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CLINICAL RESEARCH
Heart failure/cardiomyopathy

Comparing biomarker profiles of patients with heart failure: atrial fibrillation vs. sinus rhythm and reduced vs. preserved ejection fraction

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Aims The clinical correlates and consequences of atrial fibrillation (AF) might be different between heart failure with reduced vs. preserved ejection fraction (HFrEF vs. HFpEF). Biomarkers may provide insights into underlying pathophysiological mechanisms of AF in these different heart failure (HF) phenotypes.

Methods and results We performed a retrospective analysis of the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF), which was an observational cohort. We studied 2152 patients with HFrEF [ejection fraction (EF < 40%)], of which 1419 were in sinus rhythm (SR) and 733 had AF. Another 524 patients with HFpEF (EF ≥50%) were studied, of which 286 in SR and 238 with AF. For the comparison of biomarker profiles, 92 cardiovascular risk markers were measured (Proseek® Olink Cardiovascular III panel). The circulating risk marker pattern observed in HFrEF was different than the pattern in HFpEF: in HFrEF, AF was associated with higher levels of 77 of 92 (84%) risk markers compared to SR; whereas in HFpEF, many more markers were higher in SR than in AF. Over a median follow-up of 21 months, AF was associated with increased mortality risk [multivariable hazard ratio (HR) of 1.27; 95% confidence interval (CI) 1.09–1.48, $P = 0.002$]; there was no significant interaction between heart rhythm and EF group on outcome.

Conclusion In patients with HFrEF, the presence of AF was associated with a homogeneously elevated cardiovascular risk marker profile. In contrast, in patients with HFpEF, the presence of AF was associated with a more scattered risk marker profile, suggesting differences in underlying pathophysiological mechanisms of AF in these HF phenotypes.

Keywords Atrial fibrillation • Heart failure • Preserved ejection fraction • Biomarkers

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Clinical perspective

In patients with heart failure with reduced ejection fraction (HFrEF), cardiovascular risk markers were homogeneously higher in atrial fibrillation (AF) patients compared to patients in sinus rhythm (SR). This was in contrast to patients with heart failure with preserved ejection fraction (HFpEF), where the risk marker profile was more scattered. Even though these findings do not have direct clinical implications, these different risk marker profiles might suggest that AF has a different pathophysiological role in HFrEF than it has in HFpEF. A better understanding of this potential difference of AF in the two heart failure phenotypes should be further investigated, since this might also give insights into potential differences in (response to) treatment of AF in HFrEF vs. HFpEF. Moreover, the differences in risk marker profiles could potentially be helpful in finding a biomarker (panel) that is more accurate in diagnosing HFpEF in patients with concomitant AF than currently recommended diagnostics that are not specific for AF nor HFpEF (a combination of signs and/or symptoms, elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and structural or functional cardiac abnormalities assessed by echocardiography). Ideally, the biomarker pattern of patients with 'pure' AF (without HFpEF) should be compared to the markers of patients with HFpEF without AF, and those with both AF and HFpEF, in order to find a biomarker with a higher discriminative capacity than NT-proBNP has.

Introduction

Atrial fibrillation (AF) and heart failure (HF) share common risk factors, predispose to each other, and together herald a worse prognosis than either condition alone.[1–3] The majority of our knowledge on the AF–HF relationship stems from series based on heart failure with reduced ejection fraction (HFrEF). However, heart failure with preserved ejection fraction (HFpEF) accounts for up to half of HF diagnoses, and AF has a high prevalence in both HFrEF and HFpEF.[4–6]

Heart failure with preserved ejection fraction is a more heterogeneous syndrome than HFrEF, with highly prevalent comorbidities and a higher prevalence among elderly, obese, and women.[7] The diagnosis of HFpEF in the setting of AF is challenging because risk factors and symptoms overlap. Moreover, levels of biomarkers, such as circulating natriuretic peptides, are influenced by both AF and HF, which further complicates the diagnosis of HFpEF.[5,8] Therefore, in most current HF trials, separate cut-offs for these natriuretic peptides are used for patients in sinus rhythm (SR) and those in AF.[9] However, the specific cut-offs that are used are still arbitrary and widely debated.

Since distinct differences in pathophysiology are seen between HFrEF and HFpEF, with pronounced differences in age, sex, aetiology, and response to therapy, it is possible that AF also plays a different role and reflects different pathophysiological processes in these HF phenotypes.[10–12] Biomarkers might have the potential to help us understand these possible differences in the underlying pathophysiological role of AF. Therefore, we performed a *post hoc* analysis of the BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) to study biomarker profiles of patients in AF vs. SR in both HFrEF and HFpEF.

Methods

Patient population and study design

We performed a retrospective analysis of BIOSTAT-CHF, which was an observational study and has been previously published.[13,14] In brief, a total of 4254 patients with new-onset or worsening signs and/or symptoms of HF from 11 European countries were included in BIOSTAT-CHF. Patients had to have objective evidence of cardiac dysfunction documented either by left ventricular ejection fraction (LVEF) of ≤40%, or plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) >2000 pg/mL. We included patients with either SR or AF/atrial flutter at baseline for our analysis. Those with a pacemaker rhythm and unknown atrial rhythm ($n = 466$), other rhythm ($n = 63$) or unknown rhythm ($n = 111$) were excluded. A flowchart of the selected patients is presented in Supplementary material online, *Figure S1*. Patients were categorized into two groups based on LVEF assessed by transthoracic echocardiography: HFrEF (<40%) and HFpEF (≥50%). Patients with unknown LVEF were excluded ($n = 345$). Patients with a LVEF between 40% and 49% [HF with mid-range ejection fraction (EF)] were excluded in order to make a greater distinction between the two HF phenotypes ($n = 593$). Quality of life (QoL) was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ).[15] Higher scores indicated a better QoL. Primary outcome was time to all-cause mortality. The study complies with the Declaration of Helsinki, medical ethics committee of participating centres approved the study, and all patients provided written informed consent.

Definition of atrial fibrillation

A standard 12-lead electrocardiogram (ECG) was performed at baseline. Patients were classified into AF or SR according to their heart rhythm at time of blood collection, registered on the baseline ECG.

Biomarkers

The Olink Cardiovascular III panel was used to create the biomarker profiles in the two HF phenotypes. This panel comprises 92 cardiovascular disease-related biomarkers, which were selected based on literature searches, disease association in the Coremine database, and in collaboration with experts within the cardiovascular field. Measurement of these 92 biomarkers was performed by Olink Bioscience analysis service (Uppsala, Sweden), using the Proseek® multiplex Inflammatory96*96 kit.[16] The Proseek® reagents are based on the Proximity Extension Assay (PEA) technology, which binds 92 oligonucleotide-labelled antibody probe pairs to the target biomarker. For further quantification, real-time PCR was performed. Olink wizard and GenEx software were used for further data analysis. Proseek® data are presented as arbitrary units (AU) on a log2 scale. Every marker was categorized by current literature in one or more categories.[17] The abbreviations and full names of the 92 biomarkers and their categories are presented in Supplementary material online, *Table S1*.

Statistical analyses

Normally distributed variables were depicted as means ± standard deviation, non-normally distributed variables as median with the first and third quartile (Q1–Q3), categorical variables as numbers with percentages. Means of continuous variables were compared by one-way analysis of variance (ANOVA) or the Kruskal–Wallis test, while categorical variables were compared by the χ^2 test. The Kaplan–Meier survival curves were

compared using the log-rank statistic. Cox regression models were used to adjust for the effect of covariates and to calculate hazard ratios (HR). The Cox proportional hazards assumption was assessed by visually inspecting plots of Schoenfeld residuals against time, which showed proportionality in both the total cohort, as in the two HF subgroups (HFrEF and HFpEF) separately. The median level of each biomarker in the AF group was divided by the median level of this biomarker in the SR group to produce a ratio. This ratio (converted into a percentage) was visualized in *Take home figure*, where every bar represents this difference (%), which can either be positive (higher level in AF) or negative (higher level in SR). Interaction testing was performed to determine whether the effect of heart rhythm differed between the HF phenotypes, with regard to outcome (interaction term in the cox regression model) and with regard to every separate biomarker (interaction term in the linear regression model). We also tested three falsification hypotheses to see whether other important covariates gave similar biomarker patterns in HFrEF and HFpEF as found for heart rhythm. Rejection of these hypotheses would strengthen the fact that the biomarker profiles found for AF vs. SR were specific for heart rhythm, and not importantly influenced by other confounders. These three hypotheses were formulated for age (below vs. above the mean age in HFrEF and HFpEF), renal disease [above vs. below an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2], and ischaemic heart disease (previous myocardial infarction, percutaneous intervention, and/or coronary artery bypass graft, 'yes' vs. 'no'). A substantial number of the previously mentioned definitions and analyses were added or adjusted during the review process. Therefore, the findings should be considered exploratory. In general, a two-tailed *P*-value of <0.05 was considered statistically significant. In the tables where the associations of 92 biomarkers were tested, the *P*-values were controlled for the false discovery rate using the Benjamini–Hochberg method. For testing interactions, a *P*-value of <0.1 was considered significant.

Results

Patient characteristics

We studied a total of 2676 HF patients, of which 1703 were in SR (64%) and 971 had AF (36%). Baseline characteristics are presented in *Table 1*. These patients were further stratified in 2152 HFrEF patients, of which 1419 were in SR and 733 had AF, and 524 HFpEF patients, of which 286 were in SR and 238 had AF. The baseline characteristics of these four subgroups are presented in *Table 2*. In both HF phenotypes, patients with AF were significantly older than their counterparts in SR. Patients with AF and HFpEF were the oldest (79 ± 9 years), and patients in SR and HFrEF the youngest (69 ± 12 years). Men were more likely to have AF and HFrEF, whereas a similar number of men and women had AF and HFpEF. In both HFrEF and HFpEF, patients with AF less often had a history of coronary artery disease (HFrEF: 51% in SR vs. 43% in AF, $P = 0.001$ and HFpEF: 54% in SR vs. 28% in AF, $P < 0.001$). Patients with HFpEF reported the lowest QoL, where no differences were seen between patients with AF and SR. However, in HFrEF, AF patients reported significantly lower QoL (*Figure 1*).

Biomarker profiles

In HFrEF, the relative levels of 77 of 92 (84%) cardiovascular risk markers were higher in patients with AF than in those in SR, which resulted in a homogeneous risk marker pattern (*Take home figure*). This was in contrast to the pattern seen in HFpEF, where the risk marker profile of patients with AF vs. SR was much more scattered; 51 (55%) risk markers were higher in patients in SR and 36 (39%) in patients with AF (*Take home figure*). The median log2 levels of the 92 biomarkers for SR and AF are presented in Supplementary material online, *Table S2* for HFrEF and Supplementary material online, *Table S3* for HFpEF. To find out whether these differences in biomarker profiles between HFrEF and HFpEF were importantly influenced by other covariates, interactions for every biomarker between rhythm group and HF phenotype were tested in a univariable and multivariable model. This resulted in a significant interaction between rhythm and HF phenotype in 44 biomarkers, of which 26 (59%) remained significant in the multivariable model (Supplementary material online, *Table S4*).

Apart from the differences seen in overall risk marker pattern when comparing HFrEF and HFpEF, several similarities were found when studying the top five markers with the largest difference between AF and SR (being highest in AF). In both HFrEF and HFpEF, NT-proBNP was the risk marker with the largest difference between AF and SR. Beyond NT-proBNP, two other markers were found in this top five in both HFrEF and HFpEF: ST2 and SPON1. A sensitivity analysis revealed no notable differences between patients who had a history of AF vs. patients with AF on the baseline ECG. The falsification hypotheses about age, renal disease, and ischaemic heart disease showed homogeneous patterns with the most elevated risk markers in the group at risk (older, eGFR <60, and ischaemic heart disease) in both HFrEF and HFpEF (Supplementary material online, *Figure S2*), in contrast to the findings with AF vs. SR in HFrEF and HFpEF.

Outcome

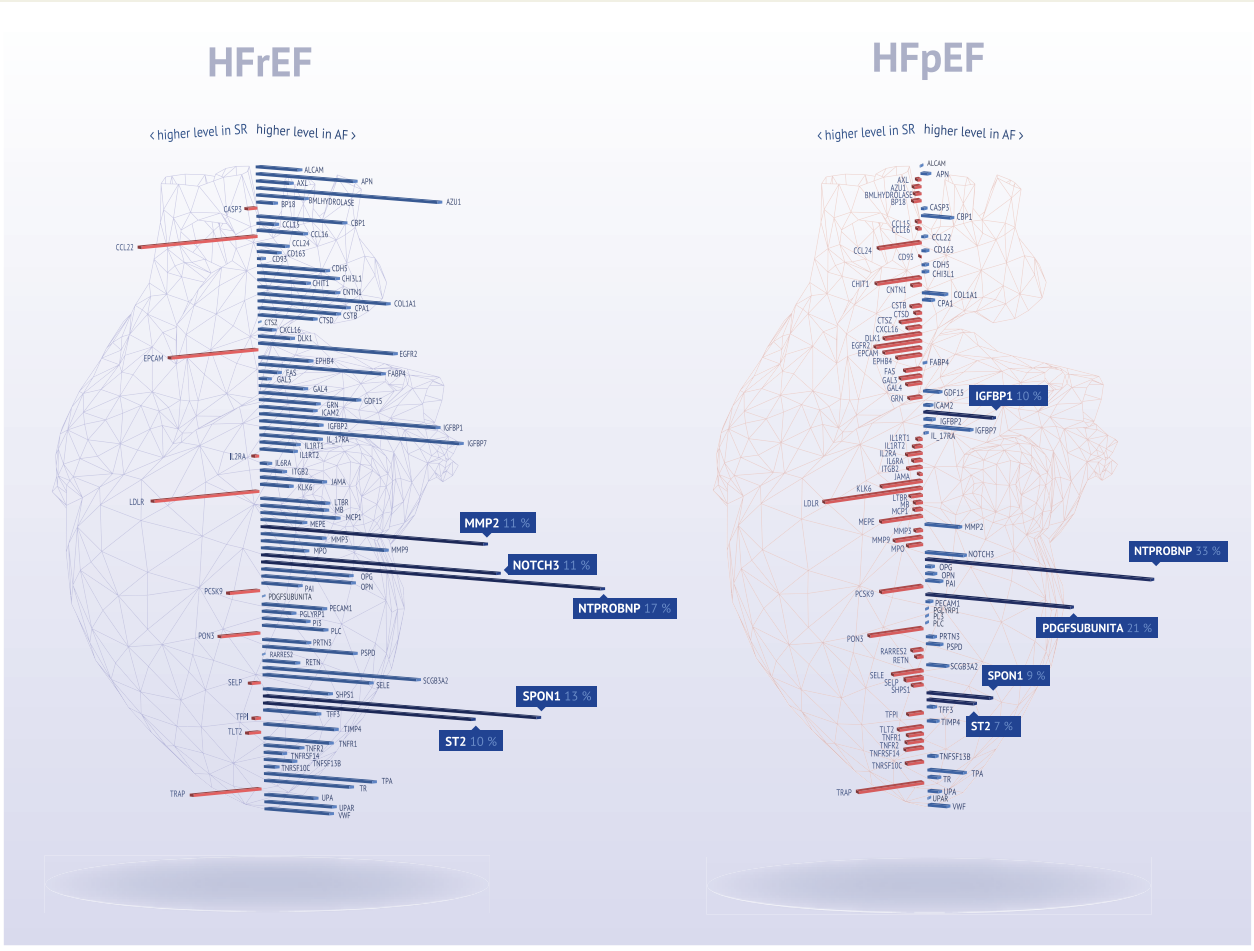
The median follow-up duration was 21 months (IQR 11–32 months). Atrial fibrillation was associated with increased mortality risk [HR 1.44, 95% confidence interval (95% CI) 1.25–1.66; $P < 0.001$) in the total cohort (*Figure 2*) and in the HF phenotypes (HFrEF: HR 1.41, 95% CI 1.19–1.68; $P < 0.001$ and HFpEF: HR 1.39, 95% CI 1.05–1.83; $P = 0.022$) (*Figure 3*). After adjustment for covariates, the association of AF on outcome remained significant in the total cohort (HR 1.27, 95% CI 1.09–1.48; $P = 0.002$), but no longer in HFpEF (*Table 3*). However, there was no significant interaction between heart rhythm and the HF phenotypes on outcome ($P = 0.71$). Of the previously mentioned top five biomarkers, NT-proBNP, ST2, and SPON1 were all strongly associated with all-cause mortality for patients in SR and AF in both HFrEF and HFpEF (Supplementary material online, *Table S5*).

Discussion

In this study, the presence of AF was associated with a homogeneously elevated cardiovascular risk marker profile in patients with HFrEF, whereas in HFpEF, the presence of AF was associated with a much more scattered risk marker profile. These findings suggest that there might be differences in underlying pathophysiological mechanisms of AF in these two HF phenotypes.

Patient characteristics

Patients with AF reported a significantly lower QoL than patients in SR in HFrEF, whereas QoL was not influenced by heart rhythm



Take home figure Graphical representation of the risk marker profile in patients with SR vs. AF in HFrEF (left) and HFpEF (right). A blue bar indicates a higher level of this marker in patients with AF, whereas a red bar reflects a higher level in patients in SR. The top five biomarkers with the largest difference between SR and AF were highlighted in blue, with the percentage indicating the magnitude of this difference. AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IGFBP1, insulin-like growth factor-binding protein-1; MMP2, matrix metalloproteinase-2; NOTCH3, neurogenic locus notch homolog protein-3; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PDGFSUBUNITA, platelet-derived growth factor subunit-A; SPON1, spondin-1; ST2, ST-2 protein; SR, sinus rhythm.

among patients with HFpEF. Interestingly, patients with HFpEF reported the lowest QoL. In our view, the overall lower QoL in our HFpEF patients could be explained by the higher age and higher number of women.[18] However, after adjustment for age and sex, AF still had a significantly negative influence on QoL in HFrEF but not in HFpEF. The levels of NT-proBNP of the patients with HFpEF were relatively high, also in the SR group, due to the natriuretic peptide entry criteria for patients with a LVEF > 40% in BIOSTAT-CHF. This might reflect the inclusion of quite severe HFpEF in our cohort, which could have directly resulted in the lower QoL.

Similar to previous studies, our study found that men are more likely to have AF, especially in HFrEF.[19,20] In HFpEF, where more women were included, the prevalence of AF in men and women was similar. Furthermore, patients without a history of coronary artery disease were more likely to have AF, in accordance with previous studies.[20–23] Exact mechanisms of the difference between the sexes and associations with aetiology are yet to be discovered.

Biomarker profiles

The biomarker profiles of patients with AF vs. SR revealed prominent differences between HFrEF and HFpEF. The great majority of these markers were elevated in patients with AF in HFrEF. We hypothesize that AF is a reflection of a more advanced disease state in HFrEF, since almost all of these markers are associated with worse prognosis. In contrast, in HFpEF, the risk marker profile was more scattered, with less than half of the biomarkers being more elevated in the AF group. Atrial fibrillation may be a separate bystander along with a high prevalence of other comorbidities in HFpEF, instead of a marker for disease severity. Furthermore, it is possible that a higher number of patients had prior AF before HFpEF developed, which is shown to have a better prognosis as compared to patients who develop AF after HF.[24,25] Another possible explanation is the misclassification of HF in patients with AF. The challenges of making an accurate diagnosis of symptomatic AF (without HF) vs. HFpEF with concomitant AF have been previously discussed.[5,9] It is plausible that patients with AF

Table 1 Baseline characteristics of heart failure patients in sinus rhythm and atrial fibrillation

	Total cohort		
	Sinus rhythm *n* = 1705 (64%)	Atrial fibrillation *n* = 971 (36%)	*P*-value
Clinical			
Age (years)	70 ± 12	75 ± 10	<0.001
Women (%)	527 (31)	263 (27)	0.041
BMI (kg/m^2)	28.0 ± 5.9	28.6 ± 5.9	0.009
NYHA (%)			0.003
I	122 (8)	43 (5)	
II	749 (48)	407 (45)	
III	570 (37)	363 (40)	
IV	117 (8)	85 (10)	
LVEF (%)	33 ± 13	36 ± 14	<0.001
Systolic blood pressure (mmHg)	126 ± 22	124 ± 21	0.161
Diastolic blood pressure (mmHg)	73 ± 13	74 ± 14	0.001
Heart rate (b.p.m.)	76 ± 18	90 ± 26	<0.001
History of (%)			
Atrial fibrillation	273 (16)	864 (89)	<0.001
Coronary artery disease[a]	874 (52)	379 (39)	<0.001
Valvular surgery	87 (5)	96 (10)	<0.001
Stroke	182 (11)	131 (14)	0.034
Hypertension	1017 (60)	586 (60)	0.756
Diabetes mellitus	541 (32)	306 (32)	0.962
COPD	305 (18)	170 (18)	0.837
Renal disease	482 (29)	357 (37)	<0.001
Physical examination (%)			
Rales	789 (48)	519 (55)	<0.001
Oedema	768 (54)	591 (69)	<0.001
JVP	323 (26)	286 (40)	<0.001
Hepatomegaly	141 (9)	131 (14)	<0.001
KCCQ			
Functional status score	52 (32–75)	45 (27–64)	<0.001
Clinical summary score	49 (30–71)	42 (24–61)	<0.001
Overall score	50 (32–70)	43 (27–60)	<0.001
Laboratory data			
NT-proBNP (pg/mL)	2030 (613–5797)	3093 (1548–6287)	<0.001
Creatinine (μmol/L)	97 (80–119)	101 (84–127)	<0.001
TSH (mU/L)	1.8 (1.0–2.7)	1.9 (1.2–3.1)	0.025
fT4 (pmol/L)	15.3 (13.2–17.9)	15.7 (13.9–18.2)	0.018
Medications (%)			
ACE/ARB	1267 (74)	658 (68)	<0.001
β-Blocker	1348 (79)	760 (78)	0.665
MRA	792 (47)	428 (44)	0.252
Diuretics	1701 (100)	961 (99)	0.014

[a]Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention, and/or coronary artery bypass graft.
ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; fT4, free thyroxine; JVP, jugular venous pressure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TSH, thyroid stimulating hormone.

Table 2 Baseline characteristics by heart failure phenotype comparing patients in sinus rhythm and atrial fibrillation

	HFrEF			HFpEF		
	SR *n* = 1419 (66%)	AF *n* = 733 (34%)	*P*-value	SR *n* = 286 (55%)	AF *n* = 238 (45%)	*P*-value
Clinical						
Age (years)	69 ± 12	74 ± 10	<0.001	75 ± 10	79 ± 9	<0.001
Women (%)	390 (27)	152 (21)	0.001	137 (48)	111 (47)	0.841
BMI (kg/m^2)	27.7 ± 5.6	28.4 ± 5.6	0.015	29.4 ± 6.9	29.5 ± 6.8	0.861
NYHA (%)			0.005			0.796
I	115 (9)	35 (5)		7 (3)	8 (4)	
II	650 (51)	325 (48)		99 (36)	82 (36)	
III	444 (35)	268 (40)		126 (46)	95 (42)	
IV	73 (6)	45 (7)		44 (16)	40 (18)	
LVEF (%)	28 ± 7	28 ± 7	0.115	58 ± 6	58 ± 7	0.857
Systolic blood pressure (mmHg)	124 ± 22	123 ± 21	0.318	133 ± 25	128 ± 21	0.024
Diastolic blood pressure (mmHg)	74 ± 13	76 ± 13	0.001	67 ± 13	71 ± 15	0.004
Heart rate (b.p.m.)	77 ± 18	91 ± 25	<0.001	73 ± 17	88 ± 27	<0.001
History of (%)						
Atrial fibrillation	227 (16)	653 (89)	<0.001	46 (16)	211 (89)	<0.001
Coronary artery disease[a]	720 (51)	314 (43)	0.001	154 (54)	65 (28)	<0.001
Valvular surgery	61 (4)	72 (10)	<0.001	26 (9)	24 (10)	0.813
Stroke	132 (9)	93 (13)	0.019	50 (18)	38 (16)	0.746
Hypertension	814 (57)	428 (59)	0.682	203 (71)	158 (66)	0.300
Diabetes mellitus	443 (31)	221 (30)	0.646	98 (34)	85 (36)	0.767
COPD	230 (16)	121 (17)	0.908	75 (26)	49 (21)	0.153
Renal disease	355 (25)	250 (34)	<0.001	127 (46)	107 (46)	1.000
Physical examination (%)						
Rales	647 (47)	368 (52)	0.032	142 (51)	151 (65)	0.003
Oedema	596 (50)	428 (67)	<0.001	172 (68)	163 (74)	0.196
JVP	256 (25)	204 (39)	<0.001	67 (31)	82 (42)	0.025
Hepatomegaly	131 (9)	113 (16)	<0.001	10 (4)	18 (8)	0.089
KCCQ						
Functional status score	55 (36–75)	46 (27–66)	<0.001	39 (23–63)	38 (21–58)	0.530
Clinical summary score	51 (32–73)	44 (26–63)	<0.001	39 (20–60)	37 (23–56)	0.691
Overall score	52 (35–71)	45 (29–63)	<0.001	42 (25–59)	39 (25–53)	0.365
Laboratory data						
NT-proBNP (pg/mL)	2642 (855–6725)	3573 (1853–7127)	<0.001	802 (261–3092)	2359 (1136–4799)	<0.001
Creatinine (μmol/L)	97 (80–118)	104 (87–130)	<0.001	95 (74–124)	95 (78–122)	0.751
TSH (mU/L)	1.8 (1.1–2.8)	1.9 (1.3–3.2)	0.009	1.6 (1.0–2.6)	1.8 (0.9–2.9)	0.695
fT4 (pmol/L)	15.1 (13.0–17.8)	15.5 (13.7–18.0)	0.055	15.7 (13.8–18.0)	16.0 (14.1–18.6)	0.328
Medications (%)						
ACE/ARB	1079 (76)	532 (73)	0.089	188 (66)	126 (53)	0.004
β-Blocker	1168 (82)	607 (83)	0.819	180 (63)	153 (64)	0.819
MRA	738 (52)	365 (50)	0.353	54 (19)	63 (27)	0.049
Diuretics	1416 (100)	729 (100)	0.373	285 (100)	232 (98)	0.076

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; fT4, free thyroxine; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; JVP, jugular venous pressure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TSH, thyroid stimulating hormone.

[a]Coronary artery disease: previous myocardial infarction, percutaneous coronary intervention (PCI), and/or coronary artery bypass graft (CABG).

Table 3 Multivariable cox regression analysis for all-cause mortality by heart failure phenotype

	Univariable analysis		Multivariable analysis[a]		Multivariable analysis[b]	
	HR (95% CI), AF vs. SR	*P*-value	HR (95% CI), AF vs. SR	*P*-value	HR (95% CI), AF vs. SR	*P*-value
HFrEF	1.41 (1.19–1.68)	<0.001	1.24 (1.04–1.47)	0.015	1.28 (1.07–1.53)	0.007
HFpEF	1.39 (1.05–1.83)	0.022	1.11 (0.83–1.48)	0.480	1.10 (0.81–1.49)	0.550
Overall	1.44 (1.25–1.66)	<0.001	1.22 (1.05–1.41)	0.009	1.27 (1.09–1.48)	0.002
					P-value for interaction: 0.71	

AF, atrial fibrillation; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; SR, sinus rhythm.
[a]Adjusted for age.
[b]Adjusted for age, sex, body mass index, previous myocardial infarction/percutaneous intervention and/or coronary artery bypass graft, hypertension, and renal disease.

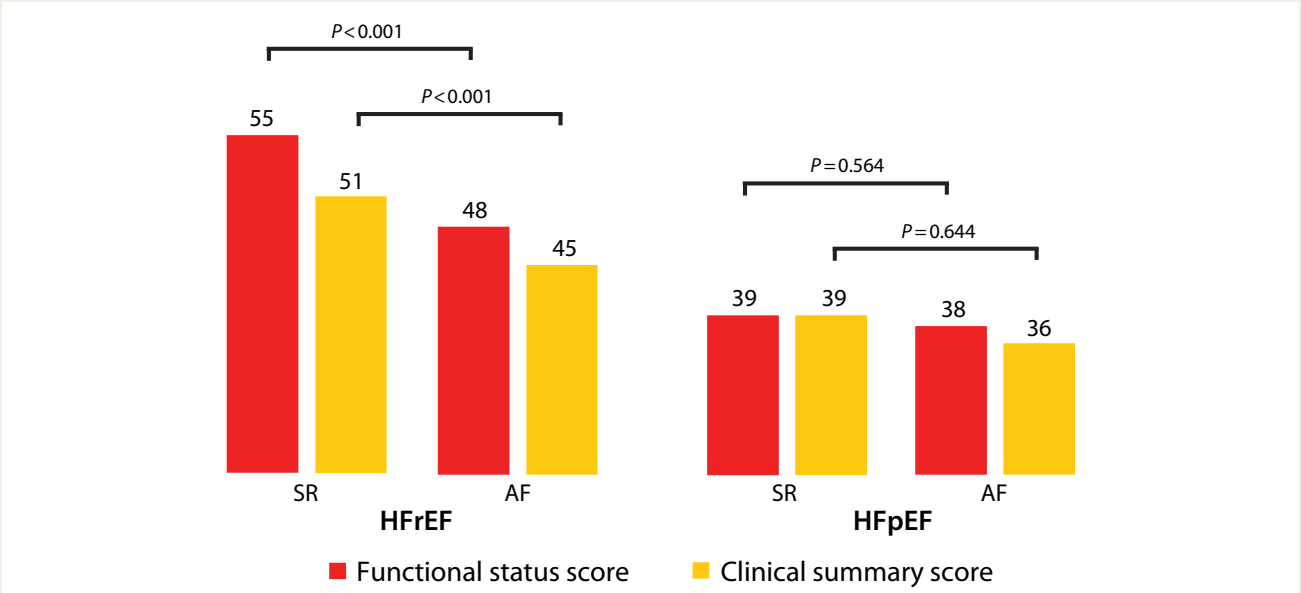


Figure 1 Quality of life; KCCQ scores for patients in sinus rhythm vs. atrial fibrillation. AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; SR, sinus rhyhtm.

but without actual HFpEF were included in this group. Furthermore, since AF itself raises natriuretic peptides, the NT-proBNP inclusion criterion above >2000 pg/mL in BIOSTAT-CHF may have led to inclusion of patients in SR having more severe HFpEF. Greater severity of HF in patients with HFpEF and SR is supported by their low QoL, high mortality rates and higher numbers of elevated risk markers compared to those in SR and HFrEF.

Despite the differences between the biomarker profiles seen in the two HF phenotypes, several similarities were found. Three out of five markers with the largest differences between AF and SR patients were seen in both HFrEF and HFpEF. NT-proBNP, the marker with the largest difference between AF and SR in both HF phenotypes, is well known to be importantly influenced by AF. The other two markers in both HFrEF and HFpEF were ST2 and SPON1. Soluble ST2 is released from the myocardium and vascular endothelial cells in response to pressure and/or volume overload, which is seen in both HFrEF and HFpEF, and which is also more pronounced in patients

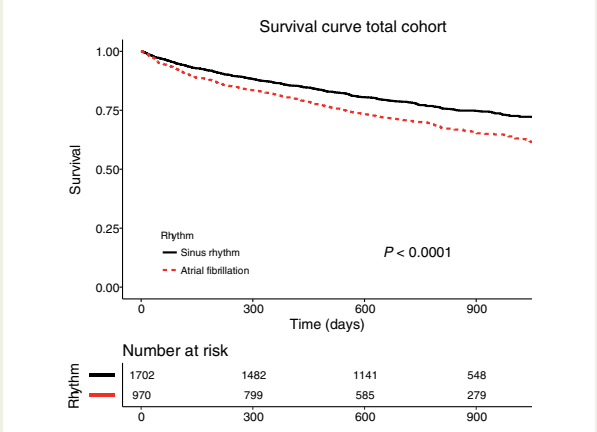


Figure 2 The Kaplan–Meier analysis showing the survival of patients in sinus rhythm vs. atrial fibrillation.

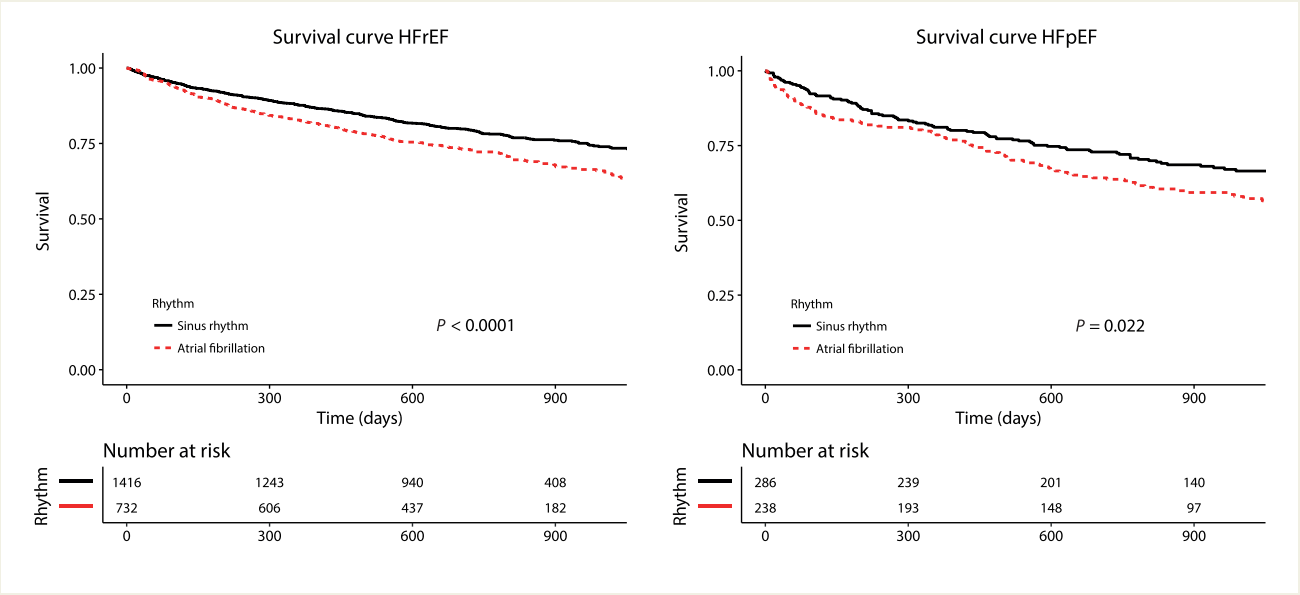


Figure 3 The Kaplan–Meier analysis showing the effect of atrial fibrillation on survival by heart failure phenotype.

with AF.[26] Spondin-1 (SPON1) has been less explored in the cardiovascular field, but associations of this marker have been identified with incident HF, worsened systolic function and hypertension.[27] No specific literature has been found about SPON1 in AF, but this biomarker has been related to angiogenesis and other prothrombotic markers, which perhaps could be linked to the mechanisms of thrombogenesis seen in AF.[17,28]

In HFrEF, the other two top five risk markers were neurogenic locus notch homolog protein 3 (NOTCH 3) and matrix metalloproteinase-2 (MMP2), which were both categorized as markers of remodelling. The two other markers that were most pronounced in patients with AF and HFpEF, were platelet-derived growth factor subunit-A (PDGFSUBUNITA) and insulin-like growth factor-binding protein-1 (IGFBP1), which are both not cardiac-specific markers, and both are linked to cellular growth factors.[29] No specific information is available about the biology and relation between AF and these two markers. Our findings encourage additional studies investigating the underlying mechanisms and the clinical relevance of our findings.

Strengths

The novelty of this study is the measurement of 92 both established and novel cardiovascular risk markers, which resulted in the comparison of the biomarker profiles in HFrEF vs. HFpEF. BIOlogy Study to TAilored Treatment in Chronic Heart Failure is a reflection of real world contemporary European HF patients, due to the inclusion of patients from eleven European countries, aiming for optimal HF treatment. Furthermore, the HF phenotypes were defined according to the latest ESC guidelines EF cut-offs.[30]

Limitations

The results of the current study are based on *post hoc* analyses. The sample size of HFpEF was smaller than in HFrEF, which could explain the differences found in outcome between HFrEF and HFpEF after adjustment for covariates. However, since there was no significant interaction between heart rhythm and HF phenotype, it is unlikely that a larger sample size of HFpEF would have resulted in a contrasting outcome of AF-HFpEF patients. As discussed above, misclassification of AF vs. HFpEF is possible, patients with more severe HFpEF in SR may have been included due to the natriuretic peptide inclusion criterion of BIOSTAT-CHF. This inclusion criterion could also have resulted in positive confounding with higher event rates in the HFpEF group, therefore we did not directly compare AF-HFrEF with AF-HFpEF. Unfortunately, we have no information about patients developing AF during follow-up. Furthermore, there is a lack of data on the type of AF (e.g. paroxysmal, persistent, and permanent) and on applied therapies for AF. The questionnaire used for assessing QoL is not generally used in AF cohorts, which could have led to ignorance of AF specific symptoms that can influence QoL.

Conclusion

This study revealed that the presence of AF was associated with a homogeneously elevated cardiovascular risk marker profile in patients with HFrEF, whereas in HFpEF, the presence of AF was associated with a more scattered risk marker profile. These findings suggest that there might be differences in underlying pathophysiological mechanisms of AF in these two HF phenotypes.

Supplementary material

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

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