

## Periprocedural Stroke and Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation With Different Anticoagulation Management

### Results From the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) Randomized Trial

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**Background**—Periprocedural thromboembolic and hemorrhagic events are worrisome complications of catheter ablation for atrial fibrillation (AF). The periprocedural anticoagulation management could play a role in the incidence of these complications. Although ablation procedures performed without warfarin discontinuation seem to be associated with lower thromboembolic risk, no randomized study exists.

**Methods and Results**—This was a prospective, open-label, randomized, parallel-group, multicenter study assessing the role of continuous warfarin therapy in preventing periprocedural thromboembolic and hemorrhagic events after radiofrequency catheter ablation. Patients with CHADS<sub>2</sub> score  $\geq 1$  were included. Patients were randomly assigned in a 1:1 ratio to the off-warfarin or on-warfarin arm. The incidence of thromboembolic events in the 48 hours after ablation was the primary end point of the study. The study enrolled 1584 patients: 790 assigned to discontinue warfarin (group 1) and 794 assigned to continuous warfarin (group 2). No statistical difference in baseline characteristics was observed. There were 39 thromboembolic events (3.7% strokes [n=29] and 1.3% transient ischemic attacks [n=10]) in group 1: two events (0.87%) in patients with paroxysmal AF, 4 (2.3%) in patients with persistent AF, and 33 (8.5%) in patients with long-standing persistent AF. Only 2 strokes (0.25%) in patients with long-standing persistent AF were observed in group 2 ( $P < 0.001$ ). Warfarin discontinuation emerged as a strong predictor of periprocedural thromboembolism (odds ratio, 13; 95% confidence interval, 3.1–55.6;  $P < 0.001$ ).

**Conclusion**—This is the first randomized study showing that performing catheter ablation of AF without warfarin discontinuation reduces the occurrence of periprocedural stroke and minor bleeding complications compared with bridging with low-molecular-weight heparin.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01006876. (*Circulation*. 2014;129:2638-2644.)

**Key Words:** atrial fibrillation ■ catheter ablation ■ catheter ablation, radiofrequency ■ stroke ■ transient ischemic attack ■ warfarin

Radiofrequency catheter ablation for atrial fibrillation (AF) is an effective therapeutic option for the treatment of symptomatic drug-refractory AF.<sup>1</sup> The complexity

of the procedure and its operator dependency expose patients to a considerable number of potential complications.<sup>2–4</sup> Periprocedural thromboembolic events represent one of the

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most worrisome complications of catheter ablation because of the potential long-term effect on patients' functionality.<sup>2-4</sup>

### Clinical Perspective on p 2644

The periprocedural anticoagulation management could play an important role in the occurrence of these complications. Although ablation procedures performed without warfarin discontinuation seem to be associated with lower thromboembolic risk compared with other strategies discontinuing warfarin before ablation, no randomized study currently exists.<sup>2-6</sup>

This study aims at exploring the risk of periprocedural thromboembolic and hemorrhagic events in continuous versus interrupted warfarin in a large, randomized, high-risk patient population undergoing radiofrequency catheter ablation for AF.

## Methods

### Study Design

The Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) trial was a prospective, randomized, parallel-group, multicenter study assessing the role of continuous warfarin therapy in preventing periprocedural thromboembolic events after radiofrequency catheter ablation. Inclusion criteria were the following: age  $\geq 18$  years, international normalized ratio (INR) in the range of 2.0 to 3.0 in the last 3 to 4 weeks before ablation, and CHADS<sub>2</sub> score  $\geq 1$ . During the study period, 2234 patients met the inclusion criteria. Of these, 1584 agreed to participate in this study.

Exclusion criteria were known bleeding disorders or inherited thrombophilic disorder, oral contraceptives or estrogen replacement therapy, prosthetic heart valves, and contraindications to warfarin therapy.

Consenting eligible subjects were randomly assigned (1:1 ratio) to an anticoagulation strategy of either discontinued warfarin (group 1) or continuous warfarin (group 2). To ensure equal group allocation within the participating centers, block randomization was performed with study center as the blocking variable. A central randomization algorithm was used to generate the randomization code. This was a nonstratified trial; no stratification on subgroup membership was performed.

The study was approved by the Institutional Review Board.

### End Points

The incidence of thromboembolic events during 48 hours after ablation was the primary end point of the study. Thromboembolic events were defined as stroke, transient ischemic attack (TIA), or systemic thromboembolism.

Secondary end points included bleeding complications defined as major (requiring intervention) and minor (not requiring intervention) bleeding. Pericardial effusions were also analyzed separately as a secondary end point of the study.

### Anticoagulation Management

All patients (groups 1 and 2) were on warfarin before the procedures to achieve 3 to 4 weeks of therapeutic INRs. Transesophageal echocardiography was performed in all patients in group 1 and when the patient presented with a subtherapeutic INR on the day of the procedure in group 2.

#### Group 1 (Off-Warfarin Group)

All patients were on warfarin before the procedure to achieve 3 to 4 weeks of therapeutic INRs, and warfarin was monitored every week for the 3 to 4 weeks preceding the ablation.

In group 1, warfarin was discontinued 2 to 3 days before the ablation, and patients were bridged with low-molecular-weight heparin. Specifically, 1 mg/kg enoxaparin was administered twice daily until the evening before the ablation procedure. A bolus of 15000 IU heparin was given intravenously before the transseptal puncture. A continuous infusion of heparin 1000 U/h was started. The infusion

was adjusted to maintain an activated coagulation time (ACT)  $>350$  seconds. During the procedures, the transseptal sheaths were continuously infused with heparinized saline. Every effort was taken to avoid air embolism.

Protamine was administered after completion of the ablation procedure to partially reverse the heparin effect. A single 325-mg aspirin was given in the electrophysiology laboratory.

Sheaths were pulled when the ACT was  $<200$  seconds. Three hours after ablation, enoxaparin 0.5 mg/kg twice daily was routinely started. It was stopped when the INR was  $>2$ . Warfarin was restarted the night of the procedure.

#### Group 2 (On-Warfarin Group)

All patients continued uninterrupted warfarin. The INR had to be therapeutic and was monitored every week for the 3 to 4 weeks preceding the ablation. If on the day of the procedure patients had an INR  $>3.5$ , they were excluded. If the INR was between 3 and 3.5, fresh-frozen plasma was administered a few hours before the procedure. Some patients presented on the day of the procedure with a subtherapeutic INR and were not excluded. A bolus of 10000 IU unfractionated heparin in male patients and 8000 IU in female patients was given before the transseptal puncture.

During the procedures, the ACT was kept  $>300$  seconds, and the transseptal sheaths were continuously infused with heparinized saline. Every effort was made to avoid air embolism.

Protamine was administered after the completed ablation procedure to partially reverse the heparin effect. Sheaths were pulled when the ACT was  $<200$  seconds.

Warfarin was administered the night of the procedure as per the patient's scheduled dose.

## Ablation Procedure

### Paroxysmal AF

Briefly, pulmonary vein antrum isolation guided by circular mapping catheter and by intracardiac echocardiography was performed. The electric isolation of the pulmonary veins could be extended to the posterior wall contained between the pulmonary veins. In all patients, isoproterenol up to 30  $\mu\text{g}/\text{min}$  was given to disclose non-pulmonary vein triggers.

If AF/atrial tachyarrhythmia was present or induced, ablation was performed to terminate the tachycardia. When ablation was unsuccessful, cardioversion was performed to restore sinus rhythm.<sup>7</sup>

### Persistent and Long-Standing Persistent AF

Briefly, pulmonary vein antrum isolation guided by circular mapping catheter and by intracardiac echocardiography was performed. 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. Ablation of complex fractionated atrial electrograms in the left atrium and in the coronary sinus was also performed if fractionated potentials were found.

In patients with AF/atrial tachyarrhythmia, ablation was performed to terminate the tachycardia. If termination was unsuccessful, cardioversion was performed to restore sinus rhythm.

In all patients, isoproterenol up to 30  $\mu\text{g}/\text{min}$  was given to disclose non-pulmonary vein triggers.<sup>8</sup>

## Neurological Evaluation

All patients underwent neurological examination before and at the end of the procedure and every 2 hours thereafter. The postprocedural and predischarge examinations were performed by a physician. The remaining evaluations were performed at 2-hour intervals by the nursing staff.

## Definitions

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 TIA. If the deficit persisted for a longer period and resulted in positive finding

on a computed tomography or magnetic resonance imaging, it was defined as a stroke. Stroke and TIA diagnoses were performed by a neurologist who was blinded to the patient's group assignment. The diagnoses of peripheral embolic events or deep venous thrombosis were performed by other physicians blinded to the group assignment.

Major bleeding was defined as the occurrence of cardiac tamponade or hemopericardium requiring intervention, causing symptoms, or requiring 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 or did not cause any symptoms.

Our definitions are in accordance with the recently published Bleeding Academic Research Consortium ones.<sup>9,10</sup>

## Statistical Analysis

The incidence of thromboembolic events during 48 hours after ablation was the primary end point of the study.

An earlier prospective study from our group reported a 0.9% thromboembolic event rate in patients who discontinued warfarin and none in patients on continuous warfarin.<sup>5</sup>

Considering a 5% type I error rate and 80% power, 1560 patients were required to capture a 1% difference in the thromboembolic incidence. The present study enrolled 1584 patients: 790 assigned to discontinued warfarin (group 1) and 794 to continuous warfarin (group 2).

Continuous data are described as mean±SD; categorical data, as counts and percents. The Student *t* test and  $\chi^2$  test (Fisher exact for cell value <10) were used to compare differences across groups. A multivariable logistic model was used to identify significant predictors of periprocedural thromboembolic events. Potential confounders were entered into the model on the basis of known clinical relevance or significant association observed in univariate analysis. Controlling variables used in the model were age, left atrial diameter, left ventricular ejection fraction, cardioversion, history of coronary artery disease, and CHADS<sub>2</sub> score.

The CHADS<sub>2</sub> score was entered into the logistic model as a continuous variable. Tests were run to examine the presence of multicollinearity of the covariates. The discriminative ability of the models in predicting periprocedural thromboembolism was assessed by C statistics and receiver-operating characteristic curve. The odds ratio (OR) and 95% confidence interval (CI) were computed for periprocedural thromboembolism. 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

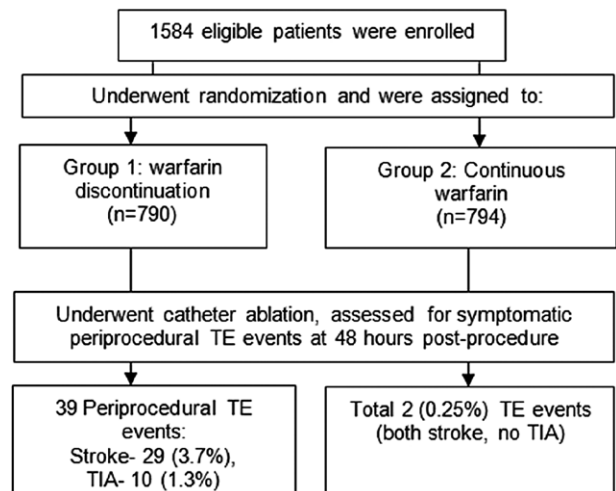
### Patient Characteristics

A total of 1584 patients presenting with AF at the participating centers between December 2009 and December 2012 were enrolled in the study. Patients were randomly assigned to the anticoagulation strategy of warfarin discontinuation before the procedure (group 1, n=790) or to undergo the procedure with continuous warfarin (group 2, n=794; Figure 1).

The baseline characteristics and risk factors were well balanced between the 2 groups. In group 1, the average age was 61±10 years; 76% were male; 29% had paroxysmal AF; 22% had persistent AF; 49% had long-standing persistent (LSP) AF; the left atrial size was 44.8±7 mm; and the left ventricular ejection fraction was 53±12%.

Patients in group 2 were 62±12 years of age; 74% were male; 25% had paroxysmal AF; 24% had persistent AF; 51% had LSP AF; the left atrial size was 45.1±7 mm; and the left ventricular ejection fraction was 52±13%.

In group 1, 561 patients (71%) had a CHADS<sub>2</sub> score ≥2 compared with 588 (74%) in group 2 (*P*=0.17). Fifty-five



**Figure 1.** Study design showing the enrollment and follow-up of study patients. TE indicates thromboembolic; and TIA, transient ischemic attack.

patients (7%) had a history of previous stroke or TIA in group 1 compared with 64 patients (8%) in group 2 (*P*=0.41). The baseline parameters are presented in Table 1.

Transesophageal echography was performed on the day before or on the day of the procedure for all patients in group 1 and only in 20% of patients in group 2 because of a

**Table 1. Baseline Characteristics**

	Group 1 (Off Warfarin; n=790)	Group 2 (On Warfarin; n=794)	<i>P</i> Value
Male, n (%)	602 (76)	590 (74)	0.40
Age, y	61±10	62±12	0.07
AF type, n (%)			
Paroxysmal	229 (29)	200 (25)	0.23
Persistent	174 (22)	189 (24)	
LSP	387 (49)	405 (51)	
CAD, n (%)	182 (23)	206 (26)	0.18
Hypertension, n (%)	640 (81)	660 (83)	0.27
CHF, n (%)	118 (15)	136 (17)	0.23
Diabetes mellitus, n (%)	302 (38)	318 (40)	0.46
Prior stroke/TIA, n (%)	55 (7)	64 (8)	0.41
CHADS <sub>2</sub> score, n (%)			
1	229 (29)	206 (26)	0.19
2	268 (34)	284 (36)	
3	170 (22)	152 (19)	
4	94 (12)	101 (13)	
≥5	32 (4.1)	48 (6.0)	
LVEF, %	53±12	52±13	0.11
LA diameter, mm	44.8±7	45.1±7	0.43
Fluoroscopy time, min	68±29	70±32	0.19
Radiofrequency time, min	76±44	77±36	0.60
Procedure time, min	170±82	168±71	0.62

There were no significant differences (*P*<0.05) between the 2 groups. AF indicates atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; LA, left atrial; LSP, long-standing persistent; LVEF, left ventricular ejection fraction; and TIA, transient ischemic attack.

subtherapeutic INR on presentation or at the discretion of the physician ( $P<0.001$ ).

### Intraprocedural Parameters

Sixty-four percent of patients (506 patients) in group 1 and 65% (516 patients) in group 2 entered the electrophysiology laboratory in AF/atrial tachyarrhythmia ( $P=0.69$ ). Persistence of AF/atrial tachyarrhythmia at end of the procedure before cardioversion was observed in 205 patients (26%) in group 1 and 224 patients (28%) in group 2 ( $P=0.31$ ).

The mean procedure time was  $170\pm 82$  and  $168\pm 71$  minutes ( $P=0.62$ ) for groups 1 and 2, respectively (Table 1).

### Study Outcomes

Periprocedural symptomatic thromboembolic events occurred in 39 patients (4.9%) in group 1 (29 strokes [3.7%] and 10 TIAs [1.3%]) and in only 2 patients (0.25%; both stroke) in group 2 ( $P<0.001$ ). Compared with group 1, patients in group 2 had significantly lower risk for periprocedural thromboembolism; the unadjusted relative risk was 0.051 (95% CI, 0.012–0.211), with a relative risk reduction of 95% in favor of uninterrupted warfarin (Figure 2).

Eighty-five percent of all the thromboembolic events (35 of 41) occurred in the LSP population. In the off-warfarin population (group 1), 1 TIA and 1 stroke were reported in patients with paroxysmal AF, 2 TIAs and 2 strokes were reported in patients with persistent AF, and 7 TIAs and 26 strokes were reported in patients with LSP AF.

In group 2 patients, both events occurred in LSP AF patients (Table 2). Both patients had subtherapeutic INR on the day of the procedure (1.6 and 1.7). Both patients had a transesophageal echocardiogram that did not show thrombus, and they did not receive low-molecular-weight heparin.

A significant reduction in thromboembolic risk in the on-warfarin group compared with the off-warfarin group was consistently observed across 6 major subgroups: female sex, age  $\geq 75$  years, diabetes mellitus, coronary artery disease, history

**Table 2. Thromboembolic Events According to AF Type**

	Group 1 (Off Warfarin; n=790), n (%)	Group 2 (On Warfarin; n=794), n (%)	P Value
Stroke/TIA combined	39 (4.9)	2 (0.25)	<0.001
Paroxysmal	2 (0.87)	0 (0.0)	0.25
Persistent	4 (2.3)	0 (0.0)	0.06
LSP	33 (8.5)	2 (0.49)	<0.001
Stroke	29 (3.7)	2 (0.25)	<0.001
Paroxysmal	1 (0.44)	0 (0.0)	0.47
Persistent	2 (1.15)	0 (0.0)	0.25
LSP AF	26 (6.7)	2 (0.49)	<0.001
TIA	10 (1.27)	0 (0.0)	<0.001
Paroxysmal	1 (0.44)	0 (0.0)	1.00
Persistent	2 (1.15)	0 (0.0)	0.50
LSP	7 (1.81)	0 (0.0)	0.016

AF indicates atrial fibrillation; LSP, long-standing persistent; and TIA, transient ischemic attack.

of cerebrovascular accident or TIA, and CHADS<sub>2</sub> score  $\geq 2$ . The relative risks with 95% CIs are shown in Figure 3.

Table 3 summarizes the major clinical characteristics of patients with and without thromboembolism.

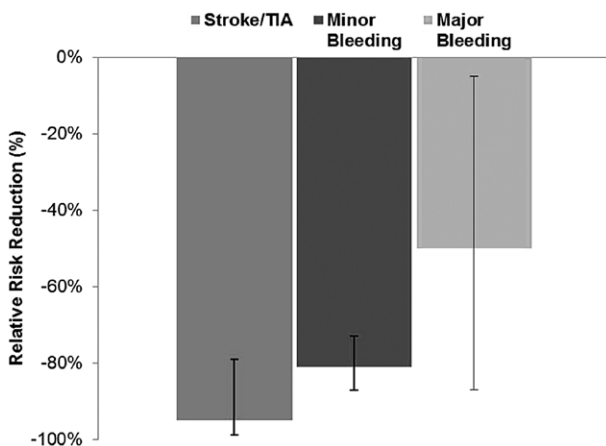
### Predictors of Periprocedural Thromboembolism

Patients were divided into 2 groups according to stroke/TIA outcome. Univariate analysis was performed comparing their clinical characteristics. Female sex, AF type, CHADS<sub>2</sub> score, history of diabetes mellitus, and history of stroke/TIA were associated with incidence of periprocedural thromboembolism (Table 3).

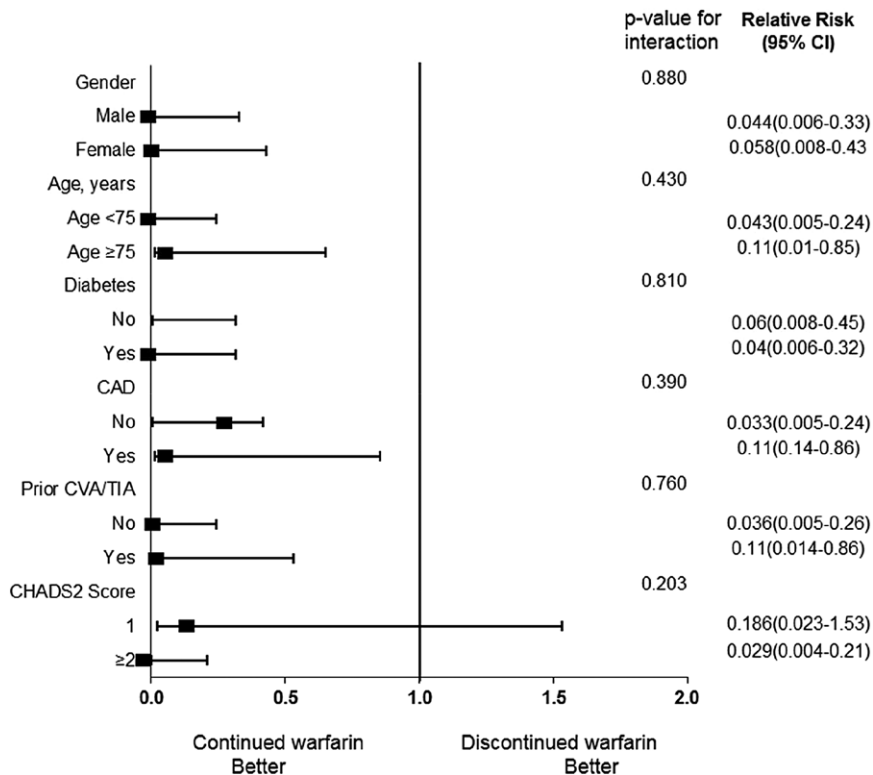
On multivariate analysis, warfarin discontinuation emerged as a strong predictor of periprocedural thromboembolism (OR, 13; 95% CI, 3.1–55.6;  $P<0.001$ ). Other significant predictors were female sex (OR, 2.2; 95% CI, 1.1–4.5;  $P=0.03$ ), CHADS<sub>2</sub> score (OR, 5.4; 95% CI, 3.5–8.1;  $P<0.001$ ), and LSP AF type (OR, 4.7; 95% CI, 2.6–8.5;  $P<0.001$ ). To evaluate the discriminatory capacity of the risk models and to assess warfarin use as a predictor of a periprocedural thromboembolic event, we fitted separate models (all above covariates with and without warfarin use) and computed the area under the curve (C statistic) and the respective 95% CIs. The C statistics for the risk models were compared by use of a nonparametric test. It was important to observe that adding warfarin use to the model significantly improved the discrimination ability (c index, 0.79; 95% CI, 0.62–0.88) compared with the model without warfarin use (c index, 0.71; 95% CI, 0.56–0.80;  $P=0.04$ ).

### Bleeding Complications

The incidence of major bleeding complications (8 in group 1 [0.76%] versus 3 in group 2 [0.38%];  $P=0.31$ ) and pericardial effusions (7 in group 1 [0.89%] versus 4 in group 2 [0.50%];  $P=0.36$ ) was not statistically different between groups. The incidence of minor bleeding complications was 174 in group 1 (22%) and 33 in group 2 (4.1%;  $P<0.001$ ). In addition, small hematoma had a higher likelihood of resulting in pseudoaneurysm (25 [3.2%] versus 4 [0.5%] for groups 1 and 2, respectively;  $P<0.001$ ).



**Figure 2.** Incidence of periprocedural thromboembolic events and bleeding complications were more frequent in the off-warfarin population (group 1). Patients on warfarin (group 2) had a 95% relative risk reduction in stroke/transient ischemic attack (TIA), 81% relative risk reduction in minor bleeding, and 50% relative risk reduction in major bleeding compared with group 1. Error bars represent 95% confidence interval of the relative risk reduction.



**Figure 3.** Relative risk and 95% confidence interval (CI) for stroke within specific subgroups. Squares represent relative risk; the error bars show the 95% CIs. CAD indicates coronary artery disease; CVA, cerebrovascular accident; and TIA, transient ischemic attack.

The management of pericardial effusion did not show any statistical difference (Table 4).

### Discussion

This is the first randomized study showing that performing catheter ablation of AF without warfarin discontinuation and with a therapeutic INR in patients at high risk for stroke significantly reduces the occurrence of periprocedural stroke/TIA and minor bleeding complications.

Warfarin discontinuation, nonparoxysmal AF, and high CHADS<sub>2</sub> score were the strongest predictors of cerebrovascular thromboembolic events. Warfarin discontinuation was associated with a 10-fold-higher chance of cerebral thromboembolism. Notably, ≈50% of the patient population had LSP AF, and ≈70% had a CHADS<sub>2</sub> score ≥2.

In addition, all patients in group 1 (off warfarin) underwent transesophageal echocardiography before ablation, whereas only 158 patients (20%) in group 2 (on warfarin) did, reinforcing the importance of warfarin in preventing thromboembolism. In addition, an important reduction in minor bleedings in group 2 (on warfarin) was found.

Many clinicians still fear performing invasive procedures in patients on therapeutic warfarin because of the perceived higher risk of bleeding complications. This randomized study showed the opposite.

Although the heparin bolus was different between groups, the ACT was kept at a high level in both arms and actually at a higher target in the off-warfarin group.

Because vascular access was obtained with the same technique and by the same operators in both groups, vascular access does not explain the higher bleeding complications of the off-warfarin strategy patients. In addition, minor bleedings

occurred after sheath removal, after partial reversal with protamine, and with similar ACT values in both groups. Therefore, it is unlikely that the larger bolus of heparin was responsible for the higher bleeding rate in the off-warfarin group. The higher bleeding rate should be attributed to the use of low-weight-molecular heparin. Notably, similar results with device implantation on warfarin have been recently published.<sup>11</sup>

In addition, both stroke/TIA and bleeding complications increase the patient's hospital stay and could result in long-term physical disability or cognitive impairment, thus influencing the total cost. Therefore, these results are clinically important for their potential socioeconomic implications.

### Previous Studies

The reported incidence of stroke/TIA varies from 0.9% to 5% even with irrigated-tip catheters.<sup>2-6</sup> Several surveys enrolling mainly paroxysmal AF patients have reported an incidence of stroke/TIA varying from 0.8% to 1.1% with open irrigated catheters.<sup>4,12</sup>

Observational and nonrandomized studies showed that performing catheter ablation on therapeutic warfarin reduces the risk of stroke and bleeding complications.<sup>5,6</sup> We first reported the possibility of performing catheter ablation while maintaining therapeutic anticoagulation with warfarin in a small and then in a large series of consecutive patients.<sup>5,13</sup> All of these studies showed that the periprocedural risk of stroke/TIA is higher in patients with nonparoxysmal AF and with a high CHADS<sub>2</sub> score.

The present study shows that, when comparing patients at high thromboembolic risk, ablation procedures performed with uninterrupted warfarin protect against the risk of periprocedural stroke.

**Table 3. Patient Characteristics With and Without Thromboembolic Events (TIA/Stroke)**

	Patients With Thromboembolic Events (n= 41)	Patients Without Thromboembolic Events (n=1543)	P
Sex, n (%)			
Male	24 (59)	1168 (77)	0.012
Female	17 (42)	375 (24)	
Age, y	63±12	60±10	0.06
AF type, n (%)			
Paroxysmal	2 (5)	427 (28)	<0.001
Persistent	4 (10)	359 (23)	
LSP	35 (85)	757 (49)	
Patients with risk factors, n (%)			
CAD	9 (22)	379 (25)	0.70
CHF	8 (20)	246 (16)	0.53
Hypertension	38 (93)	1262 (82)	0.07
Age ≥75 y	10 (24)	218 (14)	0.065
Diabetes mellitus	23 (56)	597 (39)	0.02
Prior stroke/TIA	13 (32)	106 (7)	<0.001
CHADS <sub>2</sub> score, n (%)			
1	7 (17)	428 (28)	0.15
2	11 (27)	541 (35)	
3	14 (34)	308 (20)	
4	6 (15)	189 (12)	
≥5	2 (5)	78 (5)	
LVEF, %	53±11	52±9	0.16
LA diameter, mm	44±12	45±7	0.38

AF indicates atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; LA, left atrial; LSP, long-standing persistent; LVEF, left ventricular ejection fraction; and TIA, transient ischemic attack.

Of note, when we considered the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and not the CHADS<sub>2</sub> score, the results of our study did not differ.

### Bleeding and Tamponade

No statistical differences between groups were found for major bleeding. Although not statistically different, group 2 (on warfarin) had a relative risk reduction for major bleedings of 50% compared with group 1 (off warfarin).

Of great clinical interest is the fact that in case of tamponade no major differences in patient management were found between groups with the exception of more fluid aspirated and more protamine used in group 2. In group 2, besides protamine to reverse the effect of intravenous heparin, fresh-frozen plasma was necessary to reverse the effect of warfarin (Table 4).

Minor bleeding complications were significantly higher in the off-warfarin group.

Of note is the fact that all procedures were performed under intracardiac echocardiography guidance. As reported in our meta-analysis,<sup>6</sup> the use of intracardiac echocardiography could help reducing bleeding complications, in addition to facilitating transseptal access, confirming ablation catheter contact, and improving anatomic orientation.

**Table 4. Pericardial Effusion Management**

	Off Coumadin, n=7	On Coumadin, n=4
Patients with pericardial effusion requiring pericardiocentesis, n (%)	7 (100)	4 (100)
Requiring surgery, n (%)	1 (14.3)	0 (0)
Requiring fresh-frozen plasma or transfusion, n (%)	2 (28.6)	4 (100)
Mean pericardial fluid aspiration, cm <sup>3</sup>	750±300	950±300
Mean protamine for reversal, mg	65±8	85±12*

\*Significant difference between groups ( $P<0.05$ ).

### Newer Anticoagulants

Recently, new anticoagulants such as dabigatran, rivaroxaban, apixaban, and edoxaban have been introduced into the clinical practice. Their use in the periprocedural AF ablation setting has not yet reached consensus.

Contrasting data comparing dabigatran with the on-warfarin approach are present in the literature.<sup>14-17</sup> Most of these studies discontinued dabigatran before the procedure and included mainly patients with paroxysmal AF.

We feel that the results of the COMPARE Trial should not be extrapolated to these new oral anticoagulant drugs.

We showed that on-warfarin treatment protects against periprocedural thromboembolism. Because the risk of this complication during AF ablation is confined predominantly to patients with nonparoxysmal AF, studies assessing the protective value of newer anticoagulants in paroxysmal patients are less relevant. Therefore, future studies assessing the protecting value of newer anticoagulants in the same setting should be performed in comparison with on-warfarin treatment and should enroll mainly patients with nonparoxysmal AF because these events are less prevalent in paroxysmal patients.<sup>18</sup>

### Study Limitations

Operators were not blinded to the anticoagulation management, which introduced a bias in the study. In addition, subclinical femoral vein thrombosis might have been missed in this study, although this is less likely to happen in patients on warfarin.

### Conclusions

This is the first open-label, randomized, parallel-group, multicenter study showing that performing catheter ablation of AF without warfarin discontinuation in patients at high risk for stroke and with nonparoxysmal AF statistically reduces the occurrence of periprocedural stroke/TIA and bleeding complications. The role of the newer oral anticoagulants requires further investigation in high-risk patients and should be compared with on-warfarin treatment.

### Disclosures

Dr Di Biase serves as a consultant for Hansen Medical, Biosense-Webster, and St. Jude Medical. Dr Di Biase also received speaker honoraria from Biotronik and Atricure. Dr Gallinghouse is a consultant for Hansen Medical. Dr Natale has received honoraria for serving on the speakers' bureau for St. Jude Medical, Boston Scientific, Medtronic, and Biosense-Webster. Dr Natale is consultant for Biosense Webster and St. Jude Medical. The other authors report no conflicts.

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## CLINICAL PERSPECTIVE

Periprocedural thromboembolic and hemorrhagic events represent serious complications of radiofrequency catheter ablation of atrial fibrillation (AF). Indeed, the incidence of thromboembolic events varies from 0.9% to 5%, depending on the anticoagulation strategy used in the periprocedural period. Although discontinuation of warfarin 3 to 5 days before ablation with and without bridging with low-weight-molecular heparin has shown a higher thromboembolic risk than radiofrequency catheter ablation without warfarin discontinuation under therapeutic international normalized ratio, no randomized, controlled trial on this topic existed. The Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) trial is the first randomized, multicenter study comparing AF ablation performed with and without warfarin discontinuation. Notably, the majority of enrolled patients had a high risk for stroke (nonparoxysmal AF and CHADS<sub>2</sub> score >2) in ≈70% of the cases. The incidence of thromboembolic events (primary end point) was 4.9% in group 1 (off warfarin) and 0.25% in group 2 (on warfarin;  $P<0.001$ ). The majority of events occurred in patients with nonparoxysmal AF. No significant difference in major bleeding and pericardial effusion was seen, whereas a significantly higher number of patients had minor bleeding (especially groin hematomas) in group 1 (22%) compared with group 2 (4.1%;  $P<0.001$ ). Preprocedural transesophageal echocardiography was not performed in the on-warfarin group with therapeutic international normalized ratio. AF ablation on therapeutic international normalized ratio appears safer than the off-warfarin strategy. Randomized studies assessing the protective value of newer oral anticoagulants during radiofrequency catheter ablation should be performed only in comparison with on-warfarin treatment and possibly in nonparoxysmal AF patients.

**Periprocedural Stroke and Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation With Different Anticoagulation Management: Results From the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) Randomized Trial**

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