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ANTITHROMBOTIC THERAPY IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION AND HIGH RISK OF STROKE AFTER SUCCESSFUL ENDOVASCULAR LEFT ATRIAL APPENDAGE OCCLUSION

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Aim. To assess the antithrombotic therapy after left atrial appendage occlusion (LAAO) with the Watchman device (WD) and Amplarzer Cardiac Plug (ACP) for stroke prevention in patients with nonvalvular atrial fibrillation (AF) with contraindications for long anticoagulation therapy.

Methods. 200 consecutive patients with nonvalvular AF and contraindications to oral anticoagulation therapy with contraindications for long anticoagulation who undergone LAAO implantation using WD (n=108; WD group) and ACP (n=92; ACP group) were enrolled into this study. Antithrombotic therapies were prescribed after successful LAAO implantation according to indications. Patients were followed at 45 days, 3, 6 and 12 months after enrollment. At each follow-up visit the data regarding clinical events and healthcare utilization were collected. Transesophageal echo (TEE) was perfomed at 45 days and 6 months after successful LAAO implantation. The efficacy end point was the composite of transit ischemic attack (TIA)/stroke, device thrombosis and procedure-related death.

Results. During the follow-up TIA/stroke has occurred in 4.8% of patients in the WD group with no such events in ACP group (4.8% vs 0%, p=0.062). These patients had 4 or more points on the CHA_2DS_2-VASc, and they were prescribed various combinations of antithrombotic therapy, except warfarin, while patients from the WD group with 4 or more points on the CHA_2DS_2-VASc score taking warfarin had no thromboembolic events. Device thrombosis during TEE at 45 days after successful LAAO implantation was confirmed in 3 patients (2,9%) with WD with no such events in ACP group (2.9% vs 0%, p=0.251). The efficacy end point events in all groups were 4.6%: 8 events in WD group (7.6%) and 1 case in ACP group (1.1%). One patient in the ACP group died in 6 weeks after LAAO implantation. No autopsy was performed; therefore, the exact cause of death was not determined (p=0.038). Survival rate showed significantly higher rate events in WD group versus ACP group (p=0.027).

Conclusion. Any combinations of antithrombotic therapy could be prescribed to patients with contraindications for anticoagulant therapy and high risk of stroke who undergone successful (LAAO) implantation with Amplatzer Cardiac Plug. It's possible to cancel oral anticoagulants in this patient. Patients aged 70 and older with a CHA_2DS_2-VASc $\geq$4 and a history of stroke are recommended to take warfarin after successful Watchman Device implantation.

Key words: atrial fibrillation; left atrial appendage occlusion; stroke prevention; antotrombotic therapy; Watchman device; Amplatzer Cardiac Plug

Conflict of Interests: Karapet Davtyan serves as a proctor for Medtronic and Abbott. Andrey Kalemberg is a consultant for Abbott. Dmitriy Lebedev has received a speaker honorarium from Medtronic and Biosense Webster. Other authors have nothing to declare.

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Atrial fibrillation (AF) is a common heart rhythm disorder that is associated with a significantly increased risk of stroke and/or systemic embolism (SE) and death. According to recent data [1-3], 20-30% of all ischemic strokes are attributable to AF, and in the structure of all strokes in patients with AF, cardioembolic strokes account for 65%. The most common source of thromboembolism in AF (90% in nonvalvular AF, 57% in valvular AF) is the left atrial appendage (LAA) [4].

The most important way to prevent thromboembolic complications in patients with AF is long-term (virtually lifelong) anticoagulant therapy. Numerous studies have shown that treatment with anticoagulants significantly reduces the risk of stroke/SE but is often associated with side effects, the most dangerous of which are hemorrhagic complications (especially intracranial and gastrointestinal bleeding), which in some cases can be fatal [5]. In such cases, methods of non-medical stroke prevention become relevant. One of them is endovascular implantation of special devices that isolate the LAA, so-called occluders. According to international clinical guidelines, endovascular isolation of the LAA is recommended for patients with nonvalvular AF and high risk of stroke in whom long-term anticoagulant therapy is contraindicated.

Because the occluder is a foreign body, thrombi may form on its surface, so patients should receive antithrombotic therapy until the device is endothelialized.

Considering that LAA occluders were developed for patients with contraindications to anticoagulant therapy, in clinical practice patients after LAA occluder implantation are often not prescribed these drugs. It is often that the duration of dual antiplatelet agents is shortened, oral anticoagulants (OAC) are used, or treatment variants are limited to anticoagulant monotherapy, or no antithrombotic therapy is prescribed at all [6]. At the same time, after implantation of the Watchman Device (WD), it is recommended to apply the protocol of antithrombotic support used in the randomized clinical trial (RCT) PROTECTAF [7] and PREVAIL [8]. It is reasonable to prescribe warfarin with target international normalized ratio values of 2.0-3.0 in combination with acetylsalicylic acid (ASA). After implantation of the Ampltatzer Cardiac Plug (ACP), it is common to prescribe a combination of ASA and clopidogrel [9]. All these approaches have not yet been studied in RCTs and are part of the local protocols of different medical centers and are not official treatment tactics recommended by the medical community.

In our country, in 2015-2017, for the first time, a registry was established with the participation of 5 medical centers from different regions, comparing the immediate and long-term outcomes of WD and ACP occluder implantation in patients with nonvalvular AF, who cannot take OAC for a long time. These two types of devices are the most widely used in practice worldwide and are approved in the Russian Federation. We compared the safety of the implantation procedure and the effectiveness of prevention of cardioembolic complications in the postoperative period. These data are presented in another journal [10].

The aim of the research is to determine the specifics of antithrombotic therapy after implantation of the LAA occluder used in this study.

MATERIALS AND METHODS

An open-label, multicenter, prospective, nonrandomized comparative study was conducted between May 2015 and December 2017 in five centers of the Russian Federation: National Medical Research Center for Therapeutic and Preventive Medicine, Ministry of Health of the Russian Federation (Moscow); National Medical Research Center for Cardiology, Ministry of Health of the Russian Federation (Moscow); Almazov National Medical Research Center, Ministry of Health of the Russian Federation (St. Petersburg); Meshalkin Medical Research Center, Ministry of Health of the Russian Federation (Novosibirsk); Multidisciplinary Clinic No.1 of Volgograd State Medical University (Volgograd). The study was sponsored by the Ministry of Health of the Russian Federation, which selected the clinics participating in this study and divided the number of included patients by clinic.

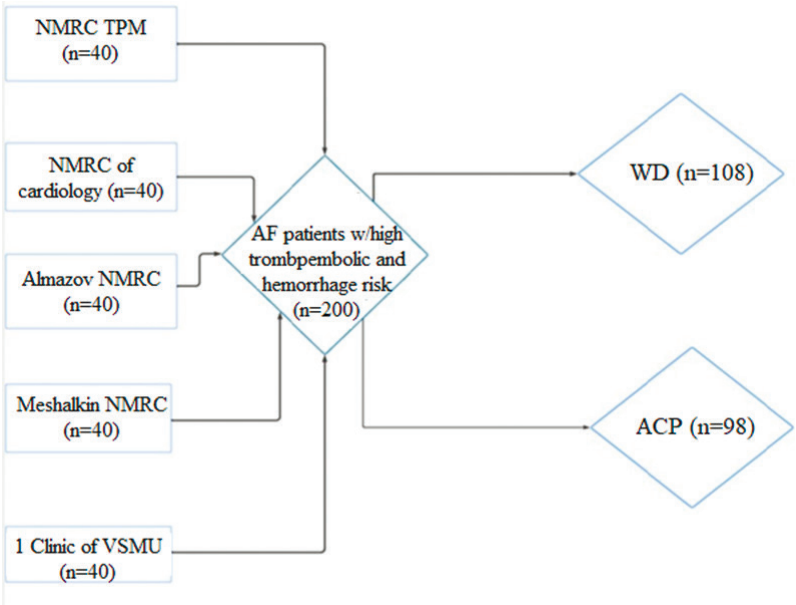

Fig. 1. Study design.

Inclusion criteria for the study were the following: age over 18 years, paroxysmal, persistent, or permanent nonvalvular AF, high risk of stroke/SE (sum of CHA_2DS_2-VASc scores > 2 in men and > 3 in women), no possibility of long-term OAC therapy, written informed consent to participate in the study.

Exclusion criteria: severe concomitant disease with a life expectancy of less than 1-year, valvular pathology requiring surgical correction, refusal to participate in the study.

After a preliminary examination, all patients were implanted with one of the occlusion systems - WD (Boston Scientific, Natwick, MA, USA) or ACP (St. Jude Medical, Plymonth, MA, USA). Accordingly, patients were divided into 2 groups:

WD (n=108) and ACP (n=92) (Fig. 1). The study was not randomized, so the choice of occluding device was at the discretion of the physician and depended on the LAA anatomy and the skills of the respective surgical team. After successful implantation of the LAA occluder, patients were prescribed antithrombotic therapy, which was not strictly regulated by the study protocol and was at the discretion of the treating physician.

The duration of the prospective study was 12 months. During the follow-up period, visits at 45, 90, and 180 days after the procedure were offered, as well as telephone contact with the patient or relatives at 12 months. At 45 and 180 days after implantation of the LAA occluder, a transesophageal echocardiographic examination was performed, and at 180 days, a transthoracic echocardiographic examination was performed. During the transesophageal echocardiographic examination the position of the device, the presence of thrombosis on its surface, and residual blood flow in the LAA were assessed.

The end points for stroke / SE prevention efficacy were 1) stroke / SE; 2) device thrombosis; and 3) procedure-related death. When stroke occurred, diagnosis was confirmed by computed tomography scan or magnetic resonance imaging of the brain. Device thrombosis was verified by the transesophageal echocardiographic examination performed at follow-up visits at 45 and 180 days.

Statistical analysis

Data were statistically analyzed using the statistical program SPSS 23.0 for Windows (SPSS Inc, USA). The nature of the distribution of quantitative characteristics was analyzed using the Kolmogorov-Smirnov one-sample test. The mean (M) and standard deviation (SD) were calculated for a parametric distribution; results are presented as M±SD. The median (Me) and interquartile range (25th percentile; 75th percentile) were calculated for qualitative ordinal and quantitative characteristics whose distribution was nonparametric; results are presented as Me (25%; 75%). When comparing the two groups, we used the Mann-Whitney test for quantitative variables and Fisher's two-sided exact test or Pearson's chi-square for qualitative and ordinal variables. The dynamics of qualitative indicators were assessed with the McNemar chi-square test. Relationships between variables were analyzed using Spearman correlation analysis. Survival analysis was performed by the Kaplan-Meier method; the log-rank criterion was used to compare survival curves.

Table 1.

Non-valvular AF patient characteristics (n=200)

Parameter	All patients (n=200)	Group WD (n=108)	Group ACP (n=92)	p
Age, years (M±SD)	66.8±7.8	67.0±7.9	66.7±7.6	0.488
Males, n (%)	112 (56)	59 (54.6)	53 (57.6)	0.672
Paroxysmal AF, n (%)	58 (29)	30 (27.8)	28 (30.4)	0.539
Persistent AF, n (%)	49 (24.5)	24 (22.2)	25 (27.2)	
Permanent AF, n (%)	93 (46.5)	54 (50)	39 (42.4)	
CHA_2DS_2-VASc*, Me (25%; 75%) M±SD	4 (3; 5) 4.01±1.58	4 (3; 5) 3.99±1.64	4 (3; 5) 4.03±1.51	0.670
HAS-BLED*, Me (25%; 75%) M±SD	3 (2; 3) 2.87±1.02	3 (2; 4) 2.98±0.93	3 (2; 3) 2.74±1.12	0.076
HAS-BLED >3, n (%)	124 (62)	74 (68.5)	50 (54.3)	0.040
Bleeding history, n (%)	79 (39.5)	36 (33.3)	43 (46.7)	0.053
Hypertension, n (%)	166 (83)	98 (90.7)	68 (73.9)	0.002
Hypertension, stage 1, n (%)	24 (14.5)	8 (8.2)	16 (23.5)	0.011
Hypertension, stage 2, n (%)	44 (26.5)	31 (31.6)	13 (19.1)	
Hypertension, stage 3, n (%)	98 (59)	59 (60.2)	39 (57.4)	
Diabetes mellitus, type 2, n (%)	60 (30)	33 (30.6)	27 (29.3)	0.853
Myocardial infarction history, n (%)	33 (16.5)	19 (17.6)	14 (15.2)	0.652
Stroke / TIA, n (%)	67 (33.5)	32 (29.6)	35 (38)	0.209
Ischemic stroke	51 (76.1)	21 (65.6)	30 (85.7)	0.054
Hemorrhagic stroke	8 (11.9)	5 (15.6)	3 (8.6)	0.464
TIA	12 (17.9)	7 (21.9)	5 (14.3)	0.418
2 strokes/TIA	4 (6)	1 (3.1)	3 (8.6)	0.615
Heart failure, n (%)	150 (75)	73 (67.6)	77 (83.7)	0.009
functional class 1 (NYHA), n (%)	9 (6.1)	7 (9.9)	2 (2.6)	0.125
functional class 2 (NYHA), n (%)	100 (68)	44 (62)	56 (73.7)	
functional class 3 (NYHA), n (%)	38 (25.9)	20 (28.2)	18 (23.7)	
Erosive gastritis, n (%)	30 (15)	4 (3.7)	26 (28.3)	<0.001

Notes: AF - atrial fibrillation; TIA - transient ischemic attack; * - scores on a scale.

Differences were considered statistically significant at a two-tailed $p < 0.05$.

RESULTS

Patient characteristics

The study included 200 patients with nonvalvular AF (56% men) aged 40 to 86 years (mean age 67±8 years), with 80% older than 60 years. The sum of CHA_2DS_2-VASc scores ranged from 2 to 8 (Me 4). The sum of HAS-BLED scores ranged from 0 to 6 (Me 3). Table 1 shows the main characteristics of the patients included in the study. As suggested by the data presented, the study included patients at high risk not only for stroke but also for bleeding. One in three patients with AF already had an episode of cerebral circulatory disorder, including four patients who had two episodes each. Of note were the high rates of arterial hypertension (83%), chronic heart failure (75%), and type 2 diabetes mellitus (30%). Although there were statistically significant differences in the incidence of arterial hypertension and chronic heart failure between the WD and ACP groups, the risk of stroke on the CHA_2DS_2-VASc score, which includes both conditions, was almost identical in both groups and averaged 4 points. The median HAS-BLED bleeding risk score was 3 in both groups, allowing us to conclude that patients in both groups were completely comparable in all important characteristics.

Before occluder implantation, the transesophageal echocardiographic examination was performed in all patients to determine the absence of thrombosis in the left atrium and LAA. After successful occluder implantation, 197 patients received antithrombotic therapy (three patients did not have the WD occluder implanted due to failure, so they were not included in further calculations) (Table 2). The following combinations of antithrombotic therapies were prescribed: ASA + clopidogrel, ASA + clopidogrel + warfarin, warfarin, OAC, aspirin + OAC. There were also patients who were not prescribed antithrombotic therapy.

Table 2 shows that antithrombotic therapy was prescribed in 90.9% of patients after successful occluder implantation, with the combination of ASA and clopidogrel used in approximately half of the cases, although the frequency was significantly higher in the ACP group, which may be since this antithrombotic treatment strategy for ACP occluder implantation has been studied and recommended in numerous registries. Similarly, warfarin monotherapy was used significantly more often in the WD group, which is likely since administration of warfarin in combination with antiplatelet therapy was recommended in WD implantation before endothelialization in a single RCT of this device, but to reduce the risk of bleeding, physicians most likely opted for warfarin monotherapy. It is important to emphasize that the prescription of antithrombotic therapy was not regulated by the study protocol and was at the discretion of the treating physician.

One-year follow-up was completed, or primary efficacy/safety end points were met in 186 (93%) of the 200 patients. Three patients were excluded from the study due to failure of WD implantation. Eleven patients discontinued the study during follow-up because they refused treatment, lost contact, or did not show up for another appointment. In these cases, the duration of prospective follow-up was 90 days in 4 patients and 180 days in 7 patients.

During the observation period, ischemic stroke occurred in 5 patients in the WD group (Table 3); there were no cases of SE. No episodes of stroke were observed in the ACP group. Table 3 shows that the incidence of ischemic stroke was 2.5% in all patients with AF. There was a trend toward a higher incidence of ischemic stroke in the WD group (p=0.062).

Of note, patients with nonvalvular AF and high risk of stroke were enrolled in the study: the mean CHA_2DS_2-VASc score was 4.01±1.58. The predicted stroke incidence based on the CHA_2DS_2-VASc scale in these patients was 4.84% per year: 4.76% in the WD group and 4.93% in the ACP group (p=0.531). In all patients, the actual stroke rate was lower than the calculated rate (2.5% vs. 4.8%), which corresponded to a 48% reduction in the risk of stroke, i.e. implantation of any occluder correlated with a reduced risk of ischemic stroke. At the same time, the reduction in stroke risk was 100% in the ACP group and 0% in the WD group, because the actual stroke rate matched the calculated one.

The characteristics of pa-

Table 2.

Frequency and structure of antithrombotic therapy after successful occluder implantation (n=197)

Drugs	All patients (n=197)	Group WD (n=105)	Group ACP (n=92)	p
As+Cl, n (%)	95 (48.2)	43 (41)	52 (56.5)	0.029
As+Cl+warfarin, n (%)	7 (3.6)	5 (4.8)	2 (2.2)	0.452
Warfarin, n (%)	22 (11.2)	18 (17.1)	4 (4.3)	0.004
NOAC, n (%)	34 (17.3)	21 (20)	13(14.1)	0.277
NOAC+As, n (%)	21 (10.7)	11 (12)	10 (9.5)	0.581
Without atithrombotics, n (%)	18 (9.1)	7 (6.7)	11 (11.9)	0.430

Notes: As - aspirine; Cl - clopidogrel; NOAC - non-vitamin-K antagonist oral anticoagulants

Table 3.

Frequency and timing of ischemic stroke in patients with AF (n=197)

Time period	All patients (n=197)	Group WD (n=105)	Group ACP (n=92)	p
First 45 days, n (%)	0	0	0	-
46-90 days, n (%)	2 (1)	2 (1.9)	0	0.500
91-180 days, n (%)	1 (0.5)	1 (1)	0	1.0
181-365 days, n (%)	2 (1.1)	2 (2.1)	0	0.498
Total, n (%)	5 (2.5)	5 (4.8)	0	0.062

tients in the WD group who experienced ischemic stroke during the follow-up period are shown in Table 4. As shown in Table 4, strokes occurred predominantly in patients aged 70 years or older who had a CHA_2DS_2-VASc score > 4 and a history of stroke. Of note, strokes occurred in patients taking various combinations of antithrombotic therapies and none of the patients in the warfarin group.

A follow-up transesophageal echocardiography 45 days after LAA occluder implantation was performed in 192 patients. In the WD group, 3 of them were found to have thrombosis of the device without systemic thromboembolic complications. These patients received subcutaneous injections of enoxaparin sodium at a therapeutic dose for 21 days. In the control group transesophageal echocardiographic examination, no thrombus was found on the surface of the device after 3 weeks. No hemorrhagic complications were noted during treatment with enoxaparin. There were no statistically significant differences in the incidence of device thrombosis between the WD and ACP groups. When a follow-up transesophageal echocardiography was performed 180 days after implantation of a LAA occluder, none of the patients' showed signs of device thrombosis.

The cumulative incidence of performance endpoint events was 4.6%: 8 events (7.6%) in the WD group and 1 event (1.1%) in the ACP group (1 patient in the ACP group died within the first 3 months after successful LAA occluder implantation; no pathological autopsy was performed, so the exact cause of death was unknown) (p=0.038). Kaplan-Meier survival analysis confirmed that the risk for adverse events of the efficacy endpoint was significantly higher in the WD group than in the ACP group (chi-square=4.87; p=0.027) (Fig. 2).

DISCUSSION

After implantation of the Watchman device, it is recommended to use the antithrombotic support protocol used in the RCTs PROTECT-AF and PREVAIL. It is reasonable to administer warfarin with a target international normalized ratio of 2.0-3.0 in combination with ASA at a dose of 75 mg q.d. for at least 45 days after the procedure. After 45 days, a transesophageal echocardiography is performed to clarify the positioning of the occluder. When the device is optimally installed (complete occlusion of the LAA orifice, residual blood flow not exceeding 5 mm) and there is no evidence of thrombosis on its surface, warfarin is discontinued and dual antiplatelet therapy (ASA combined with clopidogrel 75 mg q.d.) is prescribed for up to six months. Six months after implantation, patients should be switched to indefinite ASA monotherapy. If the device is not adequately positioned, warfarin should be continued until the residual blood flow diameter has disappeared or decreased to less than 5 mm [7, 8]. This therapeutic regimen showed greater efficacy than registry data. Therefore, we recommend adherence to this protocol for postoperative platelet aggregation inhibition.

After ACP device implantation, a combination of ASA 75 mg q.d. and clopidogrel 75 mg q.d. is usually prescribed for 3 to 6 months, followed by a transition to ASA monotherapy [9]. Thus, the main difference in the recommended antithrombotic strategy in the case of ACP occluder implantation is that warfarin does not need to be prescribed. However, it should be noted that in this study, the different antiplatelet agents did not lead to thrombotic complications.

In the PROTECT-AF RCT study [7], the reduction in stroke risk with implantation of the Watchman device was 46% in 707 patients with a median follow-up of 18 months; in the CAP study [11], 78% in 566 patients with a median follow-up of 50 months; in the CAP2 study [11], 69% in 578 patients with a median follow-up of 50 months.

The ACR/Amulet device trial registries showed a 60-65% reduction in stroke risk: a 59% reduction in 1,001 patients with a mean follow-up of 1.3 years [9]. In these studies, the efficacy of LAA occluder implantation was assessed not only by the incidence of thromboembolic events

Table 4.

Characteristics of patients from the WD group who had ischemic stroke during the follow-up

Parameter	# of patient				
	1	2	3	4	5
Age, years	79	70	62	72	70
Sex	male	male	male	female	female
AF type	persistent	permanent	paroxysmal	permanent	permanent
CHA2DS2-VASc*	7	6	4	5	4
HAS-BLED*	5	2	5	3	3
Stroke history	yes	yes	yes	yes	no
Antithrombotics**	no	As + Cl	NOAC + As	As + Cl	NOAC
LA dilatation	yes	yes	yes	yes	yes
LV EF <40%	yes	no	no	no	no
SPAP >30 mm Hg	yes	no	no	yes	yes
SEC	yes	yes	yes	yes	yes
SEC grade	2	2	2	2	4

Notes: AF - atrial fibrillation; ** - after implantation of a left atrial appendage occluder; LA - left atrium; LV EF - left ventricular ejection fraction; SPAP - systolic pulmonary artery pressure; SEC - spontaneous echocontrasting

such as stroke/ SE, device thrombosis, and cardiovascular/ unexplained death, but also by the reduction in stroke risk compared with the predicted incidence calculated using the CHA_2DS_2-VASc score.

In our study, immediately after ACP device implantation, anticoagulant drugs were discontinued in 63 patients (68.5%), whereas no antithrombotic medications were prescribed in 11 cases (11.9%). In the patient group WD, only 50 cases (49.0%) did not receive anticoagulant therapy after successful LAA occluder implantation. No thromboembolic events or device thrombosis were observed in the ACP group.

In our study, the reduction in the risk of stroke in all patients with AF was 48% (0% in the WD group, 100% in the ACP group). During the follow-up period, 5 cases of ischemic stroke were observed in the WD group, whereas there were no strokes in the ACP group. When comparing the groups in terms of stroke incidence, there was a tendency for an increase in the WD group (4.8% vs. 0%; p=0.062). A possible reason for this could be a design feature of the WD, namely the presence of a permeable polyethylene membrane on the left atrium. Thrombus may form on the surface of this membrane before endothelialization is complete. We should note right away that the same property of the occluder may be the main cause of device thrombosis, the incidence of which was also slightly higher in the WD group (2.9% vs. 0%; p=0.251); there were no cases of device thrombosis in the ACP group.

The cumulative incidence of ischemic events was evaluated in 32 of 66 studies (n=7689): it was 13.2% (37/280) in patients with device thrombosis and 3.8% (285/7399) in patients without thrombosis (OR 5.27; 95% CI 3.66-7.59; p < 0.001). In a sensitivity analysis including only RCTs and prospective multicenter registries, the device thrombosis rate was 3.7%, and thrombosis was also associated with a higher rate of ischemic events (13.5% versus 4.4% in patients without thrombosis; OR 4.15; 95% CI 2.77-6.22; p < 0.001) [12].

In our study, the thrombosis rate of the WD was similar to the meta-analysis data (2.9% versus 3.1%), whereas the thrombosis rate of the ACP device was lower (0% versus 3.6%). In all three cases identified in our work, device thrombosis was not accompanied by systemic thromboembolic complications. We should also note that all episodes of WD thrombosis were detected by transesophageal echocardiographic examination at 45 days, against a background of 3 weeks of therapy with therapeutic doses of enoxaparin, thrombus were completely resolved, and no thrombus was detected on the device surface in any patient 180 days after implantation of the LAA occluder.

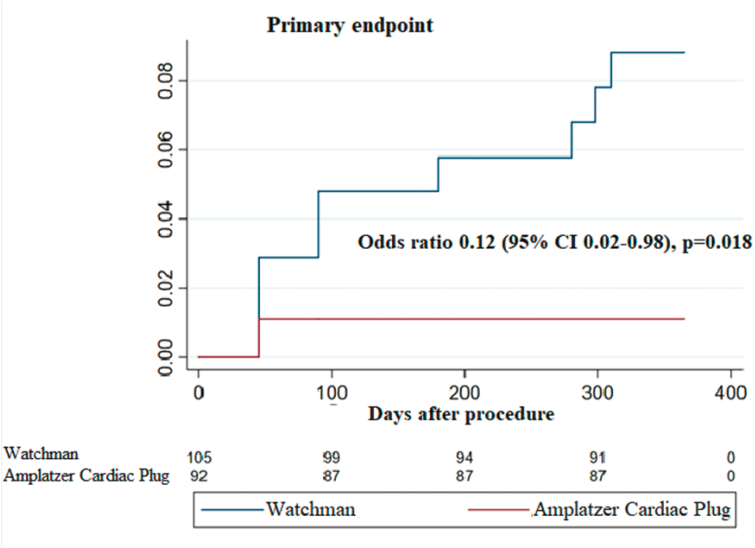

Fig. 2. The primary efficacy endpoint's adverse events depend on the occluding device (n=197).

CONCLUSION

After implantation of the ACP Occluder, it is possible to discontinue OAC and prescribe one of the combinations of antithrombotics accepted in clinical practice. This is particularly important for patients with contraindications to anticoagulant therapy and a very high risk of stroke who require effective non-drug stroke prevention. Warfarin is recommended for patients aged 70 years or older with a CHA_2DS_2-VASc score > 4 and a history of stroke after implantation of the Watchman Device closure device. It is not recommended to implant the Watchman Device in these patients if warfarin is not available.

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