

**Safety and efficacy of contemporary catheter ablation for atrial fibrillation patients with a history of cardioembolic stroke in the era of direct oral anticoagulants**

(直接経口抗凝固薬時代における、脳梗塞既往を有する心房細動患者に対する最新のカテーテルアブレーション治療の安全性と有効性)

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### Abstract

**Backgrounds:** Safety and efficacy of the contemporary atrial fibrillation (AF) ablation in patients with a recent or previous history of cardioembolic stroke (CS) or transient ischemic attack (TIA) remain to be established.

**Methods:** The total of 447 patients who underwent first-ever contact force (CF)-guided AF ablation with circumferential pulmonary vein isolation were included. Of these, 17 had CS or TIA within 6 months before ablation (Group 1), 30 more than 6 months before ablation (Group 2), and the other 400 without CS or TIA (Group 3). Procedural complications and recurrence of AF and atrial tachyarrhythmias were compared among the 3 groups.

**Results:** The mean age was  $71\pm 7$ ,  $66\pm 9$ , and  $61\pm 11$  years in Groups 1, 2, and 3, respectively ( $p<0.05$ , Group 1 versus Group 3). The oral anticoagulants were warfarin ( $n=108$ , 24.1%), dabigatran ( $n=101$ , 22.6%), rivaroxaban ( $n=147$ , 32.9%), apixaban ( $n=87$ , 19.5%) and edoxaban ( $n=4$ , 0.9%), and did not differ among the 3 groups. Median follow-up period was 14 [IQR 12-22], 13 [12-14], and 12 [10-16] months, respectively. One episode of cardiac tamponade, 2 episodes of arteriovenous fistula, and some minor complications occurred in Group 3, but no complications

occurred in Groups 1 and 2 in the periprocedural period. Although one episode of CS occurred 11 days after the procedure in Group 3, there were no periprocedural CS, TIA or major bleedings in Groups 1 and 2. AF recurrence free rate after the procedure was 76.5%, 86.7% and 79.1% in Groups 1, 2 and 3, respectively, and there was no difference in Kaplan-Meier curves among the 3 groups.

**Conclusion:** The safety and efficacy of CF-guided AF ablation in the era of direct oral anticoagulants in patients with a recent or previous history of CS or TIA are similar to those in patients without it.

## Introduction

Atrial fibrillation (AF) is a common arrhythmia in clinical practice and plays a key role as a cause of cardioembolic stroke (CS) [1]. Recent pooled study in Japanese non-valvular atrial fibrillation (NVAF) patients (n=3588) without anticoagulation showed that age  $\geq 75$  years, hypertension, and prior cerebral infarction or TIA among CHADS<sub>2</sub> score components are a significant risk factor for incidence of ischemic stroke components [2]. Notably, prior cerebral infarction or TIA shows the highest hazard ratio (HR)=3.25 among them, suggesting that it is of significant importance to manage adequately NVAF patients with prior cerebral infarction or TIA in order to prevent recurrence of CS [2]. Although anticoagulation therapy significantly reduces the incidence of thromboembolic events including CS [3,4], prior cerebral infarction or TIA still remains being a significant risk after adjusting for anticoagulation therapy [5,6].

Catheter ablation is an effective treatment for the patients with drug-refractory symptomatic AF [7], since successful AF ablation may reduce the risk of cardiovascular events including CS and death [8,9]. We and others demonstrated that recently developed contact force (CF)-guided AF ablation is more effective and safe than the conventional AF ablation without use of CF systems [10-12]. Furthermore, direct oral anticoagulants (DOACs) are shown to be comparable to warfarin in patients undergoing AF ablation [13-15]. Although recent report showed that AF patients with a prior history of cerebral infarction can safely undergo AF ablation, mostly non CF-guided ablation with warfarin, without periprocedural thromboembolic complications [16], little is known about safety and efficacy of AF ablation with use of CF systems and DOACs for those patients at high risk of

thromboembolic events. The purpose of this study was to investigate the safety and efficacy of CF-guided AF ablation in patients with a recent or prior history of CS or TIA in the era of DOACs.

## **Methods**

### Study population

A total of 466 patients undergoing their first-ever CF-guided AF ablation from October 2012 to December 2015 were included. Patients with left ventricular ejection fraction (LVEF) < 30% (n=7) or left atrial diameter > 55 mm (n=12) were excluded. The remaining 447 patients were divided into 3 groups according to the history of CS or TIA: 17 with CS or TIA within 6 months before AF ablation (Group 1), 30 more than 6 months before the ablation (Group 2), and the other 400 without CS or TIA (Group 3). Flow chart of the study patients is shown in Figure 1. Clinical characteristics, anticoagulant use, ablation protocol, procedural complications, and follow-up data were retrospectively obtained from the medical records. The study protocol was approved by the Ethics Committee of our institution (2016-1035).

### Cardiac catheterization and ablation protocol

Cardiac catheterization and CF-guided AF ablation procedure were performed as described previously[10,11,17,18]. A 6 Fr double decapolar steerable catheter (BeeAT, Japan Lifeline Co, Tokyo, Japan) was inserted into the coronary sinus via the internal jugular vein under local anesthesia. Two 8.5 Fr long sheaths (Daig SL1, St.Jude Medical, St Paul, MN, USA) were inserted into the left atrium (LA). A 10 Fr SoundStar ultrasound catheter (Biosense Webster, Diamond Bar, Ca, USA) was inserted into the right atrium, and anatomic mapping of the LA by CartoSound

module equipped in a CARTO3 system (Biosense Webster) was performed.

Intracardiac echography (ICE) images were displayed through the CartoSound module using an Acuson X300PE echocardiography system (Siemens Medical Solutions USA, Mountain View, CA, USA). The ICE image of LA was integrated with computed tomography (CT) image as previously described [17].

AF ablation was performed by way of circumferential pulmonary vein isolation (CPVI) for all patients using a Thermocool SmartTouch catheter (Biosense Webster). Isolation of superior vena cava and left atrial linear ablation were performed for selected patients with persistent AF at operator discretion. Carvotricuspid isthmus (CTI) ablation was performed for all patients with a history of typical atrial flutter. The ablation catheter was advanced into the LA via the long sheath, which was then pulled back to the right atrium in order to reduce systemic thromboembolic risk. The endpoint of CPVI was elimination of all PV potentials recorded by a circular catheter (Lasso Nav or PentaRay NAV, Biosense Webster) placed at the ostium of the PV, and LA-PV block during pacing from the circular catheter at 10-V output with 1-ms pulse width. When there was a conduction gap in the encircling linear ablation line, touch-up ablation targeting the earliest electrogram site was performed until complete elimination of the gap.

#### Periprocedural anticoagulation therapy

All patients took warfarin with therapeutic prothrombin time-international normalized ratio (PT-INR) or DOACs for at least 4 weeks before the procedure. Preprocedural transthoracic and transesophageal echocardiography were performed for all patients to assess cardiac function, LA diameter, and mitral regurgitation grade, and to confirm the absence of left atrial thrombi. Contrast enhanced CT was also

performed. A bridge therapy using heparin after warfarin interruption was not performed before and after the procedure. When a PT-INR was  $< 2.0$  on admission, warfarin was continued. When a PT-INR was  $\geq 2.0$ , warfarin was stopped on the day of the procedure. All DOACs were skipped only on the morning of the procedure day.

During ablation, we administered 5000 units of heparin after transseptal puncture, measured activated clotting time (ACT) every 10 minutes, and administered additional dose of heparin to maintain ACT between 300 and 350 seconds.

In patients with a PT-INR  $< 2.0$  on the day of the procedure, 600 units per hour of intravenous heparin was infused every 3 hours after the procedure until the next morning. In patients with a PT-INR  $\geq 2.0$  on the day of the procedure, or on rivaroxaban or edoxaban, oral anticoagulant was resumed after the procedure. In patients on dabigatran or apixaban, oral anticoagulant was restarted on the evening of the day of the procedure.

#### Follow-up and outcomes

All patients were seen in the clinic at 1 and 3 months after CPVI and every 3 months thereafter until 12 months to perform 12-lead electrocardiogram (ECG) and a 24-h Holter ECG. After 12 months follow-up, every 6 months follow-up was performed if the patients were seen in our clinic. The efficacy outcome was freedom from AF and any atrial tachyarrhythmias, which were defined as any asymptomatic or symptomatic AF and atrial tachyarrhythmias lasting more than 30 seconds detected by either a 12-lead ECG or a 24-h Holter ECG at every visit to the clinic,

beyond a blanking period defined as 3 months after CPVI. The safety outcomes were the incidence of periprocedural complications and the recurrence of CS or TIA.

### Statistical analysis

Data were expressed as mean±standard deviation, median (interquartile range [IQR]) or n (%). Comparisons of parametric data were performed using one-way analysis of variance (ANOVA) followed by Turkey's honestly significant difference test. Comparisons of nonparametric data were performed using Kruskal-Wallis test followed by Dunn's multiple comparisons test. Categorical variables were compared by Fisher's exact test. Kaplan-Meier analysis was performed to compare outcomes among the groups. Multivariate Cox regression analyses were performed to determine significant risks for recurrence of AF and any atrial tachyarrhythmias. Data were analyzed using JMP pro (version 12.0, SAS, NC, USA). A p-value of <0.05 was considered significant.

## **Results**

### Baseline characteristics

The clinical characteristics of the patients are summarized in Table 1. The mean age was significantly older in Group 1 than in Group 3 [70.8±6.8 versus 61.0±11.1 years (p<0.05)]. CS or TIA occurred at a 3.7±1.8 and 39.2±35.0 months before AF ablation in Groups 1 and 2, respectively. Furthermore, 47% of patients (n=8) in Group 1 had CS within 3 months before the ablation. CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were both significantly higher in Groups 1 and 2 than in Group 3. No significant differences in sex, prevalence of paroxysmal AF, left ventricular ejection fraction, and LA diameter were found among the 3 groups.



Total procedure time and total fluoroscopy time did not differ among the 3 groups. The bidirectional LA-PV blocks were successfully completed in all the cases. CTI ablation was performed in 3 (17.7%), 5 (16.7%), and 63 (15.8%) patients in the Groups 1, 2, and 3, respectively.

All patients were on oral anticoagulation before the ablation. The oral anticoagulants were warfarin (n=108, 24.1%), dabigatran (n=101, 22.6%), rivaroxaban (n=147, 32.9%), apixaban (n=87, 19.5%) and edoxaban (n=4, 0.9%). No difference in its ratio was found among the 3 groups.

#### Periprocedural complications

One episode of cardiac tamponade (requiring cardiocentesis), 2 epicarditis, 2 episodes of arteriovenous fistula (managed conservatively), 2 groin hematoma (not requiring transfusion), 2 phrenic nerve palsy (remission in the next day), and one episode of minor bleeding occurred during the periprocedural period. No such periprocedural complications occurred in Groups 1 and 2. One episode of CS occurred 11 days after the procedure in Group 3. There were no periprocedural CS, TIA or major bleedings in Groups 1 and 2.

#### Follow-up outcomes

Follow-up information was obtained from 421 (94.2%) patients (17/17, 30/30, and 374/400 in Groups 1, 2, and 3, respectively). Median follow-up period was 14 [12-22], 13 [12-14], and 12 [10-16] months, respectively. The recurrence free rate for AF and any atrial tachyarrhythmias after the ablation was 76.5% (13/17), 86.7% (26/30), and 79.1% (296/374) in Groups 1, 2, and 3, respectively, and Kaplan-Meier curves showed no significant difference among 3 groups (p=0.58 by log rank test) (Figure 2). Multivariate Cox regression analysis showed no significant difference in

the recurrence between Groups 1 and 3 (HR 1.13, 95% confidence interval (CI) 0.34-2.80, p=0.83), and between Groups 2 and 3 (HR 0.56, 95% CI 0.17-1.37, p=0.30) (Table 2A). Furthermore, we also compared the outcome between the patients with a history of CS or TIA (Groups 1 and 2 together) and those without it (Group 3). We found no significant differences between the two groups (Table 2B, Figure 3). These findings indicate that the recent or prior history of CS or TIA was not associated with the recurrence of AF and any atrial tachyarrhythmias. Persistent AF was an independent risk factor for the recurrence (Table 2A and 2B). LVEF and LA diameter were not an independent risk factor, although close to significance. Although one patient in Group 3 was hospitalized due to hemorrhagic stroke (thalamic bleeding, 8 months after the procedure), none of the patients in Groups 1 and 2 had recurrence or incidence of CS or TIA.

## **Discussion**

### Major findings

In the present study, we showed that the none of the patients with a history of CS or TIA suffered from stroke, TIA, and any major bleedings during the CF-guided AF ablation. Furthermore, there was no difference in the recurrence of AF and any atrial tachyarrhythmias during follow-up period between patients with and without a history of CS or TIA. Notably, more than 70% of the patients in this study administered DOACs as an anticoagulation therapy. These findings indicate that the CF-guided AF ablation in the era of DOACs is likely safe and effective in patients with a history of CS or TIA, even in those occurring CS within 6 months before AF ablation.

### The safety of CF-guided AF ablation in patients with a history of CS or TIA

The incidence of periprocedural thromboembolism during AF ablation varies between 0% and 7%, depending on the center experience, ablation protocol, periprocedural anticoagulation and comorbidities [7]. A CHADS<sub>2</sub> score  $\geq 2$  and a prior history of cerebral infarction are shown to be independent predictors of periprocedural complications [19]. On the other hand, recent report by Hussein et al. showed that AF patients with a prior history of cerebral infarction can safely undergo AF ablation without periprocedural thromboembolic complications [16]. It should be noted that these studies, although conflicting, were performed mostly by the conventional catheter ablation without use of CF systems and under anticoagulation therapy with warfarin. The present study was performed by the contemporary AF ablation with the use of CF systems and recent anticoagulation therapy with DOACs, and supports Hussein's findings showing that the safety of AF ablation in patients with a history of CS or TIA during the procedure. The periprocedural use of DOACs in AF ablation was increased from 0% in 2005 to 69.8% in 2014 [13, 20]. Accordingly, the results of our study may be successfully applied for the clinical practice, even in patients occurring CS within 6 months before AF ablation.

Typically, most of periprocedural thromboembolic events occur within the first 24 hours after the ablation [21]. In our protocol, almost all patients undergoing catheter ablation stayed in the hospital for two days after the procedure. Therefore, most of the acute complications can be monitored during the hospital stay and therefore the risk for oversight of periprocedural complications is very small.

Cardiac tamponade is also a major complication in AF ablation and its incidence varies 0% to 6% [7]. The most common causes of cardiac tamponade are

misdirected transeptal puncture and direct mechanical perforation. In this study, the incidence of cardiac tamponade was only 0.2% (1/447) and was not occurred in Groups 1 and 2. Preprocedural anatomical evaluation of LA and the periprocedural guide of ICE and CF are shown to reduce the periprocedural complication including cardiac tamponade [22,23]. We showed that their advantages were preserved during AF ablation in patients with recent or prior history of stroke or TIA. Although we routinely perform transthoracic echocardiography after the procedure to detect asymptomatic epicardial effusion, possibility of asymptomatic delayed cardiac tamponade cannot be completely excluded [24].

#### The efficacy of CF-guided AF ablation in patients with a history of CS or TIA

We recently showed that CF-guided CPVI is safe and more effective in reducing not only the procedure time but also the AF recurrence than the conventional CPVI, possibly due to reduced residual conduction gaps during CPVI procedure [10,11]. In the present study, we showed no difference in recurrence of AF and atrial tachyarrhythmias between patients with and without a history of CS or TIA evaluated by Kaplan-Meier analysis and multivariate Cox regression analysis. Thus, the present study expands the evidence on the efficacy of CF-guided CPVI to the patients with a history of CS or TIA, who are at high risk for recurrence of CS, although the study patients are relatively small.

Persistent AF is known to be a predictive factor for AF recurrence after the ablation [25]. The present study also supports this finding, and shows that this may be true even in patients with a history of CS or TIA.

#### Limitations

Our study has several limitations. First, this is a retrospective observational study and only 10% of patients with a history of stroke underwent AF ablation, and therefore generalization of our results may be limited. Also small number of study patients would be at risk of being statistically underpowered. More number of the patients is certainly needed to confirm our result. Second, we did not routinely perform magnetic-resonance imaging to detect cerebral infarction, unless the patients complain neurological symptoms, so the occurrence of silent cerebral ischemia (SCI) may be underestimated. However, the majority of acute SCI after the AF ablation are reported to occur after 2-week follow up [26] and its impact on the outcome of AF ablation remains to be established. Third, although we performed 12-lead ECG and 24-h Holter ECG for all patients at every follow-up visit to the clinic, possibility of overlooking the asymptomatic AF recurrence cannot be excluded. Finally, we did not evaluate the disability of patients with a history of CS or TIA. Accordingly, our results cannot be applied for all patients with a history of stroke.

### **Conclusions**

The safety and efficacy of CF-guided AF ablation in patients with a recent or prior history of CS or TIA were similar to those without it in the era of DOACs. Because those patients are at high risk for recurrence of CS, indication for AF ablation should not be restricted only by the recent or prior history of CS or TIA. Further large scale study is warranted.

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### **Figure legends**

**Figure 1. Flow chart of the study patients.** CF indicates contact force, AF; atrial fibrillation, LVEF; left ventricular ejection fraction, LAD; left atrial diameter, CS; cardioembolic stroke, TIA; transient ischemic attack.

**Figure 2. Arrhythmia-free survival curves for atrial fibrillation (AF) and any atrial tachyarrhythmias after blanking period evaluated by Kaplan–Meier analysis among the 3 groups.** Group 1 indicates 17 patients with cardioembolic stroke (CS) or transient ischemic attack (TIA) within 6 months before AF ablation, Group 2; 30 patients with CS or TIA more than 6 months before the ablation, Group 3; 374 patients without CS or TIA.

**Figure 3. Arrhythmia-free survival curves for atrial fibrillation (AF) and any atrial tachyarrhythmias after blanking period evaluated by Kaplan–Meier analysis between the patients with a history of CS or TIA and those without it.** Groups 1 and 2 indicate 47 patients with cardioembolic stroke (CS) or transient ischemic attack (TIA), Group 3; 374 patients without CS or TIA.

**Table 1. Baseline characteristics and procedural data of the study patients**

Variable	Group 1	Group 2	Group 3	p-value
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	(n=17)	(n=30)	(n=400)	
Age (years)	70.8±6.8	65.7±9.4	61.0±11.1	< 0.001*
Male	11 (64.7%)	22 (73.3%)	263 (65.6%)	0.68
PAF	14 (82.4%)	21 (70.0%)	289 (72.3%)	0.60
CHADS <sub>2</sub> score	3.3±1.1	3.0±0.6	0.9±0.8	< 0.001* <sup>†</sup>
CHA <sub>2</sub> DS <sub>2</sub> -VASc score	4.5±1.4	4.0±0.9	1.8±1.2	< 0.001* <sup>†</sup>
Heart failure	1 (5.9%)	2 (6.7%)	43 (10.6%)	0.61
Hypertension	11 (64.7%)	20 (66.7%)	230 (57.5%)	0.53
Diabetes mellitus	4 (23.5%)	4 (13.3%)	65 (16.3%)	0.67
Vascular disease	0	3 (10.0%)	16 (4.0%)	0.19
Periprocedural OAC (WF/Dabi/Riva/Api/Edo)	2 / 2 / 10 / 3 / 0	9 / 8 / 9 / 4 / 0	97/ 91/ 128/ 80/ 4	0.47
LVEF (%)	66.9±7.7	67.3±10.1	66.0±9.7	0.75
LAD (mm)	39.7±5.8	40.6±6.3	38.7±6.1	0.21
MR grade (mild/moderate/severe)	7 / 1 / 0	13 / 0 / 0	129 / 14 / 1	0.73
SEC	2 (11.8%)	3 (10.0%)	29 (7.25%)	0.71
Procedure time (min)	156±38	173±53	171±43	0.34
Fluoroscopic time (min)	13.3±5.6	15.3±7.2	14.1±7.4	0.65
CTI ablation	3 (17.7%)	5 (16.7%)	63 (15.8%)	0.97
Additional ablation	1 (5.9%)	3 (10.0%)	62 (15.5%)	0.35
AAD after ablation (none / class I / AMD)	13 / 2 / 2	26 / 2 / 2	284 / 18 / 72	0.41
Follow-up period (month)	14 [12-22]	13 [12-14]	12 [10-16]	0.17

Data are given as mean±standard deviation, median (interquartile range) or number (%). \* p<0.05, Group 1 versus Group 3, †p<0.05, Group 2 versus Group 3. PAF indicates paroxysmal atrial fibrillation, OAC; oral anticoagulant, LVEF; left ventricular ejection fraction, WF; warfarin, Dabi; dabigatran, Riva; rivaroxaban, Api;

apixaban, Edo; edoxaban, LAD; left atrial diameter, MR; mitral regurgitation, SEC; smoke-like echo, CTI; cavo tricuspid isthmus line, AAD; antiarrhythmic drug, AMD; amiodarone.

**Table 2. Multivariate Cox regression analysis for recurrence of AF and atrial tachyarrhythmias**

(A) Analysis using the 3 groups (Group 1, Group 2, and Group 3) as a variable

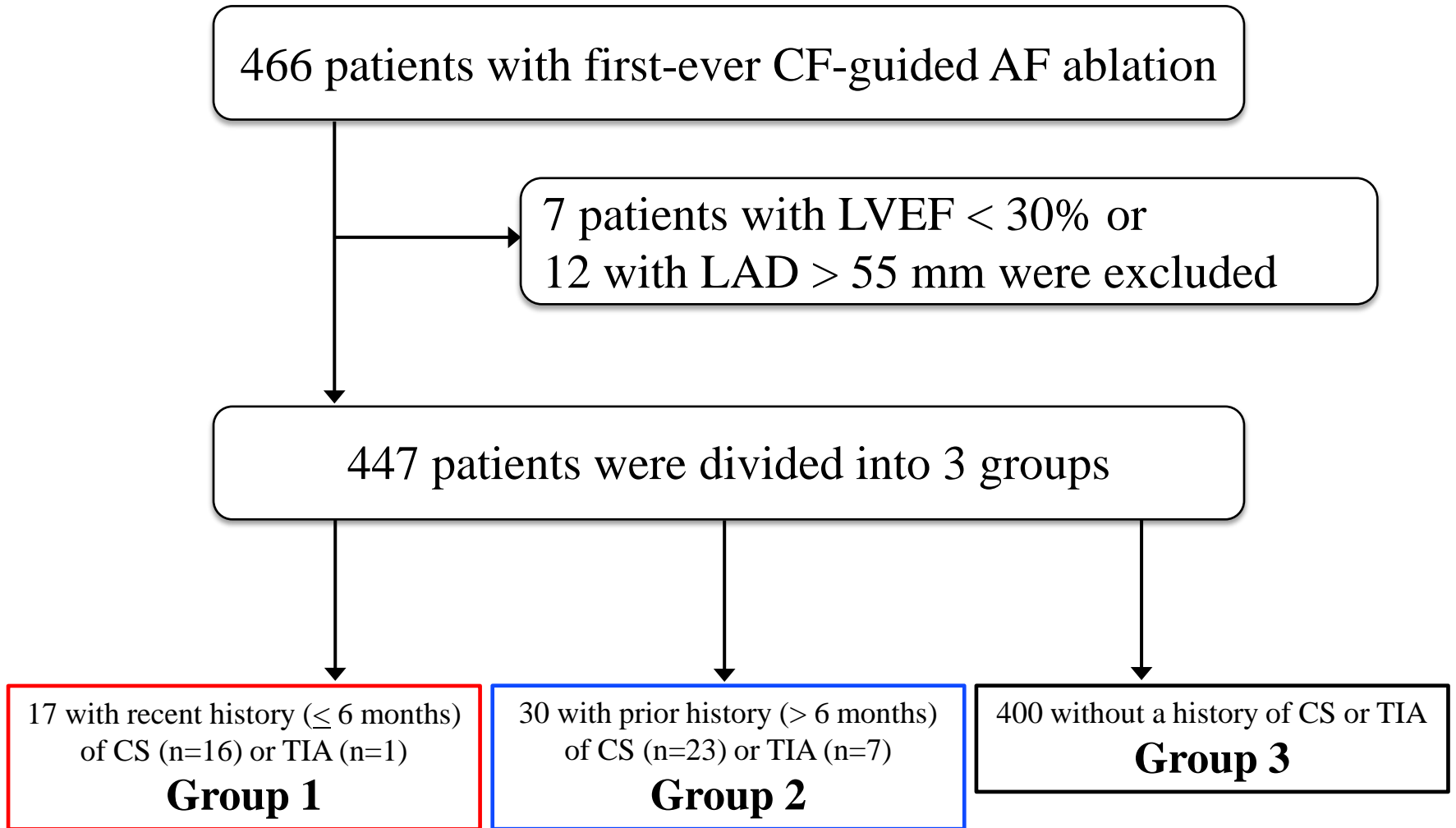
Variable	HR	95% CI	p-value
Group 1 (Group 3 as a reference)	1.12	0.34-2.80	0.83
Group 2 (Group 3 as a reference)	0.56	0.17-1.37	0.30
PRAF (PAF as a reference)	1.67	1.03-2.69	0.04
LVEF (%)	1.02	0.99-1.05	0.08
LAD (mm)	1.04	0.99-1.08	0.05

**(B)** Analysis using the 2 patient groups (Groups 1+2 and Group 3) as a variable

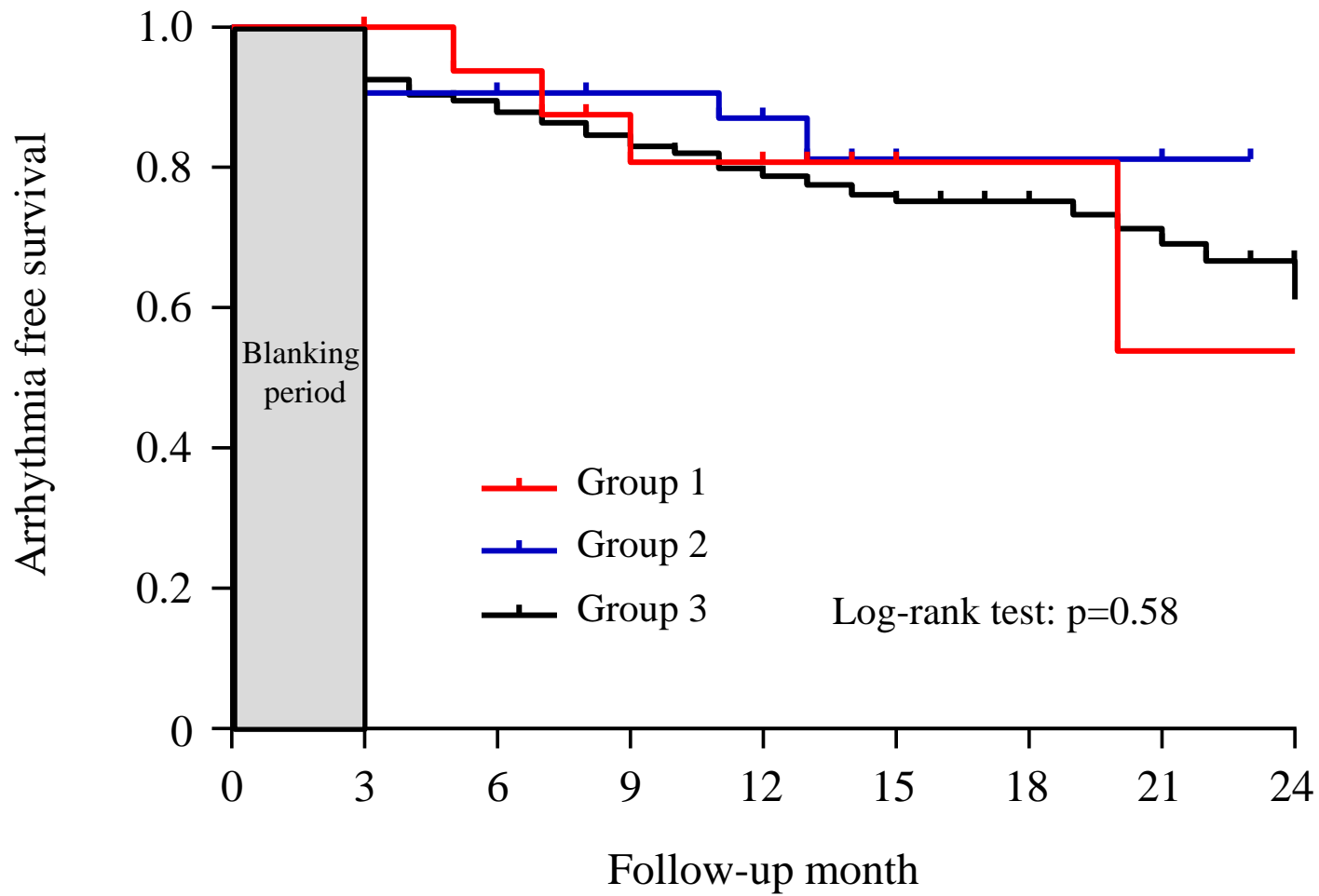
Variable	HR	95% CI	p-value
Groups 1+2 with a history of CS or TIA (Group 3 as a reference)	0.75	0.33-1.48	0.42
PRAF (PAF as a reference)	1.67	1.03-2.67	0.04
LVEF (%)	1.02	0.99-1.05	0.08
LAD (mm)	1.04	0.99-1.07	0.06

Analysis was performed after adjusting for age and sex. HR indicates hazard ratio, CI; confidence interval, PRAF; persistent atrial fibrillation, PAF; paroxysmal atrial fibrillation, LVEF; left ventricular ejection fraction, LAD; left atrial diameter, CS; cardioembolic stroke, TIA; transient ischemic attack.

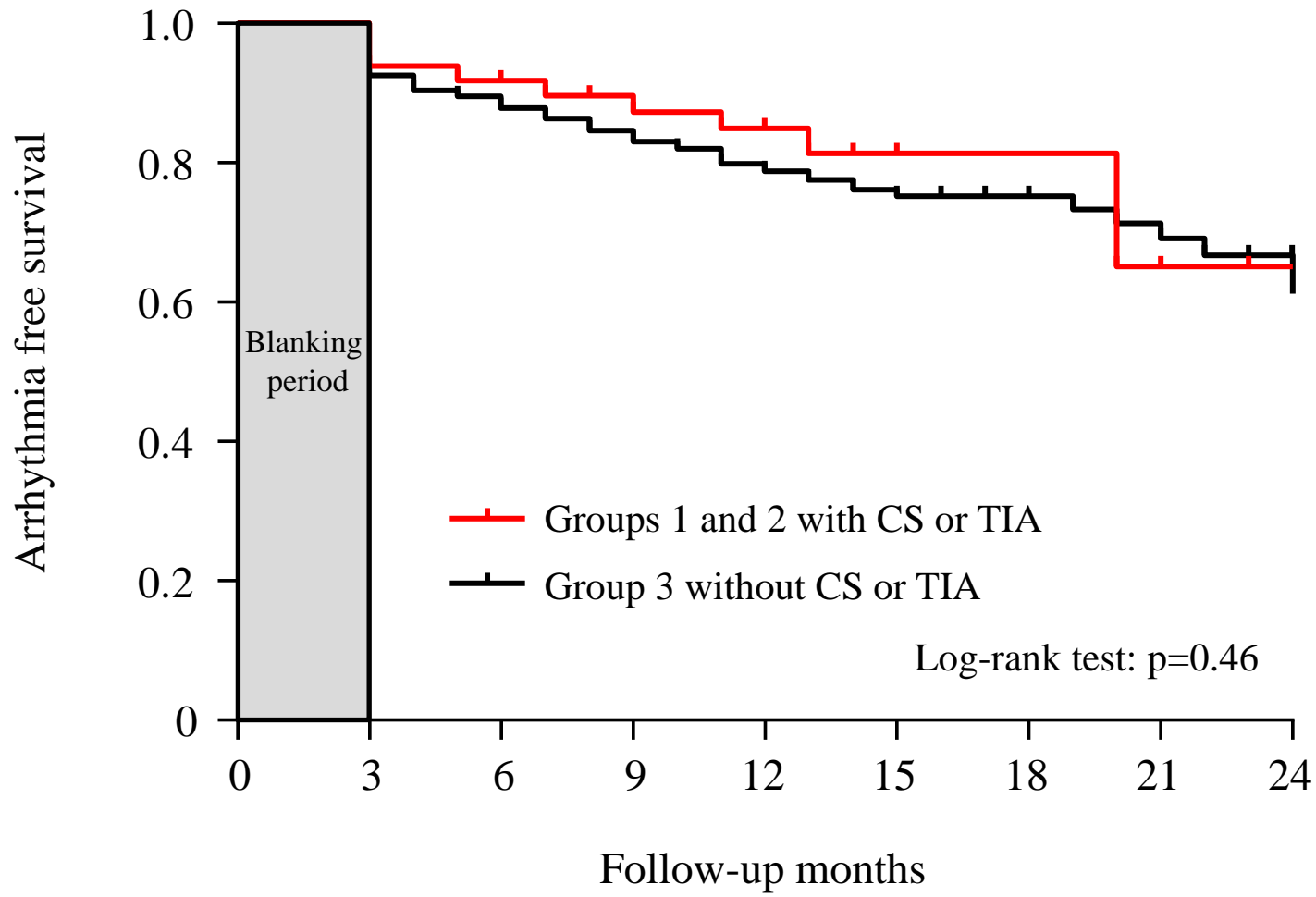




**Figure 1**



**Figure 2**



**Figure 3**