Periprocedural Stroke and Bleeding Complications in Patients undergoing
Catheter Ablation of Atrial Fibrillation with Different Anticoagulation
Management: Results from the "COMPARE" Randomized Trial

Running title: Di Biase et al.; AF ablation on Warfarin

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Abstract

**Background**—Periprocedural thromboembolic (TE) 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 TE 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 TE and hemorrhagic events after radiofrequency catheter ablation. Patients with CHADS2 score ≥ 1 were included. Patients were randomly assigned in a 1:1 ratio to the off-warfarin or on-warfarin arm. Incidence of TE events in the 48 hours post-ablation was the primary end point of the study. The study enrolled 1584 patients; 790 assigned to discontinue warfarin (group I) and 794 to continuous warfarin (group II). No statistical difference in the baseline characteristics was observed. There were 39 TE [3.7% (29) strokes and 1.3% (10) TIA] events in group I; 2 (0.87%) in PAF (paroxysmal), 4 (2.3%) in persistent AF, and 33 (8.5%) in long standing persistent (LSP) AF. Only 2 (0.25%) strokes in LSP patients were observed in group II (p < 0.001). Warfarin discontinuation emerged as a strong predictor of periprocedural TE (odds ratio (OR) 13, 95% CI 3.1 to 55.6 p < 0.001).

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

**Clinical Trial Registration Information**—www.clinicaltrials.gov/. Identifier: NCT01006876.

**Key words:** radiofrequency, warfarin, periprocedural, stroke, ablation, atrial fibrillation
Introduction

Radiofrequency catheter ablation (CA) for atrial fibrillation is an effective therapeutic option for the treatment of symptomatic drug refractory atrial fibrillation\(^1\).

The complexity of the procedure and its operator dependency, expose patients to a considerable number of potential complications\(^2-4\).

Periprocedural thromboembolic (TE) events represent one of the most worrisome complications of CA because of the potential long term effect on patients' functionality\(^2-4\).

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 TE risk, when compared to other strategies discontinuing warfarin before ablation, no randomized study currently exists\(^2-6\).

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 radio-frequency CA for AF.

Methods

Study Design

“COMPARE” was a prospective, randomized, parallel-group, multicenter study assessing the role of continuous warfarin therapy in preventing periprocedural thromboembolic (TE) events after radio frequency catheter ablation. Inclusion criteria were: age 18 or above, INR in the range of 2.0-3.0 in the last 3-4 weeks prior to ablation and CHADS2 score \(\geq 1\).

During the study period, 2234 patients met the inclusion criteria and 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 anticoagulation strategy of either discontinued warfarin (group I) or continuous warfarin (group II). To ensure equal group allocation within the participating centers, block randomization was performed with study center as blocking variable. A central randomization algorithm was used to generate the randomization code. This was a non-stratified trial; no stratification on subgroup membership was performed.

The study was approved by the IRB.

End Points

Incidence of TE events during 48 hour post-ablation was the primary end point of the study. Thromboembolic events were defined as stroke, transient ischemic attack (TIA), or systemic thrombo-embolism.

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

Anticoagulation management

All patients (groups I and II) were on warfarin before the procedures to achieve 3-4 weeks of therapeutic INRs. Transesophageal echocardiogram (TEE) was performed in all patients from Group I and when the patient presented with a sub-therapeutic INR on the day of the procedure in group II.

Group I (off Warfarin Group).

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

In this group, Warfarin was discontinued 2-3 days before the ablation and bridged with low molecular weight heparin.

Specifically, 1 mg/kg of enoxaparin was administered twice daily until the evening prior to ablation procedure.

A bolus of 15000 intravenous (i.v.) UI heparin was given prior to the trans-septal puncture.

A continuous infusion of heparin of 1000 U/hr was started. The infusion was adjusted to maintain an activated coagulation time (ACT) above 350 seconds.

During the procedures, the trans-septal sheaths were continuously infused with heparinized saline.

Every effort was taken to avoid air embolism.

Protamine was administered after the ablation procedure was completed to partially reverse the heparin effect and a single Aspirin 325 mg was given in the EP lab.

Sheaths were pulled when activated clotting time (ACT) was <200 seconds.

Three hours after ablation, enoxaparin 0.5 mg/kg twice daily was routinely started and was stopped when the INR was >2 and warfarin was restarted the night of the procedure.

**Group II (on Warfarin Group)**

All patients continued uninterrupted Warfarin. The INR had to be “therapeutic” and was monitored every week for the 3-4 weeks preceding the ablation. If the day of the procedure patients had INR>3.5 they were excluded, while if 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 sub-therapeutic INR and were not excluded.
A bolus of 10000 unfractionated heparin (UI) in males and 8000 in females was given prior to the trans-septal puncture.

During the procedures the ACT was kept above 300 seconds.

During the procedures, the trans-septal sheaths were continuously infused with heparinized saline.

Every effort was taken to avoid air embolism.

Protamine was administered after the completed ablation procedure to partially reverse the heparin effect.

Sheaths were pulled when activated clotting time (ACT) was <200 seconds.

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

Ablation Procedure

Paroxysmal AF

Briefly, pulmonary vein antrum isolation (PVAI) guided by circular mapping catheter and by intracardiac echocardiography (ICE) was performed.

The electrical isolation of the pulmonary veins could be extended to the posterior wall contained between the pulmonary veins.

In all patients, isoproterenol up to 30 mcg/min was given to disclose non-PV triggers.

If AF/AT (AT=atrial tachyarrhythmia) was present and/or induced, ablation was performed to terminate the tachycardia and when unsuccessful, cardioversion was performed to restore sinus rhythm.

Persistent and Long Standing Persistent AF

Briefly, pulmonary vein antrum isolation (PVAI) guided by circular mapping catheter and by intracardiac echocardiography (ICE) was performed;
The electrical 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 (CFAEs) in the left atrium and in the coronary sinus was also performed if fractionated potentials were found.

In patients with AF/AT, 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 mcg/min was given to disclose non PV triggers.

**Neurologic Evaluation**

All patients underwent neurologic examination before and at the end of the procedure and every 2 hours thereafter. The post procedure and pre-discharge examinations were performed by a physician while the remaining evaluations at 2 hours intervals were performed by the nursing staff.

**Definitions**

Stroke was defined as the onset of a new neurologic deficit that occurred anytime during or within 48 hours of the procedure. If the duration of the deficit was less than 24 hours, it was defined as a transient ischemic attack (TIA). If the deficit persisted for a longer period and resulted in positive finding on a computed tomography (CT) or magnetic resonance imaging (MRI), it was defined as a stroke. Stroke and TIA diagnosis were performed by a neurologist who was blinded to patient’s group assignment, while the diagnosis of peripheral embolic events or deep venous thrombosis were performed by other physicians blinded as well to the group assignment.

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

Our definitions are in accordance with the recently published BARC consortium ones\textsuperscript{9, 10}.

**Statistical Analysis:**

Incidence of TE events during 48 hour post-ablation was the primary end point of the study.

An earlier prospective study from our group reported 0.9% TE event in patients who discontinued warfarin and none in continuous warfarin group\textsuperscript{5}.

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

Continuous data are described as mean ± standard deviation (SD) and as counts and percent if categorical. Student’s t-test, chi-square test (Fisher’s exact for cell value <10) test were used to compare differences across groups. Multivariable logistic model was used for identifying significant predictors of periprocedural TE events. Potential confounders were entered into the model based on known clinical relevance, or significant association observed in univariate analysis. Controlling variables used in the model were: age, LA diameter, LV EF\%, cardioversion, history of coronary artery disease and CHADS2 score.

CHADS2 score was entered in the logistic model as a continuous variable. Tests were run to examine the presence of multi-collinearity of the covariates. The discrimination ability of the models in predicting periprocedural TE was assessed by c-statistics and receiver operating characteristic (ROC) curve. The odds ratio (OR) and 95\% confidence interval (CI) were computed for periprocedural TE. All tests were two-sided and a P-value <0.05 was considered
statistically significant. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

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 I, n=790) or undergo the procedure with continuous warfarin (group II, n=794) (figure 1).

The baseline characteristics and risk factors were well balanced between the two groups. In group I the average age was 61±10 years, 76% male, 29% paroxysmal (PAF), 22% persistent, 49% long-standing persistent (LSP) AF, LA size 44.8±7 mm, and LVEF 53±12%.

Patients in group II were 62±12 years, 74% male, 25% PAF, 24% persistent, 51% LSP AF, LA size 45.1±7 mm, and LVEF 52±13%.

In group I, 561(71%) patients had CHADS2 score ≥2 compared to 588(74%) in group II (p= 0.17). Fifty-five (7%) patients had history of previous stroke or transient ischemic attack (TIA) in group I compared to 64 (8%) patients in group II (p=0.41).

The baseline parameters are presented in table 1.

Transesophageal echo (TEE) was performed on the day before or the day of the procedure for all patients in Group I, and only in 20% of patients in Group II because of a subtherapeutic INR on presentation or at physician discretion (p<0.001).

Intra-Procedure Parameters

Sixty-four percent of patients in Group I (506 patients), 65% (516 patients) in Group II entered the electrophysiology laboratory in AF/AT (p=0.69). Persistence of AF/AT at end of the
procedure before cardioversion was observed in 205(26%) patients in group I, and 224(28%) patients in group II (p=0.31).

The mean procedure time was 170±82 min and 168±71 min (p=0.62) for group I and II respectively (table 1).

Study Outcomes

Periprocedural symptomatic TE events occurred in 39 (4.9%) patients in group I [29(3.7%) stroke and 10 (1.3%) TIA] and only in 2 (0.25%) patients (both stroke) in group II (p <0.001).

Compared to group I, patients in group II had significantly lower risk for periprocedural TE; the un-adjusted relative risk was 0.051 (95% CI 0.012 to 0.211), with a relative risk reduction of 95% in favor of the uninterrupted warfarin (figure 2).

Eighty-five percent of all the TE events (35/41) occurred in the LSP population. In the off warfarin population (group I), one TIA and one stroke were reported in PAF, 2 TIAs and 2 strokes in persistent AF patients while 7 TIAs and 26 strokes were reported in LSP AF patients.

In group II patients, both events occurred in LSP AF patients (table 2). Both patients had subtherapeutic INR the day of the procedure (1.6 and 1.7 respectively). Both patients had a TEE that did not show thrombus and did not receive LMWH.

Significant reduction in TE risk in the “on” warfarin group, as compared to the “off” warfarin, was consistently observed across six major subgroups- female gender, age ≥75 years, diabetes, coronary artery disease, and prior history of cerebro vascular accident (CVA) and or /TIA, and CHADS2 score ≥2. The relative risks with 95% CI are shown in figure 3.

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

Predictors of Periprocedural TE

Patients were divided into two groups according to stroke/TIA outcome and univariate analysis.
was performed comparing their clinical characteristics. Female gender, AF type, CHADS2 score, history of diabetes, prior history of stroke/TIA were associated with incidence of periprocedural TE (table 3).

At multivariate analysis, warfarin discontinuation emerged as a strong predictor of periprocedural TE (odds ratio (OR) 13, 95% CI 3.1 to 55.6 p<0.001). Other significant predictors were female gender [OR 2.2 (1.1 to 4.5), p .03], CHADS2 score [OR 5.4 (3.5 to 8.1), p<0.001], and LSP AF type [OR 4.7(2.6 to 8.5), p<0.001]. To evaluate the discriminatory capacity of the risk models and assess the ability of warfarin use in predicting periprocedural TE event, we fitted separate models (all above covariates ± warfarin use) and computed the area under the curve (C statistic) and the respective 95% confidence intervals. The C statistics for the risk models were compared using a nonparametric test. It was important to observe that, adding warfarin use to the model significantly improved the discrimination ability [c-index 0.79 (0.62-0.88)] compared to the one without [c-index 0.71 (0.56-0.80)], (p=0.04).

Bleeding Complications

The Incidence of major bleeding complications [8(0.76%) in group I vs. 3(0.38%) group II, p= .31] and pericardial effusions [7(0.89%) in group 1 vs. 4(0.50%) group 2, p=.36] was not statistically different between groups. The incidence of minor bleeding complication was 174 (22%) in group I and 33 (4.1%) in group II (p<.001).

In addition, small hematoma had a higher likelihood of resulting into pseudo aneurysm 25(3.2%) vs 4(0.5%) respectively for group I and II (p<.001).

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 atrial fibrillation without warfarin discontinuation and with a therapeutic INR in patients at high risk for stroke significantly reduces the occurrence of peri-procedural Stroke/TIA and minor bleeding complications.

Warfarin discontinuation, non paroxysmal atrial fibrillation and high CHADS$_2$ score were the strongest predictors of cerebrovascular thromboembolic events. Warfarin discontinuation had a ten-fold higher chance of cerebral thromboembolism. Notably, around 50% of the patient population had LSP AF and around 70% had CHADS$_2$ score greater than or equal to two.

In addition, all patients in group I (off warfarin) underwent TEE before ablation while only 158 patients (20%) of group II patients (on warfarin) did, reinforcing the importance played by warfarin in preventing TE.

In addition an important reduction of minor bleedings in group II (on warfarin) was found.

Despite many clinicians still fear performing invasive procedure on therapeutic warfarin due to the perceived higher risk of bleeding complications, this randomized study showed the opposite.

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

Since vascular access was obtained with the same technique and by the same operators in both group, this does not explain the higher bleeding complications of the “off” warfarin strategy patients. In addition, minor bleedings occurred after sheath removal, following partial reversal with protamine and with similar ACT values in both groups. Therefore it is unlikely that the
larger bolus of heparin was responsible of 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^{11}.

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

**Previous studies**

The reported incidence of stroke/TIA varies from 0.9 up to 5% even with irrigated tip catheters (2-6). Several surveys mainly enrolling paroxysmal AF patients have reported an incidence of TIA/Stroke varying from 0.8% to 1.1% with open irrigated catheters^{4,12}.

Observational and not randomized studies showed that performing catheter ablation on therapeutic warfarin reduces the risk of stroke and bleeding complications^{5,6}.

We first reported the possibility of performing CA while maintaining therapeutic anticoagulation with warfarin in a small and then in a large series of consecutive patients^{5,13}.

All these studies showed that the periprocedural higher risk of TIA/stroke is higher in patients with non paroxysmal AF and with a high CHADS2 score.

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

Of note, when considering the CHA2DS2-VASc Score and not the CHA2DS2 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 II (on warfarin) had a relative risk reduction for major bleedings of 50% when compared to group I (off warfarin).

Of great clinical interest is the fact that in case of tamponade no major differences in the patients’ management were found between groups with the exception of more fluid aspirated and more protamine utilized in group II. In group II, besides protamine to reverse the effect of i.v. 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 ICE guidance. As reported in our metanalysis\(^6\), the use of ICE could help reducing bleeding complication, in addition to facilitate transseptal access, confirm ablation catheter contact and improve anatomical orientation.

Newer Anticoagulants

Recently new anticoagulants such as dabigratan, rivaroxaban, apixaban and edoxaban have been introduced in the clinical practice.

Their use in the periprocedural AF ablation setting has not yet reached consensus.

Contrasting data comparing dabigratan to the “on warfarin” approach are present in the literature\(^{14-17}\). Most of these studies discontinued dabigratan before the procedure and mainly included 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 peri procedural TE. Since the risk of this complication during AF ablation is predominantly confined to patients with
nonparoxysmal AF, studies assessing the protecting 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 mainly enroll pts with non paroxysmal AF since in paroxysmal patients these events are less prevalent.

**Study limitation**

Operators were not blinded to the anticoagulation management thus introducing 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 atrial fibrillation without warfarin discontinuation in patients at high risk for stroke and with non paroxysmal atrial fibrillation, statistically reduces the occurrence of peri-procedural stroke/TIA and bleeding complications.

The role of the newer oral anticoagulants requires further investigation in high risk patients and should be compared to on warfarin treatment.

**Conflict of Interest Disclosures:** Luigi Di Biase serves as consultant for Hansen Medical, Biosense-Webster and St Jude Medical. G. Joseph Gallinghouse is a consultant for Hansen Medical. Andrea Natale has received honoraria to the speakers’ bureau from St.Jude Medical, Boston Scientific, Medtronic, and Biosense-Webster. Dr. Natale is consultant for Biosense Webster and St Jude Medical. All the remaining authors have no disclosures.
References:


Table 1. Baseline characteristic.

<table>
<thead>
<tr>
<th></th>
<th>Group I off Coumadin (N= 790)</th>
<th>Group II on Coumadin (N= 794)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>602(76)</td>
<td>590(74)</td>
<td>0.40</td>
</tr>
<tr>
<td>Age, Years</td>
<td>61±10</td>
<td>62±12</td>
<td>0.07</td>
</tr>
<tr>
<td>AF Type, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>229(29)</td>
<td>200(25)</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>174(22)</td>
<td>189(24)</td>
<td>0.23</td>
</tr>
<tr>
<td>LSP</td>
<td>387(49)</td>
<td>405(51)</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>182(23)</td>
<td>206(26)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>640(81)</td>
<td>660(83)</td>
<td>0.27</td>
</tr>
<tr>
<td>CHF</td>
<td>118(15)</td>
<td>136(17%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes</td>
<td>302(38)</td>
<td>318(40)</td>
<td>0.46</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>55(7)</td>
<td>64(8)</td>
<td>0.41</td>
</tr>
<tr>
<td>CHADS2 Score, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>229(29)</td>
<td>206(26)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>268(34)</td>
<td>284(36)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>170(22)</td>
<td>152(19)</td>
<td>0.19</td>
</tr>
<tr>
<td>4</td>
<td>94(12)</td>
<td>101(13)</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>32(4.1)</td>
<td>48(6.0)</td>
<td></td>
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<tr>
<td>LVEF, %</td>
<td>53±12</td>
<td>52±13</td>
<td>0.11</td>
</tr>
<tr>
<td>LA Diameter, mm</td>
<td>44.8±7</td>
<td>45.1±7</td>
<td>0.43</td>
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<tr>
<td>Fluoroscopy Time, min</td>
<td>68±29</td>
<td>70±32</td>
<td>0.19</td>
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<tr>
<td>Radio-frequency Time, min</td>
<td>76±44</td>
<td>77±36</td>
<td>0.60</td>
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<tr>
<td>Procedure Time, min</td>
<td>170±82</td>
<td>168±71</td>
<td>0.62</td>
</tr>
</tbody>
</table>

AF- atrial fibrillation, LSP- long standing persistent, CAD- coronary artery disease, CHF- congestive heart failure, LVEF- left ventricular ejection fraction, TIA- transient ischemic attack, LA- left atrial. There was no significant difference (at P<0.05) between the two groups.
Table 2. TE events according to AF type.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (off-warfarin, n=790)</th>
<th>Group 2 (on-warfarin, n=794)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA Combined, n(%)</td>
<td>39(4.9%)</td>
<td>2(0.25%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>2(0.87%)</td>
<td>0(0.0%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Persistent</td>
<td>4(2.3%)</td>
<td>0(0.0%)</td>
<td>0.06</td>
</tr>
<tr>
<td>LSP</td>
<td>33(8.5%)</td>
<td>2(0.49%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stroke, n(%)</td>
<td>29(3.7%)</td>
<td>2(0.25%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>1(0.44%)</td>
<td>0(0.0%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Persistent</td>
<td>2(1.15%)</td>
<td>0(0.0%)</td>
<td>0.25</td>
</tr>
<tr>
<td>LSP</td>
<td>26(6.7%)</td>
<td>2(0.49%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TIA, n(%)</td>
<td>10(1.27%)</td>
<td>0(0.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>1(0.44%)</td>
<td>0(0.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Persistent</td>
<td>2(1.15%)</td>
<td>0(0.0%)</td>
<td>0.50</td>
</tr>
<tr>
<td>LSP</td>
<td>7(1.81%)</td>
<td>0(0.0%)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

LSP- long standing persistent atrial fibrillation, TIA- transient ischemic attack

Table 3. Patient characteristics with and without TE (TIA/Stroke).

<table>
<thead>
<tr>
<th></th>
<th>Patients with TE Events (n= 41)</th>
<th>Patients without TE Events (n=1543)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24(59)</td>
<td>1168(77)</td>
<td>0.012</td>
</tr>
<tr>
<td>Female</td>
<td>17(42)</td>
<td>375(24)</td>
<td></td>
</tr>
<tr>
<td>Age, Years</td>
<td>63±12</td>
<td>60±10</td>
<td>0.06</td>
</tr>
<tr>
<td>AF Type, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>2(5)</td>
<td>427(28)</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>4(10)</td>
<td>359(23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long-standing Persistent</td>
<td>35(85)</td>
<td>757(49)</td>
<td></td>
</tr>
<tr>
<td>Patients with risk factors, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>9(22)</td>
<td>379(25)</td>
<td>0.70</td>
</tr>
<tr>
<td>CHF</td>
<td>8(20)</td>
<td>246(16)</td>
<td>0.53</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38(93)</td>
<td>1262(82)</td>
<td>0.07</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>10(24)</td>
<td>218(14)</td>
<td>0.065</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23(56)</td>
<td>597(39)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>13(32)</td>
<td>106(7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHADS2 Score, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7(17)</td>
<td>428(28)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11(27)</td>
<td>541(35)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>14(34)</td>
<td>308(20)</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>6(15)</td>
<td>189(12)</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>2(5)</td>
<td>78(5)</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>53±11</td>
<td>52±9</td>
<td>0.16</td>
</tr>
<tr>
<td>LA Diameter, mm</td>
<td>44±12</td>
<td>45±7</td>
<td>0.38</td>
</tr>
</tbody>
</table>

LSP- long standing persistent atrial fibrillation, CAD- coronary artery disease, CHF- congestive heart failure, TIA- transient ischemic attack, LVEF- left ventricular ejection fraction.
Table 4. Pericardial Effusion Management.

<table>
<thead>
<tr>
<th></th>
<th>Off-Coumadin, n=7</th>
<th>On-Coumadin, n=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Pericardial Effusion requiring pericardiocentesis</td>
<td>7(100%)</td>
<td>4(100%)</td>
</tr>
<tr>
<td>Requiring Surgery</td>
<td>1(14.3%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Requiring Fresh Frozen Plasma and or transfusion</td>
<td>2(28.6%)</td>
<td>4(100%)</td>
</tr>
<tr>
<td>Mean Pericardial Fluid Aspiration, cm3</td>
<td>750±300</td>
<td>950±300</td>
</tr>
<tr>
<td>Mean Protamine for Reversal, mg</td>
<td>65±8</td>
<td>85±12*</td>
</tr>
</tbody>
</table>

Significant differences between groups is indicated by * for P < 0.05

Figure Legends:

Figure 1. Study design showing enrollment and follow-up of study patients

Figure 2. Incidence of periprocedural TE events and bleeding complications were more frequent in off-warfarin population (group I). Patients on warfarin (group II) had a 95% relative risk reduction of stroke/TIA, 81% of minor bleeding, and 50% of major bleeding when compared to group I. The error bars represent 95% confidence interval of relative risk reduction.

Figure 3. The figure displays the relative risk and 95% confidence interval for stroke within specific subgroups. The squares represent relative risk and the error bars show the 95% confidence intervals. CAD: coronary artery disease, CVA/TIA: cerebro vascular accident/transient ischemic attack.
1584 eligible patients were enrolled

Underwent randomization and were assigned to:

Group 1: warfarin discontinuation (n=790)

Group 2: Continuous warfarin (n=794)

Underwent catheter ablation, assessed for symptomatic periprocedural TE events at 48 hours post-procedure

39 Periprocedural TE events:
- Stroke- 29 (3.7%),
- TIA- 10 (1.3%)

Total 2 (0.25%) TE events (both stroke, no TIA)
Figure 2
Figure 3
Periprocedural Stroke and Bleeding Complications in Patients undergoing Catheter Ablation of Atrial Fibrillation with Different Anticoagulation Management: Results from the "COMPARE" Randomized Trial

Luigi Di Biase, David Burkhardt, Pasquale Santangeli, Prasant Mohanty, Javier Sanchez, Rodney Horton, G. Joseph Gallinghouse, Sakis Themistoclakis, Antonio Rossillo, Dhanunjaya Lakkireddy, Madhu Reddy, Steven Hao, Richard Hongo, Salwa Beheiry, Jason Zagrodzky, Rong Bai, Sanghamitra Mohanty, Claude S. Elayi, Giovanni Forleo, Gemma Pelargonio, Maria Lucia Narducci, Antonio Dello Russo, Michela Casella, Gaetano Fassini, Claudio Tondo, Robert A. Schweikert and Andrea Natale