A Prospective Protocol Increases Oral Anticoagulant Prescription in Patients With Chronic, Nonvalvular Atrial Fibrillation

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Introduction and objectives. Observational studies have shown that oral anticoagulants (OAC) prescription is suboptimal in patients with nonvalvular atrial fibrillation (NVAF). Our objective was to evaluate the usefulness of a prospective protocol for increasing OAC usage in these patients.

Patients and method. From 1 february 2000 until 31 october 2002 we enrolled all patients with chronic NVAF seen in two outpatient cardiology clinics, excluding candidates for cardioversion. Each patient was studied to identify cardioembolic risk factors (CERF) and contraindications for OAC. Anticoagulation was suggested to all patients with ≥ 2 CERF and without contraindications for OAC. The decision to prescribe OAC was made by the physician in charge when there was only one CERF.

Results. 721 patients fulfilled the inclusion criteria. Mean age was 73 ± 8 years; 44% were men. In most cases NVAF was related with hypertension (57%), followed by no structural heart disease (25%) or ischemic heart disease (9%). The most frequent CERFs were hypertension (66%), age ≥ 75 years (45%) and diabetes (24%). A total of 663 patients had ≥ 1 CERF (92%), and 125 (19%) of these presented at least one contraindication for OAC. Of the 538 remaining patients (90%), 485 (67% of the whole series) were treated with anticoagulation. Of the patients with ≥ 2 CERF and without contraindications for OAC, 95% were treated.

Conclusions. A prospective protocol for use in the outpatient cardiology clinic allows to prescribe OAC in a large percentage of patients with NVAF.

Key words: *Atrial fibrillation. Anticoagulants. Prevention. Stroke.*

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Un protocolo prospectivo permite incrementar la utilización de anticoagulación oral en pacientes con fibrilación auricular crónica no valvular

Introducción y objetivos. Los estudios observacionales han constatado una infrautilización de la anticoagulación oral (ACO) en la fibrilación auricular no valvular (FANV). Nuestro objetivo ha sido valorar si un protocolo prospectivo es útil para aumentar la utilización de ACO en estos pacientes.

Pacientes y método. Desde el 1 de febrero de 2000 hasta el 31 de octubre de 2002 se han seleccionado todos los sujetos con FANV permanente, no candidatos a cardioversión, revisados en dos consultas de cardiología. Se estudió a cada paciente para identificar factores de riesgo cardioembólicos (FRCE) y contraindicaciones para ACO. Se ofreció ACO a todos los enfermos con ≥ 2 FRCE y sin contraindicación para ACO. Se dejó a juicio del cardiólogo responsable la ACO de los que tenían un solo FRCE.

Resultados. Cumplieron los criterios de inclusión 721 pacientes. Su edad media fue 73 ± 8 años, con un 44% de varones. La FANV se asoció más frecuentemente a hipertensión (57%), seguida de ausencia de cardiopatía (25%) y cardiopatía isquémica (9%). Los FRCE más frecuentes fueron: hipertensión (66%), edad ≥ 75 años (45%) y diabetes (24%). Un total de 663 pacientes presentaron ≥ 1 FRCE (92%). De éstos, 125 (19%) tuvieron al menos una contraindicación para ACO. De los 538 restantes fueron anticoagulados 485 pacientes (el 90%; un 67% del total). Fueron anticoagulados el 95% de los pacientes con ≥ 2 FRCE y sin contraindicaciones para ACO.

Conclusiones. La utilización de un protocolo prospectivo en la consulta de cardiología hace posible la aplicación de ACO en pacientes con FANV en un alto porcentaje de casos.

Palabras clave: *Fibrilación auricular. Anticoagulantes. Prevención. Accidente cerebrovascular.*

INTRODUCTION AND OBJECTIVES

Nonvalvular atrial fibrillation (NVAF) is a common condition with a high associated risk of embolism,

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ABBREVIATIONS

OAC: oral anticoagulation.
NVAF: nonvalvular atrial fibrillation.
EAFT: European Atrial Fibrillation Trial.

particularly stroke. According to the Framingham study, embolic risk is 5.6-fold higher in patients with this condition than in the general population.[1] Nonvalvular atrial fibrillation is present in 15%-20% of strokes.[2,3] Computed tomography studies in patients with NVAF also indicate a high frequency of silent cerebral infarction, ranging from 13% to 35%.[4,5] Prevention of thromboembolic complications is one of the main objectives of therapy for this condition.

Various clinical trials conducted in the late 20th century have studied the role of oral anticoagulation (OAC), aspirin and the combination of these agents in primary and secondary prophylaxis[6-16] for thromboembolic events in NVAF. The predictive factors for stroke,[17-22] as well as the factors predisposing to bleeding complications, have been analyzed in patients treated with OAC.[23,24] Based on these studies, various medical societies, including the Sociedad Española de Cardiología (Spanish Society of Cardiology), have developed clinical practice guidelines[25-28] that provide precise instructions for stratification of stroke risk and the indications for OAC in this population. These virtually unanimous recommendations suggest anticoagulant therapy for all NVAF patients with no absolute contraindications and a history of transient ischemic attack or stroke, or risk factors for embolic stroke, whether medical (advanced age, hypertension, diabetes mellitus, history of ischemic heart disease or heart failure) or echocardiographic (left atrial enlargement, ventricular dysfunction).

Despite these guidelines, observational studies in Spain[29-35] and other countries[36-41] have shown that OAC is underutilized in patients with NVAF.

In light of this situation, we designed a prospective study to 1) characterize the patients with NVAF seen at our hospital with regard to risk factors and contraindications for OAC, and to 2) design a protocol that would increase the outpatient use of OAC in line with current guidelines. Although the literature contains at least one study designed to improve OAC prescription and management in NVAF,[42] to our knowledge there are no similar publications reporting on any study of this kind in Spain.

PATIENTS AND METHODS

Inclusion criteria

We included all consecutive patients with established NVAF seen from 1 February 2000 to 31 October 2002 in 2 outpatient cardiology clinics associated with the Hospital Universitario Reina Sofía, supervised by 2 of the investigators. All patients were assessed for cardioversion, and any patient with successful reversion to sinus rhythm was excluded.

Study protocol

All patients underwent a complete work-up that included clinical history, physical examination, blood tests (blood count, glucose, urea, creatinine, sodium, potassium, liver enzymes, thyroid hormones and coagulation), electrocardiogram and chest x-ray. In addition, all patients with suspected structural heart disease and no contraindication for OAC or clinical risk factors also underwent echocardiographic study to determine the decision on anticoagulation.

The following were considered risk factors for embolic stroke, as specified in the guidelines of the Sociedad Española de Cardiología:[27-28] age ≥75 years, hypertension, diabetes mellitus, history of stroke, history of ischemic heart disease or heart failure, left atrial enlargement (anteroposterior diameter ≥50 mm) and left ventricular dysfunction (ejection fraction ≤0.45). Age is a continuous risk factor, as risk[17] increases with age. However, there is no consensus as to the cut-off point for stroke risk in the medical societies' recommendations. The guidelines of the Sociedad Española de Cardiología for cardiac arrhythmia[27] consider age >65 years as a risk factor for embolic stroke and that OAC is a Class 1 indication in patients with at least one risk factor. Nevertheless, guidelines on the use of anticoagulants and antiplatelet agents in cardiology[28] designate both anticoagulant therapy and antiplatelet therapy with aspirin as a Class IIA indication in patients aged 65 to 75. Lastly, the guidelines of the American College of Cardiology/American Heart Association/European Society of Cardiology consider aspirin as a Class 1 indication in patients 60 to 75 years old without risk factors, and OAC in patients over 75.

Absolute contraindications for OAC were defined as a recent history of severe bleeding, poorly controlled hypertension, gastrointestinal disease with a high risk of bleeding, probable noncompliance with therapy, unrelated severe anemia, high probability of frequent trauma and refusal of therapy by the patient. Gastrointestinal disease with a high risk of bleeding included peptic ulcer, hiatus hernia, esophageal varices and diverticulosis of the colon, provided there had been significant bleeding in the past month or the gastroenterologist recommended that anticoagulation

be avoided (the Gastroenterology Department was always consulted before contraindicating OAC for this reason). Noncompliance with therapy was considered probable if the patient had any of the following factors: persistent noncompliance with therapy in the past, illiteracy and/or serious visual or cognitive impairment without adequate support from the family or social service. All risk factors for embolic stroke and absolute contraindications for anticoagulation were prospectively recorded.

Protocol for thromboembolic prophylaxis

Aspirin or other antiplatelet agents were prescribed for all patients who had no risk factors and those who had one or more risk factors and at least one absolute contraindication for OAC. Oral anticoagulation was recommended to all patients who had 2 or more risk factors and no contraindications, after carefully explaining the advantages of therapy to minimize patient refusal caused by incomplete or inadequate information. In patients with no contraindications and only one risk factor, the decision regarding coagulation was made by the cardiologist. In this subgroup of patients, the guidelines of the Sociedad Española de Cardiología[27,28] recommend OAC. Others, such as the Guidelines of the American College of Cardiology/American Heart Association/European Society of Cardiology,[26] acknowledge some discrepancies on the need for OAC in the group classified as «intermediate risk,» i.e., patients with only one of the following risk factors for stroke: age 65 to 75, diabetes, ischemic heart disease or history of hypertension. Patients with only one risk factor for stroke are, of course, at lower risk[26] and therefore obtain the least absolute and relative benefit from OAC. In these patients, the physician´s criteria play an important role when weighing any potential minor contraindications and patient preferences against OAC, which in cases of higher risk would be overshadowed. Lastly, our study required that each physician record the therapy actually prescribed to the patient.

Statistical analysis

All data were entered by the physician in a database created in SPSS 8.0 (SPSS Inc. Chicago, Illinois, USA.). Quantitative data are shown as mean±one standard deviation. Qualitative parameters are expressed as percentages. SPSS 8.0 was used for the statistical analysis.

RESULTS

Demographic characteristics and symptoms

By 31 October 2002, 721 patients (mean age, 73±8 years; men, 44%) had been enrolled in the study. Distribution by age was as follows: 49% were 70 to 79 years old, 26% were 60 to 69, 20% were age 80 or older and only 5% were under 60 years old. Among the study patients, 75% were asymptomatic, 21% had dyspnea, 2% had palpitations and 2% had chest pain.

Risk factors for embolic stroke and contraindications to anticoagulation

Nonvalvular atrial fibrillation was most frequently associated with hypertension, and secondly with the absence of structural heart disease (Figure 1). The most frequent risk factors for embolic stroke were hypertension, followed by age ≥75 years and diabetes (Table 1). Most patients in our series had one or two risk factors, and only 8% had no risk factors (Table 2). Thus, 663 patients (92%) presented one or more risk factors. Among these, 125 (19%) had at least one contraindication for OAC. The contraindications for OAC are listed in Table 3. The most frequent was probable noncompliance with therapy. A total of 467 patients (65% of the series) presented two or more risk factors; 93 (20%) of these had at least one contraindication for OAC.

Patients treated with anticoagulation

Among the 538 patients with one or more risk factors and no contraindications for OAC, 485 (90%;

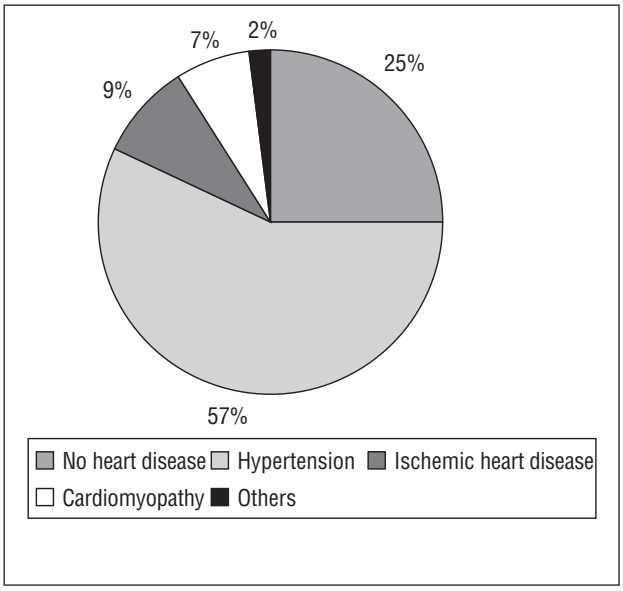

Fig. 1. Conditions associated with nonvalvular atrial fibrillation in the study population;

TABLE 1. **Frequency of risk factors for embolic stroke**

Hypertension	66%
Age ≥ 75 years	45%
Diabetes	24%
Left atrial enlargement	20%
Previous cardioembolic event	14%
Heart failure	14%
Ischemic heart disease	9%
Left ventricular systolic dysfunction	9%

TABLE 2. **Number of risk factors for embolic stroke**

	N (%)
None	58 (8)
1	196 (27)
2	266 (37)
3	128 (18)
4 or more	73 (10)

TABLE 3. **Contraindications for anticoagulation in our series (patients with at least one risk factor for embolic stroke)**

	No. (%)
Expectation of poor compliance	67 (54)
Gastrointestinal disease 10 (8)	
Patient refusal	23 (18)
History of severe bleeding	8 (6)
Poorly controlled hypertension	6 (5)
Unrelated severe anemia	5 (4)
Frequent trauma	6 (5)
Total	125

67% of the entire series) received anticoagulation. Among the patients with no contraindications, anticoagulation was achieved in 85% of patients aged 75 or older, 94% of those with hypertension, 95% of those with diabetes, 97% of those with ischemic heart disease, 90% of those with heart failure, 98% of those with a history of stroke, 98% of those with left ventricular dysfunction and 98% of all patients with left atrial enlargement. Moreover, anticoagulation was achieved in 80% of patients with one risk factor for embolic stroke, 92% with two, 96% with three and 100% with four or more risk factors and no contraindications for OAC. Anticoagulation therapy was prescribed for 354 patients with two or more risk factors and no contraindications (95% of this group; 76% of all with two or more risk factors).

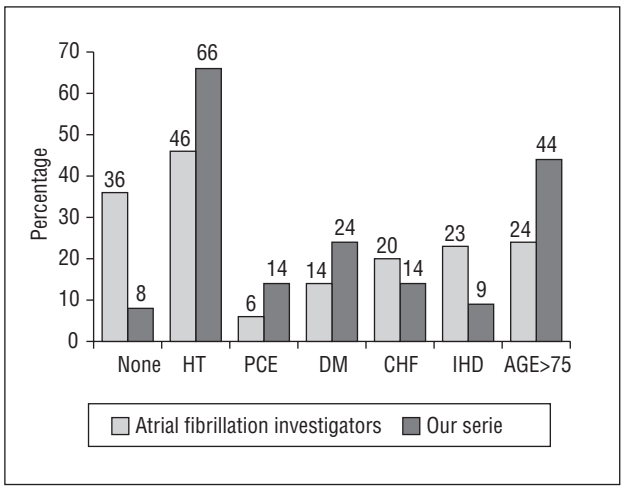

Fig. 2. Risk factors for embolic stroke in our series and in the Atrial Fibrillation Investigators meta-analysis. IHD indicates ischemic heart disease; PCE, previous cardioembolic event; DM, diabetes mellitus; HT, hypertension; CHF, congestive heart failure

DISCUSSION

The NVAF population seen by our Cardiology Outpatient Clinic differed from the populations included in most clinical trials. In comparison to the Atrial Fibrillation Investigators meta-analysis[17] (Figure 2), our series had a higher incidence of hypertension, advanced age, diabetes mellitus and previous cardioembolic event. Moreover, there were fewer patients with heart failure or ischemic heart disease, and fewer patients with no risk factors for stroke. This meta-analysis includes NVAF data from five clinical trials on anticoagulation,[6-10] all involving highly selected patients. One trial[10] included only men, and only 525 patients were enrolled after screening 7982 patients. In another,[6] 2546 patients were asked to participate, but only 1007 were enrolled. Another study[8] rejected more than 17 000 patients to obtain a final sample of 1330 subjects. In the combined analysis of the data, 70% of the patients were men. One cause for the differences in the population characteristics between these studies and ours could, therefore, be the stringent criteria for patient selection. Our study population, however, is quite similar to the population of the CARDIOTENS project,[30] which included all outpatients seen on a specific day in 1999 by 1159 physicians throughout Spain (21% cardiologists and 79% primary healthcare physicians). The aim of CARDIOTENS was to investigate the frequency of atrial fibrillation in the population sample. Among 32 051 patients studied, 1540 had atrial fibrillation. The study found a high rate of atrial fibrillation in women, an older population (>40% were aged 70 to 79) and a high frequency of hypertension (60%). The inclusion method used by those authors (cross-sectional study with routine screening of the

population) probably gives an accurate idea of the characteristics of outpatients with atrial fibrillation seen by physicians in Spain.

The EAFT (European Atrial Fibrillation Trial)[11] was a secondary prevention study that analyzed OAC contraindications in significant detail by looking at all patients with paroxysmal or chronic atrial fibrillation and a history of transient ischemic attack or stroke in the previous three months. The total population of 1007 patients was divided into eligible (n=669) or ineligible (n=338; 34%) for OAC. Patients in the first group were randomized to OAC, aspirin or placebo, and those in the second group, to aspirin or placebo. The ineligibility criteria for OAC were similar to those of our series, although the age limit defined as an indication was decided by the physician. A comparison with our study population (Figure 3) shows that OAC was contraindicated in 19% of our patients versus 34% in this clinical trial, possibly because the most frequent contraindication observed in the EAFT study was age (55%). In our series, anticoagulation was not contraindicated on the basis of age alone. At the time of the EAFT study, physicians were generally reluctant to prescribe OAC in the elderly. Secondly, it is noteworthy that the most frequent contraindication in our study is probable noncompliance with therapy (54% of all contraindications). This is probably because our population included a high percentage of elderly persons living alone, patients with visual, cognitive or other impairments that hinder adequate compliance with anticoagulant therapy, and individuals living in an underprivileged environment. In these patients, anticoagulant therapy should only be ruled out if there is no social or health support or family members able to assist with compliance. Poor compliance with therapy is one of the predictive factors of excessive anticoagulation in outpatients with heart disease, a situation that increases the risk of bleeding.[43]

Previous studies conducted in Spain[29-35] and other countries[36-41] on the use of OAC in NVAF show that this therapy is underutilized, although this trend is changing in Spain.[44] There are a number of potential reasons: a delay in the use of newly published guidelines in daily practice, hesitation to implement a therapy with a potentially high risk of complications and/or impose limitations on patients. Other studies published in this journal[45] show that intentional changes in healthcare procedures can be helpful in adapting clinical practice to the recommendations. Cabrera et al. used a quality assurance program to improve the prescription of appropriate medications for secondary prevention in ischemic heart disease. To our knowledge, our research is the first study in Spain aimed at increasing OAC prescription for NVAF in daily clinical practice. Anticoagulation has been achieved to date in 67% of all patients enrolled and

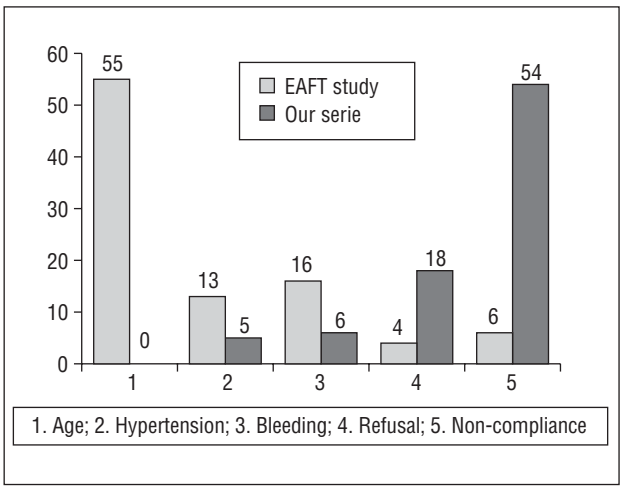

Fig. 3. Contraindications for anticoagulation in the EAFT study and in our series; EAFT indicates European Atrial Fibrillation Trial.

90% of those with an indication specified in the guidelines of the Sociedad Española de Cardiología. Observational studies published in Spanish journals in the last five years[29-35] report rates of anticoagulation between 12% and 39%. Because our protocol was first implemented in February 2000, OAC use in the series has gradually increased. By February 2001, 515 patients had been enrolled and 58% of them were receiving anticoagulant therapy (85% of those with one or more risk factors and no contraindications).[46]

The present study has several limitations. First, some subjectivity in the assessment of contraindications could not be avoided, primarily because poor compliance with therapy was expected, but hard to assess. In fact, noncompliance was the leading contraindication in the study population. Secondly, the protocol was implemented by only two physicians (the authors of this article) and we do not know whether it will be useful and well accepted by an unselected sample of physicians. Thirdly, no baseline study on anticoagulation prescription was conducted at our center before the protocol was implemented, and therefore our results could only be compared to those reported in the literature. A small percentage of patients did not receive anticoagulant therapy, despite an indication for anticoagulation and no absolute contraindications. Thus, improvements are still needed to achieve optimal prescription of OAC in these patients.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Despite the limitations, our study shows that a prospective protocol in cardiology outpatient clinics

would allow OAC to be prescribed for more NVAF patients in daily practice, even when the working environment is less than «ideal» (specialty centers with a high patient flow). A coordinated effort among all the staff involved in managing this disease is needed, to ensure that the majority of eligible patients benefit from these results and continue to do so over time.

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