

Differences among Clinical Classification Schemes for Predicting Stroke in Atrial Fibrillation: Implications for Therapy in Daily Practice

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Abstract

Background: Several clinical classification schemes (CCSs) for predicting stroke in nonvalvular atrial fibrillation (NVAF) have been developed to help identify patients eligible for anticoagulation. **Objectives:** To estimate the agreement in predicting the risk of stroke among four widespread CCSs, and to determine their implications for thromboprophylaxis in clinical practice. **Methods:** The authors conducted a prospective, multicenter, observational study of adults with NVAF in 12 emergency departments (EDs) in July 2000 and February 2001. The proportions of patients classified as having high, moderate, and low risk of stroke among the following CCSs were compared: the Atrial Fibrillation Investigators (AFI), the Stroke Prevention in Atrial Fibrillation (SPAF), the CHADS₂ (an acronym for congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack), and the American College of Chest Physicians (ACCP). **Results:** One thousand two hundred twenty patients were included. The proportions of patients strati-

fied as having high/moderate/low risk of stroke according to each CCS were: 70%/22%/8% (AFI), 38%/41%/21% (SPAF), 13%/45%/42% (CHADS₂), and 86%/7%/7% (ACCP). The agreement was medium between AFI and ACCP ($\kappa = 0.52$) and poor among the rest of them (AFI/SPAF, $\kappa = 0.01$; AFI/CHADS₂, $\kappa = 0.02$; SPAF/CHADS₂, $\kappa = 0.18$; SPAF/ACCP, $\kappa = 0.11$; CHADS₂/ACCP, $\kappa = 0.03$). The agreements in selecting patients as eligible for antiplatelet therapy or anticoagulation were: AFI/SPAF, $\kappa = 0.45$; AFI/CHADS₂, $\kappa = 0.22$; AFI/ACCP, $\kappa = 0.91$; SPAF/CHADS₂, $\kappa = 0.47$; SPAF/ACCP, $\kappa = 0.11$; CHADS₂/ACCP, $\kappa = 0.03$. **Conclusions:** In the ED population studied, these CCSs showed relevant differences in the risk of stroke stratification and, therefore, in the identification of patients with NVAF eligible for anticoagulation. **Key words:** emergency service, hospital; atrial fibrillation; embolic stroke; risk factors for stroke; anticoagulants. *ACADEMIC EMERGENCY MEDICINE* 2005; 12:828-834.

Atrial fibrillation is an independent risk factor for embolic stroke.¹ Although this is well defined in patients with mitral valve disease, the risk of stroke varies widely in patients with nonvalvular atrial fibrillation (NVAF),² depending on the presence or absence of certain risk factors.^{3,4} Since rhythm control does not seem to reduce the rate of stroke,⁵ anti-thrombotic treatment is the mainstay for stroke prevention.⁶ Oral anticoagulation reduces the risk of

stroke by approximately 65% and by 45% with respect to antiplatelets,⁷ and also reduces its severity and the risk of death from stroke.⁸ However, anticoagulation gives rise to an increased probability of complications, principally hemorrhage.^{9,10} Therefore, it is crucial to differentiate patients with NVAF who have an increased risk of stroke, and would benefit from long-term anticoagulation, from those with a risk low enough to use antiplatelet therapy.⁴

Various clinical classification schemes (CCSs) derived from the results of several clinical trials have been proposed for predicting the risk of stroke associated with NVAF.^{3,4,11-13} However, the risk factors for stroke included in these schemes are not the same, and resulting recommendations for therapy have several differences. Additionally, there is limited information available concerning the impact of these differences in risk stratification on the eligibility for anticoagulation in nonselected populations not included in the clinical trials.^{14,15} Emergency departments (EDs) account for a large, and increasing, number of visits of patients with NVAF.¹⁶ In this setting, the conditions of the ED and the patients'

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clinical profiles are different from the highly selected study populations and conditions of clinical trials, and could provide helpful information about the real management of NVAF in daily clinical practice.

The objectives of this study were to estimate the agreement in predicting the risk of stroke in NVAF between four widespread CCSs, and their implications for the prescription of thromboprophylaxis in a representative patient population in the acute setting of daily clinical practice.

METHODS

Study Design. The study cohort was constructed with the patients of the GEFAUR (Spanish Atrial Fibrillation in Emergency Medicine Study Group)-1 and GEFAUR-2 studies. Detailed descriptions of the GEFAUR studies' methodology and the characteristics of emergency medicine in Spain have been published elsewhere.^{16,17} Briefly, the GEFAUR-1 was a prospective, multicenter, observational study performed in the EDs of 12 hospitals of the National Health System in Madrid, Spain, between June 15 and August 1, 2000; and GEFAUR-2 was carried out in the same way in four of these hospitals between February 1 and 15, 2001. Both studies were promoted by the Scientific Committee of the Spanish Society of Emergency Medicine (SEMES). The protocol was blinded to guarantee patients' and physicians' confidentiality. The Institutional Review Board of the Spanish Society of Emergency Medicine approved the study protocols.

Study Setting and Population. All patients above 14 years of age without evidence of heart valve disease, who were treated in the ED, and in whom atrial fibrillation (AF) was demonstrated in an electrocardiogram (ECG) (obtained when the emergency physician considered it necessary during clinical evaluation), were eligible for inclusion. The diagnosis of NVAF and the determination of the type (paroxysmal, persistent, or permanent) were made by a staff emergency physician using criteria from Levy et al.¹⁸ Valvular heart disease was considered to be present in: 1) patients with a previous diagnosis in their medical records of mitral valve disease, valve repair surgery, or mitral and/or aortic valve replacement, and 2) patients whose clinical evaluation in the ED suggested a diagnosis of mitral valve disease. Comorbidity was defined according to the criteria from the Framingham Heart Study.²

Study Protocol. The treating emergency physicians prospectively filled out data forms for each patient, and a separate researcher daily reviewed the ED medical records to avoid recruitment losses, and to confirm the data collected. The following information was included on the data-collection sheet¹⁷: demographic variables, risk factors for stroke, comorbidity

(structural heart disease, reduced left ventricular fraction shortening, recent heart failure, hypertension, diabetes, disability, previous embolic event), current stroke prophylaxis, clinical evaluation in the ED, whether rate and/or rhythm control was attempted and its effectiveness, patient disposition (discharge, observation, or admission, and the reason), and stroke prophylaxis prescribed in the ED [anticoagulation (coumarin and/or low-molecular-weight heparin) or antiplatelet therapy (aspirin, clopidogrel, or ticlopidine)]. No therapeutic recommendation or specific education about NVAF was done by the study group during data collection. To reduce interobserver variability, the data-collection sheet variables were encoded according to a single table established by the coordinating committee.¹⁷ The following were considered by the study group as factors that contraindicated anticoagulation in the ED: disability, frequent falls, uncontrolled hypertension (>180/100 mm Hg), drug abuse (alcohol or illicit substances), inability to monitor treatment, allergy to anticoagulant therapy, recent major hemorrhage, previous bleeding related to anticoagulants, surgery or severe trauma during the previous three months, or potential high risk of hemorrhage (neoplasm, gastrointestinal, vascular, or genitourinary diseases with a high risk of bleeding, among others).^{3,4,11,12}

Measurements. Four CCSs for predicting the risk of ischemic stroke in patients with NVAF were considered: the Atrial Fibrillation Investigators (AFI),¹¹ the Stroke Prevention in Atrial Fibrillation (SPAF),³ the CHADS₂ index (an acronym for congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack [TIA]) obtained from a synthesis of the two aforementioned schemes,⁴ and the Sixth Consensus on Antithrombotic Therapy of the American College of Chest Physicians (ACCP).¹² A brief summary of the risk factors for stroke and risk stratification provided by these CCSs is listed in Table 1.

Data Analysis. Statistical analysis was done using SAS for Windows statistical software package (version 8.0, SAS Institute, Inc., Chicago, IL). The χ^2 test was used to compare proportions (with $p < 0.05$ considered significant), and the weighted kappa (κ) statistical test¹⁹ was used to determine the degree of concordance in the estimation of the risk of stroke associated with NVAF between the different CCSs. A κ value close to 0 indicates agreement at the level of chance, whereas a κ of 1 is perfect agreement.

RESULTS

During the study period, 1,220 patients with NVAF were included (974 during GEFAUR-1 and 246 during GEFAUR-2), with a mean (\pm SD) age of 75.6 (\pm 11.6)

TABLE 1. Clinical Classification Schemes for Predicting Stroke in Nonvalvular Atrial Fibrillation^{3,4,11,12}

AFI	SPAF	CHADS ₂	ACCP
		Prior stroke/TIA 2	<i>High RF</i> Prior stroke/TIA
		Age >75 years 1	Age >75 years
		Hypertension 1	Hypertension
		Diabetes 1	↓LVF/HF
		Heart failure 1	<i>Moderate RF</i> 65–75 years
		Score 0–6	Diabetes
			CAD
High risk: Prior stroke/TIA Hypertension Diabetes	High risk: Prior stroke/TIA Age >75 years (women) Age >75 years + hypertension sBP >160 mm Hg	High risk: 6, 5, 4	High risk: ≥1 High RF or ≥2 Moderate RFs
Moderate risk: Age >65 years	Moderate risk: Age <75 years + hypertension Diabetes	Moderate risk: 3, 2	Moderate risk: 1 Moderate RF
Low risk: No RF	Low risk: No RF	Low risk: 1, 0	Low risk: No RF

AFI = Atrial Fibrillation Investigators; TIA = transient ischemic attack; SPAF = Stroke Prevention in Atrial Fibrillation; ACCP = American College of Chest Physicians; ↓LVF = reduced left ventricular fraction shortening; HF = heart failure; CAD = coronary artery disease; RF = risk factor; CHADS₂ index = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or TIA.

years, and 684 (56.1%) of them were female. There was no protocol violation of clinical importance in the recruitment: only 14 eligible patients were missed or the data-collection forms were not accurately filled out. In 159 (13%) patients, NVAF was paroxysmal; in 729 (60%), it was persistent or permanent; and 332 (27%) of patients did not have a history of previous episodes of NVAF. Risk factors for stroke in the study population are listed in Table 2. The agreement between the different CCSs in stratifying patients according to high, moderate, and low risk of stroke is shown in Table 3.

Due to their implications for therapy, a comparison was also made of the proportions of patients classified by the different schemes within the low-risk group in which antiplatelets could be an acceptable alternative to anticoagulation (Table 4). The AFI scheme classified 8.3% (101 patients) as at low risk, compared with 20.8% (234) by SPAF, 41.9% (511) by CHADS₂, and 7.5% (91) by ACCP. An excellent agreement was observed in the estimation of risk between AFI and

ACCP ($\kappa = 0.91$), only moderate between AFI and SPAF ($\kappa = 0.45$) and CHADS₂ and SPAF ($\kappa = 0.47$), and fair between AFI and CHADS₂ ($\kappa = 0.22$), SPAF and ACCP ($\kappa = 0.11$) and CHADS₂ and ACCP ($\kappa = 0.03$).

Finally, we also analyzed the prescription of stroke prophylaxis in the ED. Of the 1,220 patients included, 930 patients (76.2%) were not taking anticoagulants when they visited the ED. Anticoagulation was prescribed in the ED to 221 (23.8%) of these patients. Table 5 shows the prescription of anticoagulants in each risk stratum according to the different CCSs. Anticoagulation was equally prescribed for patients with different levels of risk according to the AFI and ACCP schemes, and was more frequently prescribed to patients classified as at low risk by the SPAF ($p = 0.008$) and CHADS₂ ($p < 0.001$) schemes. When analyzing the impact of the type of NVAF in stroke prophylaxis, the emergency physicians prescribed anticoagulants to 56 (35%) patients with paroxysmal and to 132 (18%) patients with persistent/permanent NVAF.

TABLE 2. Risk Factors for Stroke in the Study Population (N = 1,220)

Risk Factor	No. Patients (%)
Age >65 years	1,021 (83.7%)
Age >75 years	682 (55.9%)
Hypertension	738 (60.5%)
Diabetes	277 (22.7%)
↓LVF/HF	265 (21.7%)
CAD	254 (20.8%)
sBP >160 mm Hg	205 (16.8%)
Stroke/TIA	195 (16%)

↓LVF/HF = reduced left ventricular fraction shortening/heart failure; CAD = coronary artery disease; TIA = transient ischemic attack.

DISCUSSION

In our acute setting population, agreement between the four schemes in the classification of patients into groups at risk (high, intermediate, and low) of stroke associated with NVAF is practically nonexistent, with the exception of a moderate agreement between AFI and ACCP ($\kappa = 0.52$). This is a logical consequence of including different risk factors, and with distinct weighting, by the CCSs. Such differences are explained by variations in the prevalence of risk factors for stroke among patients from clinical trials on whom the CCSs are based, and the daily practice population

TABLE 3. Agreement among the Four Schemes in the Stratification of Patients as Being at High, Moderate, and Low Risk for Stroke (N = 1,220)

Classification Scheme ^{3,4,11,12}	Risk of Stroke	Classification Scheme ^{3,4,11,12} No. Patients (%)		
		SPAF	CHADS ₂	ACCP
AFI	Low	89 (7.5%)	95 (8.3%)	86 (7.1%)
	Moderate	0 (0%)	38 (3.3%)	66 (5.5%)
	High	347 (29.3%)	144 (12.6%)	839 (69.7%)
		$\kappa = 0.01$	$\kappa = 0.02$	$\kappa = 0.52$
SPAF	Low		222 (19.6%)	81 (6.8%)
	Moderate		215 (18.9%)	5 (0.4%)
	High		70 (6.2%)	443 (37.4%)
			$\kappa = 0.18$	$\kappa = 0.11$
CHADS ₂	Low			85 (7.5%)
	Moderate			0 (0%)
	High			144 (12.6%)
				$\kappa = 0.03$

AFI = Atrial Fibrillation Investigators; SPAF = Stroke Prevention in Atrial Fibrillation; ACCP = American College of Chest Physicians; CHADS₂ index = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack.

in which the CCSs are applied.^{4,12-16} Thus, ED patients are older, with a higher prevalence of age-related comorbidity (hypertension, diabetes), compared with those included in clinical trials on stroke prophylaxis in NVAF.^{11,20}

When the lack of agreement in the estimation of risk is transferred to clinical practice, and an analysis is made of the classification of patients into two groups, low risk (indication for antiplatelet therapy) and moderate to high risk (eligible for anticoagulation), the disparity in classification means that the number of patients for whom anticoagulation must be prescribed would vary as much as 33% (from 91% [AFI] to 58% [CHADS₂]). Such variation is of clinical relevance because it could have profound effects on the incidence of stroke and bleeding complications, and would lead to substantial differences in the use of resources, particularly anticoagulation clinics. Other studies have also detected relevant differences in the number of patients eligible for anticoagulation using different CCSs in outpatient populations,^{14,15} and in

cohorts of NVAF patients enrolled in clinical trials.^{20,21} More than 90% of this difference is attributable to the different roles played by age and gender as risk factors among the different CCSs.^{14,21} Given that the risk of stroke increases notably with age,²² its inclusion as a risk factor could be a limitation common to all schemes. Its repercussions would be different according to what age is considered the threshold above which the risk of stroke is increased, and could result in the anticoagulation of older patients with NVAF who have a rate of stroke similar to that of age-matched control subjects in sinus rhythm. A recent study demonstrated that, independent of age, patients with NVAF, but without a history of stroke/TIA, treated hypertension, systolic blood pressure ≥ 140 mm Hg, coronary artery disease, or diabetes, have a rate of stroke when receiving prophylaxis with antiplatelet therapy that is comparable to that in a community cohort of the same age.²³ According to these data derived from six clinical studies, 24% of patients with NVAF (16% of those older than 75 years) would have a low risk of stroke and would not benefit from anticoagulation. Patient age can lead by itself to the indication for anticoagulation; therefore, the elimination of age as a risk factor for stroke from CCSs could increase the agreement between them in the estimation of risk, without reducing the effectiveness of stroke prophylaxis. Further prospective investigation is warranted to clarify the role of patients' age as a risk factor for stroke in NVAF.

As in other health care settings, it is important to know physicians' daily practice patterns to facilitate the translation of guidelines' recommendations into effective clinical care.^{4,16} In our study, the prescription of anticoagulation as stroke prophylaxis by the treating physicians was insufficient and did not follow the risk stratification provided by any of the widespread CCSs. Although the efficacy of anticoagulation has been demonstrated in numerous clinical trials,¹¹

TABLE 4. Agreement among the Four Schemes in Stratification of Patients as Eligible for Antiplatelet Therapy (Low Risk of Stroke)

Classification Scheme ^{3,4,11,12}	Classification Scheme ^{3,4,11,12} (No. Patients at Low Risk)		
	SPAF (234)	CHADS ₂ (511)	ACCP (91)
AFI (101)	89 (7.5%)	95 (8.3%)	86 (7.1%)
	$\kappa = 0.45$	$\kappa = 0.22$	$\kappa = 0.91$
SPAF (234)		222 (19.6%)	81 (6.8%)
		$\kappa = 0.47$	$\kappa = 0.11$
CHADS ₂ (511)			85 (7.5%)
			$\kappa = 0.03$

AFI = Atrial Fibrillation Investigators; SPAF = Stroke Prevention in Atrial Fibrillation; ACCP = American College of Chest Physicians; CHADS₂ index = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack.

TABLE 5. Anticoagulation Prescribed by the Treating Physicians and Its Distribution According to the Risk Stratification Provided by the Four Classification Schemes (Patients without Previous Prophylaxis with Anticoagulants: N = 930)

Risk of Stroke	Classification Scheme ^{3,4,11,12}			
	AFI	SPAF	CHADS ₂	ACCP
Low	22/87 (25.3%)	55/214 (25.7%)	116/406 (28.6%)	22/77 (28.6%)
Moderate	54/227 (23.8%)	106/352 (30.1%)	85/403 (21.1%)	20/72 (27.8%)
High	145/616 (23.5%)	60/364 (16.5%)	20/121 (16.5%)	179/781 (22.9%)

Number of patients in whom anticoagulation was prescribed/number of patients in each risk stratum (%). AFI = Atrial Fibrillation Investigators; SPAF = Stroke Prevention in Atrial Fibrillation; ACCP = American College of Chest Physicians; CHADS₂ index = congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack.

various studies have highlighted a low prescription in various daily practice settings such as hospitals,^{24,25} primary care,²⁶ EDs,^{16,27} and geriatric units.²⁸ Thus, in daily practice, anticoagulation is prescribed to only 15–44% of eligible patients,²⁹ consistent with the 24% of prescriptions found in our study.

The decision to prescribe anticoagulants as stroke prophylaxis by the emergency physicians may be controversial, but literature on improving medical treatment supports a multidisciplinary approach to decreasing morbidity and mortality from cardiovascular disease and stroke.²⁷ Additionally, NVAF is the most frequently managed arrhythmia in the ED, and is often the point of first medical attention for patients with symptoms related to the arrhythmia. Finally, our ED population had a high risk of stroke, and considering the devastating consequences of stroke in these patients, stroke prophylaxis must be initiated as soon as possible. Therefore, and according to other authors,²⁷ anticoagulants could be accurately prescribed by emergency physicians in patients with NVAF and high risk of stroke. Patients discharged from the ED should then be sent for cardiology consultation for further workup, whereas control of oral anticoagulation should be performed in the primary care setting.

The deficiency found in adapting the prescription of anticoagulation by the treating physicians to the risk of stroke provided by the CCSs may have various explanations. In some cases, anticoagulation could be prescribed in young patients with persistent NVAF and without risk factors for stroke, with the aim of performing elective cardioversion three to four weeks later, and this might explain the prescription of anticoagulation in patients with low risk of stroke according to the CCSs. Although carefully evaluated by the study group, we could be underestimating contraindications for anticoagulation, and this could contribute to the low prescription of anticoagulants in older patients with high risk of stroke. Other factors that could have an influence in the low prescription of anticoagulation in our study are physicians' distrust in the validity of clinical trials that support these CCSs,³⁰ the uncertainty about whether the CCSs' benefits are applicable to clinical practice,³¹ or their reticence to initiate anticoagulation for older pa-

tients,^{16,27,30,32} despite the available evidence.³³ In addition to this, in some cases, the emergency physicians could be following the recommendations of local clinical practice guides, and the rate of anticoagulation would vary as much as 13% to 100%, depending on the guideline used.³⁴

Finally, the type of NVAF had an impact on the prescription pattern: anticoagulation was more frequently indicated in patients with paroxysmal NVAF than in those with persistent or permanent NVAF. Patients with paroxysmal NVAF usually presented with acute symptoms,¹⁶ and frequently attended the ED for medical attention, so the emergency physicians could be more concerned about its management. However, and despite the limited number of patients with paroxysmal AF included in clinical trials,⁴ anticoagulation has demonstrated an effectiveness on stroke prevention, similar to that of patients with persistent or permanent NVAF.^{12,14} Therefore, and according to the recommendations of all the CCSs tested, it is not the type of NVAF but the presence of risk factors for stroke that should be the deciding factor in whether anticoagulation is indicated.^{3,4,11,12}

LIMITATIONS

Limitations in the GEFAUR studies should be acknowledged. Due to the heterogeneity of the large number of physicians involved, we could not use the physician as the unit of analysis and, therefore, the information about the prescription of anticoagulation in the ED is not complete. In addition, for most of the patients, their cardiologists and/or family physicians do not initiate anticoagulation in the presence of risk factors for stroke. Although carefully evaluated by the study group, we could be underestimating contraindications for anticoagulation. In this way, the limited number of reasons listed for avoiding anticoagulation noted in the data-collection sheet may have prevented us from capturing all the contraindications.

We included patients in whom AF was demonstrated in an ECG performed when the treating physician obtained one during clinical evaluation. Therefore, the prevalence of AF in ED patients could be greater, but we selected this inclusion criterion

with the aim of stating the impact of AF in the ED daily setting.

In a number of cases, the emergency physicians could be following the recommendations of local guidelines different from those studied and, therefore, the prescription of stroke prophylaxis would follow other risk-stratification schemes. Finally, knowledge of the existence of a study protocol and the required completion of a data form could have an impact on the treating physicians. They could be more concerned about this topic, and the number of patients for whom anticoagulation was prescribed might be higher than would normally be seen.

CONCLUSIONS

Clinical classification schemes for predicting stroke in NVAF based on the results of clinical trials differ widely in risk stratification when applied to an acute setting daily practice population. Therefore, the proportion of patients eligible for anticoagulation would have relevant differences depending on the CCS followed, and this could have profound effects on the incidence of stroke and hemorrhagic complications, and in the use of resources. An effort to homogenize the risk of stroke stratification provided for the CCSs appears warranted (selecting the most appropriate one to the acute setting population or validating a new scheme) to help improve the suitability of stroke prophylaxis in ED patients with NVAF.

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• APPENDIX A

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