CLINICAL RESEARCH
Heart failure/cardiomyopathy

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

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Aim	To investigate the characteristics long-term prognostic implications (up to ~2.2 years) of atrial fibrillation (AF) compared to sinus rhythm (SR), between acute and chronic heart failure (HF) with reduced (HFrEF < 40%), mid-range (HFmrEF 40–49%), and preserved (HFpEF ≥ 50%) ejection fraction (EF).
Methods and results	Data from the observational, prospective, HF long-term registry of the European Society of Cardiology were analysed. A total of 14 964 HF patients (age 66 ± 13 years, 67% male; 53% HFrEF, 21% HFmrEF, 26% HFpEF) were enrolled. The prevalence of AF was 27% in HFrEF, 29% in HFmrEF, and 39% in HFpEF. Atrial fibrillation was associated with older age, lower functional capacity, and heightened physical signs of HF. Crude rates of mortality and HF hospitalization were higher in patients with AF compared to SR, in each EF subtype. After multivariable adjustment, the hazard ratio of AF for HF hospitalizations was: 1.036 (95% CI 0.888–1.208, $P = 0.652$) in HFrEF, 1.430 (95% CI 1.087–1.882, $P = 0.011$) in HFmrEF, and 1.487 (95% CI 1.195–1.851, $P < 0.001$) in HFpEF; and for combined all-cause death or HF hospitalizations: 0.957 (95% CI 0.843–1.087, $P = 0.502$), 1.302 (95% CI 1.055–1.608, $P = 0.014$), and 1.365 (95% CI 1.152–1.619, $P < 0.001$), respectively. In patients with HFrEF, AF was not associated with worse outcomes in those presenting with either an acute or a chronic presentation of HF.

Conclusions	The prevalence of AF increases with increasing EF but its association with worse cardiovascular outcomes, remained significant in patients with HFpEF and HFmrEF, but not in those with HFrEF.
Keywords	Heart failure • Atrial fibrillation • Hospitalizations • Mortality • Ejection fraction • Prognosis

Introduction

Heart failure (HF) is a leading cause for morbidity and hospital readmissions.

With the ageing of the population, atrial fibrillation (AF) often coexists with HF; they are mechanistically linked to each other, can adversely impact cardiovascular outcomes and mortality, and together are expected to increase in prevalence in future years because of the ageing of the population.[1,2] Improvements in thrombo-embolic risk prediction and anticoagulation therapy in recent years have led to a reduction in stroke and thromboembolism-related mortality in patients with AF, and cardiac complications are now the leading cause of adverse events, with a significant HF burden in patients with AF.[3,4] Therefore, the inter-relationship of these frequently co-existing conditions will have a significant impact on future healthcare economics and there is a need for a better understanding of the clinical features and prognostic relevance of AF across the recognized subpopulations with HF.

A new distinct HF category of mid-range ejection fraction heart failure (HFmrEF) was recently designated in order to stimulate research into the underlying characteristics, pathophysiology, and potential for treatment of this population with ejection fraction (EF) between 40% and 49%.[5] The optimal HFmrEF treatment potential remains uncertain; but similar to preserved ejection fraction heart failure (HFpEF), it is increasing in prevalence and is associated with older age, non-cardiac comorbidities, higher rates of AF, and more limited treatment options. In contrast, heart failure with reduced ejection fraction (HFrEF) is more commonly associated with coronary artery disease and has gained solid evidence-based therapies.[5] Although there is a close association between AF and HF, there is heterogeneity in research evidence regarding the clinical features and prognostic significance of AF in HFpEF compared to HFrEF subtypes,[6–13] with some contrasting findings reported, even in meta-analyses.[14–16]

Therefore, the purpose was to investigate the clinical characteristics and prognostic impact of AF compared to sinus rhythm (SR) in patients with both with both acute heart failure (AHF) and chronic heart failure (CHF), within the three subtypes of HF defined by left ventricular EF in.

Methods

Study design

The HF Long-Term Registry of the European Society of Cardiology (ESC) is a prospective, multicentre, observational study of inpatients and outpatients at 211 diverse cardiology centres in 21 European and Mediterranean countries that are members of the ESC. The names of the countries, their geographical area, and patient distribution have been previously reported.[17,18] We analysed the ESC-HF Long-Term Registry,

offering a unique opportunity to investigate a large, contemporary, and multinational prospective cohort of HF patients around Europe, outside of randomized clinical trials, with comparative data on long-term outcomes (up to 800 days; ~2.2 years) of survival or HF hospitalizations in both outpatients with CHF and inpatients admitted for AHF. Enrolment period continued from May 2011 to April 2013. The EURObservational Research Programme (EORP) Department of the ESC was appointed to co-ordinate the project operationally, provide support to the committees, National Coordinators, and participating centres, and to oversee the methodological concepts of the survey and statistical analysis.

Patient population and clinical setting

Enrolment was based on a 1 day per week recruitment for 12 consecutive months. On the screening day, entering to the registry were: (i) all outpatients with CHF diagnosed according to the clinical judgement of the responsible cardiologists at the participating centres; and (ii) all inpatients admitted to the hospital's Cardiology Ward or Intensive Cardiac Care Unit for AHF, for whom an intravenous therapy (inotropes, vasodilators, or diuretics) was needed. There were no specific exclusion criteria, with the exception that all patients must be aged over 18 years. The registry was approved by each local Institutional Review Board according to the rules of each participating country. No data were collected for the registry purposes before detailed information was provided to the patient, and a signed informed consent was obtained. Patients were followed up in accordance with the usual practice of the centres, with the exception of a mandatory follow-up visit at 12 months to collect information on morbidity and mortality. In cases where the patient was unable to reach the clinical centre, a phone call replaced this follow-up clinical visit (Supplementary material online, *Table S1*).

Biochemical blood measurements were determined using local standard laboratory procedures. Conventional trans-thoracic echocardiogram was used to measure left ventricular EF according to international standard criteria. Patients were categorized into three EF groups: HF with reduced (HFrEF < 40%), mid-range (HFmrEF 40–49%), and preserved (HFpEF ≥ 50%) EF. The presence of AF was defined according to the rhythm documented by a 12-lead electrocardiogram performed most adjacent to the time of the patient's enrolment, as determined by the screening cardiologist in each centre. Study outcomes included 1-year follow-up data from the ESC-HF Long-Term Registry regarding all-cause mortality and/or HF hospitalizations. Data on mortality were available for 94% of the whole cohort ($n = 14\,061$), whereas data on HF hospitalizations were available for 84% ($n = 12\,555$) of the study participants.

Statistical analysis

Categorical variables are reported as numbers and percentages and compared using the χ^2 test or a Fisher's exact test in cases of small numbers. Continuous variables are reported as means ± standard deviation or median and interquartile range (IQR) as appropriate. Among group comparisons were made using a non-parametric test (Kruskal–Wallis). Baseline characteristics, laboratory tests, and types of treatments are reported stratified by EF groups and the presence of AF rhythm compared to SR. Age- and sex-adjusted logistic regression models were applied to estimate the association between baseline AF and baseline clinical

characteristics in each of the HF EF subtypes. Plots of Kaplan–Meier curves for time to all-cause death and/or HF hospitalizations according to the presence of AF and EF groups were performed and survival distributions compared using the log-rank test. Missing baseline or follow-up covariate data were considered as missing values and no imputation was performed.

The descriptive statistics for the long-term outcome in patients with and without missing data, demonstrated the excluded patients to be older, with lower BMI, less often HFpEF and more often AF (Supplementary material online, Tables SA1–SA3).

A Cox regression was used to determine the hazard ratio of all-cause death and HF hospitalizations associated with AF in each of the HF EF subtypes. The first model was adjusted for age and sex. The covariates included in the second multivariable regression model (detailed in the Supplementary material online, Appendix) were chosen based on their clinical relevance and the significance in univariable analyses with a P-value of <0.10 and with at least 80% of data available, entered into the model with an automatic stepwise selection.

As HFpEF vs. HFmrEF vs. HFrEF, are well-established three distinct clinical syndromes, we performed three separated models as we found a significant interaction between HF group and rhythm (<0.001) (Supplementary material online, Table SB).

A two-sided P-value <0.05 was considered to be statistically significant. All analyses were performed with SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Patients' characteristics

Enrolled in the ESC-HF Long-Term Registry were 19 134 patients giving informed consent. We excluded from current analysis patients with missing information on EF or documented heart rhythm other than AF or SR. Study population flowchart is presented in Figure 1. Final study population included 14 964 patients. Mean age was 66 ± 13 years and 67% were male. Of the total study population, 26% had HFpEF, 21% had HFmrEF, and 53% HFrEF. The corresponding rates of AF were 39%, 29%, and 27%, respectively. The prevalence of AF was generally age dependent in both genders, reaching 50% in HF patients above 80 years of age (Figure 2).

Association of clinical features with atrial fibrillation according to ejection fraction subtypes

Compared to SR, AF was associated in each of the three EF subtypes with older age, reduced functional capacity, previous HF hospitalizations, higher heart rates, as well as more significant HF signs of congestion such as peripheral oedema and elevated jugular venous pressure. Medical history of patients with AF was characterized by less ischaemic heart disease in contrast to higher prevalence of stroke and more significant mitral regurgitation on echocardiogram (Supplementary material online, Table S1a). Atrial fibrillation was associated with higher representation of women in HFpEF and HFmrEF but not in HFrEF. Baseline treatment with mineralocorticoid receptor inhibitors, oral diuretics, digoxin, and anticoagulation was more prevalent in patients with AF, different from angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), statins, and antiplatelets, which were less common in those

with AF in each of the EF groups (Supplementary material online, Table S1b).

N-terminal pro-brain natriuretic peptide test results were available in only 30% of the patients; levels were elevated in AF compared to SR in each of the EF groups and were generally higher in patients with HFrEF. The age- and sex-adjusted odds ratios for the association of baseline characteristics with the presence of AF according to EF subtypes are presented in Supplementary material online, Table S1.

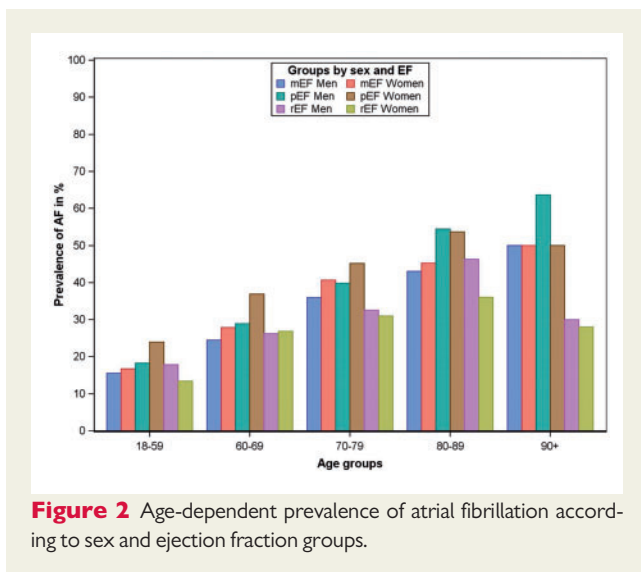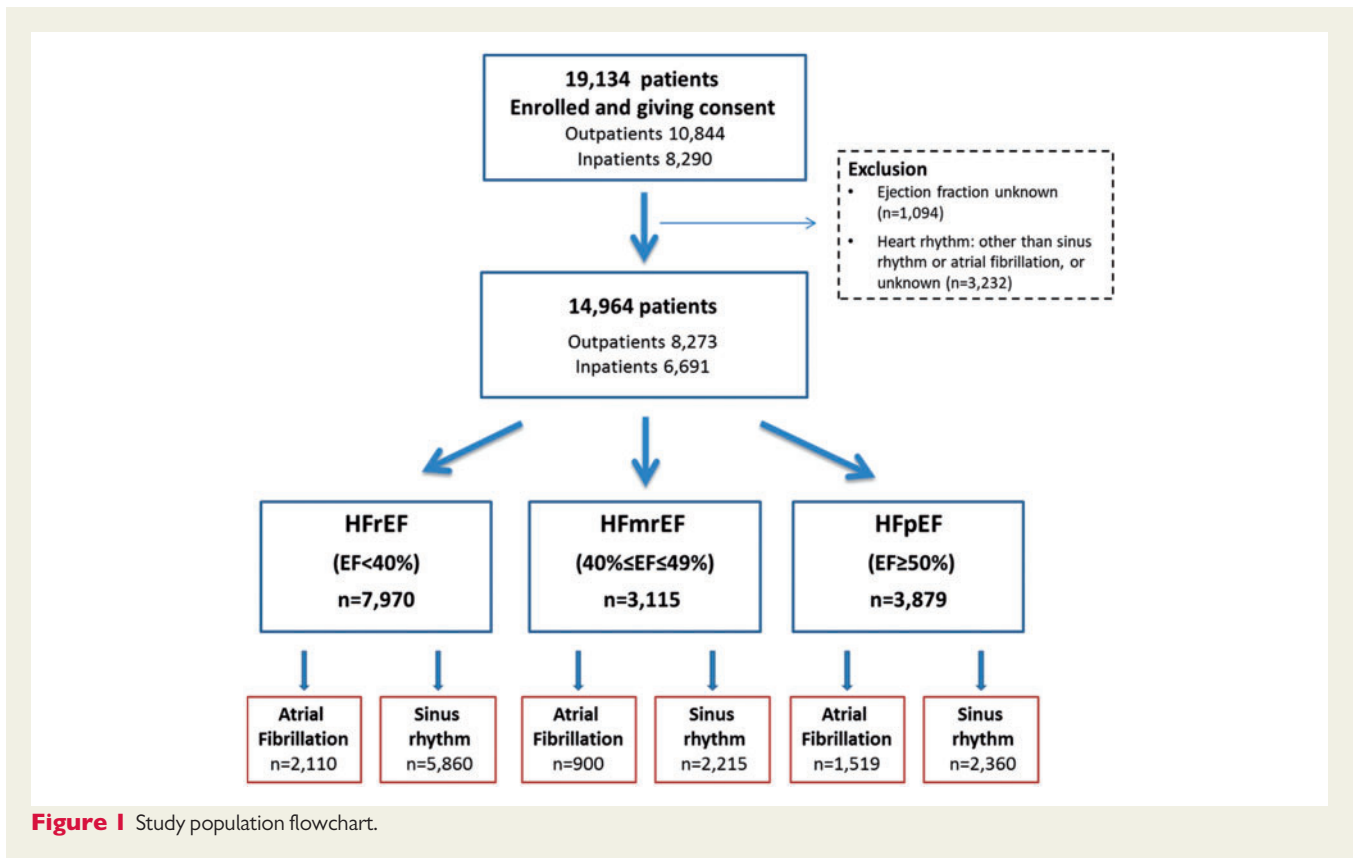## Outcomes associated with atrial fibrillation according to ejection fraction subtypes

All-cause death and HF hospitalization rates during the long-term follow-up were worse in patients with AF compared to SR in each of the three EF groups, as shown in Supplementary material online, Table S2 presenting crude outcomes and events per 100 patient-years. The Kaplan–Meier event free survival curves are presented in Figure 3, showing consistently worse outcomes over time in patients with AF compared to SR in each of the three EF groups. The gap in outcomes between HFrEF and the two subgroups with more preserved EF was wider in patients in SR than in patients with AF; this was observed for both all-cause death (Figure 3A) and HF hospitalizations (Figure 3B), and the combined outcome of all-cause mortality or HF hospitalizations (Figure 3C).

Adjusted KM curves based on the COX multivariate regression in each of the three HF groups are presented in Supplementary material online, Figures S4a–c, respectively.

The age- and sex-adjusted vs. multivariable-adjusted association between AF and all-cause death and/or HF hospitalizations is shown in Supplementary material online, Table S3. After multivariable adjustment, the long-term hazard ratio of AF for all-cause death was: 0.923 (95% confidence interval (CI) 0.782–1.091, $P = 0.347$) in HFrEF, 1.296 (95% CI 0.993–1.691, $P = 0.057$) in HFmrEF, and 1.198 (95% CI 0.954–1.504, $P = 0.120$) in HFpEF; and for HF hospitalizations: 1.036 (95% CI 0.888–1.208, $P = 0.652$), 1.430 (95% CI 1.087–1.882, $P = 0.011$), and 1.487 (95% CI 1.195–1.851, $P < 0.001$), respectively. Following this multivariable adjustment, the combined endpoint of long-term all-cause death or HF hospitalizations in the HFrEF, HFmrEF, and HFpEF groups was: 0.957 (95% CI 0.843–1.087, $P = 0.502$), 1.302 (95% CI 1.055–1.608, $P = 0.014$), and 1.365 (95% CI 1.152–1.619, $P < 0.001$), respectively.

Comparison between ambulatory and hospitalized heart failure patients

Of the overall study population, 8273 were outpatients with CHF and 6691 were inpatients hospitalized with AHF. Compared to CHF, patients with AHF were older (68 ± 13 vs. 64 ± 13 years), more were females (37% vs. 30%), their heart rate was elevated (92.3 ± 25.7 vs. 73.3 ± 16.3 beats/min), and the functional class significantly reduced [New York Heart Association Grade III/IV 84% vs. 26%] with more prevalent physical signs of HF congestion. In addition, patients with AHF had increased burden of cardiovascular risk factors and comorbidities. The prevalence of AF was higher in AHF compared to CHF patients, in each of the EF groups (43% vs. 35% HFpEF, 34% vs. 25% HFmrEF, and 31% vs. 23% HFrEF). The baseline characteristics of patients with AHF and CHF according to the heart rhythm and EF

Figure 1 Study population flowchart.

Figure 2 Age-dependent prevalence of atrial fibrillation according to sex and ejection fraction groups.

subgroups are shown in Supplementary material online, *Table S2a,b*. The corresponding age and sex adjusted odds ratios for the association of baseline characteristics with AF rhythm according to the EF subgroups are presented in Supplementary material online, *Table S3a,b*. The odds ratio distribution across EF subtypes associated with AF was similar between AHF and CHF patients for most clinical characteristics. However, stroke was associated with AF in each of the EF subgroups presenting with CHF but not AHF. In addition, treatment with ACEI or ARBs was inversely associated with AF in CHF but not in AHF patients.

After multivariable adjustment, the hazard ratio for long-term total mortality or HF hospitalizations associated with AF was not increased in HFrEF patients presenting with either AHF or CHF as shown in *Figure 4*. This was in contrast to the statistically significant increase in the hazard ratio for the same outcome event associated with AF in both AHF and CHF presentations of patients with HFpEF, while in those with HFmrEF AF was associated with increased risk for mortality or HF hospitalization that was statistically significant in AHF and borderline in those with a CHF presentation (*Figure 4*).

Discussion

In this large multinational European registry of HF patients stratified by EF subtypes, AF was progressively more common with the increase in EF and associated with clinical signs and symptoms of HF. Additionally, worse long-term cardiovascular outcomes were seen in HF patients with AF compared to SR in each of the EF subtypes. Nevertheless, after multivariable adjustment, the independent association of AF with either HF hospitalizations by itself or combined with mortality remained significant only in patients with HFpEF and HFmrEF. In contrast to the 'common belief', AF in HFrEF was not related to worse outcomes compared to SR either in chronic presentation or in acute decompensation of these patients.

Atrial fibrillation is common in patients with HF and often coexists, emerging in recent years into a dual epidemic.[19] The prevalence of
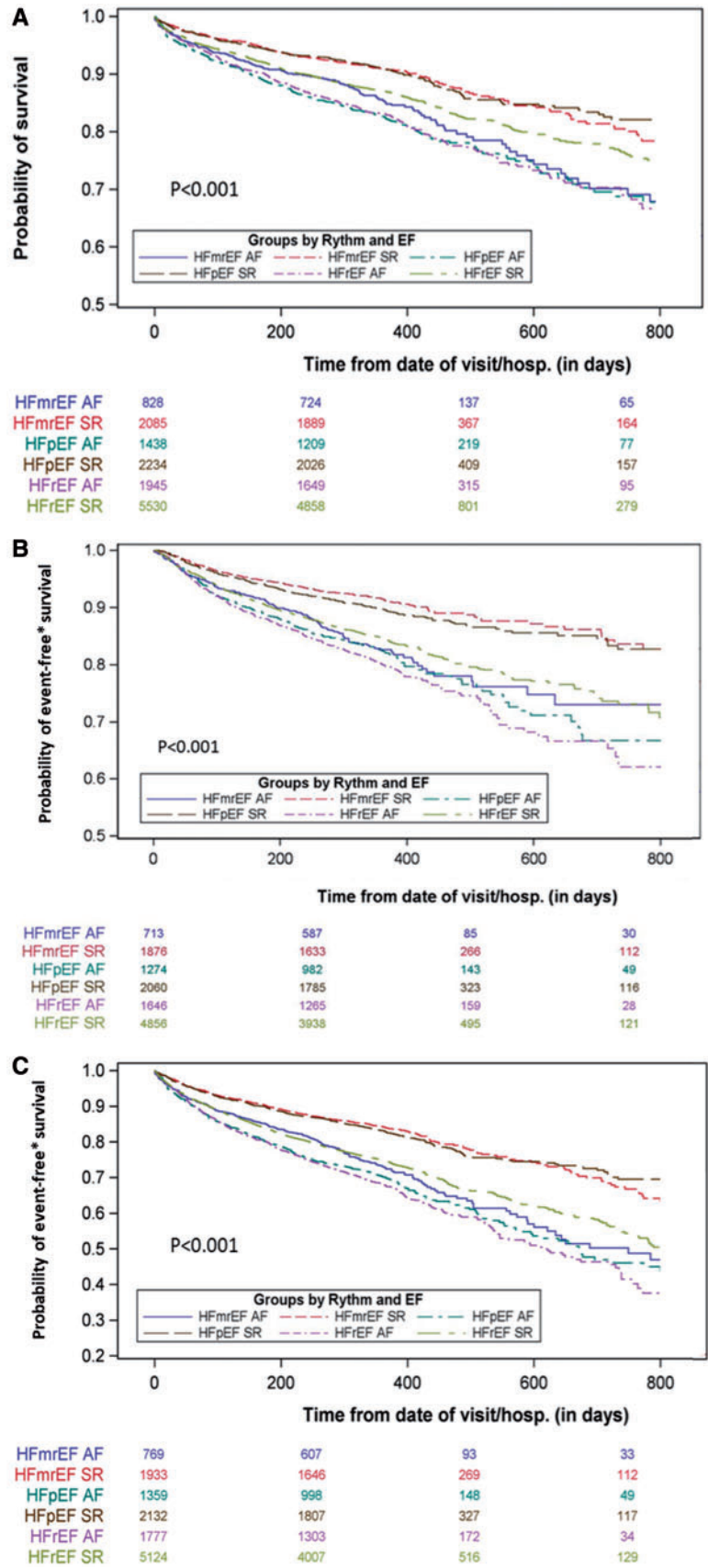
Figure 3 The Kaplan–Meier curves stratified by the three ejection fraction groups and rhythm for: (*A*) long-term total mortality, (*B*) long-term heart failure hospitalizations, and (*C*) long-term mortality or heart failure hospitalizations.
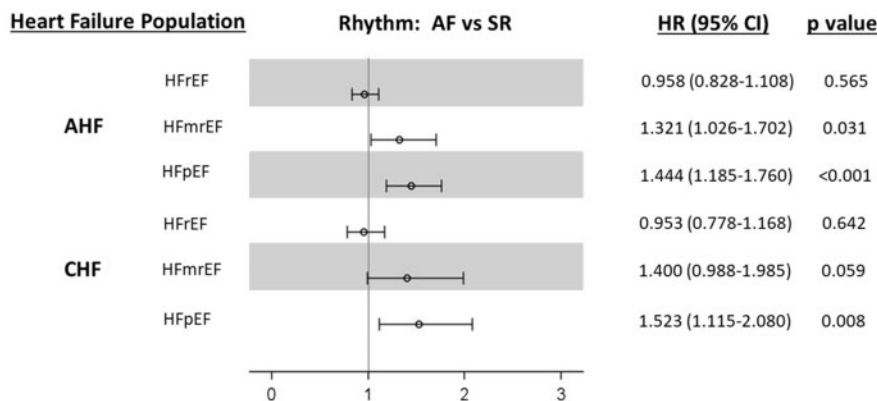
Figure 4 Multivariable hazards ratios for long-term total mortality or heart failure hospitalizations associated with atrial fibrillation, according to ejection faction groups in acute and chronic heart failure presentation.

AF in HF varies according to study design and criteria used for defining both variables. In the current study, a progressive increase in the prevalence of AF was observed in HFpEF and HFmrEF compared to HFrEF. Similar findings were recently observed in other large cohorts with data on heart rhythm across the three HF subtypes.[10,20,21] AF is commonly reported to be more prevalent in HFpEF, associated with comorbidities and older age while modifiable risk factors such as diabetes, obesity, hypertension, and smoking were shown to be accountable for the significant portion of population risk of incident HF in patients with new-onset AF.[22] Similar to previous reports, we also observed that AF prevalence in HFrEF patients increases with age, in both genders, except for the oldest-old. Albeit in the current study, we may not directly link AF to HF acute clinical deterioration, we noted a higher prevalence of AF in AHF compared to CHF presentation and with clinical manifestations of HF in each of the EF subtypes, including significant mitral regurgitation.

The prognostic significance of AF may vary according to the type of HF. In our study, the independent association between AF and risk for both long-term HF hospitalizations *per se* and its combination with total mortality was observed only in patients with HFpEF and HFmrEF. However, no similar independent significant association between AF and these adverse outcomes was observed after multivariable adjustment in patients with HFrEF, irrespective of presentation, i.e. with AHF or CHF. Over the years, the clinical and prognostic relevance of AF in HFpEF vs. HFrEF was investigated in several studies of various HF populations, with conflicting results, as clinical studies and meta-analyses suggested higher, lower, or similar mortality rates in HFpEF comparing to HFrEF patients.[6–16]

Interestingly, recent data from an open-label randomized trial of AF ablation in HFrEF patients with EF < 35% showed that patients who were assigned to ablation had reduced incidence of death or HF admissions with a rising trend in EF level post-ablation.[23] The benefit was seen with a decrease in the burden of AF from 60% of time with medical therapy to 25% with ablation, suggesting that a reduction in the amount of time in AF may be sufficient for clinical benefit. These data may seem in contrast to the current study results. However, it was an open-label study with a relatively small number of participants,

and a relatively high number of drop-outs and patients lost to follow-up. In addition, the survival curves started to separate only after 3 years, whereas our follow-up data were shorter. It is also possible that ablation for AF may have additional beneficial effects improving outcomes in HFrEF irrespective of AF response, such as an effect on the autonomic nervous system.[24] In addition, recent retrospective data support similar effects of catheter ablation in AF patients with HFpEF compared to HFrEF, with similar arrhythmia-free survival, and a trend towards greater symptomatic improvement post-ablation in patients with HFpEF.[25]

As both AF and HFpEF share similar pathophysiological mechanisms, common predisposing risk factors, and comorbidities, and are associated with structural and functional remodelling of the left atrium, it is difficult to assess the potential interaction between these two entities.[22] HFpEF in AF is associated with impaired relaxation, loss of atrial kick, shorter diastolic filling time, and elevated filling pressures, related to rapid ventricular response. Moreover, irregular ventricular rhythm with loss of atrioventricular synchrony as well as an increase in prevalence of mitral regurgitation and pulmonary hypertension may worsen HF clinical manifestation. The haemodynamic consequences of AF in HFpEF may be more significant as it is associated with increased left atrial stiffness and higher wall stress comparing to HFrEF patients.[22]

A plausible explanation for the differential association of AF with adverse cardiovascular outcome between the EF subtypes might be that with higher EF, AF may contribute to progression of HF and worsen outcomes, whereas with lower EF, the HF disease itself and its severity determines the outcomes, and not primarily AF, which may be more of a bystander. The particularly greater role of AF in HFpEF may also be related to the lesser response to HF therapy. Indeed, in recent analyses from a beta-blocker meta-analysis[26] and from CHARM,[27] beta-blockers and candesartan were found to be much less effective in HFpEF compared to HFrEF patients.

Of note, the lack of a significant association between AF and mortality in HFpEF patients may be at least partially explained by masking of such potential association by our meticulous multivariate adjustments in which we actually may have neutralized potential

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contributions of mortality mechanisms related to AF. Indeed, in the HFpEF patients, significant mitral regurgitation, a known prognostic parameter for mortality by itself in HF, was almost twice as common in the AF patients compared to patients with SR.[28]

The new ESC terminology HFmrEF is defined by left ventricular EF in the range of 40–49%,[5] a grey area in phenotype and outcomes between HFrEF and HFpEF, aiming to stimulate research into the underlying characteristics, pathophysiology, and treatment of this group of patients who were usually excluded from HFrEF clinical trials and variably included in HFpEF trials.[20,21,27] A call for further study of AF patients with HFmrEF before particular treatment strategies can be recommended, was recently noted in the 2016 ESC Guidelines for the management of AF.[29]

A recent analysis of the Swedish HF registry showed that AF was progressively more common with increasing EF and associated with similar clinical characteristics in HFmrEF compared to HFpEF and HFrEF.[10] Differing from the Swedish registry concluding that AF was associated with similarly increased risk of death and HF hospitalization in all three EF groups, our data suggest that at least in regard to the clinical adverse implications of AF in HF, HFmrEF has a similar pattern to HFpEF, which is very different from that of HFrEF. These two registries' dissimilar conclusions may be a reflection of the different nature of cohorts as in the Internet-based registry Swedish registry, participating centres online HF patient's records were reordered and transferred. In the Swedish HF registry, patients were significantly older than in our registry and the prevalence of AF was significantly higher – 53%, 60%, and 65% in HFrEF, HFmrEF, and HFpEF, respectively.[10] To the contrary, in the present ESC-HF Long-Term registry analysis, AF prevalence in HFrEF, HFmrEF, and HFpEF was 27%, 29%, and 39%, respectively, similar to the prevalence of recent analysis from the CHARM trial database, 26.2%, 25.6%, and 31.3%, respectively.[27]

The strengths of this study include the large multinational sample that is representative of many European and Mediterranean countries, which is important for the generalization of the results. Of note, the diagnosis of AF was determined according to a 12-lead electrocardiogram interpreted by a cardiologist, different than electronic-based code diagnosis often used in studies to identify AF. This ensures a more accurate assessment of heart rhythm. The ESC Long-Term HF Registry is also novel in analysing comparable data of AF patients with both AHF and CHF presentations. That said, several limitations of the present study should be acknowledged. Albeit the requirements for diagnosis of AF in our study were firm, it may have omitted patients with previous episodes of paroxysmal AF who were not noted as AF patients. It is also possible that there are additional potential confounders that were not accounted for in our study, although the ESC-HF Long-Term registry consists of numerous variables including medical history, signs and symptoms of HF, laboratory examinations, medications, and device therapy. We acknowledge that our registry reflects variable rates of recruitment per centre/country as it was conducted on a voluntary basis. Of note, consecutiveness of enrolment was not validated. Moreover, as patients were recruited in cardiology clinics and hospital wards, our findings may be relevant to this specific population rather 'real ward' HF population.

It should be noted that the associations between AF and adverse outcomes described in this registry analysis do not prove causation.

Conclusions

In a multinational European registry of HF patients, AF was progressively more common with the increase in EF and associated with signs and symptoms of HF regardless of EF subtype. Compared to SR, AF was associated with worse long-term cardiovascular outcomes across the EF subtypes. Nevertheless, the independent association of AF with HF hospitalizations, with or without total mortality, was significant only among patients with either HFmrEF or HFpEF. In contrast, AF in HFrEF patients was not related to worse outcomes in either AHF or CHF presentation.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

References

1. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol* 2013;**112**:1142–1147.
2. Lane DA, Skjøth F, Lip GYH, Larsen TB, Kotecha D. Temporal trends in incidence, prevalence, and mortality of atrial fibrillation in primary care. *J Am Heart Assoc* 2017;**6**:e005155.
3. Piccini JP, Hammill BG, Sinner MF, Hernandez AF, Walkey AJ, Benjamin EJ, Curtis LH, Heckbert SR. Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke. *Eur Heart J* 2014;**35**:250–256.
4. Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández AI, Calvo-Rojas G, Suárez-Gea ML, Vargas-Castrillón E. Causes of death in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2016;**68**:2508–2521.

5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.

6. Eapen ZJ, Greiner MA, Fonarow GC, Yuan Z, Mills RM, Hernandez AF, Curtis LH. Associations between atrial fibrillation and early outcomes of patients with heart failure and reduced or preserved ejection fraction. *Am Heart J* 2014;**167**: 369–375.e2.

7. Pandey A, Kim S, Moore C, Thomas L, Gersh B, Allen LA, Kowey PR, Mahaffey KW, Hylek E, Peterson ED, Piccini JP, Fonarow GC. ORBIT-AF Investigators and Patients. Predictors and prognostic implications of incident heart failure in patients with prevalent atrial fibrillation. *JACC Heart Fail* 2017;**5**:44–52.

8. Linssen GC, Rienstra M, Jaarsma T, Voors AA, van Gelder IC, Hillege HL, van Veldhuisen DJ. Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction. *Eur J Heart Fail* 2011;**13**:1111–1120.

9. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA, Charm I. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**: 1997–2004.

10. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail* 2017;**5**: 565–574.

11. 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**:e005694.

12. 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.

13. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, Fauchier L. Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley Atrial Fibrillation Project. *Eur J Heart Fail* 2012;**14**:295–301.

14. 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.

15. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016;**203**: 660–666.

16. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009;**11**:676–683.

17. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L; Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013;**15**:1173–1184.

18. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016; **18**:613–625.

19. Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation* 2009;**119**:2516–2525.

20. Pascual-Figal DA, Ferrero-Gregori A, Gomez-Otero I, Vazquez R, Delgado-Jimenez J, Alvarez-Garcia J, Gimeno-Blanes JR, Worner-Diz F, Bardají A, Alonso-Pulpon L, Gonzalez-Juanatey JR, Cinca J; MUSIC and REDINSCOR I Research Groups. Mid-range left ventricular ejection fraction: clinical profile and cause of death in ambulatory patients with chronic heart failure. *Int J Cardiol* 2017;**240**: 265–270.

21. Guisado-Espartero ME, Salamanca-Bautista P, Aramburu-Bodas Ó, Conde-Martel A, Arias-Jiménez JL, Llàcer-Iborra P, Dávila-Ramos MF, Cabanes-Hernández Y, Manzano L, Montero-Pérez-Barquero M; RICA Investigators Group. Heart failure with mid-range ejection fraction in patients admitted to internal medicine departments: findings from the RICA Registry. *Int J Cardiol* 2018;**255**:124–128.

22. Kotecha D, Lam CS, 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.

23. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–427.

24. Link MS. Paradigm shift for treatment of atrial fibrillation in heart failure. *N Engl J Med* 2018;**378**:468–469.

25. Black-Maier E, Ren X, Steinberg BA, Green CL, Barnett AS, Rosa NS, Al-Khatib SM, Atwater BD, Daubert JP, Frazier-Mills C, Grant AO, Hegland DD, Jackson KP, Jackson LR, Koontz JI, Lewis RK, Sun AY, Thomas KL, Bahnson TD, Piccini JP. Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. *Heart Rhythm* 2018;**15**:651–657.

26. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Böhm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson Å, Wikstrand J, Kotecha D. Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J* 2018;**39**:26–35.

27. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, McMurray JJV, Solomon SD. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* 2018;**20**:1230–1239.

28. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. Left ventricular heart failure and pulmonary hypertension. *Eur Heart J* 2016;**37**: 942–954.

29. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.