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Adherence of patients with atrial fibrillation after acute coronary syndrome to antithrombotic therapy at stage III of cardiac rehabilitation: data from the local register of the Kirov region

Aim	To evaluate the quality of antithrombotic therapy (ATT) in patients with atrial fibrillation (AF) after acute coronary syndrome (ACS) at stage 3 of rehabilitation.
Material and methods	The registry included 163 patients with AF (mean age, 65.0 [59.0; 72.0] years; 55.8% men) undergoing rehabilitation after ACS (ACS <1 month ago) in the hospital of the Kirov State Medical University.
Results	Recommendations for 73.6% of patients on ATT provided upon discharge from the hospital after stage 2 of rehabilitation were consistent with clinical guidelines (CG). During the entire stage 3, 25.8% of patients had acute cardiovascular complications (CVC) or urgent interventions (8.0% died). Furthermore, the ATT was actually consistent with CG only in 9.2% of patients; in 21.5%, errors in changing the ATT timing were detected; and in 84.1%, various mistakes in the control of international normalized ratio were observed. On the whole, 3.6% of patients incorrectly adjusted their ATT independently, and for 15.3%, the attending physician made incorrect APT adjustments.
Conclusion	In AF patients after ACS who were undergoing stage 3 of rehabilitation, the quality of the ATT was low despite the recommendations at discharge from the hospital, which depended not only on the patient but also on the attending physician.

Keywords	Acute coronary syndrome; atrial fibrillation; rehabilitation; outpatient stage; antithrombotic therapy; compliance with treatment
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Coronary artery disease (CAD) is the major cause of high mortality in patients with cardiovascular diseases (CVDs), with atrial fibrillation (AF) being the most common cardiac rhythm disorder. According to various recent studies, the incidence of AF in acute coronary syndrome (ACS) is between 5% and 23% [1–12].

The assessment of long-term and medium-term outcomes of ACS, which can be modified by comprehensive rehabilitation, is the most significant aspect of evaluating the quality of care for patients with ACS at all stages of rehabilitation [7, 8]. Providing the best possible drug treatment following the clinical guidelines is an important aspect of rehabilitation [6–11].

The outpatient stage (stage III), which lasts up to 12 months from the onset of ACS, is the longest and consequently most important period of rehabilitation. Its quality depends on many patient-related factors (adherence to the prescribed treatment) and physician-related factors (compliance with the clinical guidelines), as well as drug-related factors (features of the best possible drug treatment that affect patient adherence to long-term treatment) [6, 7, 11, 13, 14].

Although largely dependent on the prior inpatient treatment, the outpatient stage can significantly improve patient adherence to long-term treatment since it provides careful selection of the best possible drug treatment and the most extensive patient information support [6, 7, 13, 14]. Moreover, discharge summary is very important [7]. It should contain precise information not only for the patient, but also for the outpatient physician, regarding the best possible drug treatment for the patient, and the target levels of indicators taking into consideration the patient's individual characteristics [6, 7, 13, 14].

Of all the best possible drug treatments indicated to patients in stage III of rehabilitation, antithrombotic therapy (AT) is of particular importance [1–5, 7–9]. According to the clinical guidelines in effect at the time of our study, a triple AT (direct oral anticoagulant (OAC) + two antiplatelet

agents) was indicated to all patients with AF and a history of ACS if they had no corresponding contraindications [1, 2]. Otherwise, dual AT (OAC+one antiplatelet agent) was indicated, or, depending on the clinical situation, two antiplatelet agents [1, 2]. If the risk of bleeding is low (HAS-BLED <3), triple AT is indicated for up to 3 months, followed by dual AT for up to 12 months from the onset of ACS; if the risk of bleeding is high (HAS-BLED ≥ 3), the duration of triple AT is reduced to one month with subsequent dual AT [1, 2]. Information on the situation in clinical practice is obtained by monitoring the best possible drug treatments, assessing the compliance of prescriptions with the available clinical guidelines, and tracing the effect of the best possible drug treatment on the long-term prognosis [6–9, 14].

This topic has not been previous studied in the Kirov region. The article presents partial data of the register of patients with AF and a history of ACS, with a particular focus on the evaluation of the AT quality at stage III of rehabilitation.

Objective

To evaluate the quality of AT in patients with AF and a history of ACS at stage III of rehabilitation.

Material and methods

This study presents part of the local register of patients with AF who underwent stage II cardiac rehabilitation in the Kirov State Medical University hospital for previous ACS (not older than 1 month) from June 1, 2013, to June 1, 2015 (during two years after the opening of the cardiac rehabilitation department). The endpoint in this study was 12 months after the onset of reference ACS or death. A total of 163 patients with AF were included in the register by the method of continuous sampling, which was 15.9% of 1,023 patients who underwent stage II cardiac rehabilitation in the Kirov State Medical University hospital for ACS during this period. The median age of patients was 65.0 (59.0; 72.0) years (55.8% of male patients). More detailed characteristics of the study cohort, including the quality of diagnosis and prehospital treatment, have been presented earlier [8–11]. All data were depersonalized and registered in the electronic database for later analysis.

The statistical analysis of was performed using Statistica 10.0. The median with the lower and upper quartiles (Me [LQ; UQ]), as well as the Mann-Whitney U-test and the Yates chi-squared test or Fisher's exact test, the Wilcoxon W-test, and the McNemar test were calculated [15].

Results

The following AT was recommended at the end of stage II for self-administration at stage III of rehabilitation: continuation of triple AT was recommended for 24.5% of patients for 6 months given the use of this therapy at stage I and stage II of rehabilitation, followed by dual AT (OAC+one antiplatelet agent) until the end of stage III of rehabilitation (up to 12 months from the onset of ACS) or in other treatment is required; if its correction was not needed, dual AT was recommended to 50.3% of patients throughout stage III; administration of two antiplatelet drug throughout stage III of rehabilitation (due to inability to take OACs for various reasons) was recommended to 25.2% of patients if its correction was not needed or if OACs could not be added (Table 1).

OACs were recommended to a total of 74.9% of patients: vitamin K antagonists (VKAs) to 70.6% of patients and DOACs to 4.3% of patients. VKAs warfarin and phenylin were recommended to 99.1% and 0.9% of patients, respectively. DOACs dabigatran and rivaroxaban were recommended to 85.7% and 14.3% of patients. Antiplatelet agents were recommended within AT to the entire study cohort: acetylsalicylic acid and clopidogrel were recommended to 54.6% and 95.1% of patients, respectively.

Treatment was mainly selected on the basis that the majority of patients were at a high risk of stroke (CHA2DS2 VASc ≥ 2) and bleeding (HAS-BLED ≥ 3), i.e., 96.3% and 67.5% of patients, respectively. At the same time, the remaining patients were at a low risk of stroke (CHA2DS2-VASc 1) and bleeding (HAS-BLED ≥ 1–2): 3.7% and 32.5%, respectively.

Table 1. Retrospective evaluation of the recommended AT and proton pump inhibitors for self-administration during stage III rehabilitation upon discharge from hospital for patients with AF and a history of ACS

AT	Number of patients	
	абс.	%
Triple AT	40	24,5
Dual AT	82	50,3
Two antiplatelet drugs	41	25,2
Total OACs	122	74,9
Total VKAs	115	70,6
Warfarin	114	70,0
Phenylin	1	0,6
Total DOACs	7	4,3
Dabigatran	6	3,7
Rivaroxaban	1	0,6
Total antiplatelet drugs	163	100
Acetylsalicylic acid	89	54,6
Clopidogrel	155	95,1
Proton pump inhibitors indicated and prescribed	78	47,9

AT – antithrombotic therapy; AF – atrial fibrillation; ACS – acute coronary syndrome; OAC – oral anticoagulant; VKA – vitamin K antagonist; DOAC – direct oral anticoagulant.

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Refusal criteria for OAC prescription were the inability to purchase DOACs (21.5%), a high risk of bleeding (17.2%), the lack of possibility to control international normalized ratio (INR; 14.1%), and a patient's refusal to take VKA (12.3%).

Proton pump inhibitors were additionally indicated and prescribed to 47.9% of patients for the prevention of gastropathy (see Table). Thus, AT complying with clinical guidelines was recommended to 73.6% of patients discharged from hospital after stage II of rehabilitation; AT roughly complying with clinical guidelines was recommended to 26.5% of patients with comorbidities. Although the correct frequency of regular medical checkups was recommended to all patients, this advice was not always followed.

Only 49.7% of patients received AT during the entire period as recommended at discharge. The mean duration of AT was 5.0 months. 74.2% of patients received OACs during stage III of rehabilitation: 65.6% took VKA, while 14.7% took DOACs. The mean duration of OAC therapy was 11.0 months (VKA 11.0 months and DOACs 6.0 months). AT including two antiplatelet agents was used in 42.9% of patients while one antiplatelet agent was used in 12.3%; the mean duration of administration was 10.0 and 6.0 months, respectively. It should be noted that there were both short-term (tooth extraction, scheduled coronary artery revascularization, and other surgeries) and long-term (mean duration of 9.5 months) periods without AT, in 3.1% and 1.2% of patients, respectively.

The analysis of the frequency of INR control demonstrated that 84.1% made various deviations: 19.6% of patients performed no INR control, 11.2% carried out control only during repeated hospitalizations, 53.4% had irregular control (less than once a month or without increasing the frequency of control in case of non-target INR), while only 13.1% of patients had regular INR control. The target INR was 2.0–2.5 during the combination AT; the INR therapeutic range of 25.0% was determined by only 2.8% of patients.

During the entire period of stage III rehabilitation, 61.4% of patients had no adverse cardiovascular events, 12.9% of patients underwent scheduled interventions (coronary angiography or coronary artery revascularization in 12.2%), while 25.8% of patients required emergency care (thrombosis in 20.3%, thromboembolism in 4.3%, and death in 8.0% of adverse cardiovascular events). The mean time to the onset of adverse cardiovascular events was 5.0 months. Thrombosis developed in 15.3% of patients during AT not complying with the clinical guidelines.

The analysis of hemorrhagic events occurring during stage III rehabilitation as assessed by the BARC scale showed that 82.2% of patients had no bleeding, 12.9% had clinically insignificant bleeding, 4.4% had minor bleeding, while only 0.6% of patients had major bleeding. Hemorrhagic events developed in 17.2% of patients taking VKA (mean INR 3.7) and 0.6% of patients taking two antiplatelet drugs. INR control deviations were detected in a total of 14.1% of patients, while 3.1% of patients had labile INR during adequate control.

Throughout stage III rehabilitation, gastroduodenoscopy carried out in 33.1% of patients revealed various gastropathies in 7.4%: erosive disorders in 3.1%, non-erosive disorders in 4.3%, including 3.7% having exacerbation of existing pathologies. It was also shown that all patients with gastropathies took antiplatelet drugs, including 4.3% of them in combination with OACs, and other 4.3% of patients in combination with proton pump inhibitors.

An analysis of factors influencing the choice of AT during stage III rehabilitation, excluding the end of the recommended period of AT and/or the presence of repeated cardiovascular events, found that 91.4% of patients had ≥ 2 factors, while only 8.6% of patients had 1 factor. The most common factor, affecting 88.3% of patients, was the inability to buy DOACs. However, other leading factors were also the inability to control INR (61.4% of patients), a patient's low adherence to treatment (55.8%), and a high risk of bleeding (37.4%). Such factors as an artificial cardiac valve and intolerance of warfarin and acetylsalicylic acid were very uncommon (0.6% each). It was established that AT was incorrectly modified by 43.6% of patients on their own and in 15.3% of patients by the attending physician. A trend towards an increase in the risk of bleeding (HAS-BLED) with unchanged risk of stroke (CHA2DS2 VASc) should also be noted, p=0.06. Together, these factors resulted in AT compliance failure with the clinical guidelines in 65.0% of patients, roughly compliance (given the comorbidities) in 25.8% of patients, and completely compliance in only 9.2% of patients throughout stage III rehabilitation, which is significantly worse than at the end of stage II rehabilitation (p<0.001).

Discussion

The study was carried out as a part of the local register of patients with AF who underwent stage II rehabilitation for ACS in the Kirov State Medical University hospital. All patients were residents of Kirov and the Kirov Region, which has high cardiovascular mortality rates [8–11, 16], hence the high relevance of the study.

Although the literature data on the composition of AT typically focuses on a particular moment of treatment, we failed to find data on similar registers providing information about the compliance of the best possible drug treatment with the clinical guidelines. Our analysis of AT recommended to patients with AF at discharge at

the end of stage II rehabilitation for ACS found that 73.6% of patients complied with the AT clinical guidelines, while the remaining 26.5% of patients roughly complied, which formed a good background for the stage III rehabilitation. However, further analysis of AT throughout stage III of rehabilitation produced almost completely opposite data: AT was not provided in compliance with the clinical guidelines in 65.0% of patients; full compliance was only recorded in 9.2% of patients ($p<0.001$).

Although VKAs were rarely administered in patients with AF and MI in most countries investigated in studies conducted over the last 15–20 years, such as EPICOR, AMIS Plus, and RIKS-HIA, the reasons for this failure were not analyzed [17–21]. In more recent studies, such as WOEST, PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS, AT was shown to be effective and safe in patients with AF and a history of ACS/PCI; such studies also discussed the reasons for AT modifications. However, it is impossible to compare those findings with our study since no data were provided for patients with ACS [3–5, 19–24].

In our study, errors in modifying the timing of AT recommended at discharge at the end of stage II rehabilitation were identified in 21.5% of patients; deviations in INR control frequency affected 84.1% of patients; regular INR control was carried out in only 13.1% of patients taking VKAs. The time of the therapeutic range of INR, which was determined in only 2.8% of patients, turned out to be only 25.0%; i.e., the control was inadequate, but AT was ineffective. Although Sycheva et al. show somewhat better values as compared to our findings, the quality of AT was generally unsatisfactory [3]. In 12 months following hospital discharge, 24.8% of patients regularly controlled INR. The authors used the INR therapeutic range of more than 70% as the criterion of regular INR control, along with an INR determination frequency of at least once a month [3].

Throughout stage III rehabilitation, 12.9% of patients underwent scheduled interventions, while 25.8% had emergency interventions, including 8.0% who died as a result of adverse cardiovascular events. Sycheva et al. [3] showed that, among 142 patients with AF and a history of ACS who continued taking DOACs by the end of 12-month period after hospital discharge, 12.7% had thrombosis, while 11.47% had thromboembolism; cardiovascular mortality of 16.2% compared with all-cause mortality of 18.9% in the entire cohort (n=206) [3]. The same paper provided data of AT efficacy in patients with ACS only for a subgroup of patients (n=102), to whom triple AT was recommended at discharge [4]. The mortality in this subgroup was 12.8% in the follow-up period (6–24 months after the ACS episode depending on the time of inclusion in the register) [4].

The evaluation of AT safety throughout stage III of rehabilitation found that few patients had hemorrhagic complications as assessed by the BARC scale: 12.9% of patients had clinically insignificant bleeding, 4.39% had minor bleeding, while only 0.6% had major bleeding. INR control deviations were detected in a total of 14.1% of patients; 3.1% had labile INR during adequate control.

Sycheva et al. [3] provided the following data regarding the safety of AT containing DOACs: hemorrhagic events were detected in a total of 31.2% of patients. This is consistent with our findings regarding the types of bleeding of BARC 1–5, detected in 17.2% of patients, which is almost half the value provided by Sycheva et al. In our study, all hemorrhagic events developed during the VKA therapy (17.2% of patients taking VKAs). There were no such complications during the administration of DOACs. Sycheva et al. [3] observed hemorrhagic events in 46.8% of patients taking VKAs and 18.3% of patients taking DOACs, which is significantly more than in our study.

When analyzing the factors that were reducing the quality of AT, we discovered that 91.4% of patients were affected by two or more factors. These included the impossibility to buy DOACs (88.3% of patients), failure to control INR (61.4%), a patient's low adherence to treatment (55.8%), and a high risk of bleeding (37.4%). Additionally, we discovered not only that patients self-modified AT incorrectly (43.6%), but that attending physicians also adjusted AT incorrectly (15.3% of patients).

In the study by Sycheva et al., the main reasons for discontinuation of DOACs in patients with AF and MI were the same as in our study: failure to control INR while taking VKAs (42.2%) and inability to buy DOAC (47.4%) [3]. Less frequent reasons for discontinuation of DOACs were high risk of bleeding (31.11% and 15.79% of patients taking OACs and DOACs, respectively) and self-cancellation of DOACs (11.11% and 26.32% of patients taking OACs and DOACs, respectively) [3].

Several researchers [6, 13, 14] have also highlighted in recent studies the significant influence of attending physicians on the quality of the best possible drug treatment and, in general, compliance with the clinical guidelines. However, this issue has received less attention than patients' adherence to the best possible drug treatment [14]. In general, problems of patients' adherence to the prescribed treatment and compliance by physicians with the clinical guidelines comprise independent aspects of secondary prevention of adverse cardiovascular events [6].

Conclusion

The quality of antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome stage III during rehabilitation was very low in the Kirov Region.

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There was almost no control of treatment efficacy and safety, which largely depended not only on the patient, but also on the attending physician. Thus, there is an urgent need in the Kirov Region to implement training programs including psychological training to raise patients' awareness of their disease and develop their adherence to the recommended treatment, as well as improving physicians' compliance with clinical guidelines and increased knowledge.

No conflict of interest is reported.

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