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ORIGINAL PAPER

Oral anticoagulation is frequently discontinued after ablation of paroxysmal atrial fibrillation despite previous stroke: data from the German Ablation Registry

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Abstract
Aims Atrial fibrillation (AF) is the most common cause of ischemic stroke. Recent data suggest that AF patients after successful ablation have the same risk for thromboembolic events (TE) as patients without AF. Despite current guideline recommendations it is still under debate if oral anticoagulation (OAC) can be safely discontinued after ablation. We analyzed follow-up (FU) after ablation of paroxysmal AF (PAF) in a high- (previous stroke; group 1) and a low-risk group (no previous stroke; group 2) based on data from the German Ablation Registry to reveal real-life prescription behavior.
Methods Overall 29 centers in Germany participated by performing AF-ablation. Between April 2008 and April 2011, 83 patients in group 1 and 377 patients in group 2 with a first ablation of PAF were included in the registry.
Results Mean CHA_2DS_2-VASc-Score was 4.2 ± 1.4 (group 1) vs. 1.6 ± 1.2 (group 2) ($p < 0.0001$). No peri-interventional TE was observed. Arrhythmia recurrence was seen in 47.4 vs. 48.4 % ($p = 0.79$) during a median FU of 489 (453–782) days, resulting in a repeat procedure in 20.0 vs. 20.7 % ($p = 0.88$), respectively. OAC was discontinued in 38.6 % in group 1 vs. 66.3 % in group 2 ($p < 0.0001$) during FU. TE during FU occurred more often in group 1 than in group 2 (4.3 vs. 0.3 %, $p < 0.05$).
Conclusion Even in patients with previous stroke, OAC was frequently discontinued during FU after PAF ablation in this observational study. However, TE occurred significantly more frequent in these high-risk patients. These data argue against OAC discontinuation after ablation in patients with previous stroke.

Keywords Atrial fibrillation · Pulmonary vein isolation · Thromboembolic complications · Anticoagulation · Stroke

Abbreviations

AF	Atrial fibrillation
ASA	Acetylsalicylic acid

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CFAE	Complex fractionated atrial electrogram
FU	Follow-up
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiac and cerebrovascular events: death, myocardial infarction, stroke
Min	Minutes
OAC	Oral anticoagulation
PAF	Paroxysmal atrial fibrillation
PVI	Pulmonary vein isolation
RF	Radiofrequency
SAE	Severe non-fatal adverse events: myocardial infarction, stroke, major bleeding
TE	Thromboembolic events
TIA	Transient ischemic attack

Introduction

Atrial fibrillation (AF) is the most common cause of ischemic strokes [1]. Data from the Framingham study report a twofold increased relative risk of stroke in patients with AF compared to the general population [1]. In clinical routine the $CHADS_2$/CHA_2DS_2-VASc-Score is used for individual risk stratification [2]. Oral anticoagulation (OAC) for the prevention of thromboembolic events (TE) is recommended in patients with a $CHADS_2$-Score $\geq$1 or a CHA_2DS_2-VASc-Score $\geq$2.

Pulmonary vein isolation (PVI) has become an established curative therapeutic option in patients with paroxysmal atrial fibrillation (PAF) and achieves 5-year success rates up to 80 % [3, 4]. Despite this fact, the guidelines recommend to continue OAC after AF-ablation depending on the individual $CHADS_2$/CHA_2DS_2-VASc-Score, irrespective of the procedural success [2].

However, recent data suggest that patients after successful AF-ablation have the same risk for TE as patients without AF [5–7]. Hunter et al. [6] observed an annual stroke rate of 0.5 % per year after ablation. Still, most of these studies only included patients with a low $CHADS_2$-Score and therefore a low risk for TE. Only Guiot et al. [8] included patients aged $\geq$65 years, thus having an increased risk for TE. The annual stroke rate after AF-ablation in this cohort was 1.1 %. Of note, mean $CHADS_2$-Score was 1.1 $\pm$ 0.9 in these patients, which is not markedly increased.

It is yet unclear, whether patients at high risk, with previous stroke, develop TE after ablation more often than patients at low risk. Furthermore—despite current guidelines—it is still under debate whether OAC can be safely discontinued after ablation of PAF. Thus, we performed a centralized follow-up (FU) regarding the frequency of discontinuation of OAC after AF-ablation in clinical routine. A high-risk group, defined by a history of previous stroke before ablation, was compared to a low-risk group without previous stroke. Furthermore, we were interested in TE after ablation of PAF.

Methods

Recruiting sites

A total of 55 German electrophysiological centers agreed to participate in this prospective multicenter registry. 29 centres performed ablation of atrial fibrillation and included patients for this study.

Patient population

All patients aged $\geq$18 years who underwent a de novo catheter ablation of PAF in their respective centers were enrolled between April 2008 and April 2011 after written informed consent was obtained. Patients with a relevant valvular heart disease (Grade $\geq$ 2) or undergoing atrioventricular node ablation were excluded. The minimum FU was 12 months. A total cohort of 460 patients was divided into two groups: a high-risk group with previous stroke before ablation (n = 83, 18.0 %), and a low-risk group without previous stroke (n = 377, 82.0 %).

Catheter ablation procedure

The mode of the catheter ablation, such as the ablation catheter, ablation energy, non-fluoroscopic navigation system, magnetic or remote navigation, as well as the pre- and peri-procedural management were chosen at the physician's discretion according to the institutional standards. All ablation strategies aimed at electrical isolation of the pulmonary veins which probably impacts both trigger and substrate of AF [9, 10].

Transesophageal echocardiography was performed routinely before the ablation procedure to exclude intracardiac thrombus formation.

OAC was administered at the discretion of the treating physician for an individual period, but at least for 3 months. Antiarrhythmic drugs were also continued at the discretion of the treating physician.

Follow-up

The postinterventional monitoring regarding arrhythmia recurrences and adverse events was chosen at the physician's discretion according to the institutional standards.

A centralized FU was conducted via telephone interviews. A thromboembolic event was defined as either stroke or transient ischemic attack (TIA).

Registry management

This registry was carried out by the Institute for Research in Myocardial Infarction (Ludwigshafen, Germany) which was responsible for project development, project management, data management, clinical monitoring and the telephone interviews. The institute was the central contract research organization for the study. Documentation and data management were paperless and carried out as an internet-based case report form system. All site information was confidential and transmitted data were encrypted with a secure socket layer. The development of the biometric model as well as planning and performing all statistical analyses was also done by the institute.

Statistical analysis

Data are shown as absolute values, percentages, means with standard deviation or medians with 25 and 75 % quartiles (interquartile range, IQR). For statistical comparisons, the Chi-square test was used with categorical or dichotomous variables and the non-parametric Kruskal–Wallis test with metric variables. All statistical comparisons were two sided, with $p < 0.05$ being accepted as statistically significant. All analyses were performed using the Statistical Analysis System (SAS, Version 9.2, SAS Institute Inc., Cary, NC, USA).

Results

Baseline data

Between April 2008 and April 2011, 83 patients in the high-risk group and 377 patients in the low-risk group with a de novo catheter ablation of non-valvular PAF were included in the registry. The baseline data of these patients are shown in Table 1. Mean $CHADS_2$-Score was 0.7 ± 0.7 vs. 2.9 ± 0.7 ($p < 0.0001$), mean CHA_2DS_2-VASc-Score was 1.6 ± 1.2 vs. 4.2 ± 1.4 ($p < 0.0001$) in the low- vs. the high-risk group, respectively. 59.5 % (100/168) of those patients with a CHA_2DS_2-VASc-Score >1 in the low-risk group were female. Mean age [60 years (52–67) vs. 66 years (62–72), $p < 0.0001$] was higher and a greater portion of patients aged ≥75 years (3.4 vs 8.4 %, $p < 0.05$) was found in the high-risk group. The respective proportions of the different score groups are shown in Fig. 1. The FU was significantly longer in the high-risk group (625.5 vs. 493.0 days, $p < 0.0001$).

Procedural data

The procedural data are shown in Table 2. There were no significant differences between the two groups, neither regarding the ablation technique, the energy source, nor the procedure related complications. The procedural success was also comparable. No peri-interventional TE was observed. Severe procedural-related complications (defined as myocardial infarction, stroke, major bleeding) occurred in 1.6 vs. 2.4 % ($p = 0.61$), in the high-risk group vs. the low-risk group, respectively. Of note, only major bleeding was observed while no procedural-related myocardial infarction or stroke occurred. Moderate procedural-related complications (defined as aneurysm, pneumothorax, cardiac tamponade, 3rd degree atrioventricular (AV)-block) occurred in 3.0 vs. 3.7 % ($p = 0.75$) and minor procedural-related complications (defined as minor bleeding, 1st and 2nd degree AV-block) in 5.2 vs. 4.9 % ($p = 0.92$), in the high-risk group vs. the low-risk group, respectively. No 1st or 2nd degree AV-block was observed in this registry cohort. No atrial esophageal fistula was observed.

Table 1 Baseline data

	Low-risk-group $n = 377$	High-risk-group $n = 83$	p value
Age (years)	60 (52–67)	66 (62–72)	<0.0001
Female sex (%)	40	51	0.09
$CHADS_2$-Score	0.7 ± 0.7	2.9 ± 0.7	<0.0001
CHA_2DS_2-VASc-Score	1.6 ± 1.2	4.2 ± 1.4	<0.0001
Congestive heart failure (%)	0	3	0.12
Hypertension (%)	58	64	0.36
Age ≥ 75 (%)	3.4	8.4	<0.05
Diabetes (%)	9	12	0.35
Stroke (%)	0	100	–

Arrhythmia recurrence

Recurrence of any atrial arrhythmia was seen in 47.4 vs. 48.4 % ($p = 0.79$, Fig. 2), resulting in a repeat procedure in 20.0 vs 20.7 % ($p = 0.88$), in the high- vs. the low-risk group, respectively. At the 1-year follow-up, 69.8 vs 74.3 % ($p = 0.46$) patients were on betablocker-, 14.8 vs 11.4 % ($p = 0.46$) on class-I-AAD- and 12.7 vs. 11.4 % ($p = 0.77$) on class-III-AAD-treatment in the high- vs the low-risk-group, respectively.

Anticoagulation during FU

At the time of hospital discharge all patients were on OAC or bridging low-weight heparin therapy. During FU, OAC was—despite current guideline recommendation—discontinued in 38.6 % in the high-risk group vs. 66.3 % in the low-risk group ($p < 0.0001$) as shown in Fig. 3. At the same time, the proportion of patients on acetylsalicylic acid (ASA) medication increased, this increase was more pronounced in the low-risk group (18.6 vs 33.4 %, $p < 0.05$).

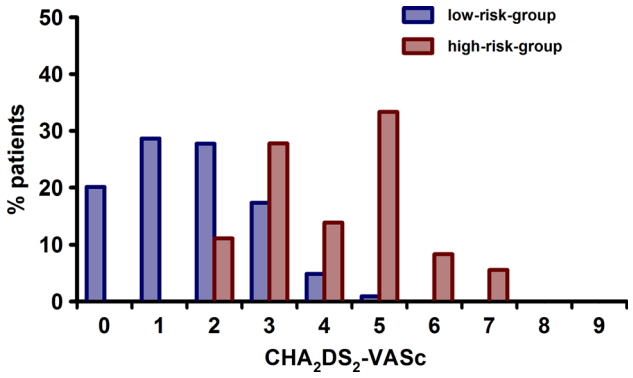

Fig. 1 CHA_2DS_2-VASc-Score: distribution of CHA_2DS_2-VASc-Scores in the high- vs the low-risk group

A combined therapy with ASA and OAC was present in 3 vs. 9 patients with ASA therapy. Thus, 24 % of patients in the high-risk group neither received anticoagulation nor platelet inhibition during FU.

Table 3 shows frequency in OAC discontinuation with respect to arrhythmia recurrence.

Thromboembolic and other adverse events during FU

TE during FU occurred more often in the high-risk group than in the low-risk group (Table 4; Fig. 4). The calculated annual thromboembolic stroke rate was 1.4 vs. 0 % in the high- vs. the low-risk group, respectively. Data of the four individuals with TE during FU are shown in Table 5.

Other adverse events, such as myocardial infarction (1.4 vs. 0 %, $p < 0.05$) or combined endpoints such as MACCE (major adverse cardiac and cerebrovascular events: death, myocardial infarction, thromboembolic stroke; 4.3 vs. 0.6 %, $p < 0.05$) or severe non-fatal adverse events (myocardial infarction, thromboembolic stroke, major bleeding; 5.8 vs. 0.03 %, $p < 0.001$) also occurred more often in the high-risk group, while there was no significant difference in major bleeding (1.4 vs. 0.3 %, $p = 0.21$). Two sudden cardiac deaths occurred in the low-risk group, while no death was observed in the high-risk group ($p = 0.5$).

Discussion

Main findings

We report on the continuation of OAC as well as the occurrence of TE after ablation of PAF in a large observational registry. First of all, OAC was discontinued after AF-ablation in over 60 % in the low-risk group and in nearly 40 % of high-risk patients despite having a history of previous stroke. In addition, recurrent TE occurred

Table 2 Procedural data

	Low-risk-group $n = 377$	High-risk-group $n = 83$	p value
Circumferential PVI, (%)	83	84	0.69
Segmental PVI, (%)	15	12	0.44
Linear lesions, (%)	14	11	0.40
CFAE Ablation, (%)	2	5	0.16
Procedural success, (%)	97	99	0.28
RF-ablation, (%)	75	84	0.07
Fluoroscopy time, (min)	26 (18–40)	22 (15–34)	<0.05
Maximum RF energy, (W)	30 (30–40)	35 (30–40)	0.18
RF time, (min)	39 (24–50)	40 (26–52)	0.47

CFAE complex fractionated atrial electrogram, *min* minutes, *PVI* pulmonary vein isolation, *RF* radiofrequency, *W* watt

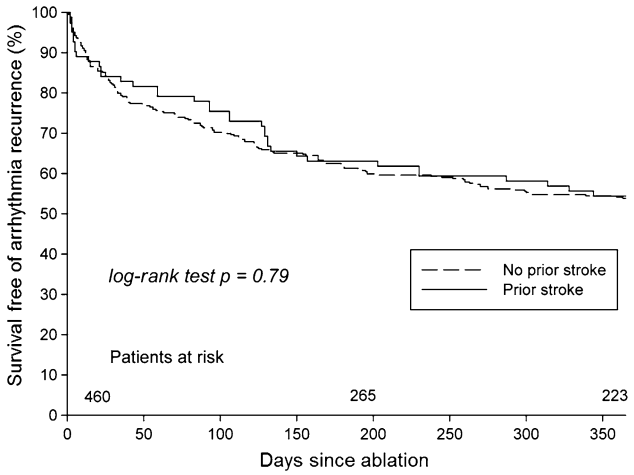

Fig. 2 Arrhythmia recurrence: Kaplan–Meier-curve shows the rate of arrhythmia recurrence was comparable in the high-risk group (prior stroke) and the low-risk group (no prior stroke) ($p = 0.79$)

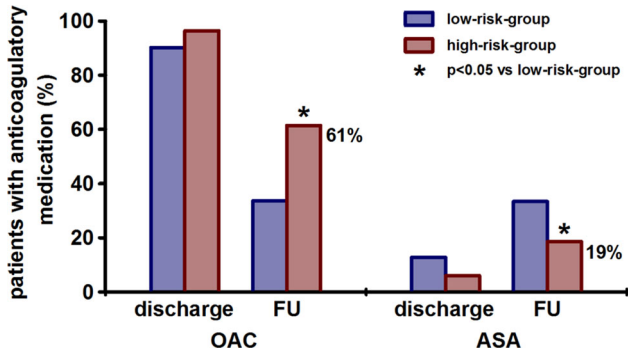

Fig. 3 Anticoagulatory medication: OAC was frequently discontinued during FU while patients on acetylsalicylic acid (ASA) medication increased. *FU* follow-up, *OAC* oral anticoagulation

significantly more often in the high-risk group, that is with previous stroke before ablation, of this registry cohort.

The proportion of patients with stroke prior to ablation in this cohort is higher than in other population-base cohorts. In comparison, the Leipzig Heart Center AF-ablation registry found 9 % of their AF-ablation patients to have had a previous stroke [11]. Of note, an additional FU of patients with previous stroke which otherwise would not have been able to be included because of a too short FU was conducted. Therefore, patients in the low- (29.04.2008–26.10.2010) and in the high-risk group were included during two different periods of time (10.02.2009–18.04.2011).

Anticoagulation during FU

Surprisingly, this real life registry showed that OAC was discontinued frequently after AF-ablation in both groups, despite the current guideline recommendations [2]. A current survey in Canada also found that physicians are likely to discontinue OAC when there is no evidence for arrhythmia recurrence [12]. As to be expected and in line with previous studies [8], withdrawal of OAC occurred more often in low-risk patients. Still, these patients had a mean $CHADS_2$-Score of 0.7 ± 0.7 and were thus predominantly recommended to receive ongoing OAC after AF-ablation regardless of the procedural outcome.

Furthermore, even in the high-risk group—that is in patients with previous stroke and thus a minimum $CHADS_2$-Score of 2—OAC was discontinued in over a third of patients, although a previous stroke is one of the strongest predictors for recurrent TE [13]. Whether to receive OAC or not should be decided regardless of procedural outcome, in part because the risk factors for AF and stroke overlap and those risk factors predominantly remain even after successful AF-ablation. AF might even only be a risk marker for TE rather than the cause [14].

Moreover, as procedural success rates of AF-ablation still need to improve and even late recurrences after several years are observed [15], the definition of long-term ablation success remains difficult. Therefore, patients who were considered to have had a successful ablation procedure may experience late arrhythmia recurrence and are then again at high risk for TE due to underlying risk factors. In one study, late recurrences were even more frequent in patients with high $CHADS_2$-Score [15].

Table 3 Discontinuation of OAC based on arrhythmia recurrence

	Arrhythmia recurrence	No arrhythmia recurrence	*p* value
Low-risk-group (%)			
OAC discontinued	56	75	$p = 0.0004$
OAC continued	44	25	
High-risk-group (%)			
OAC discontinued	18	59	$p = 0.0005$
OAC continued	82	41	
All patients (%)			
OAC discontinued	49	72	$p < 0.0001$
OAC continued	51	28	

Table 4 Adverse events during follow-up

	Low-risk-group $n = 351$	High-risk-group $n = 80$	p value
Thromboembolic stroke	0	2 (2.9 %)	<0.01
TIA	1 (0.3 %)	1 (1.4 %)	0.21
Thromboembolic events (stroke + TIA)	1 (0.3 %)	3 (4.3 %)	<0.05
Myocardial infarction	0	1 (1.4 %)	<0.05
Death	2 (0.6 %)	0	0.5
Major bleeding	1 (0.3 %)	1 (1.4 %)	0.21
Servere non-fatal adverse events	1 (0.3 %)	4 (5.8 %)	<0.001
MACCE	2 (0.6 %)	3 (4.3 %)	<0.05

MACCE major adverse cardiac and cerebrovascular events: thromboembolic stroke + myocardial infarction + death, severe non-fatal adverse events: thromboembolic stroke + myocardial infarction + major bleeding, *TIA* transient ischemic attack

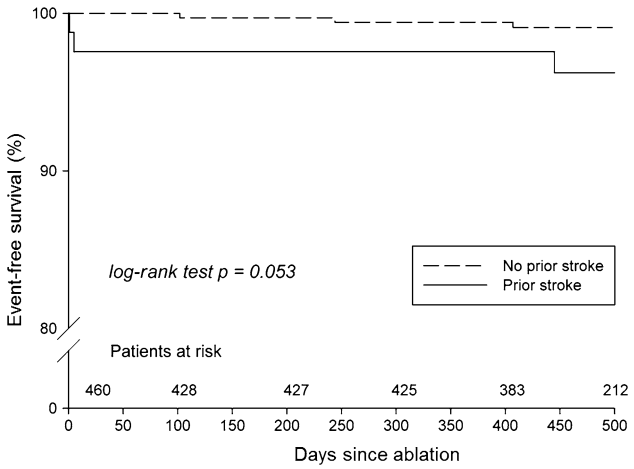

Fig. 4 Thromboembolic events and death during follow-up: Thromboembolic events during follow-up occurred more often in the high-risk group (4.3 %) than in the low-risk group (0.3 %, $p < 0.05$)

Increase of ASA therapy during FU might be related either to changing OAC to ASA or to discontinuation of OAC and prescription of ASA due to comorbidities, such as coronary artery disease. The first explanation however, would not meet the current guidelines as ASA is no longer recommended as an alternative to OAC in patients with low CHA_2DS_2-VASc-Score [2].

Thromboembolic events

The rate of recurrent TE in this study was higher than previously reported [5, 6]. Of note, the mean $CHADS_2$-/CHA_2DS_2-VASc-Score and therefore the risk for TE in this cohort, was markedly increased compared to those studies. In addition, in previous studies those patients with higher risk factors and especially patients with previous stroke mostly continued OAC which might underestimate the actual stroke rate [6].

Recurrent TE in this study occurred significantly more often in the high-risk group. This finding is in line with previous studies [16]. However, it has to be kept in mind, that the overall event rate was very low. Despite this low event rate and the differences in FU time, the calculated annual thromboembolic stroke rate was still increased in the high-risk group compared to the low-risk group as well as compared to previous studies and the estimated risk in the general population [6]. Although all patients with recurrent TE also had recurrence of an atrial arrhythmia, the overall recurrence rate of atrial arrhythmias was comparable in both groups. Thus, recurrence of TE might be determined rather by the risk profile than by the arrhythmia recurrence. While we did not observe group differences regarding arrhythmia recurrence, a previous study found a poorer outcome after AF-ablation in patients with a high $CHADS_2$-Score [6, 17, 18].

Interestingly, in those individuals with a TE during FU, OAC was not discontinued. This does not exclude insufficient time in therapeutic range as a cause for these TE. Unfortunately, the INR at the time of the TE cannot be investigated, as it was not included in the case report form. However, this finding also emphasizes that OAC can only reduce the risk for a TE, but not completely prevent it. Keeping those patients at high risk for a TE in sinus rhythm should therefore be pursued.

Study limitations

First of all, the current investigation relies on single-country registry data and was not a prospective randomized trial. Therefore, important data such as the mean time to OAC discontinuation as well as the time in therapeutic range are missing. If OAC can safely be discontinued after

Table 5 Individual data on patients with recurrent thromboembolic event

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	61	71	61	79
Female sex	y	y	y	n
$CHADS_2$-Score	2	2	1	3
CHA_2DS_2-VASc-Score	3	4	2	4
Congestive heart failure	n	n	n	n
Hypertension	n	n	y	n
Age $\geq$ 75	n	n	n	y
Diabetes	n	n	n	n
Previous stroke	y	y	n	y
Arrhythmia recurrence	y	y	y	y
TIA during FU	y	n	y	n
Stroke during FU	n	y	n	y
TE within first year	y	y	y	n
Betablocker	y	y	y	y
Antiarrhythmic drugs class I	n	n	y	n
Antiarrhythmic drugs class III	n	y	n	n
OAC during FU	y	y	y	y
ASA during FU	n	n	n	n

ASA acetylsalicylic acid, *FU* follow-up, *n* no, *OAC* oral anticoagulation, *TE* thromboembolic events, *TIA* transient ischemic attack, *y* yes

AF-ablation or if it really needs to be maintained irrespective of the procedural success has to be answered in randomized clinical trials. Still, the data reflect a real-life scenario in patients with a high risk for thromboembolic events and give insight in clinical routines apart from a study setting. Especially in terms of OAC prescription, this seems to be of particular interest.

Second, as a major limitation the event rate in this cohort was very low. However, the calculated annual thromboembolic stroke rate in the high-risk group was still markedly increased compared to the low-risk group and to the general population without AF. Due to this low event rate in our study no analysis of predicting factors for recurrent TE could be conducted as the study was not powered to detect those.

Third, the FU was significantly longer in the high-risk group. This fact is due to later addition of the variable "previous stroke" to the case report form and therefore low inclusion number of patients in the high-risk group. To increase the number of included patients an additional FU of patients with previous stroke which otherwise would not be able to be included due to FU <12 months was performed.

Finally, included patients only received warfarin as an OAC. However, novel anticoagulants impact on the event rates and the continuation after AF-ablation remains to be investigated.

Conclusion

Despite current guideline recommendations, we demonstrated that OAC is frequently discontinued during FU after AF-ablation. This happens even in patients with previous stroke and therefore a high thromboembolic risk. In addition, TE after ablation of PAF occurred significantly more frequent in these high-risk patients despite similar AF recurrence rates. These data argue against discontinuation of OAC after AF-ablation in patients with previous stroke. The predictive value of the CHA_2DS_2-VASc-Score seems to persist after ablation irrespective to the arrhythmic outcome. Randomized clinical trials are needed to answer the question whether OAC can safely be discontinued after AF-ablation in high-risk patients or if it needs to be maintained irrespective of the procedural success.

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Conflict of interest All authors declare no conflicts of interest regarding this manuscript.

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