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Anticoagulant therapy in patients with atrial fibrillation and an implanted cardiac resynchronization therapy device

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Aim. To study the efficacy and safety of direct oral anticoagulant (DOAC) therapy after implantation of cardiac resynchronization therapy (CRT) devices in atrial fibrillation (AF) patients with coronary artery disease (CAD) and dilated cardiomyopathy (DCM).

Material and methods. The study included 93 patients followed up from 2014 to 2016 (71 men and 22 women) aged 33-85 years (59,7±10,6) with stable CAD (group 1, n=44) and DCM (group 2, n=49). All patients were diagnosed with AF. The left ventricular ejection fraction (LVEF) was 30,6±3,8%; the left ventricular end-diastolic dimension was 230,9±60,8 mm. All patients received anticoagulants for the prevention of thromboembolic events: a vitamin K antagonist (warfarin) or DOAC. The analysis of medical records, as well as ECG records, echocardiographic, 24-hour ECG monitoring data and information from implanted device was carried out. The follow-up period lasted 24 months.

Results. After 24-month follow-up, positive dynamics was noted in all patients — LVEF increased from 30,6±3,7% to 39,5±5,8%). In patients with DCM, a more pronounced increase in myocardial contractile function was noted. Stroke within time interval from 12 to 24 months developed in two patients taking warfarin, from different groups. Transient ischemic attacks were observed in 6 patients: in one patient from group 1 during the period from inclusion and 12-month visit, and in 5 patients from 12 to 24 months. Out of 5 patients, two belonged to group 1 and three — to group 2, while one patient took aspirin and the other 4 — warfarin. One patient from group 1 with persistent AF and vitamin K antagonist therapy had left atrial appendage thrombosis. Hemorrhagic strokes and major bleeding have not been reported.

Conclusion. Among patients taking DOAC, regardless of the underlying disease (CAD or DCM) and response to CRT, bleeding events were less often recorded, and there were no thromboembolic events.

Keywords: cardiac resynchronization therapy, atrial fibrillation, direct oral anticoagulants.

Relationships and Activities: none.

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Introduction

Atrial fibrillation (AF) and heart failure (HF) are often combined conditions that increase the risk of stroke, HF-related hospitalization and death, and thus represent an important health problem with a poor prognosis [1-4]. AF development in a patient with HF often leads to a worsening of HF course and increases the risk of thromboembolic events (TEE) [5, 6]. A significant proportion of patients with HF have indications for the implantation of cardiac resynchronization therapy (CRT) devices, cardioverter-defibrillators, cardiac monitors detecting AF, recording decompensated HF episodes, and remotely monitoring [7, 8]. Such cardiac monitoring demonstrated that AF episodes are common in different populations [9]. Currently, with the help of implanted devices, it is possible to detect AF episodes in patients without arrhythmias and to prescribe antithrombotic prophylaxis as early as possible [10]. Some studies have reported an increased risk of embolic events in patients with atrial arrhythmias detected with implanted devices; in addition, it has been shown that the risk of death or stroke increases 2,5-fold in patients with at least one episode of atrial arrhythmia lasting >5 minutes [7]. Analysis of data from 2580 patients with implanted pacemakers or defibrillators, aged >65 years with hypertension without prior AF, showed that the TEE risk increases with AF episodes lasting >24 h [8]. Thus, the study of the efficacy and safety of direct oral anticoagulants (DOACs) in patients with AF and implanted CRT devices is an urgent task.

The aim was to study the efficacy and safety of DOAC therapy after implantation of CRT devices in AF patients with coronary artery disease (CAD) and dilated cardiomyopathy (DCM).

Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study. All patients signed informed consent.

The study included 93 patients (Table 1), observed from 2014 to 2016, (men, 71; women, 22) aged 33 to 85 years (61,0 [55,0; 66,0]), with stable CAD (n=44) and DCM (n=49). All patients had documented AF.

There were following inclusion criteria: indications for CRT implantation; AF established by electrocardiography (ECG) and 24-hour ECG monitoring. Non-inclusion criteria includes following points: patient refusal from surgery; contraindications to CRT implantation; myocardial infarction <6 months ago; life expectancy of less than a year; contraindications for anticoagulant therapy; mental illness and alcoholism.

To stratify the stroke risk in patients with AF, we used the CHA_2DS_2-VASc score (Congestive Heart failure, Hypertension, Age (2 ball), Diabetes mellitus, Stroke (2 ball), Vascular disease, Age, Sex category). The majority of patients had a high risk of TEE, on average, 3,0 [2,0; 4,0]. The risk of bleeding was calculated using the HAS-BLED score (Hypertension, Abnormal renal-liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (65 years), Drugs or alcohol concomitantly) and amount to, on average, 1,0 [0,0; 2,0]. All patients underwent transthoracic echocardiography. The left ventricular ejection fraction (LVEF) was 31,0 [28,0; 34,0]%, LV end-diastolic volume — 215,0 [187,0; 265,0] ml. All study participants received anticoagulants to prevent TEE: a vitamin K antagonist (warfarin) or DOAC (rivaroxaban, dabigatran, apixaban). For patients taking warfarin, at the time of discharge, the optimal dose of the drug was selected and the target international normalized ratio (INR) (2,0-3,0) was achieved. Follow-up outpatient monitoring of INR was recommended at least once every 4 weeks. All patients underwent follow-up examinations 12, 24 months after discharge from the hospital. During the visit, we evaluated the medical records, as well as ECG records, echocardiographic, 24-hour ECG monitoring data and information from implanted device.

The primary endpoints were TEEs (stroke, systemic embolism, or transient ischemic attack).

The secondary endpoints included bleeding events (any bleeding after study inclusion), acute myocardial infarction, and all-cause mortality.

Patients were divided into two groups according to the underlying disease: group 1 included patients with CAD (n=44), group 2 — patients with DCM (n=49). In patients with CAD, comorbidities (diabetes, chronic kidney disease) were more often observed. Therefore, risk of TEEs and bleeding was higher (Table 1).

Patients received standard therapy for CAD, HF (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, mineralocorticoid receptor antagonists, digoxin, beta-blockers, statins and diuretics), as well as for paroxysmal AF prevention — class III antiarrhythmic agent amiodarone.

The results were processed using the STATISTICA 10.0 program. The distribution was assessed using the Shapiro-Wilk test. Analysis of echocardiographic data and changes in HF class was carried out using nonparametric methods;

Table 1

Clinical and anamnestic characteristics of subjects

Parameter	Group 1, n=44, n (%), Me [LQ; UQ]	Group 2, n=49, n (%), Me [LQ; UQ]	p
Age, years	58,0 [48,0; 64,0]	62,0 [59,0; 68,0]	0,05
Men/Women	34/10	37/12	0,94/0,87
Paroxysmal AF	23 (52)	20 (42)	0,50
Persistent AF	21 (48)	28 (58)	0,61
Stroke before CRT implantation	0	1 (2)	0,94
Comorbidities			
Diabetes	12 (27)	7 (14)	0,31
HTN	36 (82)	24 (49)	0,08
CKD	18 (41)	6 (12)	0,02
Therapy			
ACE inhibitors/ARBs	44 (100)	47 (96)	0,50
Beta-blockers	42 (95)	42 (86)	0,41
Spironolactone	43 (98)	46 (94)	0,50
Loop diuretic	40 (91)	45 (92)	0,97
Digoxin	5 (11)	16 (33)	0,05
Amiodarone	40 (91)	41 (84)	0,78
Mitral regurgitation:			
no	1 (2)	9 (19)	0,02
grade 1	28 (61)	34 (70)	0,30
grade 2	15 (34)	5 (10)	0,02
grade 3	1 (2)	0	0,96
CHA_2DS_2-VASc score	2,0 [2,0; 3,0]	4,0 [3,0; 5,0]	0,00001
HAS-BLED score	1,0 [0,0; 1,0]	2,0 [1,0; 2,0]	0,000001

Note: HTN — hypertension, ARBs — angiotensin II receptor blockers, ACE — angiotensin-converting enzyme, CRT — cardiac resynchronization therapy, AF — atrial fibrillation, CKD — chronic kidney disease.

Table 2

Dynamics of clinical and echocardiographic parameters after implantation of cardiac resynchronization device

Parameter	Group 1, n=44, n (%), Me [LQ; UQ]	Group 2, n=49, n (%), Me [LQ; UQ]	p
HF class before CRT implantation	3,0 [3,0; 3,0]	3,0 [3,0; 3,0]	0,09
HF class after CRT implantation	2,0 [1,0; 2,0]	2,0 [2,0; 2,0]	0,00005
EF (B) before CRT implantation, %	30,0 [27,0; 34,0]	31,0 [29,0; 34,0]	0,09
EF (B) after CRT implantation, %	46,0 [42,0; 51,0]	39,0 [36,0; 44,0]	0,0001
EDV before CRT implantation, ml	224,0 [196,0; 278,0]	214,0 [183,0; 265,0]	0,07
EDV after CRT implantation, ml	156,0 [133,0; 177,0]	178,0 [148,0; 216,0]	0,01

Note: EDV — end-diastolic volume, EF (B) — B-mode LVEF.

Table 3

Antithrombotic therapy and endpoint incidence

Parameter	Group 1, n=44, n (%)	Group 2, n=49, n (%)	p
Antithrombotic therapy:			
Warfarin	17 (39)	14 (29)	0,30
DOACs	21 (48)	33 (67)	0,32
Aspirin	6 (14)	2 (4)	0,25
Stroke within 12 months	0	0	-
Stroke within 24 months	1 (2)	1 (4)	0,52
TIA within 12 months	1 (2)	0	0,96
TIA within 24 months	2 (4)	3 (6)	0,88
Thrombosis within 12 months	1 (2)	0	0,96
Thrombosis within 24 months	0	0	-
Bleeding within 12 months:			
— minor	3 (7)	1 (2)	0,56
— major	0	0	-
Bleeding within 24 months:			
— minor	0	1 (2)	0,94
— major	1 (2)	0	0,96
Hemorrhagic stroke within 12 months	0	0	-
Hemorrhagic stroke within 24 months	0	0	-
AMI within 12 months	0	0	-
AMI within 24 months	1 (2)	0	0,96
Death within 12 months	0	0	-
Death within 24 months	2 (4)	0	0,44

Note: AMI — acute myocardial infarction, DOACs — direct oral anticoagulants, TIA — transient ischemic attack.

the Mann-Whitney test was used in the analysis of independent groups. Data were presented as Me [LQ; UQ], where Me is the median and LQ and UQ are the lower and upper quartiles. The significance of differences between qualitative variables was assessed using the Pearson's chi-squared test. Differences were considered significant at $p<0,05$.

Results

After 24-month follow-up, positive changes were noted in all patients. In patients with CAD, there was a more pronounced increase in myocardial contractile function: LVEF increased from 30,0 [27,0; 34,0] to 46,0 [42,0; 51,0]%, while in patients with DCM, the increase in LVEF was less pronounced: from 31,0 [29,0; 34,0] to 39,0 [36,0; 44,0]%. An improvement in the HF class was also noted. In patients with CAD, HF class decreased from 3,0 [3,0; 3,0] to 2,0 [1,0; 2,0], while in the group of patients with DCM — from 3,0 [3,0; 3,0] to 2,0 [1,0; 2,0] ($p=0,00005$). In both groups of patients, a decrease in the LV end-diastolic volume was revealed. In addition, more pronounced change was noted in patients with CAD — from 224,0 [196,0; 278,0] to 156,0 [133,0; 177,0] ml ($p=0,0001$). The results are shown in Table 2.

In group 1, 17 (39%) people received warfarin, 6 (14%) — acetylsalicylic acid instead of anticoagulant therapy, while the rest (n=21, 47%) received DOACs. Aspirin monotherapy was carried out in connection with the refusal of patients from taking warfarin due to the inability to control the INR, and the DOACs due to financial difficulties. In group 2, 14 (29%) patients received warfarin, 33 (67%) — DOACs, and 2 (4%) — aspirin (Table 3).

Table 4 shows the incidence of TEE and bleeding within 24 months in patients of both groups taking

Table 4

Patterns of bleeding and TEE during DOAC and warfarin therapy for 24-month follow-up

Parameter	Patients taking DOACs, n=54, n (%)	Patients taking warfarin, n=31, n (%)	p
Stroke	0	2 (6)	0,27
TIA	0	4 (13)	0,04
LA thrombosis	0	1 (3)	0,79
All TEE	0	7 (23)	0,004
Bleeding:			
— minor	2 (4)	3 (10)	0,56
— major	0	0	-
Hemorrhagic stroke	0	0	-

Note: LA — left atrium, DOACs — direct oral anticoagulants, TIA — transient ischemic attack.

warfarin and DOACs. TEE have been observed in patients receiving warfarin and aspirin.

Ischemic stroke in the time interval from 12 to 24 months developed in two patients from different groups. One of them, the male patient with CAD, large LV sizes, a small increase in LVEF after CRT implantation, permanent AF, had a high risk of TEE on the CHA_2DS_2-VASc score (6), and received warfarin. In this patient, the target INR was not always achieved and maintained. Another 79-year-old male patient with DCM, a good response to CRT, with a CHA_2DS_2-VASc score of 4 also received warfarin, and the INR was monitored irregularly.

Transient ischemic attacks (TIA) were observed in 6 patients: in one patient from group 1 during the 12-month follow-up and in 5 patients in the period from 12 to 24 months. Out of five patients, two belonged to group 1 and three — to the second one, while two patients took aspirin, the other four — warfarin. These were elderly patients (>70 years old) with hypertension and type 2 diabetes. It was found that the INR monitoring was carried out irregularly. There was therapeutic INR range <70% of the time.

In one patient from group 1 with persistent AF, left atrial appendage thrombosis was revealed in the first year of follow-up. This patient received warfarin. The incidence of TEE is presented in Tables 3, 4.

There were no cases of hemorrhagic strokes or major bleeding in this study. Minor bleeding during anticoagulant therapy developed in 5 (6,4%) patients, while three of them received warfarin and two — DOACs. Nosebleed occurred repeatedly in one patient taking warfarin over the entire follow-up period. Two other patients had injuries with hip and head hematomas. One patient developed intraocular hemorrhage while taking DOACs, and another had moderate hematuria, which stopped when one DOAC was replaced. In all cases of minor bleeding, emergency medical intervention was not required.

During the follow-up period, 2 deaths were recorded, both from group 1 in the interval from 12 to 24 months. One patient with paroxysmal AF with a CHA_2DS_2-VASc score of 5, who received DOAC therapy, died of acute myocardial infarction. Another patient with paroxysmal AF, taking warfarin, with positive dynamics with CRT, died of cancer.

Discussion

Implantable cardioverter defibrillators, pacemakers with an atrial lead, and CRT devices allow monitoring the atrial rhythm for a long time. In this case, the identification of atrial tachycardia episodes can be used to predict the AF. It has been proven that the risk of AF is higher in patients with registered long-term episodes of atrial tachycardia [10].

By the beginning of the present study, there was an insufficient number of published works on efficacy and safety of anticoagulant therapy in patients with AF and implanted CRT. In 2015, the final results of the Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk (IMPACT) study were published (ClinicalTrials.gov Identifier: NCT00559988) [11] on anticoagulant therapy in patients with implanted cardioverter defibrillators and CRT devices. It was hypothesized that remote monitoring of atrial tachyarrhythmias with a predetermined anticoagulation plan would be better than conventional anticoagulant prescription. However, no significant effect of the remote monitoring strategy on anticoagulant prescription rate was found. In addition, the starting and stopping anticoagulation strategy, based on remote rhythm monitoring, in comparison with the usual follow-up did not prevent TEE and bleeding in patients with NYHA class II-III HF with reduced EF (~30%) [11].

The study used a standard approach to prescribing anticoagulant therapy in patients at high CHA_2DS_2-VASc risk of TEE (>2 in men and >3 in women). The choice between a vitamin K antagonist (warfarin) or DOAC was made based on patient preference. As known, warfarin therapy is associated with a number of difficulties: it has unpredictable pharmacokinetics and pharmacodynamics due to both the genetic characteristics of patients and the specificity of its drug metabolism, requires constant laboratory monitoring, as well as there is data on its interaction with food [12].

Stroke in many cases develops during the interruption of vitamin K antagonists or with non-therapeutic INR values [13].

In the present study, the majority of patients (60%) taking warfarin failed to maintain the INR within the target range. Therefore, bleeding and thromboembolic events were more often observed among patients receiving warfarin therapy. However, it cannot be said with complete certainty that warfarin was less effective as an anticoagulant in comparison with DOACs, since the INR in the target range was maintained <70% of the time.

In recent years, there has been a trend towards more common prescription of DOACs compared with vitamin K antagonists in nonvalvular AF. At the same time, the issue of rational use of DOACs in patients with a complex structure of cardiovascular disease and implanted cardiac devices remains urgent. The results obtained indicate the potential for safe DOAC therapy use in patients with CAD and DCM receiving CRT.

Conclusion

Patients with AF and HF undoubtedly belong to the high-risk group. They are more prone to an unstable disease course and drug interactions with warfarin and, to a lesser extent, with DOACs. The hypothesis on efficacy and safety of DOAC therapy was confirmed in the present work: among patients taking DOACs, regardless of the underlying disease (CAD or DCM) and response to CRT, bleeding events were less frequently recorded, while there were no TEEs. Clinical trials with larger samples in this area are promising.

Relationships and Activities: none.

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