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Relation of female sex to left atrial diameter and cardiovascular death in atrial fibrillation: The AFFIRM Trial

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ABSTRACT

Background: Female sex is associated with thromboembolism related to atrial fibrillation (AF). Left atrial (LA) diameter independently predicted incident cardiovascular (CV) major events in the general population. In AF patients, LA enlargement is associated to AF occurrence and recurrence. No data have previously been reported on the relationship between LA enlargement, sex and CV death in AF patients.

Methods and results: All patients enrolled in the AFFIRM Trial with available data about LA dimension were included in this post-hoc analysis.

Of the 2615 eligible for the present analysis, LA enlargement was recorded in 67.0%, more commonly in women than in men ($p = 0.032$). Patients with LA enlargement had higher body mass index (BMI), and were more frequently hypertensive, diabetic, and diagnosed with a structural heart disease, prior coronary artery disease (CAD) and heart failure (HF). BMI, left ventricular mass, female sex and mitral valve insufficiency ($p < 0.001$) were associated with LA enlargement.

AF female patients with LA enlargement had a higher risk for CV death ($p = 0.011$). LA diameter showed a significant association with CV death ($p < 0.001$). Cox regression analysis demonstrated that LA diameter was an independent predictor of CV death in female AF patients ($p = 0.003$).

Conclusions: LA diameter enlargement is associated with female sex, and carries a higher risk for CV death, particularly in females. LA diameter was an independent predictor of CV death in female AF patients.

1. Introduction

Atrial fibrillation (AF) is the commonest cardiac rhythm disorder which is associated with an increased risk of adverse cardiovascular (CV) outcomes, including stroke, thromboembolism, heart failure and CV death [1]. Worse clinical outcomes have been reported for female patients with AF compared to males [2].

Of note, female AF patients carry a higher risk of stroke and thromboembolism compared with males, independent of anticoagulant use [3]. Thus, female sex is included as a risk factor within the CHA_2DS_2-VASc score [4]. Independent of stroke risk, female patients with AF have higher mortality rates [5,6], even if the precise reasons accounting for this accentuated risk are poorly understood.

Left atrium (LA) enlargement has been related to higher risk of developing AF [7] and adverse CV events [8–10]. Beyond the impact on AF episode recurrences after ablation therapies [11,12], the clinical relevance of LA diameter, as assessed by trans-thoracic echocardiography, has been attributed to intracavitary thrombus formation given that LA enlargement is a surrogate marker of stroke risk [13].

On the other hand, there are conflicting results for LA enlargement in predicting all-cause death and CV events in the general population, as well as in the high risk CV population [8–10,14,15]. These discordant findings may perhaps be due to the heterogeneity of studied populations and to the lack of standardization of echocardiographic measurements. The influence of LA enlargement on CV death has been investigated in the general population showing an increased risk, particularly in males, even if this risk was mitigated by the influence of left ventricular mass (LVM) [16,17].

To the best of our knowledge, no data on LA enlargement, carefully defined according to properly echocardiographically-based sex-specific thresholds [18], and CV death have been described in AF, nor a relationship between sex and LA diameter in AF. The aim of this study

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was to investigate the relationship between LA diameter and sex in an AF population and second, the influence of LA enlargement on CV death risk related to sex. To investigate these relationships, we performed a post-hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.

2. Methods

The AFFIRM Trial was a prospective randomized trial investigating the difference of clinical outcomes between rate control *versus* rhythm control in the clinical management of patients with AF (ClinicalTrials.Gov Identifier: NCT00000556). United States National Heart, Lung, and Blood Institute (NHLBI) held the study. This post-hoc analysis is based on the original AFFIRM database, obtained from the National Institutes of Health. The study protocol and the principal trial results have been described in detail elsewhere [19,20]. For the present analysis, all patients enrolled in the AFFIRM Trial which had available echocardiographic data about LA dimension were considered. According to the joint consensus statement between American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACI) for cardiac chambers quantification, LA enlargement was defined as a LA diameter greater than 3.8 cm in female patients, or >4.0 cm in male patients [18].

Thromboembolic risk was defined according to the CHA_2DS_2-VASc risk score [4]. 'Low risk' patients were defined as those males with a CHA_2DS_2-VASc score = 0 or females with a CHA_2DS_2-VASc = 1; 'moderate risk' was defined as male patients with a CHA_2DS_2-VASc score = 1; 'high risk' was defined as patients with a CHA_2DS_2-VASc score ≥2 [21].

2.1. Statistical analyses

All continuous variables were tested for normality with the Shapiro–Wilk test. Variables with normal distribution were expressed as means and standard deviations, and tested for differences with the Student t test. Non-normal variables were expressed as median and interquartile range (IQR) and differences tested with the Mann–Whitney U test. Categorical variables, expressed as counts and percentages, were analysed by a chi-square test.

A regression analysis was performed in order to establish all clinical factors significantly associated with LA enlargement. All variables that were significantly different between the two groups at the baseline underwent a univariate analysis and those univariate predictors with a statistical significance of less than 10% were inserted into a forward multivariate logistic model. Similarly, a regression analysis was performed with the echocardiographic indexes. Next, a complete multivariable regression analysis with all variables considered in the two previous models was performed.

Kaplan–Meier (KM) curves for the occurrence of CV death, for overall population and stratified per male/female sex, according to LA enlargement and differences in survival distributors between subgroups was analysed using the Log-rank test. To establish clinical factors consistently associated with CV death a Cox proportional hazard analysis was performed according to sex. LA diameter, considered as a continuous variable, and all clinical variables significantly different between the two groups underwent a univariate analysis, and all variables associated to CV death with a p level <0.10 were inserted in the forward stepwise multivariate model. A two-sided p value <0.05 was considered as statistically significant. All analyses were performed using SPSS v. 22.0 (IBM, NY, USA).

3. Results

Of the total study population of 4060 patients originally enrolled in the AFFIRM Trial, echocardiographic data about LA diameter were available for 2615 patients (64.4%). From the overall cohort 1048 (40.1%) patients were females and median [IQR] age was 71 [65–76] years old. Median [IQR] value for LA diameter was 4.3 cm [3.9–4.8 cm]. Of the whole cohort, 71.6% (n = 1872) were diagnosed with hypertension, whilst a previous history of coronary artery disease (CAD) was reported in 35.4% (n = 927). Significant valvular disease was recorded for 331 (12.7%) patients, while a history of dilated non-ischemic cardiomyopathy was reported in 8.9% (n = 234). High thromboembolic risk was recorded for 84.0% (n = 2196).

LA enlargement was recorded for the 67.0% (n = 1751), more frequently in females than in males (p = 0.032) [Fig. 1]. Demographic and clinical characteristics according to the presence or absence of a LA enlargement are reported in Table 1. Patients with LA enlargement were more commonly female (p = 0.032) and with a higher body mass index (BMI) (p < 0.001). Both hypertension and diabetes mellitus were more frequently reported in patients with LA enlargement compared to patients with normal LA diameter (p < 0.001 and p = 0.005, respectively). Prior myocardial infarction (MI) and CAD diagnosis were more common with LA enlargement (p = 0.002), as well as heart failure (HF) p (p < 0.001). Structural cardiac diseases, e.g. dilated non-ischemic cardiomyopathy and valvular disease, were more common in patients

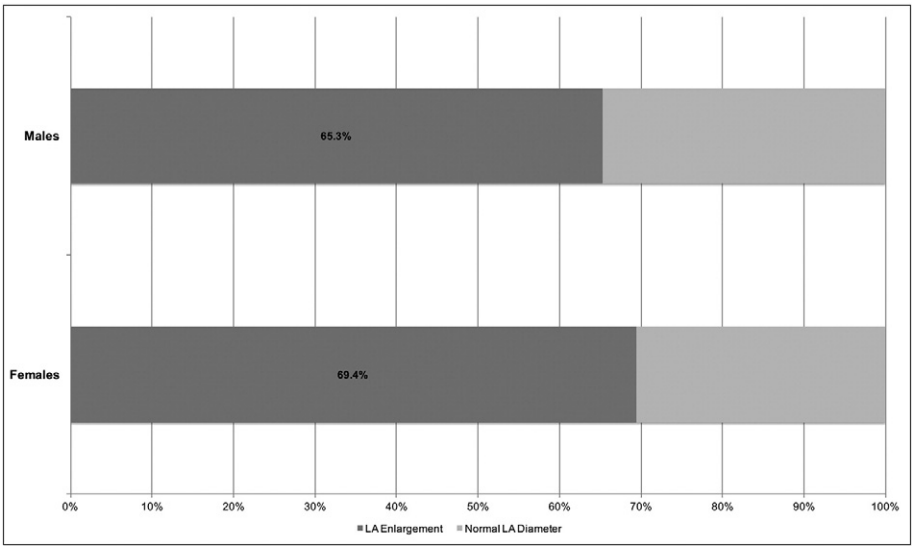

Fig. 1. Left atrial enlargement according to sex. Legend: LA = left atrium.