International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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

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ARTICLE INFO

Article history:
Received 27 November 2017
Received in revised form 16 February 2018
Accepted 20 April 2018
Available online xxxx

Keywords:
Atrial fibrillation
Heart failure
Stroke
Ejection fraction
Bleeding

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 6170 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.

1. 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

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https://doi.org/10.1016/j.ijcard.2018.04.093
0167-5273/

measurement of left ventricular ejection fraction (LVEF): HF with reduced EF (HFrEF, EF < 50) and HF with preserved EF (HFpEF, EF ≥ 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).

2. Methods

PREFER in AF was a prospective, real-world registry on 7228 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.

2.1. 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 h or causing death within 24 h 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 h.

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 min) 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].

2.2. 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%).

2.3. 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, anticoagulation treatment, CHA_2D_2VASc score (applied as indicated in the AF guidelines [22], where 1 point for congestive HF was given in patients with LV dysfunction and/or congestion at the time point of inclusion), 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.

3. Results

The flow of patients through the PREFER in AF-HF substudy is shown in Fig. 1. Out of 7228 patients enrolled in the PREFER in AF Registry, 6170 had baseline and 1-year follow-up visits, complete data on the incidence of thromboembolic events, and information on the HF diagnosis. Of these, 4571 had no HF and 1599 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 > 2) compared with 95% in patients with HFrEF ($p < 0.001$; Supplement Fig. 1S; Table 2). The proportion of patients without OAC treatment despite indication (CHA_2DS_2-VASc ≥ 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 Fig. 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).

3.1. 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;

Please cite this article as: J.M. Siller-Matula, et al., Heart failure subtypes and thromboembolic risk in patients with atrial fibrillation: The PREFER in AF - HF substudy, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.04.093