association between HF with preserved ejection fraction (HFpEF) and AF in clinical practice, as well as the role of comorbidities according to each HF phenotype is less established.

For this reason, aims of our study were to investigate (1) the difference between patients with AF with either HFpEF or HF with reduced EF/HF with mildly reduced EF (HFrEF/HFmrEF) in a real-world population, (2) the association of each phenotype of HF and all-cause mortality, and (3) the pattern of comorbidities and treatments associated with each type of HF.

METHODS

Survey on Anticoagulated Patients Register

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The START (Survey on Anticoagulated Patients Register) registry is an observational, multicenter, ongoing cohort study that includes patients (aged ≥18 years) who start anticoagulation therapy, either vitamin K antagonist (VKAs) (warfarin or acenocoumarol) or direct oral anticoagulants (DOACs), throughout Italy. Analysis was performed on patients enrolled until December 2023. Details of the START registry have been previously described.[12] The START registry has been previously registered on ClinicalTrials.gov (NCT02219984). The study protocol was accepted by the institutional review board of each participating center, and informed consent was obtained from patients at enrollment.

The study protocol complies with the ethical guidelines of the 1975 Helsinki Declaration, and informed consent was obtained from each patient.

Patients treated with low-molecular-weight heparin were excluded as well as patients already enrolled in phase 2 or 3 clinical studies. Patients enrolled in other observational or phase 4 studies were considered eligible for the study.

Baseline Characteristics

Patients' clinical features are recorded by participants on web-based case report forms. Baseline data are demographic and clinical characteristics of patients, including cardiovascular risk factors, laboratory routine data, comorbidities, EF, smoking habits, indication for anticoagulant treatment, type of oral anticoagulation, and concomitant drugs.

Previous cardiovascular disease was defined as history of coronary artery disease (either ischemic heart disease or coronary revascularization with stent or coronary artery bypass graft), while cerebrovascular disease is defined as previous ischemic stroke or transient ischaemic attack.

HFrEF/HFmrEF are defined as (1) medical history of hospital admission for HF or symptoms and signs suggestive for HF, and (2) EF <50% as reported in the electronic case report form.

Patients with history of HF or signs or symptoms suggestive for HF and EF ≥50% were classified as HFpEF.

Primary End Points

The primary end points of the studies were (1) to establish the all-cause mortality risk in patients with AF with HFrEF/HFmrEF and HFpEF, and (2) to evaluate potential concomitant comorbidities and risk factors predictive of all-cause mortality.

Statistical Analysis

Continuous variables were reported as means±SDs, and categorical variables as counts and percentages. Population characteristics were described across 3 groups: (1) patients without HF (no HF), (2) patients with HFrEF or HFmrEF (left ventricular EF ≤50%), and (3) patients with HFpEF (left ventricular EF >50%). One-way ANOVA was used to compare continuous variables across the 3 groups. Subsequently, post hoc comparisons were performed using Tukey's test, to identify differences between HFpEF and HFrEF/HFmrEF. Categorical variables were compared using the chi-square test.

Continuous variables were included in the models as linear terms, based on clinical interpretability and parsimony. Categorical variables were treated as factors, and no interaction terms were included in the final models. This modeling strategy was chosen to ensure stability and interpretability of the multivariable models and to reduce the risk of overfitting given the number of covariates considered.

Then, the cumulative incidence of all-cause mortality was estimated using a Kaplan–Meier product-limit estimator for each group, and survival curves were formally compared using the log-rank test.

Univariable and multivariable Cox proportional hazards regression analysis was used to calculate the adjusted relative hazard ratios (HRs) and 95% CI of all-cause of death by each clinical variable. In the multivariable analysis, individual variables instead of the CHA_2DS_2-VASc score were entered. Age was dichotomized at 75 years; this threshold was chosen based on its clinical relevance to cardiovascular risk, as recommended by international guidelines.[13]

A subgroup analysis was performed according to the 3 groups of study using a stepwise multivariable Cox proportional hazards regression analysis to evaluate factors associated with all-cause mortality. Results of subgroup analysis were expressed as HR and 95% CI.

The Fine–Gray model was used to estimate the cumulative incidence of cardiovascular mortality while accounting for the competing risk of noncardiovascular death. A univariate model was first fitted, accounting for HF type (reference: no HF). Subsequently, an adjusted multivariate model was performed, incorporating baseline demographic and clinical covariates, that is, sex, age, body mass index, comorbidities (hypertension, diabetes, coronary artery disease, anemia), history of cancer, kidney function, chronic obstructive pulmonary disease (COPD), liver cirrhosis, smoking status, dementia, and DOAC use. All these covariates were selected based on clinical rationale, aiming to adjust for the full range of relevant comorbidities and features and reflecting the complexity typical of patients with AF. To assess multicollinearity among the covariates, the variance inflation factor was computed for each variable in the model. Variables with variance inflation factor values >3 were considered potentially

problematic. However, no covariates in the final model had a variance inflation factor exceeding this threshold, indicating that collinearity was not a concern.

We then used propensity score matching (PSM) to account for confounding between patients with HFpEF or HFmrEF/HFrEF and without HF, in order to assess consistency of results across different modeling strategies. The propensity score was estimated using logistic regression, incorporating the following covariates: sex, age, body mass index, DOAC use, hypertension, diabetes, coronary artery disease, anemia, glomerular filtration rate, cancer, COPD/obstructive sleep apnea syndrome (OSAS), cirrhosis with varices, smoking, and dementia. These variables were chosen a priori as they reflect the most common comorbidities in patients with AF.

Patients with HFpEF and HFmrEF/HFrEF were matched 1:1 to those without HF using nearest-neighbor matching with a caliper width of 0.1, without replacement. Covariate balance post matching was assessed using standardized mean differences, with values <0.1 considered indicative of adequate balance. A summary of PSM balance for HFmrEF/HFrEF and HFpEF was reported in Table S1 top panel and B, respectively. Moreover, further balance diagnostics, that is, Love plots and propensity score distributions plots comparing before and after matching, are available in Figures S1 and S2.

After PSM, we analyzed the matched data using Kaplan–Meier curves to estimate all-cause mortality. A univariate Cox proportional hazards model was used to calculate the HR for all-cause mortality. The proportional hazard assumption was tested using Schoenfeld residuals.

No imputation was applied for missing data. Only *P* values <0.05 were considered as statistically significant. All tests were 2 tailed and analyses were performed using computer software packages (IBM SPSS-25, SPSS Inc. R Software v. 4.2.3, and MedCalc).

RESULTS

Clinical Characteristics

Overall, 2309 (22.2%) of 10369 patients with AF were affected by HF. Of these, 47.4% had HFpEF. In Table 1 were reported clinical and demographics characteristics of patients according to 3 groups: no HF, HFrEF/HFmrEF and HFpEF.

Mean age was 76.4±9.4 years with a significant difference among groups (Table 1). Patients with HFpEF were older (mean age 79.4±8.5 years) with a higher proportion of patients with age≥75 years (74.8%) compared with patients without HF and HFrEF/HFmrEF (mean age 75.9±9.4 and 76.3±9.5 years, respectively) (Table 1). A high proportion of women (53.2%) was found in patients with HFpEF with a significant difference compared with those with HFrEF/HFmrEF (35.4%) (Table 1).

Patients with HFpEF and HFrEF/HFmrEF were more commonly affected by arterial hypertension, diabetes, previous cardiovascular disease, obesity, COPD/OSAS, chronic kidney disease, anemia, and higher CHA_2DS_2-VASc score without difference in previous cerebrovascular disease compared with patients without HF (Table 1).

Furthermore, patients with HFpEF were more likely to be affected by arterial hypertension compared with HFrEF/HFmrEF. On the other hand, patients with HFrEF/HFmrEF were more commonly affected by history of cardiovascular disease and diabetes and were smokers (Table 1).

All patients in our cohort were treated with oral anticoagulants (56.3% on DOACs, 43.7% on VKAs). A higher proportion of patients with HF, especially HFrEF/HFmrEF, were treated with lipid-lowering therapy, antiplatelet, digoxin, amiodarone, and β-blockers (Table 1). On the other hand, patients without HF were likely to be treated with Class 1C antiarrhythmics (1C AADs) and calcium channel blockers compared with patients with HFrEF/HFmrEF or HFpEF. Comparing type of HF, HFrEF/HFmrEF had a higher proportion of patients treated with β-blockers, antiplatelets, lipid-lowering drugs, and renin-angiotensin system inhibitors (Table 1).

Phenotype of HF and All-Cause Mortality Risk

During a mean follow-up of 720±576 days (20747 patients/year), 727 deaths occurred (incidence rate 3.5 per 100 patient-years [95% CI, 3.3–3.8]).

Table S2 reported clinical characteristics according to survival status. Patients who were deceased were older, with a high proportion of patients with HF, persistent/permanent AF, arterial hypertension, previous cerebrovascular and cardiovascular disease, diabetes, anemia, COPD/OSAS, smoking habits, and chronic kidney disease (CKD) (Table S2).

Patients who were deceased were likely treated with digoxin, diuretics, VKAs, and β-blockers. On the other hand, there was a low proportion of patients treated with renin-angiotensin-aldosterone system inhibitors (RAASi) drugs, Class 1C AADs, and lipid-lowering therapy (Table S2).

Kaplan–Meier survival curves showed a low survival rate, both for HFpEF and HFrEF/HFmrEF, compared with patients without HF (Figure) (log-rank test *P*<0.001). However, no difference in all-cause mortality was observed between HFrEF/HFmrEF and HFpEF (univariable HR, 1.17 [95% CI, 0.91–1.50], *P*=0.211).

Multivariable Cox regression analysis indicated that overall population, age≥75 years, anemia, CKD, COPD/OSAS, peripheral artery disease, and history of cardiovascular or cerebrovascular disease were associated

Table 1. Clinical Characteristics of Patients With Atrial Fibrillation Involved in the Study According to the Presence of Heart Failure

	No.	Whole cohort (n=10 369)	No HF (n=8060)	HFrEF/HFmrEF≤50% (n=1215)	HFpEF>50% (n=1094)	*P* value among groups	*P* value HFpEF vs HFrEF/HFmrEF
Mean age, y	10 363	76.4±9.4	75.9±9.4	76.3±9.5	79.4±8.5	<0.001	<0.001
Age≥75 y, %	10 363	62.5	61.0	62.0	74.8	<0.001	<0.001
Women, %	10 369	45.8	46.3	35.4	53.2	<0.001	<0.001
Paroxysmal atrial fibrillation (vs persistent/permanent), %	10 260	37.5	39.7	30.1	29.1	<0.001	0.613
Arterial hypertension, %	10 369	80.8	79.1	85.0	88.9	<0.001	0.007
Diabetes, %	10 369	20.7	18.9	29.1	24.5	<0.001	0.013
Obesity (body mass index≥30 kg/m^2)	10 366	21.6	20.8	24.6	23.9	0.002	0.734
Previous cerebrovascular disease, %	10 369	15.6	15.9	14.9	14.2	0.273	0.680
Previous cardiovascular disease, %	10 369	17.0	13.7	33.3	22.7	<0.001	<0.001
Chronic obstructive pulmonary disease/obstructive sleep apnea syndrome, %	10 369	11.3	8.6	19.4	22.7	<0.001	0.052
Current smoking, %	10 369	4.6	4.4	6.7	3.8	<0.001	<0.001
Former smoking, %	10 369	12.2	11.3	18.2	12.8		
Anemia, %	10 369	26.2	23.3	35.7	36.4	<0.001	0.729
Creatinine clearance<30 mL/min, %	10 353	5.0	3.8	9.6	9.3	<0.001	0.831
Peripheral artery disease, %	10 369	5.9	5.1	9.2	8.1	<0.001	0.376
CHA_2DS_2-VASc score	10 363	3.7±15	3.4±1.4	4.3±1.5	4.9±1.3	<0.001	<0.001
Therapy							
Direct oral anticoagulants, %	10 369	56.3	57.5	48.5	56.1	<0.001	<0.001
Lipid-lowering drugs, %	10 369	35.3	33.9	44.3	35.8	<0.001	<0.001
Antiplatelets, %	10 369	11.9	10.7	21.0	10.9	<0.001	<0.001
Digoxin, %	10 369	8.3	6.2	14.5	16.8	<0.001	0.135
Amiodarone, %	10 369	12.4	11.2	19.6	13.2	<0.001	<0.001
Class 1C antiarrhythmic drugs, %	10 369	8.7	10.5	2.1	2.4	<0.001	0.671
β-blockers, %	10 369	47.2	43.9	63.1	53.7	<0.001	<0.001
Renin-angiotensin-aldosterone system inhibitors, %	10 369	56.3	55.2	64.8	55.0	<0.001	<0.001
Calcium channel blockers, %	10 369	22.0	22.5	17.6	23.4	<0.001	0.001
Diuretics, %	10 369	38.7	29.5	71.7	69.5	<0.001	0.273

HF indicates heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

with all-cause mortality (Table S3). Both HFpEF and HFrEF/HFmrEF were associated with all-cause mortality (HR, 1.417 [95% CI, 1.146–1.753], *P*<0.001 and HR, 1.269 [95% CI, 1.081–1.680], *P*=0.036, respectively). Conversely, female sex, paroxysmal AF, the use of DOAC, and the use of 1C AADs and lipid-lowering therapy were inversely associated with all-cause mortality in this model (Table S3).

Subgroup Analysis and All-Cause Mortality Risk

To evaluate potential differences in comorbidities and predictors of all-cause mortality in patients with HFpEF, HFrEF/HFmrEF, and without HF, we performed a subgroup analysis of study groups.

In patients without HF a stepwise multivariable Cox proportional hazards regression analysis showed a direct association between age, COPD/OSAS, diabetes, anemia, CKD, peripheral artery disease, previous cerebrovascular and cardiovascular disease, and all-cause mortality (Table 2, top panel). Conversely, paroxysmal AF, the use of DOAC, RAASi, Class 1C AADs, and lipid-lowering therapy were inversely associated with all-cause mortality (Table 2, top panel).

In patients with HFrEF/HFmrEF as shown in Table 2, middle panel, CKD, peripheral artery disease, and older age were associated with an increased risk of all-cause mortality, whereas the inverse association between RAASi use and all-cause mortality was confirmed also in this subgroup.

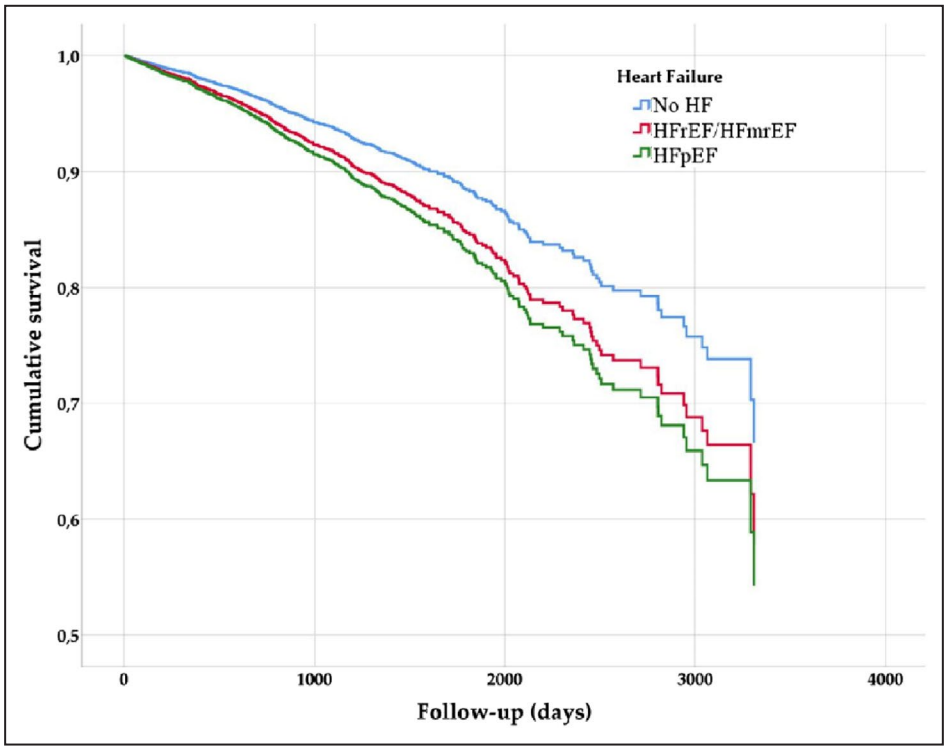

Figure. Kaplan–Meier curve for all-cause mortality according to the presence of heart failure.
HF indicates heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

On the other hand, in patients with HFpEF, as shown in Table 2, bottom panel, predictors of all-cause mortality were older and had COPD/OSAS, anemia, and CKD, whereas the use of DOACs and RAASi and paroxysmal AF were associated with lower risk of all-cause mortality (Table 2, bottom panel).

Analysis by Sex

We also performed a subgroup analysis by sex (Table S4). In men (top panel), older age, COPD/OSAS, anemia, CKD, peripheral artery disease, and clinical history of cerebrovascular or cardiovascular disease were associated with all-cause mortality. Among treatments, the use of DOACs, RAASi, lipid-lowering therapy, and Class 1C AADs were inversely associated with all-cause mortality (top panel).

On the other hand, in women (bottom panel), older age, COPD/OSAS, anemia, CKD, or HFpEF were directly associated with all-cause mortality, whereas clinical history of cerebrovascular or cardiovascular disease were directly associated with all-cause mortality.

The use of DOACs, RAASi, lipid-lowering therapy, and Class 1C AADs was inversely associated with all-cause mortality in women (bottom panel).

Competing Risk and PSM

Table S5 shows the Fine–Gray model results for cardiovascular mortality accounting for the competing risk of noncardiovascular mortality. In the univariate analysis, both HFrEF/HFmrEF (HR, 2.61 [95% CI, 1.76–3.88], $P<0.001$) and HFpEF (HR, 2.72 [95% CI, 1.81–4.10], $P<0.001$) were associated with higher cardiovascular mortality risk. After adjustment for all prespecified baseline covariates, the associations remained significant (HFrEF/HFmrEF: HR, 2.03 [95% CI, 1.30–3.16], $P=0.002$; HFpEF: HR, 1.85 [95% CI, 0.19–2.87], $P=0.006$). Of note, among covariates, older age (HR, 1.10 [95% CI, 1.07–1.13], $P<0.001$), smoking (HR, 1.59 [95% CI, 1.01–2.51, $P=0.045$]), and dementia (HR, 2.03 [95% CI, 1.11–3.72], $P=0.021$) were associated with higher risk of cardiovascular mortality, whereas the inverse association between DOAC use and cardiovascular mortality (HR, 0.49 [95% CI, 0.34–0.71], $P<0.001$) was confirmed in this model (full adjusted model was shown in Table S5).

We then used PSM to confirm robustness of our findings; Table S6 shows data for the matched cohorts. After PSM, we included in the analysis 1194 patients with HFmrEF/HFrEF and 1194 patients without HF (Table S6, top panel) with all baseline characteristics well balanced between the 2 groups. After PSM,

Table 2. Stepwise Multivariable Cox Proportional Hazards Regression Analysis of Factors Associated with All-Cause Mortality in Patients Without HF, HFrEF/HFmrEF, and HFpEF

Patients without HF	Hazard ratio	95% CI		*P* value
		Low	High	
Age≥75 y	3.067	2.381	3.951	<0.001
COPD/OSAS	1.909	1.474	2.472	<0.001
Diabetes	1.287	1.026	1.615	0.029
Anemia	1.726	1.419	2.100	<0.001
Paroxysmal atrial fibrillation (vs persistent/permanent)	0.774	0.632	0.948	0.013
Creatinine clearance <30 mL/min	2.070	1.522	2.815	<0.001
Peripheral artery disease	1.659	1.206	2.282	0.002
Previous cerebrovascular disease	1.310	1.042	1.646	0.021
Previous cardiovascular disease	1.732	1.360	2.205	<0.001
DOAC	0.475	0.386	0.585	<0.001
RAASi	0.808	0.670	0.975	0.026
Class 1C antiarrhythmic drugs	0.609	0.387	0.960	0.033
Lipid-lowering therapy	0.576	0.461	0.722	<0.001
Patients with HFrEF/HFmrEF				
Women	0.603	0.400	0.908	0.015
Age≥75 y	2.465	1.555	3.907	<0.001
Creatinine clearance <30 mL/min	3.228	2.094	4.977	<0.001
Peripheral artery disease	2.246	1.387	3.638	0.001
RAASi	0.600	0.413	0.872	0.007
Patients with HFpEF				
Age≥75 y	2.247	1.310	3.853	0.003
COPD/OSAS	2.109	1.440	3.089	<0.001
Anemia	1.482	1.028	2.136	0.035
Paroxysmal atrial fibrillation (vs persistent/permanent)	0.528	0.322	0.867	0.012
Creatinine clearance <30 mL/min	1.791	1.104	2.906	0.018
DOAC	0.575	0.390	0.845	0.005
RAASi	0.670	0.464	0.968	0.033

COPD indicates chronic obstructive pulmonary disease; DOAC, direct oral anticoagulants; HF, heart failure, HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction, OSAS, obstructive sleep apnea syndrome; and RAASi, renin angiotensin aldosterone system inhibitors.

we included in the analysis 1088 patients with HFpEF and 1088 patients without HF (Table S6, bottom panel) with all baseline characteristics well balanced.

Then, we performed Kaplan–Meier survival curves for all-cause mortality of patients with HFmrEF/HFrEF compared with those without HF in the PSM cohort (Figure S3A) and patients with HFpEF compared with those without HF in the PSM cohort (Figure S3B). Both patients with HFmrEF/HFrEF and HFpEF exhibited significantly lower overall survival over time compared with those without HF (log-rank test *P*=0.037 and *P*=0.003, respectively). In the univariate Cox proportional hazards model, HFmrEF/HFrEF and HFpEF were significantly associated with an increased risk of all-cause mortality (HR, 1.33 [95% CI, 1.02–1.74], *P*=0.037 and HR, 1.49 [95% CI, 1.14–1.94], *P*=0.004).

DISCUSSION

The analysis of our registry that included >10 000 patients with AF on oral anticoagulants showed a high prevalence of patients with HF of 22.2%, of whom nearly 50% had HFpEF. Notably, both patients with HFpEF and HFrEF/HFmrEF, compared with patients without HF, had an increased risk of death that persisted after adjustment for potential confounding factors.

We found a prevalence of HF in the with AF cohort coherent with a previous analysis performed on GARFIELD-AF (Global Anticoagulant Registry in the Field-Atrial Fibrillation) registry, in which about 18% of patients had a diagnosis of HF. However, among patients with available EF in the GARFIELD-AF cohort, only 9.8% had an EF<40%, suggesting that a high

proportion of patients with HF had a preserved or mildly reduced EF.[14]

In our cohort, patients with HFpEF were older, more frequently women, and affected by arterial hypertension compared with those with HFrEF/HFmrEF. The role of RAASi in the reduction of all-cause mortality in patients with AF has been previously investigated,[15] however, our study showed that this inverse association was consistent in patients with AF independently from type HF as RAASi use was associated with lower mortality risk both in HFpEF and HFrEF/HFmrEF.

Patients with HFrEF/HFmrEF had a higher proportion of history of cardiovascular disease, as expected by the ischemic cause commonly responsible for HFrEF/HFmrEF onset.

We found that the presence of either HFpEF or HFrEF/HFmrEF with AF was associated with an increased risk of death. A previous study performed on 23644 patients with HF (diagnosed according to *International Classification of Diseases, Ninth Revision* [*ICD-9*] codes), showed that the risk of death was increased in both HFpEF and HFrEF/HFmrEF.[16] However, the cohort of this study was represented by patients with HF only and differs broadly from our cohort. Indeed, only 23.5% of patients were treated with oral anticoagulants and had a higher proportion of patients treated with lipid-lowering therapy and antiplatelets and a higher proportion of patients with chronic lung disease.[16]

We found a mortality rate of 3.5 per 100 patient-years, similar to that reported in the COOL-AF (Cohort of Antithrombotic Use and Clinical Outcomes in Patients With Atrial Fibrillation) prospective cohort enrolling 3046 patients with AF, which showed a mortality rate of 3.6 per 100 patient-years (ranged between 2.5 per 100 patient-years in patients with paroxysmal AF and 4.4 per 100 patient-years in patients with persistent AF).[17] Although patients were younger in the COOL-AF cohort and a lower thromboembolic risk evaluated by CHA_2DS_2-VASc score was found, a similar mortality rate was observed. This could be explained by the high burden of comorbidities registered in the COOL-AF cohort despite the younger age and also the high proportion of patients who were not taking oral anticoagulants (1 out of 3 patients was taking antiplatelets). Likewise, in the GARFIELD-AF registry the mortality rate at 1 year ranged between 3.04 and 4.05.[14] In this study, patients were younger with a lower mean of CHA_2DS_2-VASc score compared with our cohort, with similar proportions of patients with paroxysmal AF. Of note, few patients were treated with DOACs in the GARFIELD-AF registry, especially in the cohort of patients enrolled retrospectively.[14] Also in this cohort, a proportion of patients ranging between 26.9% and 30.2%[14] was treated with antiplatelet drugs alone increasing the risk of cerebrovascular disease and also the mortality rate associated with stroke.

A novel finding of our work is in investigating the role of different cardiovascular and noncardiovascular comorbidities according to HF phenotype.

Compared with HFrEF, in patients with HFpEF a relevant role on all causes of death was played by comorbidities such as CKD, anemia, and respiratory disease such as COPD/OSAS.

This finding reflects the distinct pathophysiology of these conditions. In HFrEF, the primary abnormality is related to the reduced systolic function of the left ventricle, leading to impaired pumping capacity and systemic fluid overload, which is the main driver of symptoms and signs and subsequent mortality in this type of HF. Conversely, HFpEF is characterized by increased filling pressure and myocardial stiffness often driven by systemic low-grade inflammation and microvascular dysfunction.[18] Indeed, HFpEF may be the result of the presence of different comorbidities, such obesity, COPD, and pulmonary hypertension, that may lead to HF through different pathways without impairing systolic function of the left ventricle.[19]

As an example, HFpEF is the most common form of HF in patients with COPD (70%).[20] COPD further exacerbates HFpEF through 2 mechanisms: first, by promoting systemic inflammation and intermittent hypoxia, and second, by inducing pulmonary hypertension, which increases right ventricular afterload leading to right ventricular function impairment.[21,22]

For these reasons, they are now recognized as different phenotypes of HFpEF and a phenotype-base therapeutic approach is warranted.[23] As such, the identification of the comorbidity contributing the most to the HF phenotype is essential to improve cardiac status. For instance, when an “obesity phenotype” is identified, promoting a healthy lifestyle—including regular physical activity, weight loss, optimized glycemic control, and a balanced diet—should be a top priority for these patients.[21] This may also be obtained by preferring the use of drugs known to facilitate weight loss especially in patients with diabetes (ie, semaglutide, liraglutide, and tirzepatide). As a background therapy in these patients, SGLT2 (sodium/glucose cotransporter 2) inhibitors should always be considered when not contraindicated, as they allow natriuresis and improved myocardial energy, preserve renal function, and reduce the risk of HF hospitalization and mortality.[24]

Thromboprophylaxis with DOAC in patients with AF and HF is particularly important given the inverse association with all-cause mortality. This reduction may be led by the reduction of cardiovascular events associated with DOAC use as shown in a large prospective cohort of 2366 patients with AF during a long-term follow-up.[25] Further mechanisms associated with a reduction in mortality in patients treated with DOACs may be related to the lower deterioration of kidney function compared with VKAs, which is associated

with an increased risk of mortality.[26] Furthermore, patients on DOACs show a lower risk of stroke[27,28] and bleeding,[28] especially intracranial bleeding, compared with VKAs, and this may lead to a lower mortality rate in patients treated with DOACs.

Regarding drugs, we found that rhythm control with Class 1C AADs was inversely associated with all-cause mortality, whereas no associations were found with β-blockers, calcium channel blockers, or digoxin. This finding is coherent with a previous meta-analysis[29] including 5 studies with 16825 patients with AF and HFpEF. In this study,[29] rhythm control for AF was associated with lower all-cause mortality (odds ratio [OR], 0.735 [95% CI, 0.665–0.813]; $P<0.001$) compared with rate control.

In addition, patients with HFrEF were more likely to be treated with RAASi compared with patients with HFpEF despite a higher prevalence of hypertension in the latter group. This may be mainly due to the higher prevalence of ischemic heart disease in the group with HFrEF for whom RAASi treatment is mandatory in most cases.[30] However, we found an inverse association between RAASi and mortality in both groups of HF, but, given the observational nature of the study, we could not exclude the presence of a selection bias that may influence the results.

We also found a sex difference in the association between HFpEF and mortality. Indeed, HFpEF independently associated with mortality in men but not in women. A report from the ARIC (Atherosclerosis Risk in Communities) Community Surveillance Study including patients with HFpEF without AF showed a higher risk of 1-year mortality in men but not in women.[31] Our findings are coherent with previous literature: indeed, in western populations, HFpEF had a greater prevalence in women but with a lower risk of mortality compared with men.[32] This may be explained by several differences. First, the first cause of HF in men was ischemic heart disease, whereas in women it was the concomitant presence of multiple cardiovascular and noncardiovascular comorbidities such as arterial hypertension, diabetes, endocrine disorders, and rheumatic diseases.[32] A further explanation of this phenomenon could be derived from a large analysis including 4458 women and 4010 men with HFpEF.[33] In this cohort women had a higher burden of symptoms and similar rates of hospitalizations but lower rates of death compared with men. The authors found that this difference was related to a lower incidence of cardiac sudden death, which was usually associated with coronary artery disease, that affected more frequently men than women.[33]

Limitations

Our study has several limitations to acknowledge. The lack of data on natriuretic peptides in the START registry does not allow us to perfectly adhere to the definition of HF defined by the European Society of Cardiology.[30] However, this limitation is present in all registry studies that began before the introduction of the current HF classification. In addition, a recent American Heart Association/American College of Cardiology/Heart Failure Society of America guideline[34] emphasizes the role of trajectories of EF, identifying a group of patients with HF with improved EF that may have different prognosis. In our study we could not detect these patients as evaluation of EF was made only at study entry.

Furthermore, the START registry includes almost exclusively White patients, so the prevalence and role of comorbidities may be different in different ethnicities. A further limitation was the lack of information about adherence on anticoagulation over time. This aspect is of clinical relevance as taking DOAC over VKAs does not directly translate into a higher adherence to anticoagulation prescription,[35] meaning that a proportion of patients may be nonadherent during follow-up. Additionally, we have no data about implantable cardioverter-defibrillator implantation and direct current shocks.

Finaly, we dichotomized age at 75 years based on clinical relevance and consistency with established risk scores (ie, CHA_2DS_2-VASc). However, this approach may potentially obscure age-related variation and reduce statistical power. Although more flexible modeling could improve precision, we chose to prioritize clinical interpretability.

However, the analysis on a large number of patients from different centers and the adjustment for multiple cardiovascular risk factors, also after PSM and competing risk analysis, give strength to the results.

CONCLUSIONS

In patients with AF, a significant proportion of patients with HF have a phenotype of HFpEF and are at increased risk of mortality. Our results suggest that patients with HFpEF require an approach that takes into consideration noncardiovascular comorbidities associated with an elevated risk of mortality.

APPENDIX

Participating centers and investigators who contributed to the START2 AF Registry:

- Division of Angiology and Blood Coagulation, IRCCS Azienda Ospedaliero-Universitaria S. Orsola-Malpighi Bologna, Italy: Benilde Cosmi.
- SOD Malattie Aterotrombotiche, Azienda Ospedaliero Universitaria-Careggi, Firenze, Italy: Daniela Poli, Elena Lotti, Martina Berteotti, Rossella Marcucci.

- SSD Degenza Breve Internistica, Dipartimento di Medicina Interna, Ospedale di Circolo e Fondazione Macchi, ASST Sette Laghi, Varese, Italy: Walter Ageno, Giovanna Colombo.
- UOC Medicina Interna, Centro Emocoagulopatie, AOU Cagliari, Cagliari: Doris Barcellona.
- Ambulatorio Malattie Emorragiche e Trombotiche, Medicina Trasfusionale di Udine, Presidio Ospedaliero Universitario "Santa Maria della Misericordia," Udine, Italy: Giovanni Barillari, Alessandra Poz.
- Centro Trasfusionale, Centro Emostasi e Trombosi, Ospedale SS Annunziata, Taranto, Italy: Salvatore Bradamante.
- SS Medicina Vascolare e Angiologia, AUSL Romagna – Ravenna, Italy: Eugenio Bucherini, Monica Vastola, Luca Bucherini.
- Centro Diagnosi Trombosi e Sorveglianza Terapia Anticoagulanti, Immunoematologia Trasfusionale, Ospedale SS Antonio e Margherita, Tortona (AL): Paola Casasco.
- Dipartimento Medicina di Laboratorio, Laboratorio Analisi, Ospedale San Giuseppe Moscati, Avellino, Italy: Antonio Ciampa.
- Dipartimento di Medicina Traslazionale e di Precisione, Sapienza Università di Roma – Roma, Italy: Antonio Chistolini, Alessandra Serrao.
- Ambulatorio Emostasi e Trombosi, UO Patologie Trombotiche, Ospedale San Raffaele, Milano, Italy: Luciano Crippa.
- UOSD Malattie Emorragiche e Trombotiche, Dipartimento Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy: Raimondo De Cristofaro, Erica De Candia.
- Centro Emostasi e Trombosi, Medicina Generale, ASST Lecco, Lecco, Italy: Valeria De Micheli.
- Dipartimento Cardiotoraco Vascolare, IRCCS Azienda Ospedaliero-Universitaria S. Orsola-Malpighi Bologna, Italy: Igor Diemberger, Giuseppe Boriani.
- Dipartimento di Medicina e Scienze dell'Invecchiamento, SSD Medicina Interna, University "G. D'Annunzio" di Chieti-Pescara, Pescara, Italy: Marcello Di Nisio, Ettore Porreca.
- Università Bicocca Milano, Dept. Medicine and Surgery, Monza and Divisione di Immunoematologia e Medicina Trasfusionale & Centro Emostasi e Trombosi, ASST Papa Giovanni XXIII – Bergamo, Italy: Anna Falanga, Teresa Lerede.
- Centro Trombosi, Casa del Sollievo e della Sofferenza, S. Giovanni Rotondo (Foggia), Italy: Elvira Grandone, Donatella Colaizzo.
- SC Laboratorio Analisi Chimico-Cliniche e Microbiologia, AO Ordine Mauriziano, Torino, Italy: Antonio Insana.
- UO Medicina Interna, Ambulatorio Terapia Anticoagulante Orale, AO Provincia di Pavia, Pavia, Italy: Nicola Lucio Liberato.
- UOC di Patologia Clinica, Ospedale A. Perrino, Brindisi, Italy: Domenico Lione.
- Centro Emostasi e Trombosi, UO Medicina Interna, Azienda Ospedaliero-Universitaria di Parma, Italy: Rosa Maria Lombardi.
- Centro Trombosi, Ospedale Regionale F. Miulli, Acquaviva delle Fonti (Bari), Italy: Giacomo Lucarelli.
- Centro Emofilia e Trombosi, Policlinico di Bari, Bari, Italy: Giuseppe Malcangi.
- Trasfusionale, Ospedale di Galatina, Galatina (LE), Italy: Catello Mangione.
- Centro Emostasi, Spedali Civili di Brescia, Brescia, Italy: Giuliana Martini.
- UOS Angiologia Medica, Ospedale di Rovigo, Italy: Marco Marzolo.
- Dipartimento di Medicina, Azienda Ospedaliero-Universitaria di Padova, Padova, Italy: Giovanni Nante.
- Centro Emofilia – Presidio Ospedaliero Morelli, Reggio Calabria, Italy: Vincenzo Oriana.
- Laboratorio Analisi, Ospedale Maggiore Chieri, Torino, Italy: Carmelo Paparo.
- UO di Medicina Trasfusionale, Presidio Ospedaliero Dimiccoli, Barletta (Bari), Italy: Paolo Pedico.
- Servizio di Laboratorio, Istituto Ospedaliero Fondazione Poliambulanza, Brescia, Italy: Simona Pedrini.
- Dipartimento di Scienze Cardio-Toraco-Vascolari, AOU Padova, Padova, Italy: Vittorio Pengo.
- Centro Prevenzione e Cura Malattie Tromboemboliche e Centro TAO, I.R.C.C.S. Azienda Ospedaliera Universitaria San Martino-IST, Genova, Italy: Antonietta Piana, Francesco Cibecchini.
- UO Medicina Trasfusionale, Centro TAO, PO Battipaglia, Battipaglia (Salerno), Italy: Simona Pezzella.
- Centro Trombosi, Dipartimento SCIAC, Sapienza Università di Roma, Italy: Pasquale Pignatelli, Daniele Pastori.
- Centro Emostasi e Trombosi, UOC Ematologia, Azienda Ospedaliera di Cosenza, Cosenza, Italy: Vincenza Rossi.
- UO di Analisi Chimico Cliniche, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy: Lucia Ruocco, Paolo Chiarugi.
- Clinica di Ematologia, AOU Ospedali Riuniti di Ancona, Ancona, Italy: Serena Rupoli.
- Servizio Analisi, Ospedale Evangelico Internazionale, Sede di Castelletto, Genova, Italy: Domizio Serra.
- SIMT ASST Bergamo Ovest – Ospedale di Treviglio, Pavia, Italy: Carmine Spataro, Margherita Reduzzi, Chiara Ambaglio.

- Centro Emostasi e Trombosi, UUOO Laboratorio Analisi chimico-cliniche e microbiologiche, ASST Cremona, Cremona, Italy: Sophie Testa, Oriana Paoletti.
- UOC di Patologia Clinica, Ambulatorio Terapia Anticoagulante Orale, O.C. "L. Cazzavillan," Arzignano (Vicenza), Italy: Andrea Toma.
- Dipartimento di Medicina Trasfusionale e di Ematologia, ASST Santi Paolo e Carlo, Milano, Italy: Vincenzo Toschi.
- Centro Emostasi e Trombosi, UO Emofilia e Patologie della Coagulazione, Dipartimento di Ematologia, Oncologia e Medicina Trasfusionale, Azienda Ospedaliera "Pugliese Ciaccio," Catanzaro, Italy: Rita Carlotta Santoro.
- Laboratorio Patologia Clinica, Policlinico Casilino – Roma, Roma, Italy: Claudio Vasselli.
- U.O. Medicina II, Azienda Ospedaliera San Paolo di Milano, ASST Santi Paolo e Carlo, Milano, Italy: Maddalena Loredana Zighetti, Marco Cattaneo, Gianmarco Podda.

ARTICLE INFORMATION

Received March 23, 2025; accepted May 15, 2025.

Affiliations

Department of General Surgery and Surgical Specialty Paride Stefanini, Sapienza University of Rome, Rome, Italy (D.M., G.G.); Fondazione Arianna Anticoagulazione, Bologna, Italy (E.A., G.P.); Center of Atherothrombotic Disease, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy (D.P.); Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Catanzaro, Italy (G.A., A.S.); Postgraduate School of Internal Medicine, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy (G.d.C.); Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy (R.M.); Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Caserta, Italy (P.C., A.C.); Division of Clinical Cardiology, Azienda Ospedaliera di Rilievo Nazionale "Sant'Anna e San Sebastiano", Caserta, Italy (P.C., A.C.); Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy (P.P., D.P.); and IRCCS Neuromed, Località Camerelle, Pozzilli, Italy (D.P.).

Sources of Funding

None.

Disclosures

None.

Supplemental Material

Tables S1–S6
Figures S1–S3

REFERENCES

1. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation*. 2009;119:2516–2525. doi: 10.1161/CIRCULATIONAHA.108.821306
2. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. *Circulation*. 1991;84:40–48. doi: 10.1161/01.cir.84.1.40
3. Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT studies. The V-HeFT VA cooperative studies group. *Circulation*. 1993;87:VI102–VI110.
4. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT investigators. *Circulation*. 1998;98:2574–2579. doi: 10.1161/01.cir.98.23.2574
5. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol*. 2003;91:2D–8D. doi: 10.1016/s0002-9149(02)03373-8
6. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133:484–492. doi: 10.1161/CIRCULATIONAHA.115.018614
7. Tersalvi G, Bossard M, Aeschbacher S, Wiencierz A, Beer JH, Rodondi N, Gencer BF, Reichlin T, Auricchio A, Ammann P, et al. Prevalence and outcomes of heart failure phenotypes in patients with atrial fibrillation. *Int J Cardiol*. 2024;412:132320. doi: 10.1016/j.ijcard.2024.132320
8. Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart failure and atrial fibrillation, like fire and fury. *JACC Heart Fail*. 2019;7:447–456. doi: 10.1016/j.jchf.2019.03.005
9. Cheng M, Lu X, Huang J, Zhang J, Zhang S, Gu D. The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. *Eur J Heart Fail*. 2014;16:1317–1322. doi: 10.1002/ejhf.187
10. Budnik M, Gawalko M, Lodzinski P, Tyminska A, Ozieranski K, Grabowski M, Peller M, Wancerz A, Kiliszek M, Opolski G, et al. Heart failure in patients with atrial fibrillation: insights from Polish part of the EORP-AF general long-term registry. *ESC Heart Fail*. 2023;10:637–649. doi: 10.1002/ehf2.14130
11. Inciardi RM, Giugliano RP, Park JG, Nordio F, Ruff CT, Chen C, Lanz HJ, Antman EM, Braunwald E, Solomon SD. Risks of heart failure, stroke, and bleeding in atrial fibrillation according to heart failure phenotypes. *JACC Clin Electrophysiol*. 2023;9:569–580. doi: 10.1016/j.jacep.2022.11.032
12. Antonucci E, Poli D, Tosetto A, Pengo V, Tripodi A, Magrini N, Marongiu F, Palareti G, Register S. The Italian START-Register on anticoagulation with focus on atrial fibrillation. *PLoS One*. 2015;10:e0124719. doi: 10.1371/journal.pone.0124719
13. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns H, De Potter TJR, Dwight J, Guasti L, Hanke T, et al. 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024;45:3314–3414. doi: 10.1093/eurheartj/ehae176
14. Fox KAA, Accetta G, Pieper KS, Bassand JP, Camm AJ, Fitzmaurice DA, Kayani G, Kakkar AK; Investigators G-A. Why are outcomes different for registry patients enrolled prospectively and retrospectively? Insights from the global anticoagulant registry in the FIELD-Atrial Fibrillation (GARFIELD-AF). *Eur Heart J*. 2018;4:27–35. doi: 10.1093/ehjqcco/qcx030
15. Menichelli D, Poli D, Antonucci E, Palareti G, Pignatelli P, Pastori D; Investigators SR. Renin-angiotensin-aldosterone system inhibitors and mortality risk in elderly patients with atrial fibrillation. Insights from the nationwide START registry. *Eur J Intern Med*. 2024;119:84–92. doi: 10.1016/j.ejim.2023.08.019
16. McManus DD, Hsu G, Sung SH, Saczynski JS, Smith DH, Magid DJ, Gurwitz JH, Goldberg RJ, Go AS; Cardiovascular Research Network PS. Atrial fibrillation and outcomes in heart failure with preserved versus reduced left ventricular ejection fraction. *J Am Heart Assoc*. 2013;2:e005694. doi: 10.1161/JAHA.112.005694
17. Apiyasawat S, Kornbongkotmas S, Chichareon P, Krittayaphong R; Investigators C-A. Mortality risk and temporal patterns of atrial fibrillation in the nationwide registry. *J Arrhyth*. 2021;37:1434–1442. doi: 10.1002/joa3.12643
18. Fayyaz AU, Eltony M, Prokop LJ, Koepp KE, Borlaug BA, Dasari S, Bois MC, Margulies KB, Maleszewski JJ, Wang Y, et al. Pathophysiological insights into HFpEF from studies of human cardiac tissue. *Nat Rev Cardiol*. 2025;22:90–104. doi: 10.1038/s41569-024-01067-1
19. Samson R, Jaiswal A, Ennezat PV, Cassidy M, Le Jemtel TH. Clinical phenotypes in heart failure with preserved ejection fraction. *J Am Heart Assoc*. 2016;5:5. doi: 10.1161/JAHA.115.002477

20. Gulea C, Zakeri R, Quint JK. Differences in outcomes between heart failure phenotypes in patients with coexistent chronic obstructive pulmonary disease: A cohort study. *Ann Am Thorac Soc*. 2022;19:971–980. doi: 10.1513/AnnalsATS.202107-823OC
21. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart failure with preserved ejection fraction: JACC scientific statement. *J Am Coll Cardiol*. 2023;81:1810–1834. doi: 10.1016/j.jacc.2023.01.049
22. Agress S, Sheikh JS, Ramos AAP, Kashyap D, Razmjouei S, Kumar J, Singh M, Lak MA, Osman A, Zia Ul Haq M. The interplay of comorbidities in chronic heart failure: challenges and solutions. *Curr Cardiol Rev*. 2024;20:13–29. doi: 10.2174/011573403X289572240206112303
23. Anker SD, Usman MS, Anker MS, Butler J, Bohm M, Abraham WT, Adamo M, Chopra VK, Cicoira M, Cosentino F, et al. Patient phenotype profiling in heart failure with preserved ejection fraction to guide therapeutic decision making. A scientific statement of the Heart Failure Association, the European Heart Rhythm Association of the European Society of Cardiology, and the European Society of Hypertension. *Eur J Heart Fail*. 2023;25:936–955. doi: 10.1002/ejhf.2894
24. Pandey AK, Bhatt DL, Pandey A, Marx N, Cosentino F, Pandey A, Verma S. Mechanisms of benefits of sodium-glucose cotransporter 2 inhibitors in heart failure with preserved ejection fraction. *Eur Heart J*. 2023;44:3640–3651. doi: 10.1093/eurheartj/ehad389
25. Pastori D, Menichelli D, Del Sole F, Pignatelli P, Violi F; group A-As. Long-term risk of major adverse cardiac events in atrial fibrillation patients on direct Oral anticoagulants. *Mayo Clin Proc*. 2021;96:658–665. doi: 10.1016/j.mayocp.2020.06.057
26. Pastori D, Ettorre E, Lip GYH, Sciacqua A, Perticone F, Melillo F, Godino C, Marcucci R, Berteotti M, Violi F, et al. Association of different oral anticoagulants use with renal function worsening in patients with atrial fibrillation: A multicentre cohort study. *Br J Clin Pharmacol*. 2020;86:2455–2463. doi: 10.1111/bcp.14350
27. Lin DS, Lo HY, Huang KC, Lin TT, Lee JK. Efficacy and safety of direct Oral anticoagulants for stroke prevention in older patients with atrial fibrillation: A network meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2023;12:e030380. doi: 10.1161/JAHA.123.030380
28. Giugliano RP, Ruff CT, Wiviott SD, Nordio F, Murphy SA, Kappelhof JA, Shi M, Mercuri MF, Antman EM, Braunwald E. Mortality in patients with atrial fibrillation randomized to edoxaban or warfarin: insights from the ENGAGE AF-TIMI 48 trial. *Am J Med*. 2016;129:850, e852–857. doi: 10.1016/j.amjmed.2016.02.028
29. Al-Sadawi M, Aleem S, Aslam F, Jacobs R, Stevens G, Almasry I, Singh A, Fan R, Rashba E. Rhythm versus rate control for atrial fibrillation in heart failure with preserved ejection fraction. *Heart Rhythm*. 2022;3(O2):520–525. doi: 10.1016/j.hroo.2022.06.009
30. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726. doi: 10.1093/eurheartj/ehab368
31. Sharma K, Mok Y, Kwak L, Agarwal SK, Chang PP, Deswal A, Shah AM, Kitzman DW, Wruck LM, Loehr LR, et al. Predictors of mortality by sex and race in heart failure with preserved ejection fraction: ARIC Community Surveillance Study. *J Am Heart Assoc*. 2020;9:e014669. doi: 10.1161/JAHA.119.014669
32. Regitz-Zagrosek V. Sex and gender differences in heart failure. *Int J Heart Fail*. 2020;2:157–181. doi: 10.36628/ijhf.2020.0004
33. Dewan P, Rorth R, Raparelli V, Campbell RT, Shen L, Jhund PS, Petrie MC, Anand IS, Carson PE, Desai AS, et al. Sex-related differences in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2019;12:e006539. doi: 10.1161/CIRCHEARTFAILURE.119.006539
34. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the Management of Heart Failure: A report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063
35. Salmasi S, Safari A, De Vera MA, Lynd L, Koehoorn M, Bary AR, Andrade JG, Deyell M, Rush K, Zhao Y, et al. Comparative adherence between DOAC and VKA in patients with atrial fibrillation: a 23-year retrospective observational study in Canada. *Eur Heart J*. 2021;42:42. doi: 10.1093/eurheartj/ehab724.0563