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ORIGINAL RESEARCH ARTICLE

The association of heart failure across left ventricular ejection fraction with mortality in atrial fibrillation

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Abstract

Aims The aim of this study is to investigate the prognostic implications of the presence of heart failure (HF) across the range of left ventricular ejection fraction (LVEF) in patients with comorbid atrial fibrillation (AF).

Methods and results We conducted a retrospective cohort study of 1063 patients (median age 76 years), discharged from the cardiology ward with a primary or secondary diagnosis of AF between 2015 and 2018. We used Cox proportional-hazards and spline models to examine the association of the presence of HF, across the range of LVEF, with the primary outcome of all-cause mortality. HF was documented in 52.9% of patients at baseline. During a median follow-up of 31 months (interquartile range 10 to 52 months), 37.3% of patients died. The presence of HF was associated with a significantly higher risk of mortality [adjusted hazard ratio (aHR) 2.17; 95% confidence interval (CI), 1.70 to 2.77; $P < 0.001$], which was evident across HF with reduced (aHR 3.03; 95% CI 2.41 to 4.52), mid-range (aHR 2.08; 95% CI 1.47 to 2.94), and preserved LVEF (aHR 1.94; 95% CI 1.47 to 2.55). Among patients with HF, the spline curve depicted a non-linear association between LVEF and the risk of death, in which there was a steep and progressive increase in mortality for every 5% reduction in LVEF below 25% (aHR 1.97, 95% CI 1.04 to 3.73, $P = 0.04$).

Conclusions In patients with AF who were discharged from the hospital, the presence of HF at baseline was independently associated with a twofold risk of death, which was significant across LVEF-classified HF subtypes. Among patients with AF and HF, the risk of death rose significantly as LVEF was reduced below 25%.

Keywords Atrial fibrillation; Heart failure; Death; Hospitalization; Mortality; Ejection fraction

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Introduction

Atrial fibrillation (AF) is among the most common comorbidities found in hospitalized patients, and its prevalence keeps rising.[1] Heart failure (HF) occurs in more than one-third of patients with AF.[2] These entities are closely interrelated and have been designated as modern cardiovascular epidemics.[2,3] AF has been associated with significant mortality and morbidity, which rise steeply when HF coexists.[2–4]

The latest European Society of Cardiology Guidelines classified HF into three distinct subtypes, namely, HF with reduced (HFrEF), mid-range (HFmrEF), and preserved (HFpEF) left ventricular ejection fraction (LVEF).[5] Ejection fraction is the principal determinant of this classification; it is still the most widely reported index in echocardiography,[5] and historically related with the risk of mortality and cardiovascular morbidity.[6] To date, scarce data exist on the prognostic implications of the triad of LVEF-classified HF subtypes in patients with AF. On

the other hand, LVEF is measured as a continuum and can have infinite strata instead of only three. Hence, a risk stratification model incorporating continuous LVEF values would improve our understanding regarding the prognosis of patients with AF and HF. As of 2020, there is no data on the association of HF, stratified across the LVEF continuum, with the clinical course of patients with AF following acute hospitalization.

Against this background, we undertook a post hoc analysis of data from a cohort of well-characterized, unselected patients with comorbid AF who were discharged from the cardiology ward of a tertiary centre. LVEF was measured during the index hospitalization, and patients were followed-up after discharge. Our main aim was to evaluate the association of the presence of HF at baseline, further analysed by LVEF, with all-cause mortality during follow-up.

Methods

Study design

This is a retrospective cohort analysis of the MISOAC-AF (Motivational Interviewing to Support Oral AntiCoagulation Adherence in patients with non-valvular Atrial Fibrillation; ClinicalTrials.gov identifier: NCT02941978) randomized trial. The trial design and main results have been reported previously.[7,8] Briefly, MISOAC-AF demonstrated benefit from a motivational-educational intervention in improving adherence to oral anticoagulation among patients with AF, as compared with patients who had been randomly assigned to usual care. The trial conformed to the Declaration of Helsinki, and written informed consent was obtained from the participants. The first author wrote the first draft of the present manuscript and vouches for the completeness and accuracy of the analyses; all the authors participated in revisions.

Data and population sources

We used prospective data from the MISOAC-AF trial from December 2015 through June 2018. The database provided baseline clinical profiles, medical history, laboratory, and echocardiographic data relevant to the index date of hospital discharge, as well as discharge diagnoses and follow-up data on clinical outcomes. Data were manually abstracted on the basis of patient interviews, electronic hospital records, and insurance claims records by independent trained investigators.[8]

The source population included patients who participated in the MISOAC-AF trial. Patients were 18 years or older and had been discharged from the cardiology ward of an urban academic hospital in Thessaloniki, Greece, with any diagnosis, having comorbid AF. Exclusion criteria were valvular AF (moderate-to-severe mitral valve stenosis or mechanical valves), terminal illness, or conditions that could interfere with follow-up procedures. For the purposes of this study, patients whose LVEF had not been evaluated by echocardiography during the index hospitalization were also excluded.

Definition of covariates

Atrial fibrillation was defined as previously documented in the patient's history or new-onset AF during hospitalization. The latter was identified by a 12-lead electrocardiogram or a 24 h Holter monitor as irregular heart rhythm, without detectable P waves, lasting more than 30 s. A history of HF was verified by trained personnel using all available data from the patient's records and the in-person interview, according to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF.[5] New diagnoses of HF denoted by the attending physician at discharge were incorporated into the analyses. During the index hospitalization, a routine echocardiographic exam was performed. Echocardiographic images were analysed offline by an independent investigator with the use of dedicated software (EchoPAC, GE, USA). The biplane Simpson's method of disks was used to calculate LVEF, corresponding to the subtraction of the end-systolic volume from the end-diastolic volume and the difference divided by the end-diastolic volume. Values of cardiac cycles with at least two similar preceding RR intervals were chosen. In case of poor image quality, LVEF estimation was based on visual assessment. Patients with HF and an LVEF of 50% or higher were classified as having HFpEF, those with an LVEF of 40% to 49% as HFmrEF, whereas those with an LVEF of less than 40% were classified as having HFrEF.

Study outcomes and follow-up

The primary outcome was all-cause mortality, which was defined as death from any cause. The secondary outcome was the composite of cardiovascular mortality or any hospitalization during follow-up. All outcomes were adjudicated by independent physicians in the MISOAC-AF trial.[8] All deaths were additionally verified by querying the Greek web-based national general health insurance scheme.

Follow-up regarding the primary and secondary outcomes occurred annually from the index date of hospital discharge, via telephonic or in-person interviews. The follow-up period was extended for the purposes of this study and was ended in May 2020.

Statistical analysis

Characteristics of the study patients, grouped as AF without HF, and AF with HF are presented as frequencies or percentages for dichotomous variables and medians with interquartile ranges or means and standard deviations for

continuous variables. Between-group comparisons were conducted using the Pearson χ^2 or Fisher's exact test for categorical variables and the Wilcoxon rank-sum or Student's *t*-test test for continuous variables, depending on the normality of data distributions. Time-to-event outcomes are presented with the use of Kaplan–Meier plots and compared among groups by the log-rank test. In patients with AF and HF, changes in the hazard ratio (HR) for the study outcomes across the continuous spectrum of LVEF values were investigated by fitting a spline curve. A value of LVEF, whereby HR equalled one, was derived for each plot. Using regression analyses, we reported the hazard associated with each 5% change in LVEF, given a linear association with the outcome existed for the respective LVEF range. Survival analyses were adjusted by Cox proportional-hazards regression, limited by a ratio of one additional covariate per 10 events of interest. The Cox-models included up to 14 clinically relevant baseline variables: intervention/control group assignment, age, sex, AF type, the presence or absence of chronic coronary syndrome, diabetes, hypertension, the use or non-use of a beta-blocker, angiotensin-converting–enzyme inhibitor, mineralocorticoid-receptor antagonist, oral anticoagulation, and the levels of N-terminal pro-BNP (NT-proBNP), high-sensitivity cardiac troponin T and estimated glomerular filtration rate. Schoenfeld residuals were examined to confirm no violation of the assumptions of the Cox proportional hazards regression model. Follow-up data on patients were censored in the event of death. Death was categorized as cardiovascular or non-cardiovascular, based on pre-specified definitions in the MISOAC-AF trial. All outcomes are reported with 95% confidence intervals (CIs) for HF subtypes, without adjustment for multiplicity. This overall false-positive rate was kept at 5% on two-sided tests. Missing data were handled by multiple imputations by chained equations. We imputed five complete data sets; a list of the variables used in the imputation model and the missing rates before and after the imputation is provided in Supporting Information, *Table S1*. For the regression analyses, we pooled the results across all five imputed data sets into one point-estimate using Rubin's rule. A sensitivity analysis was performed on the complete-case data set. All analyses were performed with the use of Stata software, Version 13.1 (StataCorp) and R Version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) by the first author and an author who is a statistician in an academic clinical trials unit (Clinical Trials Unit Thessaloniki, Aristotle University of Thessaloniki, Greece).

Results

Study population

A total of 1063 patients with AF (median age 76 years, interquartile range 63 to 89 years, 54.6% male) were included during the study period, after excluding 57 with unavailable data on echocardiography during the index hospitalization (*Figure S1*). Of the included AF patients, 562 (52.9%) had concomitant HF. In general, patients with AF and HF were older, had more comorbidities (hypertension, diabetes mellitus, chronic kidney disease, & coronary artery disease), and more often had a prior history of stroke or transient ischemic attack, compared with patients with AF alone (*Table 1*). Patients with HF had a mean LVEF of 45 ± 13% with a normal distribution (*Figure S2*). Most patients had HFpEF (25.7%), followed by HFrEF (16.3%) and HFmrEF (10.9%). In the lower LVEF categories, the proportion of male patients; coronary artery disease; and treatment with digitalis, amiodarone, antiplatelet, mineralocorticoid-receptor antagonist, and statin increased, whereas age, body mass index, arterial hypertension, and CHA_2DS_2-VASc decreased (*Table S2*). By the end of the study, information regarding the primary and secondary outcomes was available for all patients.

Outcomes

Overall, 396 patients (37.3%) died over a median follow-up of 31 months (interquartile range 10 to 52 months), at a rate of 14.4% per year. Of these deaths, 84.1% were due to cardiovascular causes (*Table S3*).

The primary outcome of death from any cause occurred in a significantly higher percentage of patients with HF [284 of 562 (50.5%)] than patients without HF [112 of 501 (22.4%)] (unadjusted HR, 2.89; 95% CI, 2.32 to 3.60, $P < 0.001$ by the log-rank test). After adjustment for baseline measures, HF remained a significant predictor of death (HR, 2.17; 95% CI, 1.70 to 2.77; $P < 0.001$) (*Figure 1A*). The secondary outcome of cardiovascular death or any hospitalization occurred more frequently in AF patients with HF than in AF patients without HF [384 patients (68.3%) vs. 232 patients (46.3%)] (unadjusted HR, 1.99; 95% CI, 1.69 to 2.35; $P < 0.001$ by the log-rank test). The adjusted HR was similar (1.66; 95% CI, 1.38 to 2.00; $P < 0.001$) (*Figure 1B*).

Among LVEF-classified HF subtypes, both the unadjusted and adjusted HRs for the risk of the primary and secondary outcome were significantly higher compared with patients without HF (*Figures S3* and *2*). This increase in risk was evident across HFrEF (aHR 3.03; 95% CI 2.41 to 4.52, $P < 0.001$), HFmrEF (aHR 2.08; 95% CI 1.47 to 2.94, $P < 0.001$), and HFpEF (aHR 1.94; 95% CI 1.47 to 2.55, $P < 0.001$). A summary of the HRs of outcomes and the individual components of the secondary outcome in HF and HF subtypes, compared with the absence of HF, is presented in *Table S4*.

The unadjusted and adjusted spline curves depicting the risk of outcomes of AF patients with HF across the LVEF spectrum, compared with a reference LVEF value of approximately 50%, are presented in *Figures S4* and *3*, respectively. In the adjusted curve, a trend towards an elevated risk of

Table 1 Characteristics of the patients at baseline

Characteristic	Overall (*N* = 1063)	AF-no HF (*N* = 501, 47.1%)	AF-HF (*N* = 562, 52.9%)	*P*
Demographics				
Age (years), median (IQR)	76 (13)	73.5 (16)	78 (12)	<**0.001**
Male sex	580 (54.6%)	263 (52.5%)	317 (56.4%)	0.2
BMI (kg/m^2), median (IQR)	28.1 (6.1)	28 (5.9)	28.1 (6.5)	0.09
AF type				<**0.001**
First diagnosed	114 (11.2%)	75 (15.6%)	39 (7.2%)	
Paroxysmal	376 (36.8%)	233 (48.4%)	143 (26.5%)	
Persistent or permanent	531 (52%)	173 (36%)	358 (66.3%)	
HF type				
New-onset HF	40 (3.8%)	—	40 (3.8%)	
Pre-existing HF	522 (49.1%)	—	522 (49.1%)	
Medical history				
Stroke/TIA	193 (18.5%)	69 (13.9%)	124 (22.7%)	<**0.001**
Stroke under OAC	70 (6.8%)	21 (4.3%)	49 (9.1%)	**0.002**
Major bleeding	151 (14.5%)	73 (14.8%)	78 (14.3%)	0.81
Arterial hypertension	840 (81%)	379 (77.3%)	461 (84.3%)	**0.005**
Dyslipidaemia	494 (47.9%)	234 (47.8%)	260 (48.1%)	0.92
Diabetes mellitus	344 (33.2%)	133 (27.1%)	211 (38.6%)	<**0.001**
Coronary artery disease	409 (41.1%)	157 (33.3%)	252 (48.1%)	<**0.001**
Chronic kidney disease	154 (15%)	43 (8.8%)	111 (20.5%)	<**0.001**
Stroke—bleeding risk				
CHA_2DS_2-VASc score	4.4 ± 1.9	3.5 ± 1.8	5.2 ± 1.7	<**0.001**
HAS-BLED score	1.8 ± 1.0	1.6 ± 1.0	1.9 ± 1.0	**0.001**
Main diagnosis at discharge				<**0.001**
Acute coronary syndrome	104 (10.7%)	65 (14%)	39 (7.7%)	
AF	380 (39.1%)	280 (60.4%)	100 (19.7%)	
HF	273 (28.1%)	—	273 (53.8%)	
Valvular heart disease	49 (5%)	22 (4.7%)	27 (5.3%)	
Other	165 (17%)	97 (20.9%)	68 (13.4%)	
Rate control medication at discharge				<**0.001**
Beta-blocker	733 (71.2%)	327 (67.4%)	406 (74.5%)	
Beta-blocker + digitalis	54 (5.2%)	10 (2.1%)	44 (8.1%)	
Rhythm control medication at discharge				<**0.001**
Amiodarone	178 (18.3%)	100 (21.7%)	78 (15.3%)	
Sotalol	16 (1.6%)	10 (2.2%)	6 (1.2%)	
Oral anticoagulation medication at discharge				<**0.001**
VKA	267 (28.8%)	83 (19.1%)	184 (37.3%)	
NOAC	505 (54.4%)	255 (58.6%)	250 (50.7%)	
Other medication at discharge				
OAC + antiplatelet	131 (14.5%)	66 (15.6%)	65 (13.4%)	0.35
ACE inhibitor or ARB	455 (46.3%)	207 (45%)	248 (47.4%)	0.45
MRA	277 (26.4%)	54 (10.9%)	223 (40%)	<**0.001**
Statin	417 (42.6%)	185 (40.4%)	232 (44.4%)	0.20
Laboratory markers at discharge				
eGFR (mL/min/1.73 m^2)	59.5 (40)	75 (43)	53.8 (34)	**0.002**
NT-proBNP	315 (1882)	172.5 (1606)	727 (2500)	0.36
hs-cTnT	26 (39)	23 (40)	29 (38)	0.19

Data were reported as absolute numbers (%), means ± standard deviation, or medians (IQR).
ACE, angiotensin-converting–enzyme; AF, atrial fibrillation; ARB, angiotensin II–receptor blocker; BMI, body mass index; CHA_2DS_2-Vasc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category); eGFR, estimated glomerular filtration rate; HF, heart failure; HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol); hs-cTnT, high-sensitivity cardiac troponin T; IQR; Interquartile range; MRA, mineralocorticoid-receptor antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, Oral anticoagulant; NT-proBNP, N-terminal pro-BNP; TIA, transient ischaemic attack; VKA, vitamin K antagonist;

mortality was observed below 30%. As LVEF further decreased beyond the threshold of 25% (*n* = 76 patients), a steeper and progressive increase in mortality was evident (*Figure 3A*). In a multivariable-adjusted model, the HR for mortality increased by 97% for every 5% reduction in LVEF below 25% (HR 1.97, 95% CI 1.04 to 3.73, *P* = 0.04) (*Table S5*). The risk of mortality was relatively flat for values between 30% and 55%. Above 55%, the risk slowly declined, which reached statistical significance within the LVEF range of 55–65%. The risk of the secondary outcome (cardiovascular death or hospitalization) showed a similar, albeit less pronounced pattern across LVEF, as compared with the primary outcome (*Figure 3B*). In the case of the secondary outcome, the spline curve and the limits of the CI included 1.00 for all LVEF values below 55%, which implies that the risk was similar below the 55% cut-off. The results of the analyses with the imputed data sets were virtually consistent with a complete-case analysis (*Table S4*, *Figures S5* and *S6*).

Figure 1 Cumulative incidence of outcomes according to presence of HF at baseline. aHR, adjusted hazard ratio; AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; HF, heart failure.

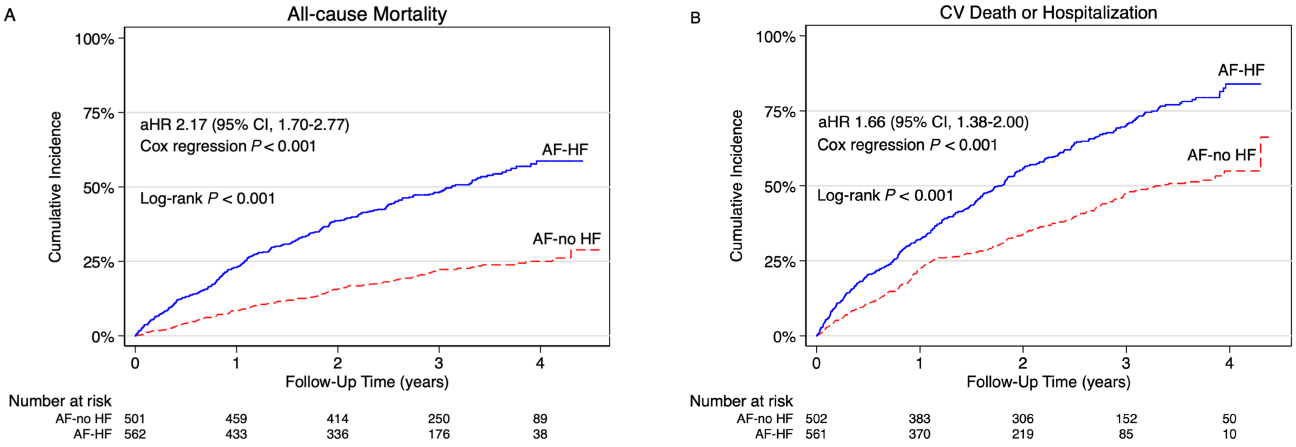
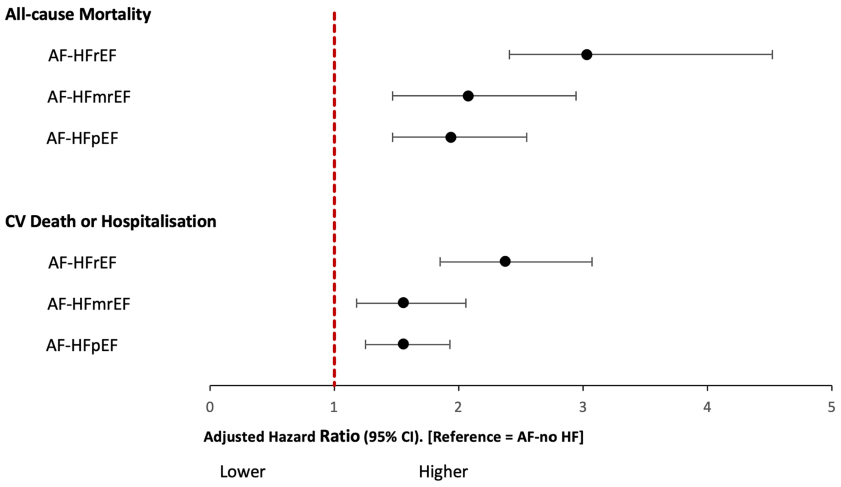


Figure 2 Type of HF at baseline compared with patients without HF: adjusted HRs of outcomes. Hazard ratios of outcomes by type of HF, using no HF as reference. HRs with 95% confidence intervals were calculated using Cox models, adjusted for intervention/control group assignment, age, sex, AF type, the presence or absence of chronic coronary syndrome, diabetes, hypertension, and the levels of N-terminal pro-BNP, high-sensitivity cardiac troponin T and estimated glomerular filtration rate. AF, atrial fibrillation; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; HFrEF heart failure with reduced ejection fraction; HFmrEF heart failure with mid-range ejection fraction; HFpEF heart failure with preserved ejection fraction.

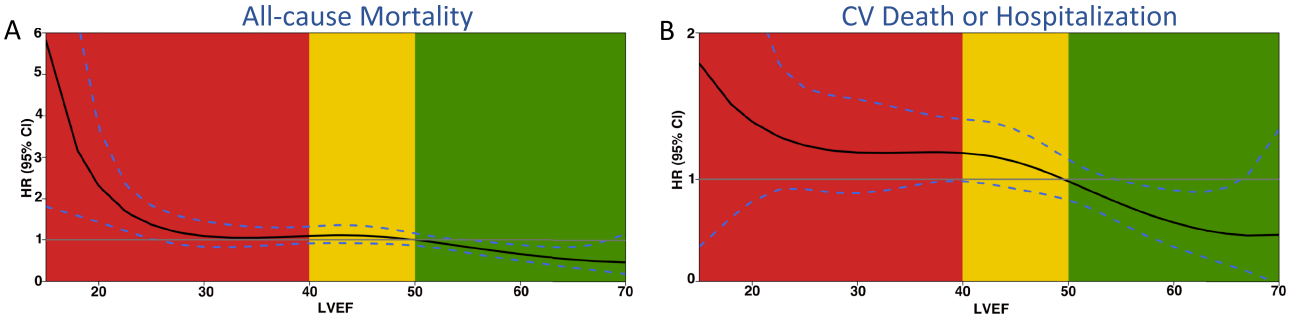


Discussion

This post-hoc analysis of a randomized clinical trial of AF patients being discharged from the hospital showed that the presence of HF at baseline was associated with an approximately twofold increase in the adjusted risk of death and the composite outcome of cardiovascular death or all-cause hospitalization. The risk of those outcomes was significantly increased across LVEF-classified HF subtypes. When LVEF was analysed as a continuous variable, the risk of mortality almost doubled for every 5% reduction in LVEF below 25%. To our knowledge, this is the first study to examine the relation of AF and comorbid HF along the continuum of LVEF with hard outcomes.

The observed two-fold increase in the adjusted risk for adverse outcomes in AF patients suffering from HF is in line with previous studies. Incident HF was first identified as an important modifier of survival in AF in a subanalysis of the Framingham Heart Study.[3] At that time, OAC treatment was restricted to warfarin, whereas background HF therapy was inferior to modern standards. In both outpatients and newly diagnosed patients with AF, HF was a powerful independent predictor of death and hospitalizations.[9–11] Corroborating evidence on the role of HF in AF has accumulated mostly

Figure 3 Adjusted association between LVEF and outcomes. Spline curves of outcomes of AF-HF patients over a median 2 year follow-up. The associations of LVEF with (A) all-cause mortality and (B) the composite of CV death and all-cause hospitalization are shown. Dashed lines represent 95% confidence intervals. The colour scale corresponds to the different HF subtypes (red, HFrEF; yellow, HFmrEF; & green, HFpEF). The models were adjusted for: intervention/control group assignment, age, sex, AF type, the presence or absence of chronic coronary syndrome, diabetes, hypertension, the use or non-use of a beta-blocker, angiotensin-converting–enzyme inhibitor, mineralocorticoid-receptor antagonist, oral anticoagulation, and the levels of N-terminal pro-BNP, high-sensitivity cardiac troponin T, and estimated glomerular filtration rate. AF, atrial fibrillation; CV; cardiovascular; LVEF, left ventricular ejection fraction; HF, heart failure; HFrEF heart failure with reduced ejection fraction; HFmrEF heart failure with mid-range ejection fraction; HFpEF heart failure with preserved ejection fraction; HR, hazard ratio.



from retrospective analyses of the landmark novel oral anticoagulation trials: In ROCKET-AF, the adjusted HR for mortality for HF was 1.75 (95% CI 1.4–2.3)[12]; in RE-LY, it reached 3.02 (95% CI 2.5–3.7).[13] The annual mortality rate in our study reached 14.4%, which is considerably higher compared with other studies.[11–15] This excess mortality could be attributed to several high-risk characteristics of our cohort. Advanced age (median of 76 years), hospitalization in an acute setting, often due to serious cardiovascular causes (38.8% myocardial infarction or acute HF), multiple coexisting conditions apart from HF, and a discordant to the high mean CHA_2DS_2-VASc score of 4.4 use of OAC (83.2%),[16] collectively formulate a cohort more prone to complications, including mortality.

We found a consistently higher adjusted risk of the primary or secondary outcome among AF patients with HFrEF, HFmrEF, or HFpEF, compared with those without HF. Nevertheless, a trend was detected towards higher risk in AF with HFrEF. Outcomes in HFmrEF more closely resembled those of HFpEF rather than those of HFrEF, which was also the case in a study of ambulatory patients with HF.[17] A meta-analysis of data from more than 50 000 patients identified a 24% increased relative risk of mortality in AF-HFrEF and similar risk of hospitalizations, compared with AF-HFpEF.[18] The totality of the data suggests that development of effective targeted interventions towards major comorbidities such as HF is necessary to improve outcomes in AF, besides applying effective anticoagulation per se. Indeed, the strategy of cardiovascular and comorbidity optimization ('C' component of the holistic pathway) is fundamental in the 2020 European Society of Cardiology AF Guidelines.[19]

Our risk-adjusted analyses identified a strong inverse association between declining LVEF values in the severely depressed range (below 25%) and the risk of mortality, whereas the nadir of adverse outcomes lied at values within the normal range (55–65%). When comparing our results with similar studies, it seems plausible that the relation of LVEF and outcomes varies by clinical setting. In older studies of patients with coronary artery disease[20] or chronic HF,[6,21,22] low LVEF was generally associated with worse survival. In contrast, a recent retrospective study indicated a non-significant relation of LVEF with prognosis in patients admitted with de novo or non-ischemic acute HF.[23] In a population-wide study published in 2020, LVEF values outside the normal range were associated with poorer survival, which remained significant after adjustment for a series confounders, including AF and HF.[24] These findings were replicated in our study. The credibility of our findings is further heightened by adjusting for an extensive set of confounders. Our study stands out for adjusting for both N-terminal pro-BNP and high-sensitivity cardiac troponin T, which are known powerful prognostic biomarkers.

Although our findings should be interpreted in the context of our sample's moderate size, they support the view that challenges subdivision of HF by a single biomarker (i.e. LVEF) as artificial and of vague prognostic significance, merely limited to the severely depressed spectrum.[25] Notably, LVEF was not useful in further risk-stratification of patients with HF and an LVEF between 30% and 55%; a finding consistent in unadjusted and adjusted analyses. It is conceivable that the prognostic significance of LVEF might be blunted in a high-risk group at baseline, namely multi-morbid patients that have sustained an acute hospitalization. In this respect, it would be of interest to explore how novel echocardiographic biomarkers perform, especially left ventricular global longitudinal strain and myocardial work index. Ultimately, we feel that efforts for comprehensive risk assessment in AF using multiple-biomarker based scores are in the right direction, as exemplified by the study of Hijazi et al[26] and a recent analysis from our cohort.[27]

Limitations

This analysis was not planned at the outset of the MISOAC-AF trial and is, therefore, both retrospective and non-randomized, confined to a single-centre data set. Accordingly, the associations of the various factors with the risk of adverse outcomes may suffer from unrecognized biases and unmeasured confounders, despite extensive adjustment for clinically relevant variables. Restricting our analysis to AF patients discharged from the hospital may limit the results' generalizability to AF outpatients, although it helped secure a more homogenous study population. The multivariable models were established based on demographics and characteristics of the patients measured at baseline. This approach could not account for newly ensuing comorbidities during follow-up or at the time of death, albeit it attenuated reverse causation in the interpretation of the results. Moreover, additional data of potential prognostic significance were unavailable, such as the duration or timing of AF and HF diagnosis prior to the index hospitalization, cardiac resynchronization therapy or implantable cardioverter defibrillator device, serial LVEF values post discharge and indices of OAC treatment quality (e.g. time in therapeutic range for vitamin-K antagonists).[28,29] A minority of cases in the database had to be excluded due to missing values on HF status or LVEF, possibly resulting in selection bias. Although assessment of LVEF was performed independently, reproducibility and validity of measurements are questionable in AF.[30] Furthermore, diagnosis of HFpEF in the context of AF may be challenging, due to the overlapping symptoms.[31] Thus, differential misclassification could have influenced our results.

Conclusions

In patients discharged from the hospital with comorbid AF, the presence of HF was independently associated with an approximately two-fold increased risk of all-cause mortality and the composite of cardiovascular mortality or all-cause hospitalization. The risk remained significant across LVEF-classified HF subtypes (HFrEF, HFmrEF, & HFpEF). The discriminatory effect of LVEF for prediction of mortality was strongest for values lower than 25%, whereby the risk doubled for every 5% decrease in LVEF.

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Conflict of interest

None declared.

Funding

Not applicable.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. List of variables imputed and amount of missing data at baseline.
Figure S1. Flowchart of the study population.
Table S2. Characteristics of Patients with Heart Failure at Baseline.
Figure S2. Distribution of LVEF values of patients with HF at baseline.
Table S3. Cause of death.
Figure S3. Type of HF at baseline compared with patients without HF: unadjusted HRs of Outcomes.
Figure S4. Unadjusted association between LVEF and Outcomes.
Table S4. Hazard ratios for outcomes at a median 31-month follow-up.
Figure S5. Adjusted association between LVEF and Outcomes (complete-case analysis).
Figure S6. Unadjusted association between LVEF and Outcomes (complete-case analysis).

References

1. Ball J, Carrington MJ, McMurray JJV, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013; **167**: 1807–1824.
2. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ, Levy D, Benjamin EJ, Ho JE. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016; **133**: 484–492.

3. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham heart study. *Circulation* 2003; **107**: 2920–2925.
4. Pandey A, Kim S, Moore C, Thomas L, Gersh B, Allen LA, Kowey PR, Mahaffey KW, Hylek E, Peterson ED, Piccini JP, Fonarow GC. Predictors and prognostic implications of incident heart failure in patients with prevalent atrial fibrillation. *JACC Hear Fail* 2017; **5**: 44–52.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016; **37**: 2129–2200m.
6. Solomon SD, Anavekar N, Skali H, McMurray JJV, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005; **112**: 3738–3744.
7. Samaras A, Kartas A, Vasdeki D, Dividis G, Forozidou E, Fotos G, Kotsi E, Paschou E, Tsoukra P, Goulas I, Karvounis H, Giannakoulas G, Tzikas A. Rationale and design of a randomized study comparing Motivational Interviewing to Support Oral AntiCoagulation adherence versus usual care in patients with non-valvular Atrial Fibrillation: the MISOAC-AF trial. *Hell J Cardiol* 2020; **61**: 453–454.
8. Tzikas A, Samaras A, Kartas A, Vasdeki D, Fotos G, Dividis G, Paschou E, Forozidou E, Tsoukra P, Kotsi E, Goulas I, Karvounis H, Giannakoulas G. Motivational interviewing to support oral anticoagulation adherence in patients with non-valvular atrial fibrillation (MISOAC-AF): a randomized clinical trial. *Eur Hear J - Cardiovasc Pharmacother* 2021; **7**: f63–f71.
9. Jani BD, Nicholl BI, McQueenie R, Connelly DT, Hanlon P, Gallacher KI, Lee D, Mair FS. Multimorbidity and co-morbidity in atrial fibrillation and effects on survival: findings from UK Biobank cohort. *Europace* 2018; **20**: f329–f336.
10. van Doorn S, Tavenier A, Rutten FH, Hoes AW, Moons KGM, Geersing GJ. Risk of cardiac and non-cardiac adverse events in community-dwelling older patients with atrial fibrillation: a prospective cohort study in the Netherlands. *BMJ Open* 2018; **8**: 1–7.
11. Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KAA, Goldhaber SZ, Goto S, Haas S, Hacke W, Kayani G, Mantovani LG, Misselwitz F, ten Cate H, Turpie AGG, Verheugt FWA, Kakkar AK. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J* 2016; **37**: 2882–2889.
12. Pokorney SD, Piccini JP, Stevens SR, Patel MR, Pieper KS, Halperin JL, Breithardt G, Singer DE, Hankey GJ, Hacke W, Becker RC, Berkowitz SD, Nessel CC, Mahaffey KW, Fox KAA, Califf RM, Anderson J, Bedwell N, Bilsker M, Bruce G, Agah R, DeSantis M, Eisenberg S, Flores A, Herzog W, Klein S, Snyder H, Krueger S, Almaguer E, Lavie E. Cause of death and predictors of all-cause mortality in anticoagulated patients with nonvalvular atrial fibrillation: data from ROCKET AF. *J Am Heart Assoc* 2015; **5**: 1–13.
13. Marijon E, le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom J, Themeles E, Ezekowitz M, Wallentin L, Yusuf S. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation* 2013; **128**: 2192–2201.
14. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KKL, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; **347**: 1397–1402.
15. Zafrir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, Anker SD, Filippatos G, Seferovic PM, Maggioni AP, de Mora Martin M, Polonski L, Silva-Cardoso J, Amir O. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J* 2018; **39**: 4277–4284.
16. Kartas A, Samaras A, Vasdeki D, Dividis G, Fotos G, Paschou E, Forozidou E, Tsoukra P, Kotsi E, Goulas I, Efthimiadis G, Karvounis H, Tzikas A, Giannakoulas G. Flaws in anticoagulation strategies in patients with atrial fibrillation at hospital discharge. *J Cardiovasc Pharmacol Ther* 2019; **24**: 225–232.
17. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017; **19**: 1574–1585.
18. McManus DD, Hsu G, Sung SH, Saczynski JS, Smith DH, Magid DJ, Gurwitz JH, Goldberg RJ, Go AS, Cardiovascular Research Network PRESERVE Study. Atrial fibrillation and outcomes in heart failure with preserved versus reduced left ventricular ejection fraction. *J Am Heart Assoc* 2013; **2**: 1–9.
19. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, la Meir M, Lane DA, Lebeau J-P, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, van Gelder IC, van Putte BP, Watkins CL, Kirchhof P, Kühne M, Aboyans V, Ahlsson A, Balsam P, Bauersachs J. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020; **42**: 373–498.
20. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR, Chaitman BR, Kaiser GC, Alderman E, Killip T. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. *Circulation* 1994; **90**: 2645–2657.
21. Wong M, Staszewsky L, Latini R, Barlera S, Glazer R, Aknay N, Hester A, Anand I, Cohn JN. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure: valsartan heart failure trial (Val-HeFT) echocardiographic data. *J Am Coll Cardiol* Elsevier Masson SAS 2004; **43**: 2022–2027.
22. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Hear Fail* 2017; **5**: 565–574.
23. Janwanishstaporn S, Feng S, Teerlink J, Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Pang P, Ponikowski P, Severin T, Gimpelewicz C, Holbro T, Chen CW, Sama I, Voors AA, Greenberg BH. Relationship between left ventricular ejection fraction and cardiovascular outcomes following hospitalization for heart failure: insights from the RELAX-AHF-2 trial. *Eur J Heart Fail* 2020; **22**: 726–738.
24. Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z, Gladding P, Good CW, Cleland JGF, Fornwalt BK. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J* 2020; **41**: 1249–1257.
25. Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, Backs J, Bauersachs J, Burkhoff D, Bonow RO, Chopra VK, de Boer RA, de Windt L, Hamdani N, Hasenfuss G, Heymans S, Hulot JS, Konstam M, Lee RT, Linke WA, Lunde IG, Lyon AR, Maack C, Mann DL, Mebazaa A, Mentz RJ, Nihoyannopoulos P, Papp Z, Parissis J, Pedrazzini T. The continuous heart failure spectrum: moving beyond an ejection fraction classification. *Eur Heart J* 2019; **40**: 2155–2163B.

26. Hijazi Z, Oldgren J, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Held C, Hylek EM, Lopes RD, Yusuf S, Granger CB, Siegbahn A, Wallentin L. A biomarker-based risk score to predict death in patients with atrial fibrillation: the ABC (age, biomarkers, clinical history) death risk score. *Eur Heart J* 2018; **39**: 477–485.
27. Samaras A, Kartas A, Akrivos E, Fotos G, Dividis G, Vasdeki D, Vrana E, Rampidis G, Karvounis H, Giannakoulas G, Tzikas A. A novel prognostic tool to predict mortality in patients with atrial fibrillation: the BASIC-AF risk score. *Hell J Cardiol* 2021. https://doi.org/10.1016/j.hjc.2021.01.007
28. Basuray A, French B, Ky B, Vorovich E, Olt C, Sweitzer NK, Cappola TP, Fang JC. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. *Circulation* 2014; **129**: 2380–2387.
29. Chamberlain AM, Redfield MM, Alonso A, Weston SA, Roger VL. Atrial fibrillation and mortality in heart failure: a community study. *Circ Hear Fail* 2011; **4**: 740–746.
30. Kotecha D, Mohamed M, Shantsila E, Popescu BA, Steeds RP. Is echocardiography valid and reproducible in patients with atrial fibrillation? A systematic review. *Europace* 2017; **19**: 1427–1438.
31. Kotecha D, Lam CSP, van Veldhuisen DJ, van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins. *J Am Coll Cardiol* 2016; **68**: 2217–2228.