Periprocedural Stroke and Management of Major Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation

The Impact of Periprocedural Therapeutic International Normalized Ratio

Luigi Di Biase, MD; J. David Burkhardt, MD; Prasant Mohanty, MBBS, MPH; Javier Sanchez, MD;
Rodney Horton, MD; G. Joseph Gallinghouse, MD; Dhanunjay Lakkireddy, MD; Atul Verma, MD;
Yaariv Khaykin, MD; Richard Hongo, MD; Steven Hao, MD; Salwa Beheiry, RN;
Gemma Pelargonio, MD; Antonio Dello Russo, MD; Michela Casella, MD; Pietro Santarelli, MD;
Pasquale Santangeli, MD; Paul Wang, MD; Amin Al-Ahmad, MD; Dimpi Patel, DO;
Sakis Themistoclakis, MD; Aldo Bonso, MD; Antonio Rossillo, MD; Andrea Corrado, MD;
Antonio Raviele, MD; Jennifer E. Cummings, MD; Robert A. Schweikert, MD;
William R. Lewis, MD; Andrea Natale, MD, FHRS, FACC

Background—Catheter ablation of atrial fibrillation is associated with the potential risk of periprocedural stroke, which can range between 1% and 5%. We developed a prospective database to evaluate the prevalence of stroke over time and to assess whether the periprocedural anticoagulation strategy and use of open irrigation ablation catheter have resulted in a reduction of this complication.

Methods and Results—We collected data from 9 centers performing the same ablation procedure with the same anticoagulation protocol. We divided the patients into 3 groups: ablation with an 8-mm catheter off warfarin (group 1), ablation with an open irrigated catheter off warfarin (group 2), and ablation with an open irrigated catheter on warfarin (group 3). Outcome data on stroke/transient ischemic attack and bleeding complications during and early after the procedures were collected. Of 6454 consecutive patients in the study, 2488 were in group 1, 1348 were in group 2, and 2618 were in group 3. Periprocedural stroke/transient ischemic attack occurred in 27 patients (1.1%) in group 1 and 12 patients (0.9%) in group 2. Despite a higher prevalence of nonparoxysmal atrial fibrillation and more patients with CHADS2 (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score >2, no stroke/transient ischemic attack was reported in group 3. Complications among groups 1, 2, and 3, including major bleeding (10 [0.4%], 11 [0.8%], and 10 [0.4%], respectively; *P*>0.05) and pericardial effusion (11 [0.4%], 11 [0.8%], and 12 [0.5%]; *P*>0.05), were equally distributed.

Conclusion—The combination of an open irrigation ablation catheter and periprocedural therapeutic anticoagulation with warfarin may reduce the risk of periprocedural stroke without increasing the risk of pericardial effusion or other bleeding complications. (*Circulation*. 2010;121:2550-2556.)

Key Words: atrial fibrillation ■ catheter ablation ■ embolism ■ stroke ■ transient ischemic attack ■ warfarin

Percutaneous radiofrequency catheter ablation (RFCA) is an effective strategy for the treatment of symptomatic drug-refractory atrial fibrillation (AF).[1–3] The "invasive" nature of the procedure and its complexity expose patients to a considerable number of potential complications.[4–9] Ablation strategies, ablation catheters, and periprocedural antico-

agulation management have evolved over time to increase the success rate of the procedures and to reduce complications.[10,11] Nevertheless, periprocedural thromboembolic and hemorrhagic events remain an insidious complication of this procedure.[4–9] Management of anticoagulation before and after RFCA could be important for the prevention of these

complications. The incidence of thromboembolic events varies from 1% to 5%, depending on the ablation and the anticoagulation strategy used in the periprocedural period.[4–9] At present, the optimal anticoagulation management that minimizes thromboembolism while not increasing hemorrhagic complications is not well established.[1,2,3,12–15] Discontinuation of warfarin 3 to 5 days before ablation, use of heparin or enoxaparin before the procedures, and "bridging" low-molecular-weight heparin with warfarin after ablation is the most frequently used protocol.[2,3] Recently, RFCA of AF without discontinuation of warfarin[16,17] at the time of the procedure has been proposed with satisfactory results. The aim of our study was to compare the incidence of periprocedural stroke and bleeding complications with different anticoagulation protocols at the time of the procedures and with different ablation catheters used over time.

<div align="center">

Clinical Perspective on p 2556

</div>

Methods

Between January 2002 and January 2009, data related to stroke and bleeding after RFCA procedures were prospectively collected from 9 centers performing the same ablation procedure with the same anticoagulation protocol over the study period. On the basis of the ablation catheter and the anticoagulation protocol used at the time of the procedure, we divided the study population into 3 groups: patients undergoing RFCA with an 8-mm catheter with warfarin discontinuation at the time of the procedure (group 1), patients undergoing RFCA with a 3.5-mm open irrigated catheter with warfarin discontinuation at the time of the procedure (group 2), and patients undergoing RFCA with a 3.5-mm open irrigated catheter without warfarin discontinuation at the time of the procedure (group 3).[10,15]

All patients included in group 3 had to show a "therapeutic" international normalized ratio (INR) the day of the procedure to meet the inclusion criteria. All patients signed informed written consent to participate in the study. The study was approved by the institutional review board.

Electrophysiological Study

Four venous accesses were obtained in each patient. The right groin accesses were used for transseptal catheterization. A double transseptal access was obtained via 2 separate puncture sites. A 20-mm decapolar circular mapping catheter was used for mapping (Lasso, Biosense-Webster, Baldwin Park, Calif); for ablation, an 8-mm-tip catheter (Celsius, Biosense-Webster) was used in group 1 and a 3.5-mm open irrigated-tip ablation catheter (Biosense-Webster) was used in groups 2 and 3.

A single left femoral 11F venous access was used to guide a 10F 64-element phased-array ultrasound imaging catheter (Acunav, Acuson, Mountain View, Calif) in the right atrium.[10,11,18] A single venous access in the right internal jugular vein was used to place a 14- to 20-pole catheter; the distal 7 to 10 poles were positioned in the coronary sinus along the mitral annulus, and the proximal 7 to 10 poles were placed along the crista terminalis.

During the procedures, patients were anticoagulated with intravenous heparin with a bolus of 15 000 U in groups 1 and 2 and 10 000 U in group 3 just before the transseptal puncture. Then in groups 1 and 2, a continuous 1000-U/h infusion of heparin was started. The infusion was adjusted to maintain an activated coagulation time >350 seconds. In group 3, noncontinuous infusion was used. The transseptal sheaths were also infused with heparinized saline during the procedure.

Antiarrhythmic drugs were discontinued 5 days before the ablation. Patients on amiodarone discontinued the medication 6 months before the procedure.

Ablation Protocol

In group 1 patients, radiofrequency energy was delivered with an 8-mm solid-tip catheter (Biosense-Webster) with a target temperature kept constant at 55°C and power titrated upward in 5-W increments from 30 to 70 W while monitoring for microbubble formation.[10,19] In groups 2 and 3, radiofrequency energy was delivered with a 3.5-mm open irrigated ablation catheter (Biosense-Webster) with a maximum temperature of 42°C, power up to 45 W, and flow rate of 30 cm^3/min.[18,19,20]

The ablation strategy was the same in all groups. Briefly, we performed pulmonary vein antrum isolation guided by a circular mapping catheter and by intracardiac echocardiography, along with empirical isolation of the superior vena cava.[21] In patients with paroxysmal AF, the pulmonary vein antra and the portion of the posterior wall contained within the pulmonary vein area were targeted during the procedures with exit block as the end point.[18,22] In patients with persistent and long-standing persistent AF, the electric isolation of the pulmonary veins was extended to the entire posterior wall down to the coronary sinus and to the left side of the septum.[18,22] Ablation of complex fractionated atrial electrograms in the right and left atria and in the coronary sinus was also performed. In all patients, challenge with isoproterenol infusion up to 30 μg/min was performed to identify extrapulmonary vein triggers.

Periprocedural Anticoagulation Management

All patients were on warfarin before the procedures to achieve 4 weeks of therapeutic INRs before ablation. In groups 1 and 2, warfarin was discontinued 3 days before the ablation procedure, and 1 mg/kg enoxaparin was administered until 12 hours before procedure. At the time of the procedure, heparin bolus was used before transseptal access (10 000 to 15 000 U).

In groups 1 and 2, all patients in AF on the day of the procedure underwent a transesophageal echocardiogram (TEE) before ablation to rule out the presence of a left atrial thrombus. At the end of the procedure, heparin was discontinued, and protamine 10 to 15 mg was given. Aspirin 325 mg was given before the patient left the electrophysiology laboratory.

Warfarin was administered the evening of pulmonary vein isolation. In addition, enoxaparin 0.5 mg/kg BID was routinely started and was stopped when the INR was >2.

Group 3 patients did not discontinue warfarin. The INR was monitored every week for the 4 weeks preceding the ablation, and it was required to be >2.0. All patients were included only when the INR was therapeutic. No TEE was performed in this group before the procedure. Patients without therapeutic INR were excluded. Before the transseptal puncture, a heparin bolus (15 000/10 000 U) was administered to all patients. During the procedure, the infusion rate was adjusted to keep the activated clotting time >350 seconds. After the procedures, heparin infusion was stopped. Heparin was reversed with 10 to 15 mg of protamine, and sheaths were pulled when the activated clotting time was <250 seconds. Patients received 325 mg aspirin before leaving the electrophysiology laboratory. They continued their warfarin dosage regimen with no changes before or after the procedure, aiming to achieve an INR of 2 to 3.0.

Neurological Evaluation

All patients underwent neurological examination at the end of the procedure and every 4 hours after ablation. The postprocedure and predischarge examinations were performed by a physician; the remaining evaluations at 4-hour intervals were done by the nursing staff.

Stroke was defined as the onset of a new neurological deficit that occurred anytime during or within 48 hours of the procedure. If the duration of the deficit was <24 hours, it was defined as a transient ischemic attack (TIA). If the deficit persisted for a longer period and resulted in a positive finding on computed tomography or magnetic resonance imaging, it was defined as a stroke. A neurologist diagnosed the events.

Table 1. Baseline Characteristics

	Group 1 (n=2488)	Group 2 (n=1348)	Group 3 (n=2618)	P
Male, n (%)	1891 (76)	1078 (80)	1911 (73)	<0.001
Age, y	55±10	57±10	58±12	<0.001
AF type, n (%)				
Paroxysmal	1144 (46)	499 (37)	942 (36)	<0.001
Persistent	448 (18)	539 (40)	1178 (45)	<0.001
Long-standing persistent	896 (36)	310 (20)	498 (19)	<0.001
Patients with risk factors, n (%)				
CAD	398 (16)	256 (19)	550 (21)	<0.001
Cardiac failure	127 (5.1)	69 (5.1)	128 (4.9)	0.9237
Hypertension	1095 (44)	634 (47)	1545 (59)	<0.001
Age ≥75 y	30 (1.2)	20 (1.5)	212 (8.1)	<0.001
Diabetes mellitus	373 (15)	148 (11)	393 (15)	0.003
Prior stroke/TIA	75 (3)	40 (3)	236 (9)	<0.001
CHADS2 score, n (%)				
0	1120 (45)	620 (46)	655 (25)	<0.001
1	1045 (42)	539 (40)	1047 (40)	0.278
≥2	323 (13)	189 (14)	916 (35)	<0.001
LVEF, %	52.3±8.06	53.5±7.82	52.1±87.61	<0.001
LVEF ≤40%, n (%)	199 (8)	94 (7)	236 (9)	0.162
LA diameter, cm	4.5±0.7	4.5±0.7	4.6±0.7	<0.001
LA diameter ≥40 mm, n (%)	1841 (74)	944 (70)	2199 (84)	<0.001

LVEF indicates left ventricular ejection fraction; and LA, left atrium.

Complications

Complications were divided into 2 categories: hemorrhagic and thromboembolic. Major bleeding complications were defined as the occurrence of cardiac tamponade or hemopericardium that required intervention or caused symptoms, the need for transfusion, hematoma requiring intervention, massive hemoptysis, hemothorax, and retroperitoneal bleeding. Minor bleeding complications were defined as the occurrence of hematoma or any bleeding that did not require any intervention and did not cause any symptoms. Thromboembolic complications were defined as occurrence of ischemic stroke, TIA, peripheral embolic events, or deep venous thrombosis.

Follow-Up

For the purpose of this study, all patients were assessed for complications during the initial 48 hours after the procedure. Follow-up was scheduled at 3, 6, 9, and 12 months. All patients had serial INR checks and were followed up by their referring physicians to maintain an INR in the range of 2 to 3.5.

Statistical Analysis

Continuous data are described as mean±SD and as counts and percent if categorical. Student t test, 1-way analysis of variance, χ^2 test, and Fisher exact test were used to compare differences across groups. When required, posthoc analysis was performed with the Tukey-Kramer multiple comparison method. Multivariable logistic regression was used to identify significant predictors of periprocedural stroke. All potential confounders were entered into the model on the basis of known clinical relevance or significant association observed in univariate analysis.

The controlling variables used in the model were age, hypertension, diabetes mellitus, coronary artery disease (CAD), congestive heart failure, prior cerebrovascular accident (CVA), and type of AF. Age was dichotomized at 75 years (≤75 and >75 years) and entered into the model as an ordinal categorical variable. Analysis of variance inflation factor was used to examine the presence of multicollinearity of the covariates. Values of variance inflation factor exceeding 3.5 were regarded as indicators of multicollinearity. The odds ratio and 95% confidence interval (CI) of periprocedural stroke were computed. All tests were 2 sided, and a value of $P<0.05$ was considered statistically significant. Analyses were performed with SAS 9.2 (SAS Institute Inc, Cary, NC).

Results

A total of 6454 pulmonary vein antrum isolation procedures were identified. Of these procedures, 2488 were in group 1, 1348 were in group 2, and 2618 were in group 3. Compared with the other 2 groups, group 3 had a sicker population with a significantly higher prevalence of nonparoxysmal AF and CHADS2 (congestive heart failure, hypertension, age >75, diabetes mellitus, stroke or TIA) score ≥2 (P from multiple comparison <0.05). The demographic characteristics of these populations are presented in Table 1. In group 3, the mean INR on the day of the procedure was 2.68±0.62.

Transesophageal Echocardiography

Preprocedural TEE was performed in all patients with long-standing persistent AF (896 patients in group 1, and 310 patients in group 2). Among paroxysmal AF patients, 240 (21%) in group 1 and 115 (23%) in group 2 had preprocedural TEE. In patients with persistent AF, 228 (51%) in group 1 and 296 (55%) in group 2 had TEE performed to exclude thrombus. None of the patients in group 3 had a TEE.

Thromboembolic Events

There were 19 strokes in group 1 (0.8%), 7 (0.5%) in group 2, and 0 in group 3. When stroke and TIA were considered together, 1.1% of group 1 and 0.9% of group 2 experienced the event. Group 3 patients did not experience stroke or TIA despite the higher prevalence of nonparoxysmal AF and a higher number of patients with CHADS2 score ≥2 (Table 2).

Table 2. Complications

Complication	Group 1 (n=2488), n (%, 95% CI)	Group 2 (n=1348), n (%, 95% CI)	Group 3 (n=2618), n (%, 95% CI)	P, Multiple Comparison Between Group 3 and Groups 1 and 2
Stroke/TIA	27 (1.1, 0.72–1.58)	12 (0.9, 0.46–1.56)	0 (0)	<0.05
Minor bleeding	498 (20, 18.3–21.9)	256 (19, 16.7–21.5)	105 (4, 3.3–4.9)	<0.05
Major bleeding	10 (0.4, 0.19–0.74)	11 (0.8, 0.41%–1.46%)	10 (0.4, 0.18–0.70)	>0.05
Pericardial effusion	11 (0.4, 0.22–0.79)	11 (0.8, 0.41–1.46)	12 (0.5, 0.24–0.80)	>0.05

Table 3. Pericardial Effusion Management

	Patients off Warfarin (n=3836)	Patients on Warfarin (n=2618)	P
Patients with pericardial effusion, n (%, 95% CI)	22 (0.57, 0.36–0.87)	12 (0.46, 0.24–0.80)	0.602
Requiring pericardiocentesis, n (%, 95% CI)	9 (0.23, 0.11–0.45)	8 (0.31, 0.13–0.60)	0.626
Requiring fresh frozen plasma, n (%, 95% CI)	0	8 (0.31, 0.13–0.60)	<0.001
Median blood units for transfusion, n (%, 95% CI)	1 (0.03, 0.00–0.15)	3 (0.11, 0.02–0.33)	0.043
Requiring surgery, n (%, 95% CI)	3 (0.08, 0.02–0.23)	1 (0.04, 0.00–0.21)	0.651
Mean pericardial fluid aspiration, cm^3	700±300	1200±200	<0.001
Mean protamine for reversal, mg	45±15	70±15	<0.001

Hemorrhagic Events

In group 1, a total of 11 pericardial effusions (0.4%) were reported. Eight were documented during the procedure, and 3 occurred 1 to 4 weeks after the procedure. Only 1 patient required surgery. In group 2, a total of 11 (0.8%) pericardial effusions occurred (9 periprocedural and 2 after 1 to 4 weeks after the procedure). Two patients required surgery.

Twelve (0.5%) pericardial effusions were reported in group 3 (10 periprocedural and 2 after 1 to 4 weeks after the procedure). In this group, fresh frozen plasma with protamine was necessary to reverse the anticoagulation status. The mean INR when bleeding stopped was 1.8±0.4. Three of the 12 patients with pericardial bleeding had termination of bleeding when the INR was <1.6. Surgery was necessary in 1 patient (Table 3). A median of 3 U blood was given in group 3. All patients requiring surgery had a steam pop during ablation along the mitral annulus.

The management strategy for pericardial effusions was compared between the on-warfarin (group 3) and off-warfarin (groups 1 and 2 combined) populations in Table 3. The incidence of pericardial effusion was comparable in the 3 groups (0.4% in group 1, 0.8% in group 2, and 0.4% in group 3; P≥0.05).

In addition, the pericardial drainage was kept overnight and removed the next day in all patients except 1 woman who continued to accumulate clear fluid in the pericardial sac for 3 days and required treatment with steroids. All patients requiring pericardiocentesis were given antiinflammatory therapy for 2 weeks.

In all patients, an echocardiogram was performed at the end of the procedure. Five of 22 patients in the off-warfarin group and 2 of the 12 patients with pericardial effusions in the on-warfarin group presented late with a pericardial effusion that was not present immediately after the procedure. No treatment was required in 3 of the 5 patients in the off-warfarin group and in 1 of the 2 patients in the on-warfarin group. In the remaining 3 patients, the fluid was removed with a pericardial window in 2 cases and with percutaneous epicardial drainage in 1 patient.

Vascular access complications resulting in major bleeding were observed in 31 patients. In 12 patients, blood transfusion was required. Three patients had retroperitoneal bleeding; other bleeding complications included hematomas requiring

no intervention but prolonged hospitalization, which was present in 16 patients.

Minor bleeding were observed more frequently in groups 1 and 2 than in group 3 (20%, 19%, and 4%, respectively; P<0.05). These data are summarized in Table 2.

Risk of Periprocedural Stroke/TIA

Patients were divided into 2 groups according to stroke/TIA outcome status, and univariate analysis was performed to compare their clinical characteristics. Male gender, CAD, diabetes mellitus, prior stroke/TIA, warfarin discontinuation, and CHADS2 score were found to be significantly associated with occurrence of periprocedural stroke (Table 4).

A multivariable analysis was performed with the logistic regression model (model 1). The significant confounders identified in the univariable test were included in the model. In addition, some other clinically important covariates (AF type, congestive heart failure, hypertension, and age >75 years) were added to the model despite their nonsignificant association in the univariate test. After adjustment for the above confounders, it was found that the anticoagulation strategy, AF type (nonparoxysmal AF), congestive heart failure, and diabetes mellitus were independent predictors of periprocedural stroke. The odds ratios from this model are presented in Table 5.

To avoid multicollinearity, a separate multivariable model was run by including CHADS2 score (categorized into 0, 1, ≥2), anticoagulation strategy, gender, CAD, and AF type (model 2). A CHADS2 score of 0 was considered the reference and was compared with the CHADS2 scores of 1 and ≥2. As observed in this model, CHADS2 score, anticoagulation strategy (on warfarin), gender, and AF type (nonparoxysmal AF) were independently associated with periprocedural stroke. Patients with CHADS2 score ≥2 had an ≈3 times (odds ratio, 3.8; P<0.001) higher risk of experiencing periprocedural stroke compared with patients having a CHADS2 score of 1 and >4 times (odds ratio, 5.7; P<0.001) higher risk compared with those with a CHADS2 score of 0 (Table 6). In both models, AF type and the anticoagulation strategy were found to be strong predictors of periprocedural stroke.

Table 4. Univariate Analysis of Clinical Risk Factors for Stroke/TIA

	Stroke (n=41)	No Stroke (n=6413)	P
Male, n (%)	26 (63)	4913 (77)	0.047
Age, y	58±9	56±11	0.275
AF type, n (%)			0.765
Paroxysmal	17 (41)	2634 (41)	
Persistent	15 (37)	1946 (30)	
Long-standing persistent	9 (22)	1833 (29)	
Patients with risk factors, n (%)			0.036
CAD	2 (5)	1107 (17)	
Cardiac failure	4 (10)	322 (5)	0.151
Hypertension	23 (56)	3027 (47)	0.275
Age ≥75 y	1 (2)	152 (2)	1.000
Diabetes mellitus	10 (24)	860 (13)	0.061
Prior stroke/TIA	10 (24)	254 (4)	<0.001
Patients off warfarin	41 (100)	3795 (59)	<0.001
Patients on warfarin	0 (0)	2618 (41)	<0.001
CHADS2 score, n (%)			<0.001
0	10 (24)	2779 (43)	
1	15 (37)	2672 (42)	
≥2	16 (39)	962 (15)	
LVEF, %	51±9	53±8	0.609
LVEF ≤40%, n (%)	37 (90)	5924 (92)	0.551
LA diameter, mm	45±7	45±7	0.961
LA diameter ≥40 mm, n (%)	31 (75)	4660 (73)	0.673

Abbreviations as in Table 1.

Discussion

Main Findings

This is the first large series of patients undergoing ablation of AF that shows that continuation of therapeutic warfarin during the procedure (RFCA) could reduce the risk of periprocedural stroke/TIA without increasing the risk of hemorrhagic events. The anticoagulation strategy, congestive heart failure, history of type 2 diabetes mellitus, and type of

Table 5. Multivariate Analysis of Clinical Variables Affecting Stroke/TIA: Model 1*

Variables	Odds Ratio (95% CI)	P
Sex	1.84 (0.92–3.65)	0.084
Age (>75 y)	1.82 (0.24–13.95)	0.563
CAD	0.60 (0.23–1.55)	0.289
AF type (nonparoxysmal AF)	2.12 (1.11–3.03)	0.023
CHF	3.38 (1.13–10.11)	0.029
DM	2.4 (1.13–5.08)	0.023
HTN	1.42 (0.72–2.82)	0.313
Prior CVA	1.55 (0.82–2.93)	0.176
Anticoagulation strategy (on warfarin)	0.54 (0.32–0.89)	0.017

*Model 1 shows the odds ratios after adjustment for gender, age (≤75 and >75 years), CAD, type of AF, congestive heart failure (CHF), diabetes mellitus (DM), hypertension (HTN), and prior history of CVA.

Table 6. Multivariate Analysis of Clinical Variables Affecting Stroke/TIA: Model 2*

Variables	Odds Ratio (95% CI)	P
CHADS2 score 0	1.0 (Referent)	
CHADS2 score 1 vs 0	1.5 (0.67–3.36)	0.326
CHADS2 score 2 vs 0	5.69 (2.49–13.00)	<0.001
CHADS2 score 2 vs 1	3.8 (1.82–7.91)	<0.001
Sex	1.95 (1.00–3.77)	0.049
CAD	0.87 (0.47–1.63)	0.661
AF type (nonparoxysmal AF)	1.53 (1.15–2.03)	0.004
Anticoagulation strategy (on warfarin)	0.52 (0.31–0.87)	0.012

*Model 2 shows the odds ratios after adjustment for CHADS2 scores (0, 1, ≥2), gender, CAD, and type of AF.

AF were independent predictors of stroke. After adjustment for CHADS2 scores, patients with CHADS2 ≥2 had the highest risk of experiencing the event, whereas patients with CHADS2 score of 0 had the lowest risk.

Of interest, group 3 consisted of a sicker population with a higher prevalence of stroke/TIA predictors. In addition, group 3 patients with long-standing persistent AF underwent a more aggressive ablation protocol, including defragmentation in the right and left atrium. Therefore, despite a more extensive ablation protocol and a higher prevalence of patients at risk for stroke, the absence of thromboembolic events in this group is of remarkable importance and is most likely related to the anticoagulation protocol in which warfarin was not discontinued because CVAs have been reported even with open irrigated catheters.[23]

Previous Studies

Many previous studies have reported the incidence of periprocedural CVA with the use of either an 8-mm ablation catheter or a 3.5-mm open irrigated ablation catheter.[10–15] We first reported the possibility of performing RCFA while maintaining therapeutic anticoagulation with warfarin.[16] In this large series of patients, we observed that the combination of therapeutic anticoagulation with warfarin and the use of a 3.5-mm open irrigated catheter significantly reduced the risk for CVA/TIA without increasing the risk for bleeding.

The reported risks of stroke/TIA vary from 0.9% to 5% after RFCA.[10–15,23] Studies have reported the incidence of TIA/stroke varying from 0.8% to 1.1% with the use of open irrigated catheters.[23] Scherr et al[23] reported a risk of periprocedural stroke of 1.4% despite the use of open irrigation catheters. Others have reported significant stroke risk reduction using a similar strategy. In a recent report, Hussein et al[17] described 3 ischemic strokes using a similar strategy in >3000 patients. However, it should be emphasized that an INR of 1.8 was considered acceptable in their series. In our series, all patients in group 3 had an INR ≥2 on the day of the procedure.

Although the expert consensus document recommends a bridging strategy, our study and others confirm the limitations of such an approach. It appears that patients who discontinue warfarin may be exposed to an increased risk of stroke during the procedure even when the TEE excludes the presence of

thrombus. In addition, achieving a therapeutic INR after the procedure may take several days. During this time, patients may be at an increased risk of stroke/TIA and may not be adequately covered with the bridging strategy. Our multicenter report and the report by Hussein et al[17] show that this anticoagulation approach is safe and efficacious in a large population of patients.

Our study found that anticoagulation strategy, nonparoxysmal AF, and higher CHADS2 scores were strongly associated with periprocedural stroke, whereas prior CVA, gender, and age did not show any impact. Patients with CHADS2 score ≥2 were ≈5 times more likely to experience the event compared with group 1 and 2 patients with a CHADS2 score of 0. The incidence of stroke was lowest among patients with CHADS2 score of 0, and each level of increase in CHADS2 score was associated with significantly higher risk. Our findings are consistent with those of Scherr et al[23] using open irrigated catheters and warfarin discontinuation.

Minor Bleeding
Minor bleeding complications were significantly higher in the group of patients using the bridging anticoagulation protocol. This may increase the cost of this strategy. For the physicians who are concerned about the risk of vascular injury while inserting sheaths under full anticoagulation, ultrasound guidance might be useful.

Major Bleeding and Tamponade
In this patient population, the majority of bleeds have been related to cardiac tamponade. The management and incidence of this complication have not shown any statistical significant difference between groups. The prevalence of pericardial effusion during and after RFCA reported in the literature is ≈1.2%, which is similar to the rate found in all 3 of our groups.

Emphasis should be put on the different modalities of anticoagulation reversal. In groups 1 and 2, protamine was usually sufficient, whereas in group 3, fresh frozen plasma was necessary. In addition, patients on warfarin were more likely to have more blood removed from the pericardial space before stabilization and were given a larger amount of blood transfusion (Table 3). The need for fresh frozen plasma and blood units, although a potential disadvantage, is mitigated by the reduced risk of stroke/TIA.

Economic Point of View
Our strategy could also be cost-effective by reducing the number of TEEs performed and the extra cost for managing complications such as stroke and bleeding. In addition, patients belonging to groups 1 and 2 incurred the additional cost of low-molecular-weight heparin, which can be substantial. On average, before warfarin was therapeutic, patients had received 6 doses of low-molecular-weight heparin.

Study Limitation
The study was not randomized, although the data were collected in a prospective fashion. This can be considered an important limitation. However, the reduced stroke rate ob-

served in group 3 despite a higher number of patients at risk is compelling.

Conclusion
Our results suggest that periprocedural therapeutic anticoagulation with warfarin can reduce the risk of procedural stroke without increasing the risk of bleeding complications.

References
1. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257–e354.
2. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, Haines DE, Haissaguerre M, Iesaka Y, Jackman W, Jais P, Kottkamp H, Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Natale A, Pappone C, Prystowsky E, Raviele A, Ruskin JN, Shemin RJ. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. *Heart Rhythm*. 2007;4:816–861.
3. Natale A, Raviele A, Arentz T, Calkins H, Chen SA, Hassaguerre M, Hindricks G, Ho Y, Kuck KH, Marchlinski F, Napolitano C, Packer D, Pappone C, Prystowsky EN, Schilling R, Shah D, Themistoclakis S, Verma A. Venice Chart international consensus document on atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2007;18:560–580.

4. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Packer D, Skanes A. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation*. 2005;111:1100–1105.

5. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A. Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. J *Am Coll Cardiol*. 2009;53:1798–1803.

6. Dixit S, Marchlinski FE. How to recognize, manage, and prevent complications during atrial fibrillation ablation. *Heart Rhythm*. 2007;4:108–115.

7. Bertaglia E, Zoppo F, Tondo C, Colella A, Mantovan R, Senatore G, Bottoni N, Carreras G, Corò L, Turco P, Mantica M, Stabile G. Early complications of pulmonary vein catheter ablation for atrial fibrillation: a multicenter prospective registry on procedural safety. *Heart Rhythm*. 2007;4:1265–1271.

8. Kok LC, Mangrum JM, Haines DE, Mounsey JP. Cerebrovascular complication associated with pulmonary vein ablation. *J Cardiovasc Electrophysiol*. 2002;13:764–767.

9. Lickfett L, Hackenbroch M, Lewalter T, Selbach S, Schwab JO, Yang A, Balta O, Schrickel J, Bitzen A, Luderitz B, Sommer T. Cerebral diffusion-weighted magnetic resonance imaging: a tool to monitor the thrombogenicity of left atrial catheter ablation. *J Cardiovasc Electrophysiol*. 2006;17:1–7.

10. Verma A, Marrouche NF, Natale A. Pulmonary vein antrum isolation: intracardiac echocardiography-guided technique. *J Cardiovasc Electrophysiol*. 2004;15:1335–1340.

11. Kanj MH, Wazni O, Fahmy T, Thal S, Patel D, Elay C, Di Biase L, Arruda M, Saliba W, Schweikert RA, Cummings JE, Burkhardt JD, Martin DO, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Forleo G, Natale A. Pulmonary vein antral isolation using an open irrigation ablation catheter for the treatment of atrial fibrillation: a randomized pilot study. *J Am Coll Cardiol*. 2007;49:1634–1641.

12. Ren JF, Marchlinski FE, Callans DJ, Gerstenfeld EP, Dixit S, Lin D, Nayak HM, Hsia HH. Increased intensity of anticoagulation may reduce risk of thrombus during atrial fibrillation ablation procedures in patients with spontaneous echo contrast. *J Cardiovasc Electrophysiol*. 2005;16:474–477.

13. Bruce CJ, Friedman PA, Narayan O, Munger TM, Hammill SC, Packer DL, Asirvatham SJ. Early heparinization decreases the incidence of left atrial thrombi detected by intracardiac echocardiography during radiofrequency ablation for atrial fibrillation. *J Interv Card Electrophysiol*. 2008;22:211–219.

14. Wazni OM, Rossillo A, Marrouche NF, Saad EB, Martin DO, Bhargava M, Bash D, Beheiry S, Wexman M, Potenza D, Pisano E, Fanelli R, Bonso A, Themistoclakis S, Erciyes D, Saliba WI, Schweikert RA, Brachmann J, Raviele A, Natale A. Embolic events and char formation during pulmonary vein isolation in patients with atrial fibrillation: impact of different anticoagulation regimens and importance of intracardiac echo imaging. *J Cardiovasc Electrophysiol*. 2005;16:576–581.

15. Mortada ME, Chandrasekaran K, NangiaV, Dhala A, Blanck Z, Cooley R, Bhatia A, Gilbert C, Akhtar M, Sra J. Periprocedural anticoagulation for atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2008;19:362–366.

16. Wazni OM, Beheiry S, Fahmy T, Barrett C, Hao S, Patel D, Di Biase L, Martin DO, Kanj M, Arruda M, Cummings J, Schweikert R, Saliba W, Natale A. Atrial fibrillation ablation in patients with therapeutic international normalized ratio: comparison of strategies of anticoagulation management in the periprocedural period. *Circulation*. 2007;116:2531–2534.

17. Hussein AA, Martin DO, Patel, D. Karim S, Batal O, Banna M, Williams-Andrews M, Sherman M, Kanj M, Bhargava M, Dresing T, Callahan T, Patrick Tchou P, Saliba WI, Di Biase L, Beheiry S, Lindsay B, Natale A, Wazni OM. Radiofrequency ablation of atrial fibrillation under therapeutic international normalized ratio: a safe and efficacious periprocedural anticoagulation strategy. *Heart Rhythm*. 2009;6:1425–1429.

18. Bhargava M, Di Biase L, Mohanty P, Prasad S, Martin DO, Williams-Andrews M, Wazni OM, Burkhardt JD, Cummings JE, Khaykin Y, Verma A, Hao S, Beheiry S, Hongo R, Rossillo A, Raviele A, Bonso A, Themistoclakis S, Stewart K, Saliba WI, Schweikert RA, Natale A. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. *Heart Rhythm*. 2009;6:1403–1412.

19. Dixit S, Gerstenfeld EP, Callans DJ, Cooper JM, Lin D, Russo AM, Verdino RJ, Patel VV, Kimmel SE, Ratcliffe SJ, Hsia HH, Nayak HM, Zado E, Ren JF, Marchlinski FE. Comparison of cool tip versus 8-mm tip catheter in achieving electrical isolation of pulmonary veins for long-term control of atrial fibrillation: a prospective randomized pilot study. *J Cardiovasc Electrophysiol*. 2006;17:1074–1079.

20. Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, Hongo R, Hao S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Arruda M, Schweikert RA, Natale A. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. *Heart Rhythm*. 2008;1:1658–1664.

21. Arruda M, Mlcochova H, Prasad SK, Kilicaslan F, Saliba W, Patel D, Fahmy T, Morales LS, Schweikert R, Martin D, Burkhardt D, Cummings J, Bhargava M, Dresing T, Wazni O, Kanj M, Natale A. Electrical isolation of the superior vena cava: an adjunctive strategy to pulmonary vein antrum isolation improving the outcome of AF ablation. *J Cardiovasc Electrophysiol*. 2007;18:1261–1266.

22. Di Biase L, Elayi CS, Fahmy TS, Martin DO, Ching CK, Barrett C, Bai R, Patel D, Khaykin Y, Hongo R, Hao S, Beheiry S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Wang P, Al-Ahmad A, Arruda M, Themistoclakis S, Bonso A, Rossillo A, Raviele A, Schweikert RA, Burkhardt JD, Natale A. Atrial fibrillation ablation strategies for paroxysmal patients: randomized comparison between different techniques. *Circ Arrhythm Electrophysiol*. 2009;2:113–119.

23. Scherr D, Sharma K, Dalal D, Spragg D, Chilukuri K, Cheng A, Dong J, Henrikson CA, Nazarian S, Berger RD, Calkins H, Marine JE. Incidence and predictors of periprocedural cerebrovascular accident in patients undergoing catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2009;20:1357–1363.

CLINICAL PERSPECTIVE

Periprocedural thromboembolic and hemorrhagic events are complications of percutaneous radiofrequency catheter ablation of atrial fibrillation. The management of anticoagulation before and after radiofrequency catheter ablation could play an important role in the prevention of these complications. The incidence of thromboembolic events varies from 1% to 5%, depending on the ablation and the anticoagulation strategy used in the periprocedural period. At present, although discontinuation of warfarin 3 to 5 days before ablation with and without bridging with low-weight heparin is the most frequently implemented protocol, the optimal anticoagulation management (minimizing thromboembolism while not increasing hemorrhagic complications) is not well established. We first reported radiofrequency catheter ablation of atrial fibrillation without discontinuation of warfarin. This is the first large series of patients undergoing ablation of atrial fibrillation with different anticoagulation protocols and with different ablation catheters showing that the continuation of therapeutic warfarin during the procedure (radiofrequency catheter ablation) reduces the risk of periprocedural stroke/transient ischemic attack without increasing the risk of hemorrhagic events. Of interest, this anticoagulation protocol eliminates the need for a preprocedural transesophageal echocardiogram. A randomized controlled trial is necessary to confirm the results of our study.

Circulation

American Heart Association

Periprocedural Stroke and Management of Major Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation: The Impact of Periprocedural Therapeutic International Normalized Ratio

Luigi Di Biase, J. David Burkhardt, Prasant Mohanty, Javier Sanchez, Rodney Horton, G. Joseph Gallinghouse, Dhanunjay Lakkireddy, Atul Verma, Yaariv Khaykin, Richard Hongo, Steven Hao, Salwa Beheiry, Gemma Pelargonio, Antonio Dello Russo, Michela Casella, Pietro Santarelli, Pasquale Santangeli, Paul Wang, Amin Al-Ahmad, Dimpi Patel, Sakis Themistoclakis, Aldo Bonso, Antonio Rossillo, Andrea Corrado, Antonio Raviele, Jennifer E. Cummings, Robert A. Schweikert, William R. Lewis and Andrea Natale

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/121/23/2550