Long-Term Predictors of Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Undergoing Electrical Cardioversion

Amaya García-Fernández, MD, PhD; Francisco Marín, MD, PhD; Vanessa Roldán, MD, PhD; José M Gómez-Sansano, MD; Diana Hernández-Romero, MD, PhD; Mariano Valdés, MD, PhD; Juan G Martínez-Martínez, MD; Francisco Sogorb-Garri, MD, PhD; Gregory YH Lip, MD

Background: Patients with nonvalvular atrial fibrillation (AF) who undergo electrical cardioversion (ECV) tend to be younger and have less comorbidity. Long-term anticoagulation after ECV should be based on thromboembolic risk. We sought to study the long-term incidence of thromboembolic events (TE), factors related to TE and compare the predictive value of the CHADS₂ and CHA₂DS₂-VASc scores in this particular population.

Methods and Results: From January 2008 to June 2012, 571 ECV were performed in 406 consecutive patients with nonvalvular AF. Risk factors for TE and factors related to anticoagulation therapy after ECV were registered. During a follow-up of approximately 2 years, the annual incidence of TE was 1.9%. Factors associated with TE were: poor quality anticoagulation control (hazard ratio [HR]: 2.91; 95% confidence interval [CI]: 1.10–7.80; P=0.03), cessation of anticoagulation after ECV (HR: 8.80; 95% CI: 3.11–25.10; P<0.001), age ≥65 years (HR: 13.65; 95% CI: 1.74–107.16; P=0.01), CHADS₂ score (HR: 1.59; 95% CI: 1.10–2.29; P=0.01) and CHA₂DS₂-VASc score (HR: 1.67; 95% CI: 1.30–2.22; P<0.001). Both risk scores predicted TE [c-statistic for CHADS₂: 0.68 (95% CI: 0.62–0.74; P=0.005), for CHA₂DS₂-VASc: 0.75 (95% CI: 0.70–0.80; P<0.001)]. Based on c-statistics, the predictive accuracy of CHA₂DS₂-VASc was superior (difference between areas: 0.064±0.031; P=0.0403).

Conclusions: Important determinants of long-term occurrence of TE after ECV were related to anticoagulant therapy (poor quality anticoagulation and cessation of this therapy over follow-up). The CHA₂DS₂-VASc score successfully predicts TE after ECV, having better predictive accuracy than the CHADS₂ score. (*Circ J* 2016; **80**: 605–612)

Key Words: Anticoagulants; Atrial fibrillation; Cardioversion; Risk factors; Thromboembolism

Nonvalvular atrial fibrillation (AF) confers a 5-fold increase in thromboembolic risk.¹ The risk of stroke and other thromboembolic events (TE) is not homogeneous and depends on the presence of underlying clinical conditions that have been grouped together in different risk stratification schemes.² Of these, the CHADS₂ score is simple,³ but has some limitations that have been extensively discussed.² The CHA₂DS₂-VASc score⁴ is better at identifying “truly low risk” patients,⁵ and is now the recommended scheme to guide anticoagulation.^{6–9} We have recently shown that CHA₂DS₂-VASc successfully predicts cardiovascular events

and mortality even among AF individuals on oral anticoagulation.¹⁰

For many years, electrical cardioversion (ECV) has been commonly used to restore sinus rhythm in AF.¹¹ However, nearly half of the patients have AF recurrence in the first months after the procedure.¹² Guidelines recommend long-term anticoagulation, regardless of procedural success after cardioversion, depending on thromboembolic risk,^{6,7} based on trials comparing rate vs. rhythm-control strategies where discontinuation of anticoagulant therapy with the rhythm-control strategy was associated with more TE.^{13,14} We have recently

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Arrhythmia Unit, Department of Cardiology, General University Hospital of Alicante, Alicante (A.G.-F., J.M.G.-S., J.G.M.-M., F.S.-G.), Spain; Department of Cardiology, Virgen de la Arrixaca General Hospital, Murcia University, Virgen de la Arrixaca Biosanitary Investigation Institute, IMIB-Arrixaca, Murcia (F.M., D.H.-R., M.V.), Spain; Hematology and Medical Oncology Unit, Morales Meseguer University Hospital, Murcia University, Virgen de la Arrixaca Biosanitary Investigation Institute, IMIB-Arrixaca, Murcia (V.R.), Spain; and University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham (G.Y.H.L.), UK

Mailing address: Francisco Marín, MD, PhD, Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, Ctra Madrid-Cartagena s/n, 30120, Murcia, Spain. E-mail: fcomarino@hotmail.com

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demonstrated that cessation of vitamin K antagonists (VKA) independently increases the risk of stroke in AF patients, even after adjusting for CHA₂DS₂-VASc score.¹⁵ On the other hand, in individuals who receive anticoagulant therapy with VKA, suboptimal anticoagulation is associated with poor outcomes and only patients who achieve a high proportion of time in the therapeutic range (TTR) show a significant reduction in the incidence of stroke.^{16,17}

Among AF patients, those who undergo a rhythm-control strategy tend to be younger, have less comorbidities and a lower incidence of thromboembolic risk factors.^{18,19}

The aims of the present study were first, to analyze the incidence of long-term thromboembolic complications after cardioversion and its relation to individual thromboembolic risk factors, cessation of oral anticoagulation and quality of anticoagulation control. Second, we tested the use of CHADS₂ and CHA₂DS₂-VASc thromboembolic risk schemes in the prediction of long-term TE in patients undergoing ECV.

Methods

Study Patients

Using an observational design, we recruited consecutive patients with persistent, nonvalvular AF who underwent one or more programmed ECV between January 2008 and June 2012 in a university hospital in Spain. Persistent AF was defined as AF lasting >7 days or requiring cardioversion for termination, and nonvalvular AF as the exclusion of rheumatic valve disease, severe valve disease, prosthetic valve or mitral valve repair surgery.

Data Collection

Data on clinical characteristics, risk factors for TE and anti-thrombotic drug treatment before ECV were obtained from the hospital medical records.

Patient Characteristics and Risk of TE

We defined lone AF as the absence of heart disease, hypertension, diabetes mellitus, pulmonary, renal or thyroid disease and those situations that could precipitate the arrhythmia, such as surgery or alcohol consumption. Hypercholesterolemia was defined as low-density lipoprotein cholesterol >130 mg/dl or actual lipid-lowering therapy. Patients with asthma, chronic obstructive pulmonary disease or obstructive sleep apnea were classified as having pulmonary disease. Thyroid disease was defined as hypo- or hyperthyroidism or treatment for either pathology. We defined severe renal disease as patients on dialysis or who had undergone renal transplant or had creatinine >200 µmol/L. For the other risk factors, included in thromboembolic risk scores, standard definitions of the different risk factors were used, as previously described,^{3,4} and the CHADS₂ and CHA₂DS₂-VASc scores at the time of ECV were calculated for every patient.

ECV and Anticoagulation Therapy Before Cardioversion

ECV was performed using a biphasic defibrillator (Medtronic Lifepak 20). The procedure was considered successful when sinus rhythm was achieved and maintained until discharge (2–3 h after ECV). Following actual recommendations²⁰ for patients on VKA, when arrhythmia duration was >48 h, international normalized ratio (INR) >2 was required in the previous 3 weeks; otherwise transesophageal echocardiography (TEE) was performed to exclude left atrial thrombus. Patients with left atrial thrombus did not enter the study, as ECV could not be performed. No anticoagulation therapy or TEE was

required before the ECV when the arrhythmia duration was <48 h. Patients on different types of anticoagulant treatment were included. Unlike other countries, acenocoumarol is the most widely used VKA in Spain and most of the subjects received this therapy. Acenocoumarol is a VKA that is used mainly in Mediterranean countries. It differs from warfarin in its shorter half-life (10 vs. 36 h), theoretically providing less stable anticoagulation. However, in studies comparing acenocoumarol and warfarin, the percentage of INRs within the therapeutic range was not shown to be better with warfarin than with acenocoumarol.^{21,22}

As non-VKA oral anticoagulants (NOACs) were first approved in Spain in 2011, only a small number of individuals were receiving these drugs when this study was conducted.

Follow-up and Adverse Events

In our region, all citizens have a personal identification number that enables healthcare professionals to consult data about all hospital admissions, visits to the outpatient clinic, deaths, as well as data about medical prescriptions and other clinical information related to the patient. Stroke and other thromboembolic complications, major bleeding episodes, AF recurrence (confirmed by a physician) and changes in antithrombotic treatment after ECV were recorded. Follow-up ended on June 2013.

TE were classified as central nervous system (CNS) or non-CNS embolic events. Ischemic stroke was defined as a sudden (minutes to hours), focal neurologic deficit in a cerebral artery territory lasting >24 h, caused by ischemia and diagnosed by a neurologist (brain imaging with CT scan or MRI was encouraged). If the duration was <24 h, it was considered a transient ischemic attack. Non-CNS embolisms comprised peripheral and embolisms of other locations outside the brain. Peripheral embolism was defined as arterial thromboembolism outside the brain, heart, eyes and lungs, documented by imaging or surgery. We considered a TE event to be related to ECV when it occurred in the first 30 days after the procedure. For major bleeding, we followed the definition of the International Society of Thrombosis and Haemostasis.²³

For the patients who received VKA, data about INR control after the ECV were collected. TTR was calculated as the percentage of tests in the therapeutic range (INR: 2.0–3.0) over the total number of tests. Controls over a maintenance period of at least 6 months were required and measurements taken during the first 6 weeks of treatment were excluded. TTR <60% was considered poor anticoagulation quality (labile INR).

Statistical Analysis

Categorical variables are expressed as percentages. Quantitative variables are expressed as mean ± standard deviation or as median (interquartile range), depending on distribution being normal or not. Kolmogorov-Smirnov test was used to analyze the normal distribution of continuous variables. In order to assess the association between the different individual risk factors and other clinical variables and the incidence of TE events, univariate Cox-regression models and a multivariate model to adjust the factors for each other were fitted. The effect of the CHADS₂ and CHA₂DS₂-VASc scores was evaluated separately, one at a time, with a Cox-regression model, which included anticoagulation variables (cessation or poor quality). The hazard ratio (HR) was obtained from the Cox-regression analysis, corresponding to the estimated increment of risk for each 1 point increment in the score. Kaplan-Meier survival curves were constructed to display the time-to-event relationship comparing groups with and without risk factors. Log-rank tests were used to assess the differences between

both groups. The ability of the CHADS₂ and CHA₂DS₂-VASc schemes to predict thromboembolism was calculated with the area under receiver operating characteristic (ROC) curve and the c-statistic. The c-statistic gives a measure of how well a risk prediction scheme identifies individuals who will have an event in the future, while the HR quantifies the increment of risk in the different strata of the stratification schemes. To compare the ability to predict TE of the 2 scores, we calculated the statistical significance of the difference between the areas under the 2 ROC curves with the method of DeLong et al.²⁴ A P-value <0.05 was considered significant. The analyses were performed using the program SPSS 20.0 for Windows (SPSS, Inc, Chicago, IL, USA) and the MedCalc statistical software for Windows (Version 14.8.1).

Ethical Issues

This study was approved by the Ethical Committee of Alicante University Hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients gave their informed consent prior to their inclusion in the study.

Results

Baseline Characteristics

During the inclusion period, 571 ECV were performed in 406 AF patients. Baseline characteristics of the patients are shown in Table 1. Median CHADS₂ score was 2 (1–2) and median CHA₂DS₂-VASc score was 3 (2–4). In 96.0% (548 procedures), patients received anticoagulant therapy before the procedure: acenocoumarol in 509 (92.9%); dabigatran in 25 (4.5%); warfarin in 12 (2.2%), and low-molecular-weight heparin in 1 (0.2%). The other 23 episodes of ECV (4.0%) were performed in patients who had not received anticoagulants pre-procedure; in 18 (78.2%) patients, the arrhythmia duration was <48 h, and in 5 (21.8%) TEE was performed, excluding the presence of left atrial thrombus, because the duration was >48 h or unknown. ECV was successful in 87.0% (495 procedures) and after 668 (293–1,186) days follow-up, AF recurred after 399 ECV (80.6%).

Post-Cardioversion Quality of Anticoagulation and Anticoagulation Withdrawal

After 99.3% of the procedures, anticoagulation therapy was continued or initiated. In 0.7% of cases, the responsible physician did not prescribe anticoagulation after ECV because the arrhythmia duration was <48 h and the patients had no risk factors. Data on INR control during follow-up was available after 542 procedures (386 patients). Of these, the percentage of TTR was <60% in 159 patients (41.2%). Median TTR was 60% (50–68%). NOACs (ie, dabigatran or rivaroxaban) were used at some time during follow-up in 15.1% of the patients.

Over the follow-up period, anticoagulant therapy was stopped after ECV in 59 patients (14.6%). Median CHADS₂ and CHA₂DS₂-VASc scores in those patients were 1 (0–3) and 2 (1–4), respectively. Of these, in most cases the reason for cessation of oral anticoagulation was cited as a return to sinus rhythm (39 patients; 62.0%). Median time to anticoagulation withdrawal was 368 (202–367) days. Distribution of CHADS₂ score in patients with anticoagulation withdrawal was as follows: 0 points: 17 patients (28.8%); 1 point: 22 patients (37.3%); ≥2 points: 20 patients (33.9%). Distribution of CHA₂DS₂-VASc score in these individuals was: 0 points in 12 patients (20.3%); 1 point in 16 patients (27.1%, 13 males); ≥2 points in 31 patients (52.7%).

Table 1. Baseline Characteristics of the 406 Spanish Patients With Nonvalvular AF Who Underwent ECV

	Median ± SD, n (%)
Age (years)	66.9 ± 10.9
Sex (male)	281 (69.2)
Previous ECV	62 (15.3)
Lone AF	37 (9.1)
Hypertension	324 (80.0)
Heart failure	110 (27.2)
Diabetes mellitus	117 (28.9)
Previous embolism	23 (5.7)
Vascular disease	90 (22.2)
Actual or previous tobacco use	186 (51.0)
Hypercholesterolemia	273 (68.3)
Pulmonary disease	118 (29.1)
Thyroid disease	41 (10.1)
Severe renal disease	20 (4.9)
Use of antiarrhythmic agents	124 (30.8)
Use of antiplatelet agents	74 (18.5)
CHADS ₂ score*	
Low risk	54 (13.3)
Moderate/intermediate risk	140 (34.6)
High risk	212 (52.1)
CHA ₂ DS ₂ -VASc score**	
Low risk	35 (8.6)
Moderate/intermediate risk	60 (14.8)
High risk	311 (76.6)
HAS-BLED score***	2 (1–3)
Low risk	214 (55.8)
High risk	170 (44.2)

CHADS₂: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack. CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female. HAS-BLED: hypertension (1 point), abnormal renal/liver function (1 point each), previous stroke (1 point), previous bleeding/predisposition (1 point), labile INR (1 point), age ≥65 (1 point), concomitant drugs or alcohol abuse (1 point each). *Low risk: 0 points; moderate/intermediate risk: 1 point; high risk: ≥2 points. **Low risk: males with 0 points, females with 1 point; moderate/intermediate risk: males with 1 point; high risk: ≥2 points. ***Low risk: 0–2 points; high risk: ≥3 points. AF, atrial fibrillation; ECV, electrical cardioversion.

Adverse Events

Median follow-up was 668 (293–1,186) days, during which lost to follow-up occurred after 42 procedures (7.4%). TE events occurred after 20 ECV procedures, amounting to an incidence of 1.9 per 100 patient-years. Mean age of the patients who experienced TE was 73.7 ± 13.0 years, most being males (n=12, 60%). Median time to first TE was 746 (149–1,180) days. The occurrence of first TE ranged between 2 and 1,463 days after ECV (Figure 1). Only one TE was considered to be related to the procedure, occurring 48 h after ECV (incidence of TE in the first 30 days after ECV was 0.17%); 7 TE occurred in the first year after ECV (after the first month) and most TE (n=13) occurred more than 1 year after the procedure.

All patients (n=20, 100.0%) who sustained TE had received acenocoumarol after the ECV. Of these patients, anticoagulation had been interrupted at a variable time during follow-up in 8 (36.4%) (median time from ECV to withdrawal: 445

Table 2. Distribution of Thromboembolic Events Among 406 Spanish Patients With Nonvalvular AF Who Underwent ECV	
Distribution of thromboembolic events	n (%)
Central nervous system	25 (96.1)
Stroke	18 (69.2)
Transient ischemic attack	7 (26.9)
Peripheral (femoral artery)	1 (3.8)

Abbreviations as in Table 1.

(128–711) days); median time from withdrawal to TE was 199 (74–700) days). In all of them the anticoagulation therapy had been withdrawn because of the presence of sinus rhythm. Additionally, in 2 of these patients the responsible physician considered other reasons (apart from sinus rhythm) for stopping VKA (1 patient had had a minor hemorrhage and another had “associated comorbidities”). In all these individuals, anticoagulation was reinitiated after TE. All the patients who stopped anticoagulants and experienced stroke or TE were high-risk patients (CHA₂DS₂-VASc score ≥2). None of the individuals with low or moderate thromboembolic risk (CHA₂DS₂-VASc score 0 or 1) in whom acenocoumarol was withdrawn experienced TE.

Of the 20 procedures after which TE happened, 4 were followed by more than 1 TE episode, making a total of 26 TE. The distribution of the 26 embolisms is shown in Table 2. Annual rate of cerebrovascular accident was 1.8%. Of the 26 embolisms, 2 were fatal, thus the mortality of TE was 7.7%. During most of the embolic episodes (n=23; 88.4%) the rhythm present was AF; at the time of hospital admission, 2 patients (7.7%) were in sinus rhythm and in 1 case (3.8%) the rhythm was not registered. The annual incidence of major bleeding was 2.0% (21 patients) and intracranial bleeding, 0.5% (5 patients).

Predictors of TE

In the multivariate analysis, independent predictors of TE were poor percentage of TTR (HR: 2.91; 95% confidence

interval [CI]: 1.10–7.80; P=0.03), cessation of oral anticoagulation during follow-up (HR: 8.80; 95% CI: 3.11–25.10; P<0.001), age ≥65 years (HR: 13.65; 95% CI: 1.74–107.16; P=0.01), CHADS₂ score (HR: 1.59; 95% CI: 1.10–2.29; P=0.01) and CHA₂DS₂-VASc score (HR: 1.67; 95% CI: 1.30–2.22; P<0.001) (Table 3). Although vascular and renal disease were associated with TE in the univariate analysis, these factors were not independent determinants in multivariate analysis. Other risk factors studied (heart failure, hypertension, diabetes, sex, previous embolism, tobacco use, hypercholesterolemia, severe renal disease, ECV success and use of antiarrhythmic or antiplatelet agents) were not independently associated with the incidence of TE in the patients studied, as shown in Table 3. Figure 2 shows the Kaplan-Meier survival curves comparing the incidence of TE in patients with good vs. poor anticoagulation control. The comparison of TE-free survival curves depending on VKA cessation is shown in Figure 3. As only high-risk patients who stopped anticoagulation experienced TE, the difference was higher among these individuals (Figure 3B).

The incidence of embolic complications increased with increasing CHADS₂ and CHA₂DS₂-VASc scores (Table 4). Those patients classified as being at “low risk” (score of 0 on CHADS₂ and score of 0 for males or score of one for females on CHA₂DS₂-VASc) had no events during follow-up. For individuals classified as moderate risk based on CHADS₂ (score of 1), the annual incidence of TE was 1.5%; for those classified as moderate risk with CHA₂DS₂-VASc (males with 1 point) this incidence was 0%. When the CHA₂DS₂-VASc score was used, all TE occurred in high-risk patients, but when the CHADS₂ was used, 25% of the embolisms occurred in the group of moderate-risk individuals (5/20 patients with TE were reclassified from the moderate to the high-risk category by CHA₂DS₂-VASc score).

On ROC curve analysis, both risk scores (CHADS₂ and CHA₂DS₂-VASc) were predictive for thromboembolic outcomes, with a c-statistic of 0.68 (95% CI: 0.62–0.74; P=0.005) for CHADS₂ score and 0.75 (95% CI: 0.70–0.80; P<0.001) for CHA₂DS₂-VASc. The predictive accuracy of CHA₂DS₂-VASc was significantly better than that of CHADS₂ (difference between areas 0.064±0.031; P=0.0403).

Table 3. Cox-Regression Analysis for Thromboembolic Events Among 406 Spanish Patients With Nonvalvular AF Who Underwent ECV

Risk factor	No. of patients with TE/no. of patients in risk category	Univariate analysis	Multivariate analysis
		HR (95% CI); P value	HR (95% CI); P value
Age ≥ 65 years	19/244	13.69 (1.83–102.29); 0.01	13.65 (1.74–107.16); 0.01
Male sex	12/281	1.53 (0.62–3.74); 0.35	
Hypertension	19/324	4.37 (0.58–32.65); 0.15	
Heart failure	8/110	1.65 (0.68–4.05); 0.27	
Diabetes mellitus	9/117	2.10 (0.87–5.07); 0.10	
Previous embolism	2/23	2.17 (0.50–9.42); 0.30	
Vascular disease	9/90	2.92 (1.21–7.06); 0.02	2.17 (0.80–5.92); 0.13
Tobacco use	2/186	0.81 (0.32–2.01); 0.64	
Hypercholesterolemia	11/173	0.49 (0.20–1.19); 0.12	
Severe renal disease	3/20	3.54 (1.03–12.09); 0.04	0.35 (0.07–1.75); 0.20
ECV success	18/351	1.16 (0.27–5.00); 0.84	
Labile INR*	14/159	3.30 (1.27–8.59); 0.01	2.91 (1.10–7.80); 0.03
Cessation of anticoagulation during follow-up	8/59	4.71 (1.93–11.54); 0.001	8.80 (3.11–25.10); <0.001
Use of antiarrhythmic agents	5/124	0.49 (0.18–1.34); 0.17	
Use of antiplatelet agents	5/74	1.51 (0.54–4.20); 0.43	
CHADS ₂ score**		1.77 (1.24–2.53); 0.002	1.59 (1.10–2.29); 0.01
CHA ₂ DS ₂ -VASc score**		1.72 (1.31–2.25); <0.001	1.67 (1.30–2.22); <0.001

*Labile INR: percentage of tests in therapeutic range (2–3) over total number of tests <60%. **Effect of the CHADS₂ and CHA₂DS₂-VASc scores was evaluated separately, one at a time, with a Cox-regression model. CHADS₂: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack. CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female. INR, international normalized ratio; TE: thromboembolism. Other abbreviations as in Table 1.

Figure 2. Kaplan-Meier curves for the incidence of thromboembolism, comparing patients with good and poor quality of anticoagulation control.

Discussion

We have shown that in patients with nonvalvular AF who undergo ECV (the great majority of them under oral anticoagulation), the periprocedural embolic incidence is very low (annual incidence of stroke or other TE $\approx 2\%$). Second, important determinants of long-term occurrence of TE after ECV

are related to anticoagulant therapy (quality of anticoagulation or cessation of this therapy during follow-up). Third, we found that TE risks are related to the CHA₂DS₂-VASc score, which is superior to the CHADS₂ score.

Incidence of TE

The rate of periprocedural TE (first 30 days) in the population

Table 4. Annual Incidence of TE Depending on CHADS₂ and CHA₂DS₂-VASc Scores Among 406 Spanish Patients With Nonvalvular AF Who Underwent ECV

Risk category	Annual incidence (%)	No. of thromboembolic events	No. of patients in category
CHADS₂ score*			
Low	0	0	76
Moderate/intermediate	1.5	5	198
High	2.7	15	295
CHA₂DS₂-VASc score**			
Low	0	0	49
Moderate/intermediate	0	0	88
High	2.5	20	432

CHADS₂: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack. CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female. *Low risk: 0 points; moderate/intermediate risk: 1 point; high risk: ≥2 points. **Low risk: males with 0 points, females with 1 point; moderate/intermediate risk: males with 1 point; high risk: ≥2 points. Abbreviations as in Tables 1,3.

analyzed is in accordance with contemporary studies, such as the X-VerT study²⁵ in which the incidence of ischemic stroke after ECV was 0% in the group receiving rivaroxaban and 0.4% in the warfarin group. Long-term incidence of stroke and TE in the present patients was approximately 2% per year, even if most of them continued receiving anticoagulation therapy after the procedure. All but one of the events occurred more than 1 month after the ECV; moreover, most of them occurred after more than 1 year of the procedure, suggesting that the incidence of TE depends on individual risk, having nothing to do with the cardioversion itself. Indeed, in a study with the goal of analyzing recurrence rates after ECV, Toso et al²⁶ found an incidence of symptomatic embolism of 2.7% in a mean follow-up of 44 months. Lower rates of embolism in that study may be explained by the greater proportion of long-term sinus rhythm maintenance and because only patients with CHA₂DS₂-VASc score <2 had oral anticoagulation replaced with aspirin or interrupted anticoagulant treatment. Similar to our data, a Danish retrospective study of more than 16,000 patients discharged after ECV of AF, reported a TE incidence within 360 days of 1.8 per 100 patient-years in the group of patients who received anticoagulation before ECV, compared with 3.2 per 100 patient-years in non-anticoagulated individuals.²⁷ Nonetheless, data about the long-term incidence of stroke and other TE events after ECV are scarce, and most of the information comes from studies in which a rhythm-control strategy was not scheduled.²⁸

Predictors of Stroke and Other TE

In AF individuals receiving anticoagulation, the rate of TE complications is associated with the quality of anticoagulation control²⁹ and withdrawal of this therapy is a risk factor for cardiovascular events and mortality.¹⁵ Of note, important long-term predictors of stroke and TE in our (specific) population of individuals who underwent ECV were a poor percentage of TTR and withdrawal of anticoagulation during follow-up.

For patients on VKA, the importance of the TTR is clearly highlighted,^{16,30} and the INR should be tightly controlled, preferably with TTR >70%, to ensure best efficacy and safety of VKA therapy.^{31,32} Current European Guidelines recommend that AF patients with stroke risk factors should receive effective stroke preventive therapy, either with a VKA (provided TTR >70% is achieved) or with a NOAC.⁶ In fact, the present patients who had poor quality anticoagulation had a 3-fold greater probability of TE. To predict which AF patients are likely to do well on VKA (good average TTR), Apostolakis et al recently proposed and validated the SAME-TT₂R₂ score,³³ which includes factors such as female sex, young age, medical conditions, rhythm-control strategy, tobacco use and race as predictors of poor anticoagulation control. We have also validated the SAME-TT₂R₂ score in a Spanish cohort of patients on acenocoumarol, showing that a high score translates into poorer quality of anticoagulation, with higher incidence of cardiovascular events, bleeding and mortality.²⁹

We also found that cessation of anticoagulation during follow-up was another important predictor of the occurrence of TE, conferring a 9-fold higher risk. We have not been able to determine the cause of anticoagulation withdrawal in all the patients, but we know that the majority were in sinus rhythm and had not had any complication related to this therapy. Among patients in whom anticoagulation was stopped, only approximately 20% had low TE risk (CHA₂DS₂-VASc score of 0), nearly 30% of them had a score of 1, and more than half of the individuals had a CHA₂DS₂-VASc score ≥2. Our study shows that anticoagulation withdrawal long-term after ECV

seems to be safe in individuals with low or moderate thromboembolic risk (CHA₂DS₂-VASc score of 0 or 1), as none of these patients experienced TE, thus we can recommend discontinuation of this therapy in this particular group of patients. Nevertheless, the incidence of TE in high-risk individuals who discontinued VKA was significant (8/31). It is likely that many of the clinicians stopped anticoagulation because sinus rhythm was present, even if the CHA₂DS₂-VASc score pointed to a high risk of TE, and international guidelines recommend the continuation of anticoagulation after ECV in patients at risk, independent of ECV success.^{6,7} Recently, we demonstrated in a population of over 500 nonvalvular AF individuals that anticoagulant therapy is stopped in more than 20% of patients, and the main cause of discontinuation is a return to sinus rhythm. Importantly, anticoagulation cessation is independently associated with increasing incidence of cardiovascular events, especially stroke and mortality.¹⁵ Thus, withdrawal of oral anticoagulation after cardioversion in patients with high thromboembolic risk (CHA₂DS₂-VASc >1) should be strongly discouraged, independent of the rhythm present.

Predictive Value of the CHADS₂ and CHA₂DS₂-VASc Scores

To our knowledge, the ability of the CHADS₂ and CHA₂DS₂-VASc scores to predict long-term TE has not been previously validated in the particular population of AF individuals who undergo cardioversion (which are usually younger and have less comorbidities).^{18,19} We have confirmed that even if both scores can predict TE after ECV, the CHA₂DS₂-VASc score has better predictive accuracy than CHADS₂ in the assessment of long-term TE risk. This risk increased almost 70% for each increment in 1 point in the CHA₂DS₂-VASc score. Olesen et al observed that in AF patients with CHADS₂ score of 0 or 1 (low or moderate risk) the TE risk was still appreciable, whereas patients with CHA₂DS₂-VASc score of 1 had lower risk, and those with CHA₂DS₂-VASc score of 0 were “truly low risk”.³⁴ Even if the initial aim of the CHA₂DS₂-VASc score was to guide the decision about anticoagulation, this score can also be applied to patients taking oral anticoagulation;¹⁰ indeed, its discriminative capacity is independent of anticoagulation status.³⁵

Study Limitations

Our study is limited by its single-center cohort and observational design. Nonetheless, it reflects a real-world situation and the results shown may be generalizable to nonvalvular AF patients who undergo ECV. However, and even if it reports extensive and reliable data, some of the information may have been missed and residual confounding remains a possibility. Because we only included programmed ECV, only patients with persistent AF (lasting >7 days or requiring ECV for termination) participated in the study, those with paroxysmal AF were excluded. Even if the number of TE is relatively low, it is in accordance with that of previous studies, and for this reason, we are quite sure that practically all the embolic complications could be registered. The majority of patients received acenocoumarol, a VKA that is most commonly used in Spain. Even if this VKA is believed to lead to less stable anticoagulation, studies comparing acenocoumarol and warfarin showed similar TTRs for both agents.^{21,22}

Conclusions

Important determinants of the long-term occurrence of TE after ECV were related to anticoagulant therapy (poor quality anticoagulation or cessation of this therapy during follow-up).

The CHA₂DS₂-VASc score successfully predicted TE after ECV, having better predictive accuracy than the CHADS₂ score.

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Disclosures

None.

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