

Predicting Embolic Events in Patients With Nonvalvular Atrial Fibrillation: Evaluation of the CHADS₂ Score in a Mediterranean Population

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Introduction and objectives. A new index for predicting embolic risk in nonvalvular atrial fibrillation has been proposed, the CHADS₂ score, which is calculated by adding 1 point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes, and by adding 2 points for a history of stroke or transient ischemic attack (TIA). Our objective was to evaluate the use of this score in a Mediterranean population.

Methods. Between February 1, 2000 and December 20, 2006, all patients with permanent nonvalvular atrial fibrillation being treated at two outpatient cardiology clinics in a university hospital in the south of Spain were offered antithrombotic therapy in accordance with scientific society recommendations and were prospectively monitored for embolic events (ie, stroke, TIA, or peripheral embolism). A CHADS₂ score was derived for each of the 296 patients who did not receive anticoagulation.

Results. The CHADS₂ score was 0 in 69 (23.3%) patients, 1 in 81 (27.4%), 2 in 99 (33.4%), 3 in 30 (10.1%), and 4 or more in 17 (5.7%). After 21 (17) months of follow-up, the embolic event rates for CHADS₂ scores of 0, 1, 2, 3, and ≥ 4 were 2.88, 5.80, 5.16, 14.78, and 22.02 per 100 patient-years, respectively ($P=0.0016$). Patients with a CHADS₂ score from 0–2 had an embolic rate of 4.63 per 100 patient-years, compared with 17.31 per 100 patient-years in those with a score ≥ 3 ($P=0.00087$).

Conclusions. The CHADS₂ score proved useful for quantifying the risk of an embolic event in Mediterranean patients with nonvalvular atrial fibrillation. In our series, the risk of embolism in patients with a low score was not negligible.

Key words: Atrial fibrillation. Prevention. Stroke.

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Predicción de eventos embólicos en pacientes con fibrilación auricular no valvular: evaluación del score CHADS₂ en una población mediterránea

Introducción y objetivos. Para predecir el riesgo cardioembólico en la fibrilación auricular no valvular (FANV) se ha propuesto un nuevo índice, el CHADS₂, que se conforma asignando 1 punto por la presencia de insuficiencia cardiaca, hipertensión, edad ≥ 75 años o diabetes y 2 puntos si hay historia de ictus o accidente isquémico transitorio (AIT). Nuestro objetivo es evaluar este índice en una población mediterránea.

Métodos. Del 1 de febrero de 2000 al 20 de diciembre de 2006, a todos los pacientes con FANV permanente atendidos en dos consultas de cardiología de un hospital del sur de España, se les indicó terapia antitrombótica según las recomendaciones de las sociedades científicas. Se siguió prospectivamente la aparición de eventos embólicos (ictus, AIT o embolia periférica). El índice CHADS₂ fue aplicado a los 296 pacientes que no fueron anticoagulados.

Resultados. El índice CHADS₂ fue 0 en 69 (23,3%) pacientes, 1 en 81 (27,4%), 2 en 99 (33,4%), 3 en 30 (10,1%) y ≥ 4 en 17 (5,7%). Tras 21 ± 17 meses de seguimiento, la tasa de eventos embólicos según su índice CHADS₂ fuera 0, 1, 2, 3 o ≥ 4 fue de 2,88, 5,80, 5,16, 14,78 y 22,02 cada 100 pacientes/año, respectivamente ($p = 0,0016$). Los pacientes con índice CHADS₂ 0-2 presentaron una tasa de embolias de 4,63, frente a 17,31/100 pacientes/año en aquellos con índices ≥ 3 ($p = 0,00087$).

Conclusiones. El índice CHADS₂ es válido para cuantificar el riesgo de eventos embólicos en una población mediterránea de pacientes con FANV. En nuestra serie, el riesgo embólico en pacientes con índice bajo no es despreciable.

Palabras clave: Fibrilación auricular. Prevención. Accidente vascular cerebral.

ABBREVIATIONS

INR: international normalised ratio
NRAF: National Registry of Atrial Fibrillation
NVAF: nonvalvular atrial fibrillation
TIA: transient ischemic attack

INTRODUCTION

Recently published guidelines on clinical practice¹⁻⁴ wholly recommend oral anticoagulation for patients with nonvalvular atrial fibrillation (NVAF) with a high risk of cardiac embolism, in the absence of contraindications. However, certain discrepancies can be observed in the different guidelines with respect to classifying patients according to the different risk groups.

Scientific recommendations for stratifying cardioembolic risk are fundamentally based on 2 studies. On the one hand, that of the Atrial Fibrillation Investigators⁵ is a meta-analysis of several randomised clinical studies on oral anticoagulation compared to a placebo or antiaggregation treatment in NVAF which establishes independent predictors of embolic events among the non-anticoagulation group, such as arterial hypertension, age, diabetes mellitus, and previous embolic events (stroke or transient ischaemic attack). On the other hand, there are the Stroke Prevention and Atrial Fibrillation⁶ studies, which also identified the following predictors of events: systolic blood pressure >160 mm Hg, previous ischaemic stroke, recent heart failure, or left ventricular systolic dysfunction in echocardiography or the combination of age ≥75, and female sex. When both criteria are applied to the same population, a significant number of patients may be classified into subgroups of differing risks requiring different therapeutic decisions.⁷⁻⁹

As a means of overcoming the above problems, in 2001 Gage et al¹⁰ put forward the CHADS₂ index (Congestive heart failure, Hypertension, Age, Diabetes, Stroke) for classifying cardioembolic risk in NVAF. This method consists of a scoring system which assigns 1 point to each one of the following conditions: recent heart failure, arterial hypertension, age ≥75, and diabetes mellitus. It also assigns 2 points for a history of stroke or transient ischaemic attack. The index was validated in the National Registry of Atrial Fibrillation (NRAF) in the United States and was proven to predict the cardioembolic risk in the present study with greater accuracy than the 2 previously described methods. The model is simple and easy to apply, however it has not been evaluated in populations other than the reference one. The objective of the present study is to present the results obtained after applying the CHADS₂ index to a Mediterranean population of NVAF patients.

METHODS

Criteria for Patient Inclusion

This is a prospective study which included all consecutive patients with permanent NVAF seen in 2 cardiology clinics within a university hospital in the south of Spain, between February 1, 2000 and December 20, 2006. The patients were referred to the clinic for primary attention, emergency services, or hospitalisation within the cardiology or internal medicine departments. Each patient was assessed for the possibility of pharmacological or electrical cardioversion, and all patients in which sinus rhythm was eventually restored were excluded. Patients with flutter were also excluded. A prospective study and thromboembolic prophylaxis protocol was followed for each patient. Those patients who did not receive anticoagulation treatment formed the study group for the present study. The project has been approved by the institution's ethics committee and all patients gave their informed consent.

Study Protocol

The study and thromboembolic prophylaxis protocols¹¹ were established by consensus among the researchers, after reviewing the Guidelines established by the Sociedad Española de Cardiología for antithrombotic treatment³ (published before the project was designed) and the scientific evidence available at the time. During the study, the American College of Cardiology/American Heart Association/European Society of Cardiology published Guidelines on atrial fibrillation¹⁻² and the Sociedad Española de Cardiología published Guidelines on cardiac arrhythmia.⁴ Having carefully reviewed these documents, the protocol remained unchanged, since it was believed that it was consistent with the basic principles of these recommendations.

A complete study was carried out on each patient. This included a clinical history, physical examination, blood analysis (blood count, glucose, urea, creatinine, sodium, potassium, hepatic enzymes, thyroid hormones, and coagulation study), electrocardiogram, and chest x-ray. An echocardiogram was performed on each patient suspected of having structural heart disease, in cases where the decision to administer anticoagulation treatment depended on the result.

The following cardioembolic risk factors were taken into consideration: advanced age (≥75), arterial hypertension, diabetes mellitus, previous cardioembolic event, history of ischaemic heart disease, recent heart failure, left atrial dilatation (anterior-posterior diameter ≥50 mm), and left ventricular dysfunction (ejection fraction <0.45).

The following were established as absolute contraindications for anticoagulation treatment: recent severe haemorrhage, severe and poorly controlled arterial hypertension, digestive disease with a high risk of

bleeding, probable therapeutic noncompliance, non-related severe anaemia, and the high probability of frequent traumas. Therapeutic noncompliance was considered likely if the patient presented any of the following factors: persistent therapeutic noncompliance in the past, illiteracy, serious visual or cognitive impairment with inadequate family or social support, etc. The risk factors and absolute contraindications for anticoagulation treatment were registered prospectively.

Thromboembolic Prophylaxis Protocol

Treatment with aspirin, other antiaggregation treatments, or no antithrombotic treatment was indicated for those patients who did not present any cardioembolic risk factors or absolute contraindications for anticoagulation treatment, according to the medical opinion of the doctor in charge. Anticoagulation treatment was given to those patients who had no absolute contraindications for anticoagulation treatment and 2 or more risk factors. Sufficient time was allocated to explain the advantages of the treatment to avoid any negativity due to incomplete or insufficient information. In those patients with no absolute contraindications who presented only 1 risk factor, the decision regarding treatment was left to the cardiologist in charge. Finally, the treatment given to each patient was registered. On completing the inclusion process, patients who deviated from the protocol were located and the clinical history was studied to find possible explanations. Patients who did not receive anticoagulation treatment formed the study group for the present analysis, regardless of whether they received treatment with antiplatelet drugs or not.

Follow-up

The patients were followed up with annual check-ups at the clinic and the appearance of embolic events was registered: stroke, transient ischaemic attack (TIA), and peripheral embolism. Diagnosis of stroke or TIA required an acute neurological deficit lasting approximately 24 hours, respectively, which could not be explained by other etiologies (haemorrhage, trauma, infection, etc) and with at least 1 image test (computed tomography or magnetic resonance) compatible with the diagnosis, as well as confirmation from a neurologist. Lethal stroke was defined as that which resulted in the death of the patient within 30 days following the stroke. A diagnosis of peripheral embolism was defined as clinically compatible and an embolus identified by vascular ultrasound, examination during surgery, or anatomopathological findings, always with the confirmation of a vascular surgeon. In patients who suffered more than 1 embolic event, only the first event was considered for the purpose of the analysis and the follow-up period was reviewed. At the end of the study, efforts were made to locate those patients lost during

follow-up by mail or by telephone contact with them or their primary care doctors.

Statistical Analysis

All baseline and follow-up data were collected prospectively and entered into a database created using the SPSS v12.0 program (SPSS Inc. Chicago, Illinois, United States). The quantitative data is presented as mean (1 standard deviation). Qualitative parameters are expressed as percentages. The gross rate of embolic events (stroke, TIA, and peripheral embolism) was obtained for every 100 patients/year for the entire series and each subgroup within the CHADS₂ index. The χ^2 test was used to compare the event rates between subgroups and Fisher's exact test when required. The Cox regression model was used to measure the effect of every one point increase in the CHADS₂ index on the hazard ratio (HR) for embolic events. The appearance of embolic events was used as a dependent variable and the CHADS₂ index as an independent one and the model was adjusted according to the use or absence of aspirin. The reduction of HR associated with the use of aspirin was calculated as 1 minus the HR associated with its use. A second Cox analysis was carried out, introducing the following variables into the model: a history of ischaemic heart disease (yes/no), left ventricular dysfunction (yes/no), and left atrial dilatation (yes/no), using the method to introduce all variables into the model (Enter). The CHADS₂ variable was introduced as a continuous variable to try and reproduce the methodology of the original work.¹⁰ A *P* value less than .05 was considered significant. The SPSS computer package was used for the statistical analysis of the information.

RESULTS

General Characteristics

During the study period, a total of 1137 patients were included in the protocol for managing atrial fibrillation and 296 did not receive anticoagulation treatment (26%). These patients form the study sample. The average age was 75 (9) years, and 44% of patients were male. A total of 58.4% were aged 75 or over, 29.1% between 65 and 74, and 12.5% were under 65. A total of 74% of patients were asymptomatic, 20% presented with dyspnoea, 3% with palpitations, and 3% with angina. A total of 92% of the patients were given antiaggregation treatment, 90% using aspirin.

Cardioembolic Risk Factors and Contraindications for Anticoagulation Treatment

NVAF was most commonly associated with arterial hypertension (50%) followed by the absence of structural

heart disease (40%), ischaemic heart disease (5%), cardiomyopathy (3%), and other types of heart disease (2%). The most common risk factors were advanced age, arterial hypertension, and diabetes (Table 1). The data for the variables included in the CHADS₂ index were taken for all patients in the series. The CHADS₂ score was 0 in 69 patients (23.3%), 1 in 81 (27.4%), 2 in 99 (33.4%), 3 in 30 (10.1%), and ≥ 4 in 17 (5.7%). The average CHADS₂ score for the sample studied was 1.49 (1.16). The reasons for not administering anticoagulation treatment were as follows: absolute contraindications in 136 patients (46%), absence of cardioembolic risk factors in 55 (19%), patient negativity in 51 (17%), and the decision of the cardiologist in charge in 54 individuals, the majority of which only presented 1 cardioembolic risk factor (41/54 or 75%). The absolute contraindications for anticoagulation treatment are outlined in Table 2. The most common was the likelihood of therapeutic noncompliance. A deviation from the protocol was observed in 13 patients, who did not present any absolute contraindications and had more than 1 risk factor but did not receive anticoagulation treatment. A retrospective analysis of the clinical histories showed that this was due to the combination of several relative contraindications not entered in the database (significant polypharmacy, with frequent changes of doses and drugs, use of high doses of anti-inflammatories, etc), as well as patient preference.

TABLE 1. Frequency of Cardioembolic Risk Factors in the Series (n=296)

Cardioembolic Risk Factors	Patients, No. (%)
Aged 75 or over	173 (58.4)
Hypertension	161 (54.4)
Diabetes mellitus	45 (15.2)
Atrial dilatation	38 (12.8)
Cardiac failure	32 (10.8)
Ischaemic heart disease	15 (5.1)
Previous cardioembolic event	15 (5.1)
Left ventricular dysfunction	11 (3.7)

TABLE 2. Absolute Contraindications for Anticoagulation Treatment in the Population Studied

Contraindication	Patients, No. (%)
High probability of therapeutic noncompliance	85 (62.5)
Digestive disease with high risk of severe bleeding	14 (10.3)
Recent severe bleeding	9 (6.6)
High probability of frequent and/or severe traumas	8 (5.9)
Uncontrolled severe hypertension	7 (5.1)
Total	136

Events During Follow-up

During an average follow-up period of 21 (17) months, with 16 patients lost to follow-up (5.4%) and a total of 484 patients per observation year, 29 embolic events were registered: 12 TIAs, 15 strokes (5 lethal and 10 non-lethal), and 2 peripheral embolisms in 5.99 per 100 patients/year. If the TIAs are excluded, the figure is 3.51 events per 100 patients/year. The embolic event rates for CHADS₂ index scores of 0, 1, 2, 3, or ≥ 4 , were 2.88, 5.8, 5.16, 14.78, and 22.02 per 100 patients/year, respectively ($P=.0016$). Patients with a CHADS₂ score between 0 and 2 had an embolic event rate of 4.63, compared to 17.31 per 100 patients/year in those with scores of ≥ 3 ($P=.00087$). In the first Cox model, adjusted to the use of aspirin, for every one point increase in the CHADS₂ index, the HR for embolic events increased by a factor of 1.44 (95% confidence interval [CI], 1.10-1.89; $P=.0078$). The use of aspirin was associated with a HR of 0.82 for embolic events (95% CI, 0.28-2.38), which corresponds to a non significant 18% reduction in the relative risk ($P=.71$). After entering variables for a history of ischaemic heart disease, left ventricular dysfunction and left atrial dilatation into the Cox model, in addition to the use of aspirin, the CHADS₂ index was associated to a HR of 1.45 for embolic events (95% CI, 1.10-1.89; $P=.0072$). This was similar to the original model and none of the variables constituted an independent predictor of events. If TIAs are excluded, the rate of stroke or peripheral embolism for CHADS₂ scores of 0, 1, 2, 3, or ≥ 4 were 0, 2.9, 4.51, 8.89, and 16.51 per 100 patients/year, respectively ($P=.0047$). Patients with a CHADS₂ score between 0 and 2 had an annual stroke or peripheral embolism rate of 2.55, compared to 11.54 per 100 patients/year in those with scores of ≥ 3 ($P=.0034$).

DISCUSSION

When the CHADS₂ index was initially published¹⁰ it was validated among a sample of 1733 patients aged between 65 and 95, which were taken from the NRAF in the United States. Table 3 shows that the present series has a lower number of patients, a reduced follow-up period, a lower average age and a lower percentage of heart failure, diabetes mellitus and stroke or previous TIA, a similar proportion of hypertensives and women, and a more common aspirin prescription. The annual rate of embolic events (stroke and TIA) in the NRAF was 4.4%, lower than the 5.99% observed among the patients included in the present study. The increase in embolic risk for each point in the CHADS₂ index was 1.5 (1.3-1.7), with a gross annual rate of embolic events of 1.2, 2.8, 3.6, 6.4, and 7.76 per 100 patients/year for CHADS₂ scores of 0, 1, 2, 3, and 4, or more, respectively. The present study is the first work to evaluate this scoring system in a different sample and the only one to do so

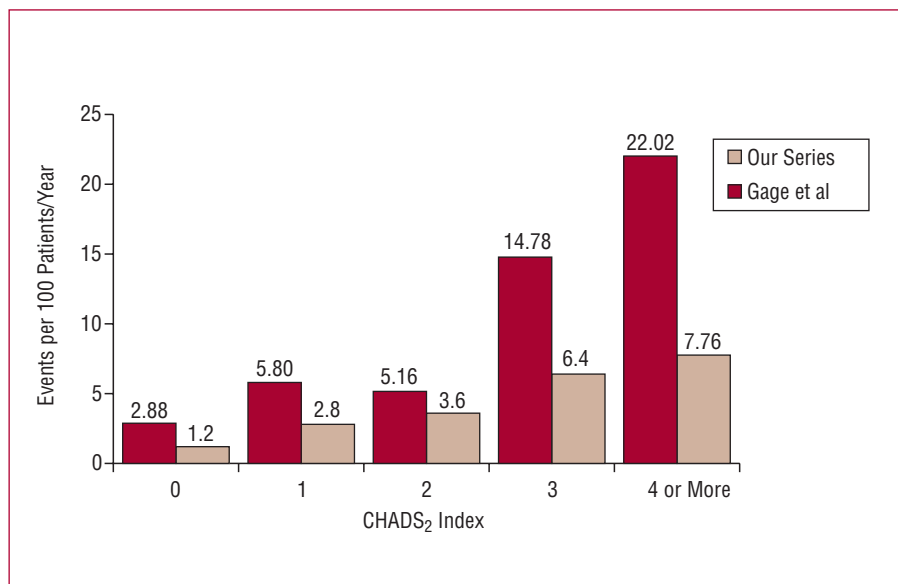


Figure 1. Annual rates for embolic events according to the CHADS₂ index in the present series and the National Register of Atrial Fibrillation (NRAF) in the United States.

among a Mediterranean population. The results for the increase in the HR of embolic risk for each point of the CHADS₂ index are very similar to those obtained for the American population (1.44 compared to 1.5). However, the gross rate of events per 100 patients/year is generally greater in this series than that included in the cited article (Figure 1). There are a number of possible reasons for this. Firstly, the study by Gage et al¹⁰ obtained the events by analysing the databases for hospital admissions and death registers, rather than a follow-up of patients within a clinic. This means that a not negligible number of TIA cases (all those patients who are not admitted to hospital but are discovered during follow-up in the clinic) were probably not detected in their work. In the sample studied, TIAs represented 41% of all embolic events, compared to just 24% in the American register. The cited study did not include peripheral embolisms in the analysis; however, it is doubtful whether this is a significant explanatory factor, given the low frequency of these events in the present series (only 2 out of 29 events were peripheral embolisms). A further 2 factors which may explain the different results are as follows: the type of atrial fibrillation, which was permanent in the present study and chronic or recurrent in the American series, and the moment in which the patients were selected, during a hospital stay in the series studied by Gage et al and an outpatient visit in the present work. Although the Guidelines from the American College of Cardiology/American Heart Association/European Society of Cardiology^{1,2} consider it reasonable to select the antithrombotic therapy without taking into account the type of atrial fibrillation and randomised studies¹¹ have found a similar incidence of ischaemic stroke in patients with paroxysmal and permanent atrial

TABLE 3. Comparison of the National Register of Atrial Fibrillation (NRAF) in the United States With the Series Studied

	NRAF	Present Series
Patients, n	1733	296
Follow-up, n, patients/year	2121	484
Average age, years	81	75
Female sex, %	58	56
Heart failure, %	56	11
Hypertension, %	56	54
Diabetes, %	23	15
Stroke or previous TIA, %	25	5
Aspirin prescription, %	31	83

TIA indicates transient ischaemic attack.

fibrillation, some cohort studies have observed a greater risk in patients with chronic NVAf.¹² Finally, the fact that there are differences in the embolic risk between both populations, which can not be explained due to methodological reasons, must also be considered. Therefore, taking into account the above exceptions, it may be said that the present study confirms the value of the CHADS₂ index in predicting embolic events among a Mediterranean population.

It is to be noted that in the sample studied, the annual rate of embolic events in patients considered as a low risk (CHADS₂=0) is 2.88%. This is mainly due to TIA, since the rate drops to 0% if these events are excluded. In patients with a CHADS₂ score of 1, the rate is 5.8% (2.9% if TIA is excluded), which is not negligible. These data therefore confirm that these patients may be considered “low risk” for severe embolic events (stroke or peripheral embolism), but not for the possibility of TIA. In terms of the practical implications,

these results indicate that the embolic risk of patients considered low risk in this centre may be greater than that initially suspected according to previous publications on patients selected for clinical trials or registers in other countries. The present group of researchers had previously published¹³ excellent results for oral anticoagulation, controlled in hospital by expert haematologists, in patients seen in daily clinical practice in this centre, including patients over 75,¹⁴ with no significant differences in the annual rate of severe haemorrhage among the entire sample studied¹⁴ (1.37% in patients receiving anticoagulation treatment compared to 1.36% in patients not receiving this treatment, the majority of which were receiving antiaggregation treatment with aspirin). These data may be useful in cases where the latest guidelines on clinical practice leave it to the clinician to decide whether to administer anticoagulation or antiaggregation treatment, as is the case for patients with only one intermediate risk factor.¹ The guidelines recognise that the estimated embolic risk is crucial when deciding whether anticoagulation treatment is required or not, and although there is general consensus regarding the need to administer anticoagulation treatment in high risk patients (annual rate of embolic events of 6% or greater) and not to administer this treatment to low risk patients (2% or less), a consensus has not been reached on the need to provide anticoagulation treatment to patients with an intermediate risk (annual rate of 3.5%).

The population included in the present study includes patients to whom, following the protocol for managing NVAF, anticoagulation treatment was not given. Although the decision-making process may be improved, the present protocol has proven useful in regulating prescriptions of anticoagulation treatment in patients with NVAF. In our initial publication¹⁵ in 2003, 33% of the patients did not receive anticoagulation treatment. In the current publication, this figure has fallen to 26%.

The CHADS₂ index is simple and can be easily applied in practice. It has therefore been recognised in the latest guidelines for managing atrial fibrillation.¹ However, until now it has not been evaluated in an independent population and it is therefore believed that the present work can provide valuable support when using this model for predicting the embolic risk in patients in this centre.

There are some limitations to the study carried out. Firstly, the sample is not as big as that of the American register. Secondly, a reduced number of patients were lost to follow-up. Thirdly, the CHADS₂ index was not evaluated statistically, which would have involved studying the behaviour of each of the index components and subsequently justifying why the index is more useful than each one of its variables, nor was the possibility that other variables may have been more useful when developing the model been taken into consideration. The objective has simply been to describe the results

obtained when this tool was applied in the daily clinical practice of this centre. Finally, the results can not be considered representative of the embolic risk in patients with NVAF in Spain, since this study was only carried out in one centre. Larger studies, with a suitable design and sample size would be required to sufficiently deal with this issue.

CONCLUSIONS

Despite the limitations, it is believed that the present work contributes to confirming that the CHADS₂ index is a valid tool for assessing the risk of embolic events in a Mediterranean population of NVAF patients. The embolic risk in patients with a low score in the present series is not negligible.

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