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Heart failure subtypes and thromboembolic risk in patients with atrial fibrillation: the PREFER in AF - HF substudy

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ABSTRACT

BACKGROUND and OBJECTIVES: To assess thromboembolic and bleeding risks in patients with heart failure (HF) and atrial fibrillation (AF) according to HF type.

METHODS: We analyzed 6,170 AF patients from the Prevention of thromboembolic events - European Registry in Atrial Fibrillation (PREFER in AF), and categorized patients into: HF with reduced left-ventricular ejection fraction (HFrEF; LVEF<40%); mid-range EF (HFmrEF; LVEF: 40-49%); lower preserved EF (HFLpEF; LVEF: 50-60%), higher preserved EF (HFHpEF; LVEF>60%), and no HF. Outcomes were ischemic stroke, major adverse cardiovascular and cerebral events (MACCE) and major bleeding occurring within 1-year.

RESULTS: The annual incidence of stroke was linearly and inversely related to LVEF, increasing by 0.054% per each 1% of LVEF decrease (95% CI: 0.013%-0.096%; p=0.031). Patients with HFHpEF had the highest CHA_2DS_2-VASc score, but significantly lower stroke incidence than other HF groups (0.65%, compared to HFLpEF 1.30%; HFmrEF 1.71%; HFrEF 1.75%; trend p=0.014). The incidence of MACCE was also lower in HFHpEF (2.0%) compared to other HF groups (range: 3.8-4.4%; p=0.001). Age, HF type, and NYHA class were independent predictors of thromboembolic events. Conversely, major bleeding did not significantly differ between groups (p=0.168).

CONCLUSION: Our study in predominantly anticoagulated patients with AF shows that, reduction in LVEF is associated with higher thromboembolic, but not higher bleeding risk. HFHpEF is a distinct and puzzling group, featuring the highest CHA_2DS_2-VASc score but the lowest residual risk of thromboembolic events, which warrants further investigation.

Key words: atrial fibrillation; heart failure; stroke; ejection fraction; bleeding.

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INTRODUCTION

Heart failure (HF) is a clinical syndrome caused by structural and/or functional cardiac abnormalities, which results in reduced cardiac output and/or elevated intracardiac pressures [1]. In recent times, HF has been classified broadly into two groups, mainly based on the measurement of left ventricular ejection fraction (LVEF): HF with reduced EF (HFrEF, EF<50) and HF with preserved EF (HFpEF, EF $\geq$50) [1, 2]. It has been estimated that approximately half of the patients with HF have HFpEF [2-6]. The European Society of Cardiology (ESC) has recently introduced a new subgroup of HF, defined as HF with mid-range EF (HFmrEF, EF 40-49%). A main shortcoming of the recent HF classification is that current knowledge about HFpEF and HFmrEF is limited, and is based on evidence mostly derived from retrospective observational cohort studies or post-hoc analyses of randomized trials [1, 2].

Atrial fibrillation (AF) and HF are tightly inter-connected entities [7-10]. Regardless of which condition arises first, the coexistence of these diagnoses confers substantially increased cardiovascular morbidity and mortality [11, 12]. HF and AF, jointly or in isolation, are likely to dominate the next era in cardiovascular disease epidemiology, in terms of prevalence, incidence, morbidity, mortality and healthcare expenditure [13-16]. Therefore, understanding predictors of outcome in AF patients according to different HF subtypes is of major clinical importance. Furthermore, the new reclassification of HF types introduced in the 2016 ESC guidelines [1] calls for a reappraisal of the thromboembolic and hemorrhagic risk stratification across different HF subtypes. To address these issues, we report on the HF sub-study of the Prevention of Thromboembolic Events European Registry in Atrial Fibrillation (PREFER in AF).

METHODS

PREFER in AF was a prospective, real-world registry on 7,228 AF patients from 461 hospitals and 7 European countries (Austria, France, Germany, Italy, Spain, Switzerland and the United Kingdom). Inclusion criteria were: age ≥18 years; at least one episode of AF in the previous one year, as demonstrated by an electrocardiogram or by an implanted pacemaker/defibrillator; and signed informed consent to be part of the study, mostly conducted in cardiology centers [17]. The first patient was included in January 2012, with the last follow-up visit being performed in January 2014. There were no explicit exclusion criteria. The study design included a baseline visit at the time of patient recruitment, and a clinical follow-up evaluation at 1 year. In this investigation we only included patients with data available from both the baseline and the 1-year follow-up visits. Only documented events were considered as relevant outcome measures, with any event occurring after the baseline assessment. The study design has been published [17, 18] and the protocol was approved by each local-site Ethics Committee. The registry was sponsored by Daiichi Sankyo Europe GmbH (Munich, Germany) via a contract research organization (SSS International Clinical Research GmbH – Munich, Germany) coordinating various local national contract research organizations.

Definitions and endpoints

The primary efficacy endpoint of this analysis was ischemic stroke. Secondary endpoints were i) the composite of major adverse cardiovascular and cerebral events (MACCE: stroke, systemic embolism, myocardial infarction and acute coronary syndrome), ii) the composite of thromboembolic events (stroke/transient ischemic attack (TIA)/arterial embolism (AE)), iii) death and iv) major bleeding occurring within 1 year of follow-up.

Stroke was defined as the abrupt onset of a focal neurologic deficit, generally distributed in the territory of a single brain artery (including the retinal artery), and not attributable to an identifiable non-vascular cause (i.e., brain tumor or trauma). The deficit had to be either characterized by symptoms lasting >24 hours or causing death within 24 hours of symptom onset. The stroke definition used in the ENGAGE-AF TIMI 48 study and in our study reflects the *Statement for Healthcare Professionals From the American Heart Association/American Stroke Association* that incorporates the *World Health Organization (WHO)* definition of stroke [19]. TIA was defined as a focal neurologic deficit associated with symptoms lasting <24 hours.

Systemic embolic event (SEE) was defined as an abrupt episode of arterial insufficiency with clinical or radiologic documentation of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation); venous thromboembolism and pulmonary embolism were also included in this outcome measure.

Acute coronary syndrome was defined as a myocardial infarction or unstable angina. Myocardial infarction (MI) was defined according to the latest version of the Universal Definition [20]. Unstable angina was defined by specific clinical findings of prolonged (>20 minutes) angina at rest; new onset of severe angina; angina that is increasing in frequency, longer in duration, or lower in threshold; or angina that occurs after a recent episode of MI, always in the absence of biochemical evidence of myocardial damage according to locally used troponin T or I tests [21].

Major bleeding was defined as fatal bleeding and/or bleeding into a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome) and/or clinically relevant bleeding with a hemoglobin drop ≥2 g/dL; this is consistent with the definition of major bleeding from the *International Society on Thrombosis and Haemostasis* [4].

HF definition and classification

Treating physicians at the enrolling sites made a clinical diagnosis of HF (HF with reduced or preserved LVEF as per HF guidelines available at the time of inclusion), without any centralized adjudication of the diagnosis. Likewise, treating physicians included data on the EF, derived from echocardiography based on the Simpson´s method, without a centralized adjudication and verification. As a second step, we grouped patients with HF into HF with reduced EF (HFrEF; EF<40%); HF with mid-range EF (HFmrEF; EF: 40-49%); and HF with preserved ejection fraction (HFpEF; EF>50%), based on the most recent ESC guidelines [1]. Thirdly, as an exploratory analysis, we further subdivided the HFpEF cohort into HF with lower preserved ejection fraction (HFLpEF ; EF: 50-60%) and HF with higher preserved ejection fraction (HFHpEF; EF>60%).

Statistics

We here report categorical variables as absolute and percent frequencies (n, %). For each continuous variables, we report the mean, median, standard deviation or 95% confidence intervals (CI), as appropriate.

We performed a complete case analysis and assumed that missing data were missing at random. We performed statistical comparisons with the t test, the Mann Whitney U test or the Chi^2-test, as appropriate. We then calculated odds ratios (OR) for independent predictors of thromboembolic events in HF patients by multivariable logistic regression, where predictors and adjusting factors were included in the model. The composite of thromboembolic events (yes/no) was the dependent variable, whereas the following factors were included into the model as independent variables: EF, HF subtype (HFrEF/HFmrEF/HFLpEF/HFHpEF), LVEF per 10% decrease, New York Heart Association

(NYHA) class, <mark>anticoagulation treatment</mark>, CHA_2D_2VASc score (applied as indicated in the AF guidelines [22], <mark>where 1 point for congestive HF was given in patients with LV dysfunction and / or congestion at the time point of inclusion</mark>), body mass index (BMI), smoking. We report ORs, 95% confidence intervals (CIs) and the corresponding p value for such analyses.

A post hoc power calculation has revealed a power of 84% for the comparison of the composite of MACCE event rates between the groups with a two-sided p value <0.05.

All analyses are to be intended as descriptive/exploratory, and therefore no adjustment for multiple testing was done. All statistical analyses were performed using SAS, version 9.4 (Cary, North Carolina, USA), with a two-tailed significance value of 0.05.

RESULTS

The flow of patients through the PREFER in AF-HF substudy is shown in **Figure 1**. Out of 7,228 patients enrolled in the PREFER in AF Registry, 6,170 had baseline and 1-year follow-up visits, complete data on the incidence of thromboembolic events, and information on the HF diagnosis. Of these, 4,571 had no HF and 1,599 had a HF diagnosis. Of these latter, 458 had HFrEF, 525 had HFmrEF and 616 had HFpEF. Among patients with HFpEF, 308 were classified with HFLpEF, and 308 with HFHpEF.

The distributions of demographic and clinical features according to HF type are indicated in **Tables 1 and 2**. Among patients with HF, patients with HFrEF were more often male, smokers and with a younger age, more often with a history of vascular disease and of chronic kidney disease. In contrast, patients with HFHpEF were more often female, with a higher age and a higher mean systolic blood pressure as compared with other HF groups (**Table 1**).

We found the highest CHA_2DS_2-VASc score in patients with HFHpEF (mean 4.7) and the lowest in HFrEF (4.1) (p<0.0001; **Table 2**). Concordantly, 99% of HFHpEF patients had a clear indication for oral anticoagulation (OAC; CHA_2DS_2-VASc $\geq$2) compared with 95% in patients with HFrEF (p<0.001; **Supplement Figure 1S; Table 2**). The proportion of patients without OAC treatment despite indication (CHA_2DS_2-VASc $\geq$2) was lowest in the HFHpEF subgroup (6%) as compared to other HF subgroups (13% in each HFLpEF, HFmrEF and HFrEF, and 15% in no HF group; p=0.0004; **Supplement Figure 1S**). Of note, due to the time period in which PREFER in AF was performed, the penetration of NOACs was <10%, and was highest in HFHpEF as compared to other groups (9.4% in HFHpEF; 5.5% in HFLpEF; 5.5% in HFmrEF; 4.6% in HFrEF; p=0.026; **Table 1**). The frequency of paroxysmal AF was in the same range in HF patients (18-21%) and was highest in no HF patients (31%; p<0.001 for trend).

Clinical outcomes

Patients with any diagnosis of HF had a higher incidence of stroke as compared to patients without HF (1.3% vs 0.6% year; respectively; p=0.007). Despite the highest CHA_2DS_2-VASc score, the yearly incidence of stroke was only 0.65% in HFHpEF, significantly lower than in other HF subgroups (1.30% in HFLpEF; 1.71% in HFmrEF; 1.75% in HFrEF; p=0.014; **Figure 2A**), and increased by 0.054% per 1% of EF decrease (95% CI: 0.013%-0.096%; p=0.031; **Figure 2B**). Also, in anticoagulated HF patients the incidence of ischemic stroke increased by 0.030% per each 1% of EF decrease (95% CI: 0.011%-0.048%; p=0.003). Stroke incidence was comparable between HFHpEF and no-HF groups (**Figure 2A;** p=0.9746).

Patients with any diagnosis of HF had a higher incidence of MACCE as compared to patients without HF (3.8% vs 2.1% per year; respectively; p<0.001). The yearly incidence of MACCE was lower in HFHpEF (2.0%) compared with other HF subgroups (4.2% in HFLpEF;

3.8% in HFmrEF; 4.4% in HFrEF; p=0.001; **Supplement Figure 2S**). MACCE incidence was comparable between HFHpEF and no-HF groups (**Supplement Figure 2S;** p=0.9234).

The incidence of major bleeding was higher in patients with HF as compared to patients without HF (3.6% vs 2.5% per year, respectively, p=0.01). There were no statistical differences in the incidences of the composite of major bleeding across the subgroups (trend p=0.161; **Supplement Figure 3S**). Of note, the incidence of major bleeding events according to bleeding type (intracranial bleeding (ICB), gastrointestinal (GI), other threatening major bleeding) was similar between HF groups, as well as in the entire study population (p>0.05; **Supplement Table 1S**).

Patients with any diagnosis of HF had a higher incidence of death as compared to patients without HF (6.0% vs 1.9% year; respectively; p<0.001). Death rate increased with decreasing EF, and was highest in the HFrEF subgroup (HFrEF: 7.2%, HFmrEF: 6.5%, HFLpEF: 5.2%, HFHpEF: 4.2%, no HF: 1.9%; p<0.001). Death incidence was higher in patients with HFHpEF vs no-HF (p=0.005).

There were no differences in the outcomes in respect to AF type in the overall population as well as there was no interaction between AF type, different HF subtypes and clinical outcomes (paroxysmal vs non-paroxysmal; p>0.05 for all comparisons).

Predictors of thromboembolic risk in HF patients

The multivariable regression analysis identified 3 factors at baseline independently associated with thromboembolic events: HF subgroup (p=0.007), NYHA class (p<0.001) and age (p=0.029). Among different HF subgroups, the highest odds for the composite of thromboembolic events were in HFmrEF patients (OR: 3.10; 95% CI: 1.12-8.56). The following estimates were calculated for the NYHA class (OR per 1 increasing NYHA point:

2.92; 95% CI: 1.60-5.30) and age (OR per 1 year of age: 1.04; 95% CI: 1.00-1.08). While, as expected, the severity of HF symptoms (NYHA class III-IV) increased with decreasing EF (**Supplement Figure 4S.A**), NYHA classes III-IV (severe HF) were associated with a higher incidence of thromboembolic events as compared to NYHA classes I-II (mild to moderate HF), which was 12.3% and 12.5% in patients with HFmrEF and HFLpEF, respectively (p<0.05 for between group comparison; **Supplement Figure 4S.B**).

Performance of the CHA2DS2-Vasc score in the prediction of stroke

In patients with no HF the CHADS-VASc score ≥ 2 performed well in terms of prediction of stroke (OR: 1.70, 95%CI: 1.34-2.16, p<0.0001; AUC: 0.73, 95%CI: 0.62-0.83). In contrast, for HF patients its performance decreased with increasing HF severity. In the overall HF population the CHADS-VASc score ≥ 2 was not predictive of stroke (OR: 1.03, 95%CI: 0.79-1.33, p=0.85; AUC: 0.50, 95%CI: 0.41-0.60). When each of the HF groups were analysed separately, the AUC for the CHADS-VASc score ≥ 2 decreased with the decreasing EF (HFHpEF AUC: 0.628, 95%CI: 0.03-1.00; HFLpEF AUC: 0.54, 95%CI: 0.36-0.72; HFmrEF AUC: 0.46, 95%CI: 0.33-0.58; HFrEF AUC: 0.44, 95%CI: 0.25-0.62) and was predictive for stroke in none of the HF subgroups in the logistic regression model.

Sensitivity analyses

When patients without OAC treatment (ranging from 6% to 19% depending on the group) were excluded from each of the analyses, the magnitude and the direction of the estimates remained unchanged (data not shown).

DISCUSSION

The central findings of the PREFER in AF – HF substudy investigating the association between HF type and thromboembolic events in this mainly anticoagulated cohort of AF patients in real-life clinical conditions under registry setting are as follows: i. the subtype of HF predicts the residual risk of thromboembolic events, with an inverse association between LVEF and hard thromboembolic endpoints, such as ischemic stroke and MACCE; ii. in HF patients, in addition to EF and age, the NYHA class is a strong and independent predictor of thromboembolic events; iii. HF patients with HFLpEF and HFHpEF represent quite distinct populations, which also differ in terms of thromboembolic risk; iv. mortality increases with decreasing EF, and was highest in the HFrEF subgroup.

The definition of HFpEF is difficult, which can be illustrated by the various classifications proposed by experts and by disparate inclusion criteria of clinical trials [2], which led to heterogeneity of HFpEF patients recruited into most studies and registries. Such difficulties in classification also affect our study. Even for the key diagnostic criterion, EF, different cut-offs have been used across trials and registries on HFpEF (ranging from ≥40% to ≥55%), of which most were applied in a post-hoc manner [12]. The validity and reproducibility of estimating systolic and diastolic function in the context of AF has also been questioned [23]. Therefore, the available evidence addressing the issue of stroke risk among different HF subtypes, is based on studies using different inclusion and exclusion criteria, end point assessments, sample sizes, patient populations and characteristics. This is mirrored in the substantial statistical and clinical heterogeneity across studies [12]. Many such limitations also apply to our study, but still the present findings add important insights into the discussion on the risk of stroke in AF across HF subtypes.

Although the prognosis of all patients with HF is poor, HFpEF has been postulated to be more benign as compared to HFrEF [8]. Indeed, considering the risk of

11

thromboembolism in the presence of AF, HFrEF was associated with the highest incidence of adverse events such as ischemic stroke, MACCE and death in our analysis, which confirms the findings of other prospective studies, such as the Studies of Left Ventricular Dysfunction (SOLVD), the Survival and Ventricular Enlargement (SAVE), the Northern Manhattan Study (NOMASS), or the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trials [24-27], showing that EF is an independent risk factor for stroke or systemic embolism [28]. In contrast, several other studies as the Loire Valley Atrial Fibrillation Project [29], the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) trial in patients not randomized to oral anticoagulation [30], or a meta-analysis of cohort studies and post-hoc sub-group analyses of randomized trials in AF patients indicated no difference in the risk of stroke between HFrEF vs HFpEF groups [12]. A possible explanation for these differences is the circumstance that in some studies patients were not or rarely anticoagulated and in the meta-analysis 50% of patients were anticoagulated [12], as compared to 90% in our study. Therefore, our study focused on the residual risk of stroke in the majority of our patients, and such residual risk is known to be affected by the type of AF and the presence of HF [31]. A third possible explanation for the inconsistent results between our study and the previous meta-analysis is the fact that the definitions of HFpEF were very heterogenous and applied only post-hoc for the majority of included studies [2, 12]. A key step that allowed more insightful information on the risk of stroke in the HFpEF population in our study was to subdivide such patients into HFLpEF and HFHpEF.

In parallel with the risk of stroke, an association between HF subtypes and mortality has been previously described [12], indicating a 1.24-fold higher risk of death for HFrEF as compared with HFpEF. Thus, we confirm this finding in the PREFER in AF - HF substudy.

A true central finding of the present analysis is the uniqueness of mainly anticoagulated AF patients with HFHpEF, apparently representing a distinct patient

population. Such patients are characterized by the highest CHA$_2$DS$_2$-VASc score, but also, surprisingly, by the lowest incidence of thromboembolic events. This association was also confirmed after exclusion of patients without a proper anticoagulant treatment. Furthermore, it is crucial to note that splitting the HFpEF into two groups, those with HFLpEF and HFHpEF, revealed a statistically significant difference in the rate of thromboembolic events between such groups. Indeed, the incidence of ischemic stroke or MACCE was half in HFHpEF compared with HFLpEF. Therefore, distinguishing a group of HFHpEF in our study might underline the complex pathophysiology and heterogeneity of the HFpEF syndrome. In contrast, we have found no significant differences in the rates of thromboembolic events between HFrEF and HFmrEF.

Guidelines encourage the use of the CHA2DS2-VASc score only for the decision making on initiation of anticoagulant treatment in AF patients [22]. Patients with a CHA2DS2-VASc score of ≥2, represent 85% of AF population being at moderate-to-high risk of thrombotic events, and who should benefit from anticoagulation. Importantly, the CHA2DS2-VASc score has never been established and is not recommended as a tool for predicting thromboembolism in patients already on anticoagulation, as it was the case in 90% of patient population included in this study. Interestingly, CHA2DS2-VASc score predicted stroke only in patients without HF in our study. In patients with HF irrespectively of the HF subtype, CHA2DS2-VASc score was not a predictor of residual risk of stroke. Moreover, the performance of CHA2DS2-VASc score to predict stroke in anticoagulated HF patients decreased with decreasing EF, which might confirm our results that EF is strongly associated with a residual risk of stroke in HF patients.

It has been reported that measures of cardiac performance, such as the LVEF, correlate poorly with HF symptoms (e.g., NYHA class) [32]. Accordingly, some patients with HFrEF may be asymptomatic, whereas some patients with HFpEF may have severe

dyspnea, as also demonstrated in our analysis. Our study, however, also showed that NYHA functional class was associated with thromboembolic events, independent of the HF type and other factors, increasing the odds for thromboembolism by 2.9 per 1 increasing NYHA point. Our observation that the clinical severity of HF in AF has independent and direct prognostic implications, confirms previous findings in the overall HF population [28]. Concordantly, the incidence of stroke was 3-fold higher in patients with more severe HF (median NYHA class 3.4) in the Prospective Randomized Milrinone Survival trial (PROMISE trial) as compared to patients with mild HF (median NYHA class 1.7) in the Studies of Left Ventricular Dysfunction (SOLVED trial) [33].

Importantly, our study design differs from a number of previously published studies on association between HF type and AF. Whereas in our analysis all patients had AF and 39% were also diagnosed with HF, other studies focused on patients who all had been diagnosed with HF, and some had also AF (prevalence ranging from 17% to 65%) [34-36]. Based on this assumption, we tested the incidence of thromboembolism in AF patients according to HF diagnosis and type. In contrast, other analyses focused on thromboembolic risk in HF patients according to rhythm disorder: AF vs no AF. Whereas results of both types of studies yield complementary information, such analyses are not interchangeable and a direct comparison of results is not feasible.

Study strengths and limitations

The strengths of our study include its focus on different types of HF, including the recent HF classification by the ESC, the large number (>6,000) of patients included, complete 1-year follow-up data on the incidence of thromboembolic events, and detailed sensitivity analyses with a focus on a new group of HFHpEF. Our study also adds data on the distribution of OAC use between the HF groups, predictors of thromboembolic events,

and the incidence of hard ischemic outcomes (such as ischemic stroke and MACCE) in each of the HF groups, as well as in relation to EF.

A major shortcoming of this study is the fact that the HF diagnosis (HFrEF or HFpEF, based on the available guidelines at the time of inclusion) was made by a treating physician at the study site and was not independently verified or adjudicated. Moreover, diagnostic criteria for HF changed over time. Due to the missing data on the levels of the brain natriuretic peptides (BNP), we could not verify the HF diagnosis. However, we performed a sensitivity analysis for a subgroup of patients with HFmrEF and HFpEF and available echocardiographic data recommended by the current guidelines for the HF diagnosis (left atrial enlargement, left ventricular hypertrophy), which confirmed the direction and the magnitude of the main study estimates. A second major shortcoming is here the use of echocardiographic assessment of the EF, known to be quite variable among operators and even within the single operator [37]. Additionally, we are lacking information whether adjustment for heart rate at the time of echo was performed, which might also influence the assessment of EF. EF derived by echocardiography with the modified Simpson formula was reported by the investigators and was not adjudicated. Much more accurate estimates of the EF are provided by magnetic resonance imaging [38], but such data were not available. The registry also did not provide data on parameters of left ventricular volumes or diastolic function, which have been shown to be potentially valuable in AF patients [23]. Moreover, imaging modalities were not adjudicated to ensure uniformity. Therefore, our study certainly lacks the standardization of HF diagnosis and of the EF measurements, and there is a risk of residual confounding. The registry also did not provide information on the underlying disease leading to HF. Mortality data were provided by the study centers following the final completion of the study, so that such data might be incomplete. Additional limitation is that the distinction between the two categories of HF with pEF (HFHpEF and HFLpEF) was a

part of post-hoc exploratory analyses. We fully acknowledge such limitations. This is however the first report in the literature describing a possible heterogeneity in the risk of stroke and bleeding within the broad category of patients with preserved EF, and calls for an independent validation of such data in independent cohorts.

CONCLUSION

In mainly anticoagulated patients with AF, the subtype of HF predicts the thromboembolic risk: patients with HFHpEF apparently represent a distinct patient population, with the highest CHA_2DS_2-VASc score but the lowest incidence of thromboembolic events. AF with HFrEF is associated with most severe adverse events, such as ischemic stroke and MACCE. HFHpEF with AF had a comparable thromboembolic risk to controls without HF but relatively high risk of bleeding. If independently confirmed, HFHpEF should be further inspected in future studies as possibly distinct from HFLpEF.

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TABLES:

Table 1. Patient demographic data according to heart failure subgroups.

	HFrEF	HFmEF	HFLpEF	HFHpEF	no HF	p between HF groups
N	458	525	308	308	4571	
Age (years)	72	73	75	76	71	<0.0001
BMI	27.4	28.0	27.9	28.1	28.0	0.0926
Male (%)	76	67	59	45	59	<0.0001
Smoking (%)	49	46	38	31	39	<0.0001
Prior stroke (%)	10	11	10	8	8	0.7993
Coronary heart disease (%)	46	41	39	27	18	<0.0001
Prior stenting (%)	24	17	11	11	8	<0.0001
Prior myocardial infarction (%)	29	22	16	8	7	<0.0001
Peripheral arterial disease (%)	7.4	7.6	7.9	5.0	3.5	0.4515
Chronic kidney disease (%)	29	16	20	22	10	<0.0001
Chronic obstructive pulmonary disease (%)	19	17	22	16	9	0.1189
Systole blood pressure (mmHg) at baseline (mean)	123	130	129	133	133	<0.0001
Diastolic blood pressure (mmHg) at baseline (mean)	74	78	76	76	78	<0.0001
Heart rate (beats/min) at baseline (mean)	82	81	80	78	78	0.0180
Prior major bleeding event (%)	5.2	3.8	9.1	7.5	3.4	0.0096
HASBLED score (mean)	2.3	2.2	2.5	2.3	1.9	0.0696
Paroxysmal AF (%)	17.9	21.0	21.1	19.2	33.8	0.6090
Valvular heart disease (moderate or severe)	35.2	26.9	26.6	24.0	13.3	0.0027
Antithrombotic therapies (%):						
No therapy	3.7	4.6	4.6	2.9	6.7	0.6336
Oral anticoagulant (VKA or VKA & antiplatelet or NOAC)	88	87	88	94	81	0.0189
VKA	65	67	75	75	66	0.0027
VKA plus antiplatelet	18.6	13.1	7.5	9.1	8.9	<0.0001
NOAC	4.6	5.5	5.5	9.4	6.1	0.0397
NOAC plus antiplatelet	0.7	1.5	0.7	1.3	1.1	0.4847
Antiplatelet only	8.5	8.2	7.8	3.3	12.6	0.0261

Legend: HFrEF: heart failure with reduced ejection fraction; HFmrEF: HF with mid-range EF: HFLpEF: HF with lower preserved ejection fraction; HFHpEF : HF with higher preserved ejection fraction; BMI: body mass index; NOAC: non-vitamin K oral anticoagulants; VKA: vitamin K oral anticoagulants; TIA: transient ischemic attack. Data are presented as n, mean or percentages as appropriate. p value for trend.

Table 2. Mean CHA$_2$DS$_2$-VASc score and its components according to heart failure subgroups.

	HFrEF	HFmEF	HFLpEF	HFHpEF	no HF	p between HF groups
CHA2DS2-VASc score	4.1	4.4	4.5	4.7	3.0	<0.0001
Points 0 (%)	0	0	0	0	6.6	0.2458
Points 1 (%)	4.9	5.4	1.7	1	12.9	0.0007
Points >2 (%)	95.1	94.6	98.3	99.0	80.5	0.0016
Congestive heart failure (%)	100	100	96.0	94.3	0.0	<0.0001
Hypertension (%)	65.9	71.4	80.4	79.3	71.2	<0.0001
Age 65–74 years (%)	33.7	30.9	30.4	26.7	33.9	0.2395
Age ≥ 75 years (%)	43.5	49.7	56.6	63.0	41.9	<0.0001
Diabetes mellitus (%)	26.4	31.6	29.6	32.3	19.1	0.2437
Prior stroke/TIA/ thromboembolic event (%)	16.2	18.8	15.5	15.7	15.2	0.5302
Vascular disease (%)	43.7	33.3	30.1	25.3	17.5	<0.0001
Female gender (%)	23.7	33.7	40.1	55.3	40.9	<0.0001

Legend: HFrEF: heart failure with reduced ejection fraction; HFmrEF: HF with mid-range EF: HFLpEF: HF with lower preserved ejection fraction; HFHpEF : HF with higher preserved ejection fraction; TIA: transient ischemic attack. p value for trend.

FIGURES
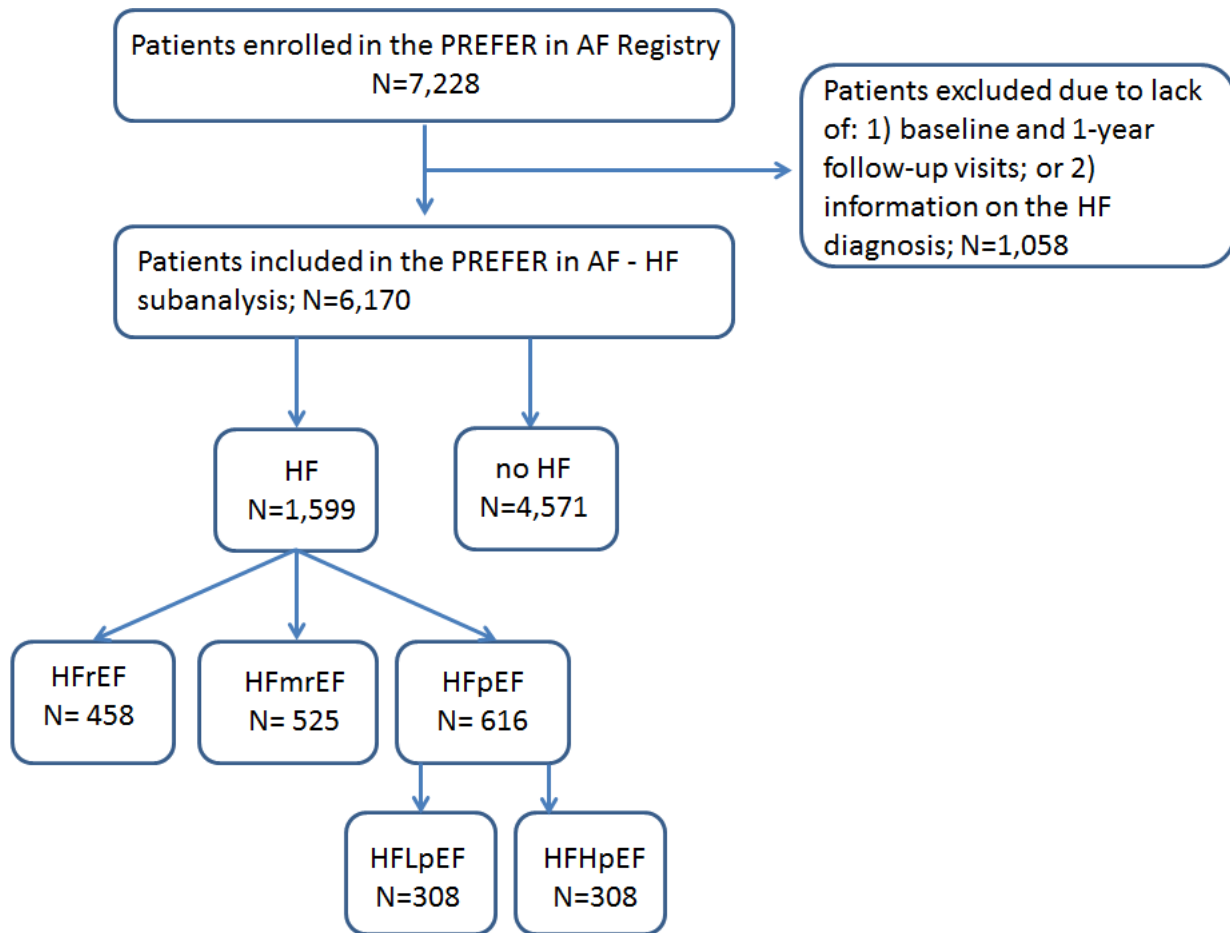
Figure 1. Flow of patients in the PREFER in AF – HF substudy. HFrEF: heart failure with reduced ejection fraction; HFmrEF: HF with mid-range EF; HFpEF: HF with preserved ejection fraction; HFLpEF: HF with lower preserved ejection fraction; HFHpEF: HF with higher preserved ejection fraction.
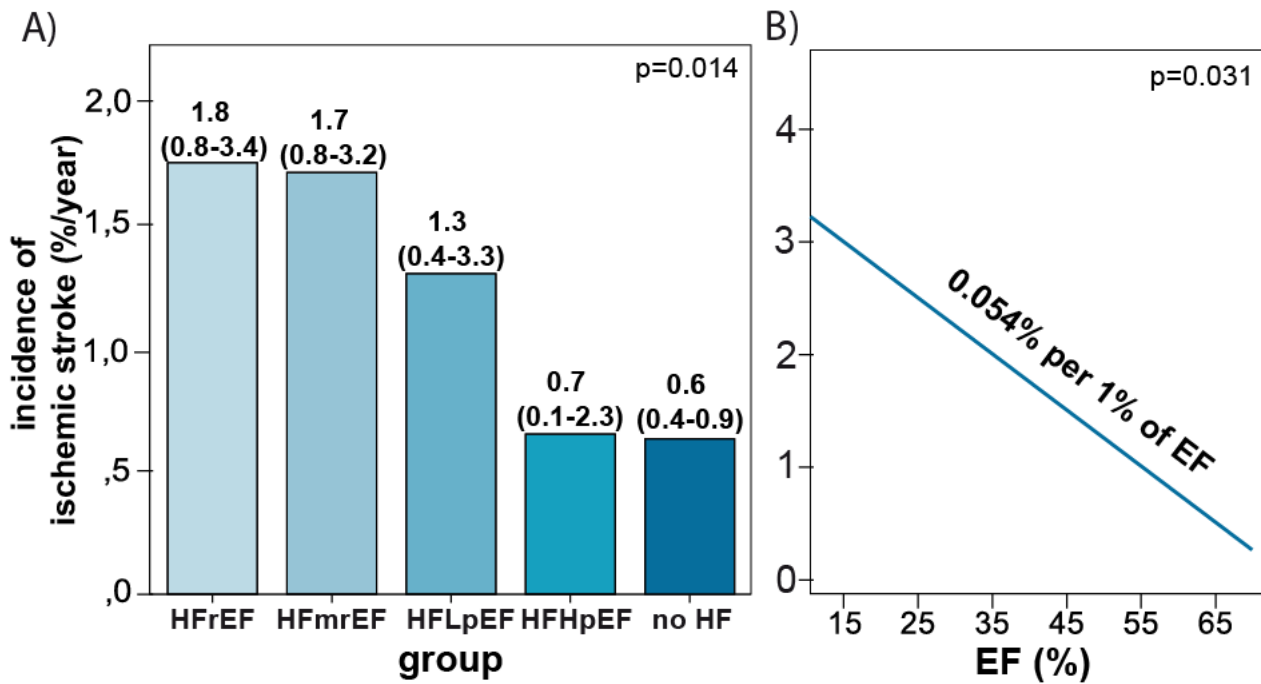
Figure 2. A) Annual incidence (mean and 95% confidence intervals, (CI)) of ischemic stroke; p value for trend; B) Linear regression model for the association between the incidence of ischemic stroke and ejection fraction (EF).

DISCLOSURES:

Author's contribution:

Jolanta M. Siller-Matula: conception and study design, interpretation of data, manuscript drafting; Ladislav Pecen: statistical analyses, interpretation of data, critical revision of the manuscript; Giuseppe Patti: interpretation of data, results discussion, critical revision of the manuscript; Markus Lucerna: interpretation of data, results discussion, critical revision of the manuscript; Paulus Kirchhof: interpretation of data, results discussion, critical revision of the manuscript; Maciej Lesiak: interpretation of data, results discussion, critical revision of the manuscript; Kurt Huber: interpretation of data, results discussion, critical revision of the manuscript; Freek W.A. Verheugt: interpretation of data, results discussion, critical revision of the manuscript; Giulia Renda: interpretation of data, results discussion, critical revision of the manuscript; Irene M. Lang: interpretation of data, results discussion, critical revision of the manuscript; Renate B. Schnabel: interpretation of data, results discussion, critical revision of the manuscript; Rolf Wachter: interpretation of data, results discussion, critical revision of the manuscript; Dipak Kotecha: interpretation of data, results discussion, critical revision of the manuscript; Marc Sellal: interpretation of data, results discussion, critical revision of the manuscript; Miklos Rohla: interpretation of data, results discussion, critical revision of the manuscript; Fabrizio Ricci: interpretation of data, results discussion, critical revision of the manuscript; Raffaele De Caterina: conception and study design, interpretation of data, manuscript drafting;