Research Article

Antithrombotic therapy and clinical characteristics of patients hospitalized for nonvalvular atrial fibrillation in Galician internal medicine clinics

Abstract

This was a multicenter, prospective, observational study that assessed the characteristics of patients with Nonvalvular Atrial Fibrillation (NVAF) admitted to internal medicine units in Galicia, Spain, as well as the antithrombotic treatment prescribed prior to hospital admission. Demographic characteristics, cardiovascular risk factors, polypharmacy, comorbidity, functional status and reasons for hospitalization were recorded for patients with NVAF admitted between January 2016 and January 2017. The antithrombotic treatment received by patients prior to hospital admission and the reasons for using this treatment were also analyzed. A total of 1419 patients were included (mean age 82.1 years; 50% male). The mean (standard deviation) number of chronic diseases per patient was 4.11(2.14) and the number of drugs being taken was 9.66(4.60). The mean CHA2DS2-VASc score was 3.09(1.26). NVAF-related hospitalizations accounted for 37.5% of all hospital admissions, with heart failure the most common reason for admission (31.4%). Most patients (75.1%) with NVAF were on anticoagulants at the time of admission and direct oral anticoagulants accounted for 13.9% of anticoagulants. Functional status was the only factor associated with the use of anticoagulation therapy. In conclusion, patients with NVAF admitted to Galician internal medicine units are a diverse population. More than one third are hospitalized for causes related to NVAF, while one in four is not receiving the appropriate antithrombotic therapy. The data suggest that, when primary care physicians or a specialist prescribe antithrombotic therapy, the patient’s functional status is more relevant than established risk factors to their decision-making.

Highlights

- Patients with nonvalvular atrial fibrillation (NVAF) admitted to the internal medicine units of Galician hospitals were generally elderly (mean age 80 years) patients with complex comorbidities who were taking multiple medications
- Most patients with NVAF were admitted to hospital for reasons other than NVAF (72.5%)
- The most common causes of hospital admission in NVAF patients were heart failure and respiratory conditions
- 75.1% of NVAF patients were taking anticoagulants at the time of admission.
- The only factor significantly associated with anticoagulant use in this population was performance status; thromboembolic or bleeding risk was not a determinant of anticoagulant prescribing.

Introduction

Atrial Fibrillation (AF) is the most common cardiac arrhythmia worldwide [1]. Its prevalence increases with age, and given the aging of population and improved management of chronic diseases, it is estimated that more than 17 million people (one in four) will have this condition in Europe in 2050 [1]. In Spain, the prevalence of AF in people aged over 80 is 16.5% [2], reaching 31.3% in hospitalized patients [3].

Patients with nonvalvular AF (NVAF) [4], are, most often, elderly with cardiovascular risk factors (CVRF) and associated chronic diseases, they take multiple drugs and have a high rate of hospitalizations [5]. In addition, AF contributes to the
increased morbidity and mortality of other common conditions such as stroke [6], Heart Failure (HF) [7,8] and systemic embolism. Therefore, AF is a serious and expensive public health problem [5,8,9].

Patients with NVAF who are admitted to a hospital are most frequently admitted to internal medicine units [9–12]. These patients have distinct characteristics from those seen in primary care units [3,11]. The rates of morbidity, mortality, frailty and comorbidity in these patients are higher due to their pluripathology and polypharmacy [11]. As a result, these patients have a decreased quality of life [13] and a high rate of hospital readmission [11,14]. However, few studies have analyzed this population, thus their condition at hospital admission has not been adequately assessed [9,10].

For this reason, the objective of this study was to describe the characteristics of patients with NVAF requiring hospitalization in the internal medicine units in Galicia and to determine the causes of hospitalization, as well as the antithrombotic treatment they were receiving at the time.

Patients and Methods

This was a prospective, multicenter study conducted at the internal medicine units of 14 Galician hospitals from January 2016 to January 2017. These centers represent the majority of the Galician Public Healthcare Network and provide treatment to 2,314,757 people (84.7% of the population of Galicia) (Galician Statistics Institute, data from 2015).

The first admission to an internal medicine unit during the study period was considered to be the index admission. The investigators participating in the study conducted an initial visit during the index hospitalization and subsequently reviewed reports on the clinical course and hospital discharge of each patient. An 86-item template was used for data collection that included demographic data, prior diagnoses, reason for hospitalization, antithrombotic therapy at the time of admission and discharge, diagnosis, duration of hospital stay, and destination at hospital discharge. Thrombotic and hemorrhagic risks at admission were assessed using CHA2DS2-VASc, CHADS2, and HAS-BLED scores [15,16]. The CHADS2 scale defines the thromboembolism risk as low if the score is 0, intermediate if the value is 1 and high when the value is ≥2. Based on the CHA2DS2-VASc score, a moderate–high risk is considered when the score is ≥1 in men and ≥2 in women [15]. Bleeding risk was assessed using the HAS–BLED scale [16], where 0 means low risk, 1–2 moderate risk and ≥3 high risk of bleeding. The patient’s functional status was assessed using the original Barthel index (0–100 items) [17], where lower values indicate higher dependence (80–100 independent, 35–80 partially dependent, 15–35 highly dependent, <15 absolute disability).

For the initial screening, all patients admitted to an internal medicine unit whose diagnosis report included AF were visited individually. The inclusion criteria were: 1) diagnosis of NVAF; 2) admission to an internal medicine unit of any hospital of the Galician Healthcare Service Network; 3) provision of informed consent to participate in the study by the patient or his/her legal representative. Exclusion criteria were: 1) patient diagnoses did not include NVAF; 2) inability to confirm diagnosis of NVAF; 3) admission to a unit other than the internal medicine unit at hospitalization; 4) life expectancy less than 6 months at the time of hospital admission; 5) contraindication for dicoumarin and direct anticoagulants (DOACs); 6) patient declined to participate.

The hospital discharge report was used to collect information about comorbidities. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9–CM) was used for classification purposes. Therefore, each diagnosis included in every hospitalization report was classified as acute or chronic. The World Health Organisation’s (WHO) definition [18], of chronic disease was used (a disease that persists for a long time and generally has a slow progression lasting more than 6 months). Chronic diseases included in the German Multicare study were evaluated [19].

We analyzed anticoagulant therapy that the patient was on at the time of admission to the hospital. Decisions relating to the use of antithrombotic treatment and the agent prescribed were made prior to the patient’s index hospital admission, usually by primary care physicians or by a specialist in an outpatient clinic. Regarding treatment with DOACs, the primary care service including a clinical pharmacist supervised and adjusted the dose for each patient based on age, weight, and renal function. The vitamin K antagonist (VKA) dose was adjusted according to the international normalized ratio (INR), which was monitored by the hematology service of each hospital.

The study was named “Tus gafas” (acronym for the Spanish translation of “treatment based on location and survival of patients with atrial fibrillation in Galicia”), received the approval of the Spanish Medicines Agency (code IBF-AUR–2015–01) and the Galician Research Ethics Committee (code 2015/461) and was conducted with the support of the Galician Society of Internal Medicine.

In the statistical analysis, a descriptive study of all variables (frequency distribution and measures of central tendency and dispersion) was performed. A Chi-squared test for trend was used to compare qualitative variables, and analysis of variance was used for quantitative variables in multiple comparisons of the means. The Duncan method was used to evaluate the difference between means. A logistic regression analysis was performed to establish which variables were independently associated with receiving anticoagulant therapy. For the construction of successive models, a “forward strategy” was followed. The terms of interaction were initially analyzed collectively, but those that were not significant were not included in the final model. For the inclusion of a variable, the usual criteria of the Wald statistic values and the maximum likelihood function were used. The statistical package SPSS 17 was used for data analysis. The level of statistical significance was set at p<0.05.

Results

Initially, 1483 patients were screened, of whom 64(4.3%) were excluded, thus the final sample size was 1419 patients.
The main characteristics of these patients are shown in Table 1. The most outstanding aspects were the high mean age (82.1, standard deviation [SD] 8.0 years), number of chronic diseases (4.11 [2.14]) and number of drugs used (9.66 [4.60]). The most frequent cardiovascular risk factors were hypertension (78.4%) and type 2 diabetes mellitus (32.6%). Mean CHADS, and CHA\textsubscript{DS}\textsubscript{2}-VASc scores were 3.09(1.26) and 4.82(1.53), respectively, and the mean HAS-BLED score was 2.14 (1.10). Only 1.2% of patients had a CHA\textsubscript{DS}\textsubscript{2}-VASc score <2. The mean original Barthel index was 72.08(35.31).

Most patients had permanent NVAF (73.2%). Paroxysmal (16.2%) and persistent (4%) forms were less frequent. No prior history of NVAF was present in 6.6% of patients.

Heart Failure (HF) and respiratory infections were the leading causes of hospitalization (31.4% and 31.2%, respectively). Table 1, whereas, thromboembolic events (stroke and systemic embolism, 2.9%) and NVAF (3.2%) were the least common causes. Considered jointly, NVAF-related causes were the reason for 37.5% hospitalizations.

Twenty seven patients (1.82%) had bleeding events at hospitalization: upper gastrointestinal bleeding (n=6), low gastrointestinal bleeding (n=4), hematuria (n=4), epistaxis (n=3), hemoptysis (n=3), gingival bleeding (n=2), retroperitoneal bleeding (n=1), muscle hematoma (n=1), intracranial hemorrhage (n=1), anal bleeding (n=1), and hemarthrosis (n=1). All patients with bleeding on admission had a HAS-BLED score >4.

Regarding antithrombotic therapy (Table 2), 75.1% of patients were on anticoagulants at the time of admission, 8.9% were on antiplatelet therapy only and 16% were not receiving any treatment. All DOAC doses were considered adequate and had been supervised by the local pharmacy service.

An analysis of patients’ main characteristics according to the type of antithrombotic treatment used is presented in Table 3. Patients on antiplatelet therapy were older and had higher CHADS\textsubscript{2}, and CHA\textsubscript{DS}\textsubscript{2}-VASc scores, whereas patients receiving no treatment had significantly fewer chronic diseases and lower Barthel index (Table 3).

An analysis of the association between thromboembolic risk factors and the use of any type of oral anticoagulant treatment is presented in Table 4. A higher number of chronic diseases, as well as a higher Barthel index were significantly associated with the use of anticoagulants (Table 4). In contrast, there was no significant association between anticoagulant treatment and either thrombotic or hemorrhagic risk scores.

**Discussion**

This study shows that patients with NVAF admitted to Galician internal medicine units are elderly, receive multiple concomitant medications and have multiple comorbidities and a high thromboembolic risk. However, 24.9% of patients were not receiving an appropriate antithrombotic therapy at the time of hospitalization according to the CHADS\textsubscript{2} and CHA\textsubscript{DS}\textsubscript{2}-VASc scores.

The characteristics of patients with NVAF receiving primary care are well described [20-22]. However, hospital studies are less frequent [3,9] and those performed in internal medicine units are even rarer [9,11,13], despite these being the units where most patients with NVAF are admitted [9,11]. Our study was conducted in the internal medicine units of hospitals servicing 84.7% of the population of Galicia. Therefore, patients included in this study comprise a representative sample in terms of characteristics and NVAF management.

From the clinical viewpoint, the characteristics of patients...
with NVAF admitted to internal medicine units were different from those seen in primary care units [22]. The population admitted to internal medicine units was older and had higher comorbidity. This population also had a higher risk of thromboembolism (according to CHADS2 and CHA2DS2-VASc scores) and bleeding (according to the HAS–BLED score) [21,22]. These data are consistent with the characteristics seen in other studies conducted in internal medicine units [9,11,13,14]. Therefore, patients with NVAF admitted to internal medicine units are a distinct subgroup of patients with greater clinical complexity and higher risk.

The reasons why patients with NVAF are admitted to internal medicine units are relevant when assessing the role of AF. AF-related diseases (HF, AF with rapid response and thromboembolism) accounted for less than half of the hospital admissions (37.5%) in our study. Specifically, HF was the leading cause of hospitalization (31.4%), which was expected because AF is a frequent cause of hospitalization for HF [7]. In contrast, hospitalizations for stroke and peripheral embolism accounted for only 2.9%, which was lower than that observed in a study conducted in several types of hospital units including internal medicine units [11], but higher than in a study that included internal medicine units only [3]. In the ARISTOTEL study that included a patient population with lower risk and comorbidity, this population also had a higher risk of bleeding complications. The percentage of patients on anticoagulant therapy was lower than in other similar studies [3,10,24,25], although not significantly lower. This study does not allow for an analysis of the reasons for this fact, but the low level of prescription of DOACs is surprising, especially when studies conducted in primary care units show that the time in therapeutic INR range is poor in patients receiving VKAs [20–22]. For example, a recent Galician study shows that more than 40% of patients do not reach the minimum time in therapeutic INR range [22]. Our study did not collect data on DOAC dosages. Current practice in our region of Spain is for the primary care service to adjust the DOAC dose at each visit based on the patient’s situation, in accordance with the guidelines of the Galician Public Health System. Given that bleeding complications (1.82%) were relatively few in our study compared with other series, and not associated with any mortality, there is no evidence to suggest that patients were receiving an incorrect dosage or that DOAC dosage had any influence on the need for hospital admission in the study participants.

In the present study, one in four patients (24.9%) in a high-risk population of patients with NVAF admitted to internal medicine units was not receiving the appropriate antithrombotic treatment, a figure slightly lower than in another similar study [20]. Of these patients, 8.9% were on anticoagulant therapy and 16% were not receiving any antithrombotic therapy. The percentage of patients on antithrombotic therapy was lower than in other similar studies [3,10,24,25], and the percentage of patients not receiving any antithrombotic therapy was slightly higher [3,9,10,25]. This reflects the fact that the use of antithrombotic therapy for NVAF is decreasing, which is consistent with clinical practice guidelines [4], that do not recommend replacing anticoagulation with antithrombotic therapy, especially in elderly patients, since the bleeding risk is the same and the benefit is small. Nevertheless, when there is a high hemorrhagic risk, some physicians are more inclined to prescribe antithrombotic therapy than an anticoagulant [26]. This was not seen in the present study where, unlike in other studies [10], high HAS–BLED score was not associated with greater use of antithrombotic therapy.

Table 3: Differences in patient’s characteristics based on anticoagulant/antiplatelet treatment received at the time of hospitalization.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>VKAs</th>
<th>Antiplatelets</th>
<th>DOACs</th>
<th>None</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>81.55(8.07)</td>
<td>85.20(6.03)</td>
<td>81.22(8.37)</td>
<td>82.82(8.49)</td>
<td>NS</td>
</tr>
<tr>
<td>CHADS2</td>
<td>3.07(1.20)</td>
<td>3.35(1.37)</td>
<td>3.33(1.32)</td>
<td>2.71(1.36)</td>
<td>0.01</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>2.07(1.09)</td>
<td>2.40(1.05)</td>
<td>2.22(1.10)</td>
<td>1.91(1.10)</td>
<td>NS</td>
</tr>
<tr>
<td>CHA2DS2</td>
<td>4.77(1.46)</td>
<td>5.20(1.73)</td>
<td>5.08(1.49)</td>
<td>4.42(1.68)</td>
<td>0.03</td>
</tr>
<tr>
<td>Barthel index</td>
<td>79.85(28.68)</td>
<td>63.38(36.83)</td>
<td>76.74(31.07)</td>
<td>37.30(43.97)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td>3.42(0.86)</td>
<td>3.36(0.84)</td>
<td>3.59(0.76)</td>
<td>2.88(1.15)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4: Thromboembolic risk factors associated with the use of anticoagulation – logistic regression analysis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>P-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.244</td>
<td>1.198</td>
<td>0.884</td>
</tr>
<tr>
<td>Age</td>
<td>0.028</td>
<td>0.977</td>
<td>0.958</td>
</tr>
<tr>
<td>Number of chronic diseases</td>
<td>0.000</td>
<td>1.438</td>
<td>1.217</td>
</tr>
<tr>
<td>CHADS2</td>
<td>0.567</td>
<td>1.043</td>
<td>0.902</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>0.061</td>
<td>0.868</td>
<td>0.749</td>
</tr>
<tr>
<td>Barthel index</td>
<td>0.000</td>
<td>1.010</td>
<td>1.005</td>
</tr>
<tr>
<td>Duration of AF at hospitalization</td>
<td>0.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Constant</td>
<td>0.507</td>
<td>1.907</td>
<td></td>
</tr>
</tbody>
</table>

AF: Atrial Fibrillation; CI: Confidence Interval; OR: Odds Ratio; VKA: Vitamin K Antagonist; NS: Not Significant.
In this study, the reasons why a high percentage of patients with high cardioembolic risk were not on anticoagulants were analyzed. The usual risk scores were not associated with antithrombotic therapy and the most important determinant for prescribing anticoagulation was the patient’s functional status (Barthel index), which was also the case in other studies [10]. If the most influential factor for prescribing anticoagulation in patients with NVAF, a complex population with a high risk and requiring hospitalization, is not based on specially designed scores, but rather depends on a discretionary assessment, inadequate treatments are likely to be prescribed in many cases. Therefore, it is necessary to find new risk assessment methods that take into account performance status, and thereby reflect clinical concerns associated with anticoagulant therapy. On the other hand, it is likely that, in some cases, the reasons for not administering treatment were potential risks, follow-up difficulties or difficulties associated with the administration of VKAs. DOACs are safer and their administration is simpler, thus they should play a more important role in these cases. It is likely that, in elderly patients with NVAF and multiple comorbidities, a number of medications (including anticoagulants) are used to preserve functional status. However, anticoagulation is often avoided in patients with poor functional status or poor life expectancy, who receive palliative therapies instead.

This study had several potential limitations. Firstly, although the study was designed to include consecutive cases, occasionally a certain degree of selection could have been applied, but if it happened, it had very little relevance. Secondly, bias in data collection is very unlikely since it was collected by experienced physicians trained to comply with study requirements. In addition, coordination workshops were conducted to ensure the homogeneity of the information collected. All of this suggests that any potential bias has not significantly altered the final study results. The strength of the study was that a large number of patients hospitalized for NVAF were recruited from most internal medicine units of the Galician Autonomous Community.

Conclusion

Patients with NVAF admitted to internal medicine units have a more complex clinical presentation than those seen in primary care. One third of the patients were hospitalized for reasons related to NVAF and one in four were not receiving appropriate antithrombotic treatment. These results suggest that absence of anticoagulation is correlated with a low functional status, but not with the established risk criteria. Thus, we believe that new scales are needed to account for patient functional status, as well as thromboembolic and bleeding risk, when deciding on the need for anticoagulant therapy in complex patients with NVAF.

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Compliance with potential ethical standards

Disclosure of potential conflicts of interest: The study was funded by Pfizer S.A. The sponsor had no involvement in the study design, collection, analysis, and interpretation of data, the writing of the manuscript, the medical writing assistance or the decision to submit the manuscript for publication.

José Manuel Cerqueiro–González has received consulting fees from Pfizer Spain. All other authors declare that they have no conflicts of interest.

Research involving human participants

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study received the approval of the Spanish Medicines Agency (code IBF–AUR–2015–01) and the Galician Research Ethics Committee (code 2015/461) and was conducted with the support of the Galician Society of Internal Medicine.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Author contributions

JM Cerqueiro, E Fernández and E Casariego contributed to the study design, recruitment and data analysis, as well as to the statistical analysis and writing of the manuscript. ML Lopez, Pesqueira P, Vazquez P, Novo I contributed in the recruitment, reading and acceptance of the manuscript. All authors approved the final version of the manuscript.

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Link: http://bit.ly/2rf4ZEv

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