Expert Opinion

Anticoagulation prescription in atrial fibrillation

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Aims: We seek to assess the factors associated with the anticoagulation prescription in a cohort of patients with atrial fibrillation (AF) collected from out-patient clinics.
Methods: A total of 1524 patients with a history of AF were collected from out-patients clinics. $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores were calculated in every patient. Variables associated with anticoagulant treatment prescription were analyzed in univariant and multivariant models.
Results: Most patients received either anticoagulant (62%) or antiplatelet treatment (37%). Anticoagulation rates increased among higher $CHADS_2$ and CHA_2DS_2-VASc score values. A logistic regression model was performed to assess the variables associated with the prescription of anticoagulant treatment; the variables with stronger association were the presence of arrhythmia at the current visit (odds ratio (OR) 33, 95% CI 27 – 40, $p < 0.001$) and lack of concomitant antiplatelet treatment (OR 0.17, 95% CI 0.14 – 0.21, $p < 0.001$).
Conclusions: Although prognosis of patients with AF is mainly determined by the long-term thrombotic risk, the prescription of antithrombotic therapy depends more on the bleeding risk and the immediate thrombotic risk perception.

Keywords: anticoagulation, antiplatelet treatment, atrial fibrillation

Expert Opin. Pharmacother. (2011) ***12****(10):1473-1479*

1. Introduction

Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia in clinical practice [1]. The prognosis of patients with AF varies widely depending on the presence of structural heart disease, the tolerance of the arrhythmia and the increased risk of thromboembolic events [2].

Controversy exists regarding anticoagulation indications in patients with AF and its implementation in clinical practice [3-6]. Current guidelines have recently extended anticoagulation indications for patients with AF [2]. The more detailed CHA_2DS_2-VASc score [7] is recommended to complement the classical $CHADS_2$ score for assessing the stroke risk and thus the anticoagulation indication. CHA_2DS_2-VASc score is recommended for evaluation of patients with $CHADS_2$ score < 2.

The final decision to start an anticoagulant treatment is not a simple reflection of the stroke risk; other variables such as bleeding risk or problems associated with oral anticoagulation compliance or security are taken into account.

We seek to assess the factors associated with the anticoagulation prescription in a cohort of patients with AF collected from out-patient clinics.

informa healthcare

10.1517/14656566.2011.584063 © 2011 Informa UK, Ltd. ISSN 1465-6566

2. Methods

2.1 Study design

CARDIOTENS 2 is an observational, transversal, multicentric study designed by the Hypertension Section of the Spanish Society of Cardiology with the aim of describing the prevalence and degree of control of arterial hypertension and other cardiovascular risk factors in clinical practice in Spain. Patients were recruited in out-patient clinics of general practitioners and cardiologists. Inclusion criteria were: age ≥ 18 years old, availability of the clinical records and previous cardiovascular diagnoses and the written acceptation of an informed consent. Exclusion criteria were illegal drugs abuse and refusal to sign the informed consent. A total of 885 physicians were selected; 89.1% were general practitioners and 10.9% cardiologists. Every physician recruited the first six patients in five consecutive days. A total of 25,856 subjects were initially collected and after excluding those who did not fulfill the inclusion criteria (639) or had any main data missing (80) a sample of 25,137 subjects constituted the final sample size; 1524 of these had current or previous history of AF and entered this sub-study. A specific questionnaire was elaborated for the study.

2.2 Variables definition

The patient was defined to have AF if the records included at least a medical report or an electrocardiogram showing it. Hypertension was defined according to the 2007 ESC/ESH guidelines if two determinations of blood pressure were ≥ 140/90 mmHg or specific treatments with previous diagnosis were present [8]. Dyslipidemia was collected if any antecedent of such diagnosis or values of total cholesterol > 220 mg/dl or low-density lipoproteins > 160 mg/dl had been registered previously. The diagnosis of diabetes mellitus was accepted if it had been previously diagnosed in a medical report, specific drug treatment or two consecutive glucose determinations were > 126 mg/dl. Obesity was considered for those with body mass index > 30 kg/m^2 and abdominal obesity if waist circumference was > 102 cm in men or > 88 cm in women. Chronic obstructive pulmonary disease was registered if specific treatments were present or previous diagnosis was present. Glomerular filtration rate was assessed by the modification of diet in renal disease equation: (186 × creatinine$^{-1.154}$ × age$^{-0.203}$) (× 0.742 in women).

The $CHADS_2$ score is based on a point system in which 2 points are assigned for a history of stroke or transient ischemic attack and 1 point each is assigned for age ≥ 75 years, a history of hypertension, diabetes or recent cardiac failure [9]. The CHA_2DS_2-VASc score was similar to $CHADS_2$, but gives 2 points for age ≥ 75 years old and 1 point for age between 65 and 74 years, 1 point for vascular disease (previous myocardial infarction, peripheral artery disease or aortic plaque) and 1 point for female gender [7]. The HAS-BLED score was assessed as the addition of 1 point for each of the following factors: systolic blood pressure > 160 mmHg, abnormal liver or renal function, stroke, bleeding history or predisposition, labile INR, age > 65 years, concomitant treatment with NSAIDs or alcohol abuse [10].

2.3 Statistical analysis

All continuous variables showed normal distribution and are presented as mean (s.d.). Discrete variables are presented as percentages. Baseline characteristics were compared between patients receiving or not anticoagulant treatment. For continuous variables, comparisons were performed by *t* test. Discrete variables were compared with the Chi^2 test or the Fisher exact test, as appropriate. Two multivariant models were performed to assess predictors of anticoagulant prescription, the first one evaluating variables included in the $CHADS_2$ risk score, and the second one performed adding to the first model those variables with significant univariant association. Results are presented as odds ratio (OR) and 95% CI. A two-sided p value of < 0.05 was considered to be significant for all analyses. All statistical analyses were performed using SPSS 13.0.

3. Results

3.1 Baseline characteristics

Table 1 describes demographic and clinical characteristics of the study population according to the prescription of anticoagulant treatment. Patients under anticoagulant treatment were older, less frequently current smokers and had more frequently history of heart failure, left ventricular hypertrophy and valvular disease, and less frequently of coronary artery disease. Most patients currently in AF were under anticoagulant treatment, whereas only a minority of those in sinus rhythm were anticoagulated. Mean $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED were 2.04 ± 1.16, 3.18 ± 1.39 and 1.19 ± 0.78, respectively. Stroke and bleeding risk scores showed significant correlation ($CHADS_2$ and HAS-BLED r = 0.570, p < 0.001; CHA_2DS_2-VASc and HAS-BLED r = 0.607, p < 0.001).

3.2 Antithrombotic treatment

Antithrombotic treatment is depicted in **Figures 1** and **2**. Most patients received either anticoagulant or antiplatelet treatment. A total of 11% did not receive any antithrombotic treatment at all. Anticoagulation rates increased among higher $CHADS_2$ (score 0 = 56%, 1 = 61% and ≥ 2 = 66%, p for the trend = 0.024) and CHA_2DS_2-VASc values (score 0 = 27%, 1 = 62% and ≥ 2 = 64%, p for the trend = 0.011), while there was no clear trend among HAS-BLED values (score 0 = 60%, 1 = 65% and ≥ 2 = 64%, p for the trend = 0.43).

3.3 Multivariate analyses

A logistic regression model was performed to assess the association between the variables included in the $CHADS_2$ risk score and the prescription of anticoagulant treatment. The model included the following variables: history of stroke or transient ischemic attack, age ≥ 75 years, a history of hypertension, diabetes and cardiac failure or left ventricular dysfunction. All

Table 1. Baseline characteristics of the study population.

N	Total N = 1524	Anticoagulant treatment N = 968	Non-anticoagulant treatment N = 556	p
Age, years	73 ± 11	74 ± 10	72 ± 13	< 0.001
Gender, females	50%	50%	49%	0.56
Risk factors				
Hypertension	87%	87%	87%	0.97
Diabetes	37%	38%	37%	0.83
Dyslipidemia	53%	52%	53%	0.87
Current smokers	9%	8%	12%	0.007
Former smokers	22%	22%	22%	0.94
Previous history				
Coronary artery disease	25%	23%	28%	0.019
Myocardial infarction	12%	11%	13%	0.16
Percutaneous coronary intervention	8%	8%	7%	0.89
Coronary artery bypass grafting	4%	4%	4%	0.48
Heart failure	35%	38%	29%	< 0.001
Left ventricular hypertrophy	38%	41%	35%	0.025
Valvular disease	29%	33%	23%	< 0.001
Cerebrovascular disease	16%	16%	17%	0.45
Chronic obstructive airway disease	19%	19%	20%	0.66
Peripheral artery disease	7%	7%	7%	0.95
Cancer	7%	7%	8%	0.59
Terminal renal failure	1%	1%	1%	0.73
Thrombosis and bleeding risk				
CHADS2	2.04 ± 1.16	1.95 ± 1.17	2.09 ± 1.15	0.887
CHADS2 ≥ 1	95%	94%	96%	0.055
HAS-BLED	1.50 ± 0.86	1.76 ± 0.85	1.35 ± 0.85	0.70
HAS-BLED ≥ 3	12%	16%	9%	< 0.001
Antiplatelet treatment	39%	73%	18%	< 0.001
Biological variables				
Weight, kg	81 ± 77	78 ± 15	77 ± 14	0.378
Height, cm	164 ± 9	164 ± 9	164 ± 9	0.776
Abdominal perimeter, cm	97 ± 14	97 ± 15	98 ± 15	0.333
Heart rate, beats per minute	74 ± 13	75 ± 13	74 ± 13	0.066
Systolic blood pressure, mmHg	137 ± 18	136 ± 17	136 ± 16	0.703
Diastolic blood pressure, mmHg	79 ± 13	79 ± 12	78 ± 12	0.399
Rhythm at evaluation				
Sinus rhythm	34%	21%	50%	< 0.001
Atrial fibrillation	76%	86%	58%	< 0.001

the variables included in the $CHADS_2$ risk score were independently associated with anticoagulation. The percentage of patients correctly classified to the prescription of anticoagulant treatment was 90% and the C statistic was 0.808.

After the addition of those variables included in the CHA_2DS_2-VASc score and not in the $CHADS_2$ risk score, age between 65 and 74 years old was also an independent predictor of anticoagulation (OR 1.45 95% CI 1.11 – 1.89, p = 0.007), while female gender was not and vascular disease showed significant interaction with antiplatelet treatment.

A second regression model was performed adding to the previous variables those associated with anticoagulant prescription in the univariate analysis. The final model was adjusted by AF at current visit, hypertension, diabetes, current smoking habit, heart failure or left ventricular dysfunction, left ventricular hypertrophy, valvular heart disease, previous stroke, antiplatelet treatment and age ≥ 75 years. Results are depicted in **Table 2**. The variables with stronger association with the prescription of anticoagulants were the presence of the arrhythmia at the current visit and lack of concomitant antiplatelet treatment. The ability of the model to predict patients correctly classified to the prescription of anticoagulant treatment increased to 93.4% and the C statistic to 0.904 (**Figure 3**).

4. Discussion

This study shows for the first time that the prescription of anticoagulant therapy in patients with AF is more tightly associated with the bleeding risk or the presence of AF at the current visit than the long-term stroke risk. In our cohort, all the variables included in the $CHADS_2$ risk score were associated with the anticoagulant prescription. Other variables such as left ventricular hypertrophy, smoking habit, antiplatelet

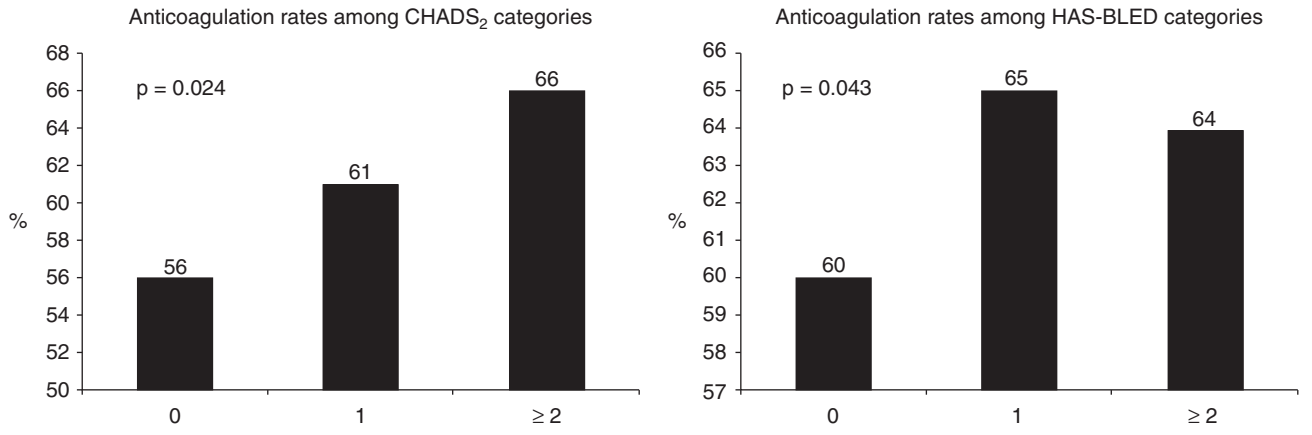

Figure 1. Anticoagulation rates among $CHADS_2$ and HAS-BLED values.

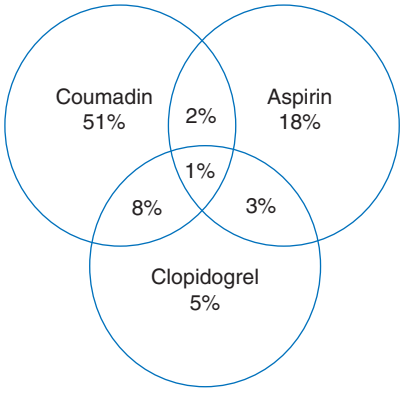

Figure 2. Antithrombotic treatment. A total of 62% received coumadin, 37% received some antiplatelet treatment and 11% did not receive any antithrombotic treatment.

treatment and the current status of AF at the moment of the evaluation were also related to the antithrombotic therapy. The variables most tightly associated with anticoagulation were the presence of AF at the evaluation and lack of concomitant antiplatelet treatment.

Anticoagulation rate in our sample was higher to that published in the last decade, but similar to currently reported series. The first edition of this registry, CARDIOTENS 99, reported a 33% of anticoagulant prescription among 999 patients with AF and hypertension recruited in out-patient clinics [11]. Comparing with more recent studies, the FAPRES study reported a 50.9% anticoagulation rate among hypertensive patients 65 years or older receiving medical care in out-patient clinics; in this study, anticoagulation rates were also higher among patients in AF at the moment of the examination, 71.2 versus 37.8% in case of sinus rhythm [12]. In a different setting, Schwammenthal *et al.* reported anticoagulation rates between 50 and 62% in a series of 586 patients with a history of AF admitted for acute ischemic stroke [13]. Investigators from the AFFECTS study reported a 64% of anticoagulation in a population of 1461 patients with AF without significant structural heart disease [14].

Several studies have underlined the underemployment of anticoagulant treatment in AF patients [6,15] and a number of articles, editorials and letters to editors have highlighted the importance of adherence to guidelines' recommendations [16]. Up-to-date studies have addressed factors associated with prognosis, but few were conducted to determine why once those factors are identified stroke is not prevented more aggressively [17-19].

Some authors have suggested that a number of patients with anticoagulation indication do not receive it due to a high bleeding risk [20,21]. Current ESC AF guidelines promote the assessment of both stroke and bleeding risk in every AF patient before the election of the antithrombotic treatment. The HAS-BLED risk score is a new tool proposed to assess the bleeding risk of a single patient [10]. Of all the variables included in the HAS-BLED score, lack of concomitant antiplatelet treatment was the most closely associated with the final decision of anticoagulation in our population and the second one in the model after the rhythm at the moment of the evaluation. A major limitation of incorporating both HASBLED and $CHADS_2$ or CHA_2DS_2-VASc score is that some of the variables are common in both models and many patients with high thrombotic risk will have also high bleeding risk; in fact, in our patients both risk scores showed significant correlation. Although patient's prognosis depends mainly on the thrombosis risk, physicians might be more concerned about bleeding risk, and fear more a complication related to a medical prescription than one caused by a medical omission, as has been previously described in different settings [22]. We speculate that a bleeding event in a patient receiving concomitant anticoagulant and antiplatelet treatment can be perceived by both patients and doctors as directly related to the medical act, and thus representing

Table 2. Multivariant analysis: including variables included in the $CHADS_2$ score and those associated with anticoagulant prescription in the univariate analysis.

	Odds ratio	95% CI		p Value
Atrial fibrillation at current visit	33.193	27.452	40.134	0
Hypertension	1.118	0.876	1.428	0.369
Diabetes	1.269	1.047	1.539	0.015
Current smoking	0.533	0.403	0.706	0
Heart failure or left ventricular dysfunction	2.388	1.908	2.987	0
Left ventricular hypertrophy	2.160	1.756	2.657	0
Valvular heart disease	2.947	2.329	3.728	0
Previous stroke	2.708	2.021	3.627	0
Antiplatelet treatment	0.171	0.138	0.213	0
Age ≥ 75 years	1.381	1.141	1.671	0.001

Percentage of correct classification: 93.4%. C-Statistic: 0.904.

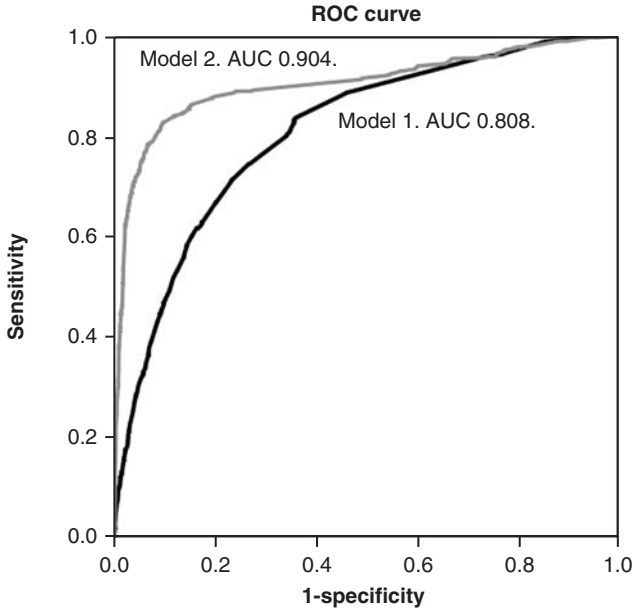

Figure 3. Receiver operator characteristic curves of multivariant models 1 and 2. Variables included in model 1: history of stroke or transient ischemic attack, age ≥ 75 years, a history of hypertension, diabetes and cardiac failure or left ventricular dysfunction. Variables included in model 2: atrial fibrillation at current visit, hypertension, diabetes, current smoking habit, heart failure or left ventricular dysfunction, left ventricular hypertrophy, valvular heart disease, previous stroke, antiplatelet treatment and age ≥ 75 years.

iatrogenia, as opposed to the natural evolution of a patient condition leading to thrombosis. It is worth noting the scarce evidence supporting guidelines' recommendations in patients with AF and coronary artery disease [2].

Previous reports have demonstrated higher anticoagulation rates among patients with permanent AF compared to those with paroxysmal AF [14,18,23]. Our results confirm these previous observations, as being in AF at the moment of the evaluation was the most powerful predictor of anticoagulant prescription in our model. This finding has been attributed to the erroneous belief that paroxysmal AF would lead to fewer embolic events, but mounting evidence exist showing similar stroke risk among different temporal patterns of AF, including paroxysmal, persistent and permanent [24-26] and guidelines and other sources have broadcast this finding. Alternatively, we propose that being in AF at the moment of the evaluation might be perceived by the physician as a higher immediate risk, as opposed to the long-term risk associated with the antecedent of past episodes of paroxysmal or persistent AF.

In the comparison of $CHADS_2$ and CHA_2DS_2-VASc risk scores for the prediction of anticoagulant treatment, we found that age was taken into account in more detail than simple dichotomization below or above 75 years old, but female gender was not considered as a variable increasing the thrombotic risk. The influence of vascular disease is difficult to interpret due to the strong interaction with antiplatelet treatment, although it has demonstrated as increasing the thrombotic risk [7].

We hypothesize that although both existing literature and guidelines recommend deciding whether or not to anticoagulate mainly on the basis of long-term stroke reduction, physicians' criteria could be more influenced by the immediate risk perception and the aphorism of *primum non nocere*.

Several limitations should be acknowledged. As in most registries, variables were collected by means of a predefined questionnaire, and some of the reasons that physicians have taken into account to prescribe a certain treatment may not be represented in the questionnaire. $CHADS_2$, CHA_2DS_2-VASc or HAS-BLED scores were not assigned by the physicians at baseline but were calculated after study completion using the recorded medical history data, which may have underestimated the real figures. Additionally, knowledge that treatment decisions were being observed might have influenced the prescribing behavior of physicians.

Further studies are needed to assess the factors that concern physicians treating AF patients and to what extent the

importance given to these factors reflect the real determining factors for patients' prognosis.

In conclusion, although prognosis of patients with AF is mainly determined by the long-term thrombotic risk, the prescription of antithrombotic therapy depends more on the bleeding risk and the immediate thrombotic risk perception.

Declaration of interest

The study was funded by an unrestricted educational grant from Recordati Spain S.A. and was endorsed by the Hypertension Section of the Spanish Society of Cardiology and the Agencia de Investigación de la Sociedad Española de Cardiología.

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