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Original Article

Women with atrial fibrillation and type 2 diabetes have a higher incidence of hospitalization and undergo ablation or pacemaker implantation less frequently than men

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ABSTRACT

Background: We reviewed trends from 2004 to 2013 in the incidence and outcomes for atrial fibrillation (AF) in Spanish patients with type 2 diabetes mellitus (T2DM) comparing women and men.
Methods: We used national hospital discharge data including all T2DM patients discharged from the hospital after AF. Patients with AF in the primary diagnosis field were selected. Discharges were grouped by sex. Incidence was calculated overall and stratified by sex. We analyzed diagnostic and therapeutic procedures, patient comorbidities, CHA2DS2-VASc score, length of hospital stay, readmission rates and in-hospital mortality (IHM).
Results: We identified a total of 214,457 admissions for AF. Patients with T2DM accounted for 21.1% (19,505 men and 25,954 women). Women with T2DM had a significantly higher incidence of AF compared to men over the study period (IRR 1.33;95%CI 1.31–1.35). Women were significantly older (77.24 ± 8.69 years) than men (72.62 ± 10.28 years), had higher prevalences of obesity and hypertension, and higher CHA2DS2-VASc score. Women less frequently underwent ablation (3.21% vs. 1.54%; $p < 0.001$) and received an implanted pacemaker (14.3% vs. 8.16%; $p < 0.001$) than men. Crude IHM was 2.81% for women and 2.48% for men ($p = 0.030$). Sex was not associated with a higher IHM after multivariable adjustment.
Conclusions: Our study demonstrates an increase in hospitalization for AF in diabetic women. Women were older, had a higher comorbidity index and had CHAD2DS2-VASc score than men. Women with AF and T2DM undergo ablation or pacemaker implantation less frequently than their male counterparts. After multivariable adjustment sex did not predict mortality during admissions for AF.

1. Background

Atrial fibrillation (AF) is the most common arrhythmia in daily clinical practice and its prevalence and incidence is increasing in recent years [1]. It is expected that in the next 25 years, the prevalence of AF will double in the Western world, mainly affecting patients over 80 years of age [2–4]. In addition, it is foreseen that there will be an increase in the prevalence of other cardiovascular risk factors such as diabetes, hypertension, and aging population [4]. The diagnosis of AF predicts, in its natural evolution, an increased risk of mortality and morbidity associated with hospitalizations due to heart failure and stroke [5]. It is therefore expected that hospitalizations for AF will increase in the coming years, subsequently leading to increased health care costs [6,7].

The Framingham Heart Study investigators reported that AF incidence increased during the period (1958–2007) in both men and women [8]. In a recent publication the authors showed that women have lower age-adjusted incidence and prevalence of AF than men; however, given the greater longevity of women, the absolute number of men and women with AF is similar. They concluded that future research is needed to address the knowledge gaps in sex-specific differences in AF [9].

Several studies have shown that type 2 diabetes mellitus (T2DM) increases the risk of AF [10–13]. Recently, our group has published an increase in hospitalization for AF in diabetic patients especially in women, elderly patients with comorbidities, and patients with high CHAD2DS2-

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VASc scores [14]. Yet we know little about the impact of sex in T2DM during hospitalization for AF. Therefore, this study aims to compare trends in the incidence rates and outcomes of AF in T2DM patients between men and women in the period 2004–2013 in Spain. Particularly, trends in the use of diagnostic and therapeutic procedures, comorbidities, CHA_2DS_2-VASc score, and in-hospital outcomes including length of hospital stay (LOHS), readmission rates, and in-hospital mortality (IHM), were compared between women and men with T2DM.

2. Methods

We performed a retrospective, observational study using the Spanish National Hospital Database (CMBD, *Conjunto Mínimo Básico de Datos*), which is managed by the Spanish Ministry of Health, Social Services and Equality (SMHSSE) and compiles all public and private hospital data, covering >95% of hospital admissions [15]. The CMBD includes patient variables (sex, date of birth), admission and discharge dates, up to 14 diagnoses at discharge, and up to 20 procedures performed during the hospital stay. The SMHSSE sets standards for record keeping and performs periodic audits of the database. We analyzed data collected between January 1, 2004 and December 31, 2013 (10 complete years) for subjects aged 18 and over.

Diseases coding and procedures were defined according to the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM), which is used in the Spanish CMBD.

Patients with a primary diagnosis of AF (ICD-9-CM code: 427.31) were selected and only the admissions with concomitant diabetes (T2DM, ICD-9-CM codes 250×0 and 250×2) were included. Patients with type 1 diabetes mellitus (ICD-9-CM codes: 250×1; 250×3) were excluded.

Clinical characteristics included information on overall comorbidities at the time of diagnosis, which was assessed by calculating the Charlson comorbidity index (CCI) [16]. We divided patients into three categories: low index, which corresponds with patients with no previously recorded disease; medium index, patients with one disease category; and high index, patients with two or more disease categories. To estimate the risk of ischemic stroke in patients with AF we used the CHA_2DS_2-VASc score [17].

Risk factors considered in the data analysis included current smoking (ICD-9-CM codes: 305.1 and V15.82), obesity (ICD-9-CM code 278.xx), hypertension (ICD-9-CM codes: 401; 401.0; 401.1; 401.9), and lipid metabolism disorders (ICD-9-CM code: 272.4) recorded during the hospitalization for AF.

In addition, we retrieved data about specific comorbidities including acute myocardial infarction, congestive heart failure, chronic pulmonary disease, renal disease, hyperthyroidism, anemia, stroke/transient ischemic attack (TIA)/thromboembolism (TE), and vascular disease as described by Quan et al. (2005) using the enhanced ICD-9-CM [18]. Also, we specifically identified the following procedures: echocardiogram (ICD-9-CM code 88.72), atrial cardioversion (ICD-9-CM code 99.61), catheter ablation (ICD-9-CM codes 37.33, 37.34), and pacemaker device implantation (ICD-9-CM code 37.70–37.74; 37.80–37.83).

We estimated the proportion of admissions from the emergency room (ER), the cost of hospitalization, the median length of hospital stay (LOHS), readmissions rate (proportion of patients that have been discharged from the same hospital in the previous 30 days before the actual admission) and in-hospital mortality (IHM). This was defined by the proportion of patients who died during admission for each year of study.

2.1. Statistical analysis

Before the analysis, we examined the database for any missing data on the following variables: sex, date of birth, admission date, discharge date, and death/survival during hospitalization. If any of these variables were missing, the record was deleted from the analysis. As all of the databases undergo quality control at the Ministry of Health before being sent to the investigators, only less than <0.1% of records were excluded.

In order to assess time trends, the incidence rates of admissions for AF in patients with T2DM were calculated per 100,000 inhabitants, according to sex using the methods previously described by our group [14].

To assess the effect of sex on the incidence of AF, we fitted multivariate Poisson regression models for men and women with T2DM hospitalizations adjusted by age and year of discharge as independent variables. The estimates then corresponded to the Incidence Rate Ratio (IRR) with their 95% confidence intervals.

Poisson regression models are a widely used technique for assessing trends in Incidence rates, offering a technique that we can use to summarize relative risk and to evaluate complex interactions with covariables. The assumptions for a Poisson regression models include: 1. Logarithm of the disease rate changes linearly with equal increment increases in the exposure variable. 2. Changes in the rate from combined effects of different exposures or risk factors are multiplicative. 3. At each level of the covariates the number of cases has variance equal to the mean. 4. Observations are independent.

To verify these assumptions, we conducted plots of residuals versus the mean at different levels of the predictor variables and other methods described elsewhere [19–22].

A descriptive statistical analysis was performed for all continuous variables and categories by stratifying admissions for AF with T2DM according to sex. Variables are expressed as proportions, as means with standard deviations, or as medians with interquartile ranges (LOHS).

For numerical data, it is important to decide if they follow the parameters of the normal distribution curve (Gaussian curve), in which case parametric tests are applied. The test of normality used was the Kolmogorov-Smirnov Test If distribution of the data is not normal we used non-parametric tests. All numerical data in our investigation was normally distributed expect LOHS.

When comparing more than two sets of numerical data, a multiple group comparison test such as one-way analysis of variance (ANOVA) or Kruskal-Wallis test were used.

To asses time trend for categorical variables for each sex we used multivariable logistic regression adjusted by age. This same method was used to compare categorical variables between men and women adjusting by year and age.

To asses time trend for continuous variables for each sex we used analysis of variance (ANOVA) or Kruskal-Wallis (LOHS). This same method was used to compare continuous variables between men and women.

Lastly, we performed logistic regression analyses with mortality as a binary outcome for men and women and for the entire diabetic population to assess the influence of sex on IHM. The independent variables included in the model were those that showed a significant association in the bivariate analysis and those considered relevant in previous investigations.

To conduct the multivariable regression models (logistic and Poisson) we did the following steps [19–23]:

i). Univariate analysis of each variable. ii). Selection of variables for the multivariate analysis. We include all the variables whose univariate test was significant and those we considered scientifically relevant according to the references reviewed. iii). Following the fit of the multivariate model the importance of each variable included in the model was verified. This included the examination of the Wald statistic for each variable and comparison of each estimated coefficient with the coefficient from the univariate model containing only that variable. Variables that do not contribute to the model based on these criteria were eliminated and a new model was fitted. The new model was compared to the old model using the LR test. Furthermore, estimated coefficients for the remaining variables were compared to those from the full model. This process of deleting, refitting and verifying continues until all the important variables are included in the model. iv). Once the