Ischemic stroke risk during long-term follow up in patients with successful catheter ablation for atrial fibrillation in Korea

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Abstract

The interruption of oral anticoagulation therapy (OAC) after CA of atrial fibrillation (AF) is controversial. The purpose of this study was to evaluate the relationship between successful long-term outcomes of catheter resection and SR maintenance and ischemic stroke risk in Korea. We studied 1,548 consecutive patients who were followed up for more than 2 years after CA of AF. We investigated the incidence of ischemic stroke during long-term follow-up. Compared to the AF recurrence group (n = 619), the sinus rhythm (SR) maintenance group (n = 929) had more paroxysmal AF (74.6% versus 44.4%, p < 0.001), smaller LA size (39.9 ± 5.7mm versus 42.3 ± 6.0mm, p < 0.001), and younger age (54.2 ± 10.9 years versus 56.4 ± 10.6 years, p < 0.001). However, CHA²DS²-VASc scores were not significantly different between the two groups (0.9 vs. 1.1, p = 0.053). The overall incidence of ischemic stroke during the mean follow-up period of 54 months after CA was 0.6%, and was significantly lower in the SR group than the AF recurrence group (0.3% vs. 1.1%, log-rank test p < 0.001). However, in sub-analysis in the SR group, the rate of ischemic stroke was significantly increasing in patients with a CHA²DS²-VASc score ≥ 4 compared to those with a CHA²DS²-VASc score < 4 (4.3% vs. 0.2%, log-rank test p < 0.001). In conclusion, this long-term follow-up data in patients with AF who underwent successful CA showed that SR maintenance was correlated with a lower rate of ischemic stroke in Korea. However, it was only observed in patients with CHA²DS²-VASc score ≤ 3.

Introduction

Current guidelines demonstrate that atrial fibrillation (AF) catheter ablation (CA) to restore sinus rhythm (SR) should not be performed only for stop of anticoagulation, which is a class III recommendation with level C evidence [1]. The CHA²DS²-VASc score is the only risk stratification tool for oral anticoagulation therapy (OAC) before and after CA [2]. This recommendation
is based on the belief that the baseline risk of thromboembolic events (TE) remains unchanged despite successful CA [3]. However, it is reasonable to speculate that elimination of AF may reduce the risk of TE.

Many studies have demonstrated that OAC can be discontinued after successful CA for patients with a relatively low risk of TE events [4–6]. Saad EB et al. showed that there is no significant TE-related morbidity of patients with antiarrhythmic drugs (AAD) and discontinuation of OAC after successful CA and CHADS

Methods

Study population

We studied 1,548 consecutive patients with AF and more than 2 years of follow-up from February 2000 to March 2013. Total 1,548 patients were divided into two groups (Fig 1). The SR maintenance group was defined as patients who underwent CA and remained in SR even after 1 year. The recurrence group was defined as patients who underwent CA and had an AF recurrence within 1 year. If a patient who had AF recurrence after 1 year, the patient was defined as SR maintenance group because that AF was not documented and SR maintenance until 1 year. This study was approved by the institutional review board in Korea University Medical Center (AN17210-002). Consent was waived by the ethics committee.

Procedures for catheter ablation

Prior to the CA procedure, all antiarrhythmic drugs were discontinued, and more than 5 half-lives were allowed to pass. Circumferentially antral pulmonary vein isolation (PVI) with electrical isolation was performed. When AF followed PVI, either linear ablation or complex fractionated electrogram (CFAE) ablation was also performed. The endpoints of the ablation were AF or AT termination. During the enrollment period, the CA strategy was changed from PVI in paroxysmal AF to combination of PVI with linear ablation or/and CFAE ablation in persistent or long-standing persistent AF.

Follow-up

To assess the efficacy of catheter ablation, we investigated freedom from atrial tachyarrhythmia (= AF or AT) after the procedure. After ablation, patients were asked to visit the outpatient clinic at 1, 3, 6, and 12 months and then every 6 months thereafter or whenever they experienced tachycardia-related symptoms. Electrocardiogram (ECG) was performed at every visit. Holter monitor recording was performed in patients who were thought to have arrhythmia-related intermittent symptoms. Recurrence of atrial tachyarrhythmia was defined as an event lasting more than 30 seconds after a 3-month blanking period. AADs were taken during the first 3 months after the ablation. Discontinuation of AADs was determined at the physicians’ discretion. During follow-up, ischemic stroke was investigated by a neurologist’s diagnosis and brain imaging.
Statistical analyses

All values are expressed as means ± SD or as numbers and percentages where appropriate. Categorical data were compared with the χ² test. Continuous variable data were compared by the independent samples t-test when the distribution was normal or by the Mann-Whitney U test if the distribution was not normal. Kaplan-Meier analysis with the log-rank test was used to determine the probability of ischemic stroke. P < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics 19.0 software (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

Clinical characteristics at baseline are summarized in Table 1. Compared to the AF recurrence group (n = 619), the SR maintenance group (n = 929) had younger age (54.2±10.9 years versus 56.4±10.6 years, p < 0.001), shorter AF onset (31.0±43.9 months versus 44.9±58.7 months, p < 0.001), lower prevalence of paroxysmal AF (74.6% versus 44.4%, p < 0.001), lower left atrium size (39.9±5.7 mm versus 42.3±6.0 mm, p < 0.001), and lower CHA2DS2-VASc score (0.9±1.1 versus 1.1±1.1, p = 0.053) compared to the SR recurrence group. In contrast, the AF recurrence group had higher prevalence of hypertension (35.1% versus 31.1%, p = 0.007), diabetes mellitus (28.5% versus 7.0%, p < 0.001), and CHA2DS2-VASc score (2.8±1.1 versus 1.0±1.1, p = 0.033) compared to the SR recurrence group.

Table 1. Clinical baseline characteristics of the study participants who underwent catheter ablation.

|                      | Total (n = 1548) | AF recurrence (n = 619) | SR maintenance (n = 929) | p value |
|----------------------|------------------|------------------------|--------------------------|---------|
| Age, year-old        | 55.0±10.8        | 56.4±10.6              | 54.2±10.9                | <0.001  |
| Male sex, n (%)      | 1228 (79.3)      | 492 (79.5)             | 736 (79.2)               | 0.949   |
| AF onset, months     | 36.5±50.8        | 44.9±58.7              | 31.0±43.9                | <0.001  |
| Paroxysmal AF, n (%) | 968 (62.6)       | 275 (44.4)             | 693 (74.6)               | <0.001  |
| LVEF, %              | 55.2±6.0         | 54.6±6.4               | 55.7±5.7                 | <0.001  |
| LA size, mm          | 40.8±5.9         | 42.3±6.0               | 39.9±5.7                 | <0.001  |
| CHF, n (%)           | 50 (3.2)         | 24 (3.9)               | 26 (2.8)                 | 0.244   |
| Hypertension, n (%)  | 482 (31.1)       | 217 (35.1)             | 265 (28.5)               | 0.007   |
| Diabetes mellitus, n (%) | 109 (7.0) | 53 (8.6)                | 56 (6.0)                 | 0.068   |
| CHA2DS2-VASc score   | 1.0±1.1          | 1.1±1.1                | 0.9±1.1                  | 0.053   |
| 0                    | 667 (43.0)       | 228 (36.8)             | 439 (47.3)               | <0.001  |
| 1                    | 492 (31.7)       | 205 (33.1)             | 287 (30.9)               | 0.193   |
| ≥2                   | 389 (25.1)       | 186 (30.0)             | 203 (21.8)               | <0.001  |

Values are expressed as means ± SDs and numbers (percentages). AF; atrial fibrillation, LVEF; left ventricular ejection fraction, LA; left atrium, CHF; congestive heart failure.
56.4±10.6 years, p<0.001), shorter time of AF onset (31.0±43.9 months versus 44.9±58.7 months, p<0.001), more paroxysmal AF (74.6% versus 44.4%, p<0.001), and smaller LA size (39.9±5.7mm versus 42.3±6.0mm, p<0.001). However, CHA2DS2-VASc scores were not significantly different between the two groups (0.9 vs. 1.1, p = 0.053).

### AAD use and antithrombotic therapy after CA

Table 2 shows AAD use and antithrombotic therapy after CA. After CA, AAD use was more frequent in the AF recurrence group compared to the SR maintenance group (64.0% versus 44.6%, p<0.001). After CA, antithrombotic therapy was more frequent in the AF recurrence group compared to the SR maintenance group (88.7% versus 72.2%, p<0.001). The SR group had more antiplatelet therapy than the AF recurrence group (58.8% versus 53.5%, p = 0.036). However, OAC was more frequent in the AF recurrence group compared to the SR maintenance group (36.5% versus 14.3%, p<0.001). Interestingly, in the SR group, the rate of OAC for patients with a CHA2DS2-VASc score ≥2 was only 16.7% and the rate of antiplatelet therapy was 70.9%.

### Ischemic stroke events after successful CA

The overall incidence of ischemic stroke after CA was 0.6% in the follow-up period of 54 months. The incidence of ischemic stroke was significantly lower in the SR maintenance group than in the AF recurrence group (0.3% vs. 1.1%, log-rank test, p<0.001, Fig 2).

1) **CHA2DS2-VASc score.** Ischemic stroke events are shown in Table 3. In the SR maintenance group, most ischemic events were reported in patients with high CHA2DS2-VASc scores: CHA2DS2-VASc score 0 (n = 1, 0.2%), CHA2DS2-VASc score 4 (n = 1, 5.5%), CHA2DS2-VASc score 5 (n = 1, 25%). However, in the AF recurrence group, ischemic stroke events were reported in patients with low and high CHA2DS2-VASc scores: CHA2DS2-VASc score 0 (n = 2, 0.9%), CHA2DS2-VASc score 1 (n = 4, 1.9%), CHA2DS2-VASc score 5 (n = 1, 11.1%). All 10 patients with stroke events were on OAC in 3 in the SR group and 7 in the recurrence group. There was no difference of OAC therapy for patients with stroke events after ablation in both groups.

2) **Risk factors for ischemic stroke.** Table 4 shows risk factors for ischemic stroke. Univariate analysis showed lower CHA2DS2-VASc score (HR 1.540, p = 0.049), AAD use after CA (HR 0.207, p = 0.048), and SR maintenance (HR 0.122, p = 0.005) reduced the risk of ischemic stroke. However, multivariate analysis showed SR maintenance (HR 0.151, p = 0.013) was the only factor that reduced risk.

### Table 2. Antiarrhythmic drug and antithrombotic therapy after catheter ablation between the AF recurrence and SR maintenance groups.

|                        | Total (n = 1548) | AF recurrence (n = 619) | SR maintenance (n = 929) | p value |
|------------------------|------------------|------------------------|--------------------------|---------|
| AAD†                   | 810 (52.3)       | 396 (64.0)             | 414 (44.6)               | <0.001  |
| Antithrombotic therapy‡| 1220 (78.8)      | 549 (88.7)             | 671 (72.2)               | <0.001  |
| Antiplatelet therapy‡  | 876 (56.5)       | 330 (53.5)             | 546 (58.8)               | 0.036   |
| Anticoagulation therapy‡| 359 (23.1)       | 226 (36.5)             | 133 (14.3)               | <0.001  |

Values are expressed as numbers (percentages). AAD: antiarrhythmic drug
† 3 months after catheter ablation
‡ 1 year after catheter ablation

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Cut off-value of $\text{CHA}_2\text{DS}_2\text{-VASc}$ score for ischemic stroke after CA

The $\text{CHA}_2\text{DS}_2\text{-VASc}$ score is already the main tool for stratification of ischemic stroke risk. Table 5 shows Cox regression analysis for stroke risk in the SR maintenance group. $\text{CHA}_2\text{DS}_2\text{-VASc}$ score was the main factor for stroke risk (HR 2.11, CI 1.08–4.12, p = 0.028). However,

Table 3. Distribution of ischemic stroke events between the AF recurrence and SR maintenance groups.

| $\text{CHA}_2\text{DS}_2\text{-VASc}$ | Total (n = 1548) | AF recurrence (n = 619) | SR maintenance (n = 929) | p value† |
|---|---|---|---|---|
| | Patients | Events | Patients | Events | Patients | Events |
| 0 | 667 | 3 (0.4) | 228 | 2 (0.9) | 439 | 1 (0.2) |
| 1 | 492 | 4 (0.8) | 205 | 4 (1.9) | 287 | 0 |
| 2 | 228 | 0 | 113 | 0 | 115 | 0 |
| 3 | 110 | 0 | 45 | 0 | 65 | 0 |
| 4 | 36 | 1 (2.7) | 18 | 0 | 18 | 1 (5.5) |
| 5 | 13 | 2 (15.3) | 9 | 1 (11.1) | 4 | 1 (25.0) |
| 6 | 2 | 0 | 1 | 0 | 1 | 0 |
| ≥7 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 1548 | 10 (0.6) | 619 | 7 (1.1) | 929 | 3 (0.3) |

Values are expressed as numbers (percentages).
† p value: compared AF recurrence versus SR maintenance
the cut-off value for differentiating stroke events was not CHA\textsubscript{2}DS\textsubscript{2}-VASc score \( \geq 2 \) (HR 0.11, CI 0.01–1.21, \( p = 0.072 \)) nor \( \geq 3 \) (HR 0.16, CI 0.01–1.89, \( p = 0.149 \)), but \( \geq 4 \) (HR 17.65, CI 1.59–195.5, \( p = 0.019 \)). In patients with CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 4 or more, the risk of ischemic stroke increased even after successful CA and SR maintenance. However, this showed the trend of low stroke event in CHA\textsubscript{2}DS\textsubscript{2}-VASc 2 or 3 in patients with SR maintenance after successful ablation.

**Discussion**

**Main findings**

This long-term follow-up data in patients with AF who underwent catheter ablation showed that SR maintenance after successful CA was correlated with a lower rate of ischemic stroke. However, it was only observed in patients with CHA\textsubscript{2}DS\textsubscript{2}-VASc score \( \leq 3 \) in Korea.

**Table 5.** Cox regression analysis for stroke risk in sinus rhythm.

| Factors                  | Hazard ratio (95% CI) univariate analysis | P value | Hazard ratio (95% CI) multivariate analysis | P value |
|--------------------------|------------------------------------------|---------|---------------------------------------------|---------|
| Age, year-old            | 1.12 (0.99–1.26)                          | 0.067   |                                             |         |
| Male sex, n (%)          | 2.16 (0.19–24.2)                          | 0.529   |                                             |         |
| Previous stroke          | 20.98 (0.00–20.98)                         | 0.849   |                                             |         |
| CHF                      | 21.30 (0.00–1.52)                          | 0.826   |                                             |         |
| Vascular diseases        | 0.06 (0.01–0.67)                           | 0.023   |                                             |         |
| AF type, paroxysmal      | 30.71 (0.00–2.78)                          | 0.556   |                                             |         |
| CHA\textsubscript{2}DS\textsubscript{2}-VASc | 2.11 (1.08–4.12)                         | 0.028   |                                             |         |
| AAD use after CA         | 0.01 (0.00–144.3)                          | 0.339   |                                             |         |
| OAC after CA             | 0.01 (0.00–5.70)                           | 0.519   |                                             |         |
| CHA\textsubscript{2}DS\textsubscript{2}-VASc \( \geq 2 \) | 0.11 (0.01–1.21)                          | 0.072   |                                             |         |
| CHA\textsubscript{2}DS\textsubscript{2}-VASc \( \geq 3 \) | 0.16 (0.01–1.89)                          | 0.149   |                                             |         |
| CHA\textsubscript{2}DS\textsubscript{2}-VASc \( \geq 4 \) | 17.65 (1.59–195.5)                        | 0.019   |                                             |         |

Values are expressed as HR (95% CI). CI; confidence interval, CHF; congestive heart failure, AAD; antiarrhythmic drug, CA; catheter ablation, OAC; oral anticoagulation therapy, SR; sinus rhythm

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Comparison of previous studies of ischemic stroke after catheter ablation

Many studies demonstrated that OAC can be discontinued after successful CA for patients with a relatively low risk of TE [4–9]. According to the current guidelines [1], even after CA of AF, anticoagulation therapy should be continued when the CHA\textsubscript{2}DS\textsubscript{2}-VASc score remains ≥2. This recommendation is based on the belief that the baseline risk of TE remains unchanged despite a successful CA [3]. However, there is no randomized study to support this, and this guideline recommendation is class III, but evidence level C. A study from a Danish cohort showed that TE risk beyond 3 months after CA was relatively low compared with a matched non-ablated AF cohort [5]. The bleeding risk score HAS-BLED increased with CHA\textsubscript{2}DS\textsubscript{2}-VASc score. Practical clinicians take bleeding risk into consideration. Karasoy D et al. also emphasized that serious bleeding risk associated with OAC seems to outweigh the benefits of TE risk reduction [5]. When considering the SR maintenance duration, another study showed that the risk of stroke is low in patients with no recurrence in first 1 year after CA [7]. In our study, we defined patients with no AF recurrence for at least 1 year as the SR maintenance group, and this was consistent with their results [7].

Another study pointed out a CHA\textsubscript{2}DS\textsubscript{2}-VASc cut-off value for stroke [4]. Saad EB et al. demonstrated that no significant TE-related morbidity was observed when AAD and OAC were discontinued after successful CA in patients with a CHADS\textsubscript{2} score ≤3 who were maintained on antiplatelet therapy during long-term follow-up. This suggests the existence of a gray zone which has a relatively low risk of ischemic stroke after successful CA. In our results, antiplatelet therapy was used more than OAC in the SR group than the recurrence group (70.9% versus 16.7%, p<0.001, respectively). CHA\textsubscript{2}DS\textsubscript{2}-VASc scores of 2 and 3 are relatively low-risk if SR is maintained after successful CA. Themistoclakis S et al. showed that the risk-benefit ratio favored the suspension of OAC after successful CA in patients at moderate-high risk of TE [10]. They also emphasized that the CHADS\textsubscript{2} score system probably is not the most appropriate system for assessing TE risk and establishing an anticoagulation strategy after CA.

On contrary, there were studies which concluded inevitable OAC after successful CA [11–15]. Oral H et al. demonstrated that sufficient safety data are as yet unavailable to support discontinuation of OAC in patients older than 65 years or with a history of stroke [11]. Patients older than 65 years or with a history of stroke have a high risk of TE events and higher CHA\textsubscript{2}DS\textsubscript{2}-VASc scores. If those patients have a history of stroke and older than 65 years, CHA\textsubscript{2}DS\textsubscript{2}-VASc scores is 3 in male and 4 in female. Our results showed that stroke events mostly occurred in patients with CHA\textsubscript{2}DS\textsubscript{2}-VASc scores ≥4, and the cut-off value for differentiating ischemic stroke events was ≤3. The number of stroke event was very low in SR group. And stroke event was mostly detected in patients CHA\textsubscript{2}DS\textsubscript{2}-VASc score ≥4 (Table 3). Therefore, this showed only trend of distribution of stroke event and further large study would be needed. The ESS-PRAFA study also showed that after CA, most patients (89.3%) continued the same anticoagulant as before CA [15]. This trend toward practical OAC was based on the CHA\textsubscript{2}DS\textsubscript{2}-VASc score, but successful CA rate and rhythm status. However, in our results, rhythm status was the most significant independent predictor of ischemic stroke.

In AFFIRM study, Corley SD et al. showed that rhythm control is not superior to rate control [16]. However, they demonstrated that OAC with warfarin improved survival, but SR was an important determinant of survival. The rhythm control strategy with CA improved more favorable outcomes than the rhythm control strategy with AAD alone or a rate control strategy [17–20]. CA has been improved and is an efficient tool for maintaining SR [21]. If TE are assessed not only by CHA\textsubscript{2}DS\textsubscript{2}-VASc score but also SR maintenance, modified OAC may be required after successful CA. However, our study showed that it was only observed in patients with CHA\textsubscript{2}DS\textsubscript{2}-VASc score ≤3. We cannot recommend discontinuation of OAC for patient...
Study limitations

First, this was not a randomized trial, but a retrospective study. However, over the past 10 years, the CA strategy has developed from PVI to linear or/and CFAE ablation, the rate of successful CA has improved, the ratio of sinus rhythm maintenance is high, and the rate of total ischemic stroke events remains low. Therefore, there were low rates of OAC for patients with CHA2DS2-VASc scores ≥2, based on rhythm status, bleeding risk, and compliance. Second, there is no analysis of asymptomatic AF episodes which were not detected by ECG or Holter monitoring. Like other AF studies, asymptomatic AF episodes are important and limit the analysis of AF recurrence. This would underestimate the recurrence of AF after ablation, and result in misallocation of some patients from recurrence group to SR group. Third, the study population included patients with a mean CHA2DS2-VASc score of 1.0 and a small number with a moderate risk of TE events. Therefore, 0.6% of the absolute ischemic stroke event rate was very low. Patients with CHA2DS2-VASc scores 0 or 1 would not be recommended OAC by current guidelines, regardless of rhythm status or success of ablation. CHA2DS2-VASc scores were not significantly different between the two groups (0.9 vs. 1.1, p = 0.053). Comparison and p value of CHA2DS2-VASc score = 0, 1, and ≥2 were <0.001, 0.193, <0.001, respectively. Patients with CHA2DS2-VASc score ≥2 were lower in SR group. This finding was also limitation of interpretation of stroke events in both groups. Large population studies with higher CHA2DS2-VASc scores are necessary to evaluate the role of sinus rhythm status after successful CA to further address our question. Finally, the ratio of male is much higher than that of female both AF recurrence (79.5%) and SR maintenance group (79.2%). This had the limitation of stroke risk for female population. Mean LVEF showed normal function both AF recurrence (54.6%) and SR maintenance group (55.7%). This also had the limitation of evaluating catheter ablation for atrial fibrillation in patients with reduced LVEF. And further study would be needed.

Conclusions

This long-term follow up study in patients with AF who underwent catheter ablation showed that sinus rhythm maintenance was correlated with a lower rate of ischemic stroke in Korea. However, it was only observed in patients with CHA2DS2-VASc score ≤3.

Author Contributions

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References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr., et al. 2014 AHA/ACC/HRS guideline 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 Heart Rhythm Society. J Am Coll Cardiol. 2014; 64(21):e1–76. Epub 2014/04/02. https://doi.org/10.1016/j.jacc.2014.03.022 PMID: 24685669.

2. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation. 2012; 126(7):860–5. Epub 2012/08/15. https://doi.org/10.1161/CIRCULATIONAHA.111.060061 PMID: 22891166.

3. Hindricks G, Pliorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. Circulation. 2005; 112(3):307–13. Epub 2005/07/13. https://doi.org/10.1161/CIRCULATIONAHA.104.518837 PMID: 16009793.

4. Saad EB, d'Avila A, Costa IP, Aryana A, Slater C, Costa RE, et al. Very low risk of thromboembolic events in patients undergoing successful catheter ablation of atrial fibrillation with a CHADS2 score ≤3: a long-term outcome study. Circ Arrhythm Electrophysiol. 2011; 4(5):815–21. Epub 2011/09/16. https://doi.org/10.1161/CIRCEP.111.963231 PMID: 21641192.

5. Karasoy D, Gislason GH, Hansen J, Johannessen A, Kober L, Hvidtfeldt M, et al. Oral anticoagulation therapy after radiofrequency ablation of atrial fibrillation and the risk of thromboembolism and serious bleeding: long-term follow-up in nationwide cohort of Denmark. European heart journal. 2015; 36(5):307–14a. Epub 2015/11/05. https://doi.org/10.1093/eurheartj/ehu421 PMID: 25368205.

6. Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. European heart journal. 2016; 37(31):2478–87. Epub 2016/03/18. https://doi.org/10.1093/eurheartj/ehw087 PMID: 26984861.

7. Kochhauser S, Alipour P, Haig-Carter T, Trought K, Hache P, Khaykin Y, et al. Risk of Stroke and Recurrence After AF Ablation in Patients With an Initial Event-Free Period of 12 Months. Journal of cardiovascular electrophysiology. 2017; 28(3):273–9. Epub 2016/12/10. https://doi.org/10.1111/jce.13138 PMID: 27933666.

8. Nademanee K, Schwab MC, Kosar EM, Karwecki M, Moran MD, Visessook N, et al. Clinical outcomes of catheter substrate ablation for high-risk patients with atrial fibrillation. J Am Coll Cardiol. 2008; 51(8):843–9. Epub 2008/02/26. https://doi.org/10.1016/j.jacc.2007.10.044 PMID: 18294570.

9. Bunch TJ, Crandal BG, Weiss JP, May HT, Bair TL, Osborn JS, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. Journal of cardiovascular electrophysiology. 2011; 22(8):839–45. Epub 2011/03/18. https://doi.org/10.1111/j.1540-8167.2011.02035.x PMID: 21410581.

10. Themistoclasis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo a et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. J Am Coll Cardiol. 2010; 55(8):735–43. Epub 2010/02/23. https://doi.org/10.1016/j.jacc.2009.11.039 PMID: 20170810.

11. Oral H, Chugh A, Ozaydin M, Good E, Fortino J, Sankaran S, et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. Circulation. 2006; 114(8):759–65. Epub 2006/08/16. https://doi.org/10.1161/CIRCULATIONAHA.106.641225 PMID: 16908760.

12. Lickfett M, Hackenbroch M, Lewalter T, Selbach S, Schwab JO, Yang A, et al. Cerebral diffusion-weighted magnetic resonance imaging: a tool to monitor the thrombogenicity of left atrial catheter ablation. Journal of cardiovascular electrophysiology. 2006; 17(1):1–7. Epub 2006/01/24. https://doi.org/10.1111/j.1540-8167.2005.00279.x PMID: 16426390.

13. Verma A, Champagne J, Sapp J, Essebag V, Novak P, Skanes A, et al. Discerning the incidence of symptomatic and asymptomatic episodes of atrial fibrillation before and after catheter ablation (DISCERN AF): a prospective, multicenter study. JAMA internal medicine. 2013; 173(2):149–56. Epub 2012/12/26. https://doi.org/10.1001/jamaintерnalmed.2013.1561 PMID: 23266597.

14. Holmquist F, Simon D, Steinberg BA, Hong SJ, Kowey PR, Reiffel JA, et al. Catheter Ablation of Atrial Fibrillation in U.S. Community Practice—Results From Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). J Am Heart Assoc. 2015; 4(5). Epub 2015/05/23. https://doi.org/10.1161/jaha.115.001901 PMID: 25999401; PubMed Central PMCID: PMCPMC4599417.

15. Potpara TS, Larsen TB, Deharo JC, Rossvoili O, Dagres N, Todd D, et al. Oral anticoagulant therapy for stroke prevention in patients with atrial fibrillation undergoing ablation: results from the First European Snapshot Survey on Procedural Routines for Atrial Fibrillation Ablation (ESS-PRAFA). Europace:
European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015; 17(6):986–93. Epub 2015/05/30. https://doi.org/10.1093/europace/euv132 PMID: 26023177.

Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation. 2004; 109(12):1509–13. Epub 2004/03/10. https://doi.org/10.1161/01.CIR.0000121736.16643.11 PMID: 15007003.

Jons C, Hansen PS, Johannessen A, Hindricks G, Raatikainen P, Kongstad O, et al. The Medical ANti-arrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) trial: clinical rationale, study design, and implementation. Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2009; 11(7):917–23. Epub 2009/05/19. https://doi.org/10.1093/europace/eup122 PMID: 19447807.

Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015; 17(3):370–8. Epub 2015/02/04. https://doi.org/10.1093/europace/euu376 PMID: 25643988.

Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, et al. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-center, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). European heart journal. 2006; 27(2):216–21. Epub 2005/10/11. https://doi.org/10.1093/eurheartj/ehi583 PMID: 16214831.

Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. J Am Coll Cardiol. 2006; 48(11):2340–7. Epub 2006/12/13. https://doi.org/10.1016/j.jacc.2006.08.037 PMID: 17161267.

Willems S, Klemm H, Rostock T, Brandstrup B, Ventura R, Steven D, et al. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. European heart journal. 2006; 27(23):2871–8. Epub 2006/06/20. https://doi.org/10.1093/eurheartj/ehi093 PMID: 16782716.