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Results of register in patients with acute coronary syndrome and atrial fibrillation receiving rivaroxaban

Aim	To evaluate outcomes in patients with acute coronary syndrome and atrial fibrillation who receive rivaroxaban and the patients' compliance with the antithrombotic therapy.
Material and methods	The study was performed from October 2017 through December 2019 and included 129 patients. Events between the discharge from the hospital and 12 months of follow-up were recorded. The primary endpoint was development of major, minor or requiring medical attention bleeding according to the TIMI scale. The secondary endpoint was a combination of recurrent myocardial infarction, nonfatal acute ischemic cerebrovascular disease, nonfatal systemic embolism, stent thrombosis, and cardiovascular mortality.
Results	32 (24.8%) patients early terminated the antiplatelet treatment and 22 (17.1%) patients terminated the rivaroxaban treatment. 26 (20.2%) patients had hemorrhagic complications. The highest incidence of hemorrhage was observed within the first 2 months after the discharge. None of the bleedings was fatal. Composite endpoint events were observed in 24 (18.6%) patients, including 14 (10.9%) who died from cardiovascular causes.
Conclusion	The compliance with the antiplatelet therapy was insufficient. The incidence of hemorrhagic complications was relatively high; minor and requiring medical attention hemorrhages mostly contributed to the structure of these complications. The observed incidence of recurrent ischemic events associated with a high mortality presents a more serious problem compared to hemorrhagic complications of the combination antiplatelet therapy and warrants a more aggressive tactics of the antiplatelet treatment in high-risk patients.

Keywords	Acute coronary syndrome; atrial fibrillation; antiplatelet therapy; rivaroxaban; thromboembolic complications; hemorrhagic complications
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Atrial fibrillation (AF) in patients with acute coronary syndrome (ACS) is a practical challenge when selecting antithrombotic therapy (ATT). When combinations of anticoagulant and antiplatelet drugs are used a balance needs to be maintained between the risk of hemorrhagic and ischemic complications [1–6]. Randomized clinical trials (RCTs) WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS show that the use of an oral anticoagulant and two antiplatelet agents (triple therapy) is associated with a larger number of hemorrhagic complications with similar efficacy, when compared to dual therapy (oral anticoagulant and antiplatelet agent) [7–10]. According to foreign registers, the prevalence of AF in patients with ACS reaches 26.6% [11–14]. Given the high prevalence and limited data on the efficacy and safety of ATT in real-world clinical practice, it needs to be studied carefully in this group of patients.

Objective

To evaluate the outcomes in patients with ACS and AF taking rivaroxaban, as well as patient compliance with ATT.

Material and methods

The study was carried out from October 2017 to December 2019. It included 129 patients with the following inclusion criteria: confirmed diagnosis of unstable angina or myocardial infarction (MI); AF confirmed by previous discharge summaries or electrocardiograms; over 18 years of age; and the signed informed consent to participate in the study.

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Exclusion Criteria: MI types 2, 4a and 5; pregnancy or lactation; active internal bleeding; cirrhosis with liver failure Child-Pugh class C; chronic kidney disease (CKD) stage 5 or programmable hemodialysis; HIV; alcoholism; drug addiction; moderate or severe mitral valve stenosis; mechanical heart valves; severe mental disorders: and allergic reactions / ATT intolerance.

All patients were assessed for thromboembolic risk (CHA_2DS_2VASc) and bleeding risk (HAS-BLED). The attending physician determined the type of ATT.

The study was approved by the ethics committee of the facility. It took into account events from discharge to 12 months of follow-up, and the decision on ATT was taken the day before the end of hospital stay. During the study, patient visits took place at 1, 3, 6, 9, and 12 months either face-to-face or on the phone. At the visits treatment compliance, as well as primary and secondary endpoints were evaluated.

The primary endpoint was the development of major bleeding, minor bleeding, or bleeding requiring intervention according to the TIMI bleeding classification. The secondary endpoint was the composite endpoint (recurrent nonfatal MI, nonfatal cerebrovascular accident (CVA) of ischemic origin, nonfatal systemic embolism, stent thrombosis, and cardiovascular mortality).

Statistical data processing was carried out using SPSS Statistics v23 software suite. The normality of distribution was evaluated using the Shapiro-Wilk test. Qualitative variables are expressed as absolute and relative rates, while quantitative variables are presented as the mean and standard deviation (M±SD) or the median and interquartile range (Me [25th percentile; 75th percentile]). The χ^2 test and the Fisher exact test were used to evaluate the significance of differences between qualitative variables. Multivariate logistic regression with stepwise elimination was used to assess the risk factors of bleeding. The differences were statistically significant at $p<0.05$.

Results

A total of 129 patients taking rivaroxaban within ATT completed follow-up: 69 (53.5%) patients had paroxysmal AF; 43 (33.3%) patients had permanent AF; and 17 (13.2%) patients newly diagnosed AF. The median age was 74 [64; 81], and 56 (43.4%) patients were female. Arterial hypertension, obesity, postinfarction cardiosclerosis, chronic heart failure, and anemia were the most common comorbidities. The median risk of thromboembolic complications was 5 [4; 6] according to the CHA_2DS_2VASc score. The risk score was 3 or more in female patients and at least 2 in male patients. The median risk of bleeding was 3 [2; 3] according to the HAS-BLED score. A high risk of bleeding (≥3) was observed in 73 (56.6%) patients. 64 (49.6%) patients had a history of non-ST-segment elevation MI. ST-segment elevation MI was diagnosed in 34 (26.4%) cases, and 31 (24.0%) patients were admitted with unstable angina. Percutaneous coronary intervention (PCI) was performed in 84 (65.1%) patients. The clinical and demographic characteristics of patients regarding the performance of PCI are provided in Table 1.

In the group of patients with a history of PCI, 67 (79.8%) and 17 (20.2%) patients received triple and dual therapy, respectively. In 40 (59.7%) patients, the duration of triple therapy was 1 month. 10 (14.9%) and 14 (20.9%) patients received triple therapy for 3 and 6 months, respectively. 3 (4.5%) patients took an anticoagulant and two antiplatelet drugs for 12 months. Rivaroxaban 20 mg was administered to 5 (5.9%) patients, rivaroxaban 15 mg to 78 (92.9%) patients, while 1 (1.2%) patient received rivaroxaban 10 mg due to reduced glomerular filtration rate (GFR) <50 mL / min / 1.73 m^2. In the dual therapy group, 8 (47.1%) patients received a reduced dose of rivaroxaban (15 mg) due to GFR ≥50 mL / min / 1.73 m^2. The triple therapy group included 43 (64.2%) such patients.

In the group of patients without a history of PCI, 19 (42.2%) and 26 (57.8%) patients received triple and dual therapy, respectively. In 16 (84.2%) cases, triple therapy was recommended for 1 month. 2 (10.5%) and 1 (5.3%) patients received triple therapy for 3 and 6 months, respectively. Rivaroxaban 20 mg was administered to 8 (17.8%) patients, 15 mg to 34 (75.5%) patients, while rivaroxaban 10 mg was used in 3 (6.7%) cases. In the dual therapy group, 7 (26.9%) patients received a reduced dose of rivaroxaban 15 mg due to GFR ≥50 mL / min / 1.73 m^2. The triple therapy group included 9 (47.4%) such patients. Patient compliance with ATT was evaluated (Figure 1).

In the group of patients with a history of PCI, 67 (79.8%) patients continued anticoagulant therapy. 66 (78.6%) patients continued antiplatelet therapy for the recommended period. In the triple therapy group, 12 (17.9%) patients discontinued rivaroxaban, while 13 (19.4%) patients discontinued antiplatelet therapy early. In the dual therapy group, 5 (29.4%) patients stopped taking rivaroxaban and antiplatelet therapy.

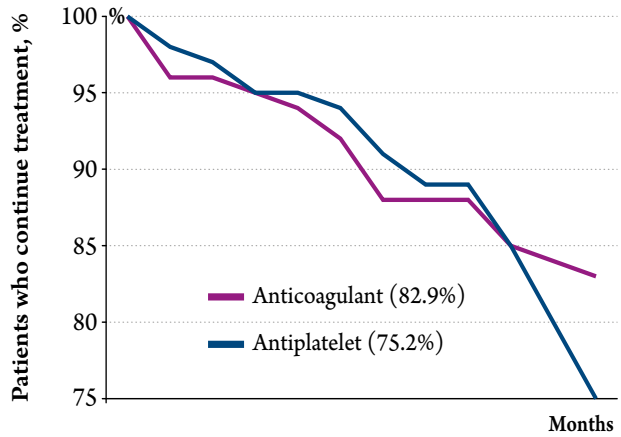
In the group of patients without a history of PCI, 40 (88.9%) patients continued taking rivaroxaban. 31 (68.9%) patients took antiplatelet drugs for the recommended period. In the triple therapy group, 3 (15.8%) subjects stopped taking rivaroxaban, while

Table 1. Clinical and demographic characteristics of patients

Parameter	Patients with a history of PCI, n=84	Patients without a history of PCI, n=45
Male/female, n (%)	32/52 (61.9/38.1)	21/24 (46.7/53.3)
Age, years	71.8±10.9	75.1±9.8
≥75 years, n (%)	37 (44.0)	24 (53.3)
≥65 years, n (%)	59 (70.2)	37 (82.2)
PCI		
• BMS stent, n (%)	36 (42.8)	–
• DES stent, n (%)	47 (56.0)	–
• Balloon angioplasty, n (%)	1 (1.2)	–
ST-segment elevation MI, n (%)	30 (35.7)	4 (8.9)
Non-ST-segment elevation MI, n (%)	40 (47.6)	24 (53.3)
Unstable angina, n (%)	14 (16.7)	17 (37.8)
CHAD2DS2 VASc, score	5 [3; 6]	6 [5; 7]
• 0–2, n (%)	8 (9.5)	1 (2.2)
• 3–9, n (%)	76 (90.5)	44 (97.8)
HAS-BLED, score	2 [2; 3]	3 [2; 4]
• 0–1, n (%)	18 (21.4)	3 (6.7)
• 2, n (%)	26 (31.0)	9 (20.0)
• 3–6, n (%)	40 (47.6)	33 (73.3)
AF pattern		
• Paroxysmal, n (%)	49 (58.3)	20 (44.4)
• Permanent, n (%)	22 (26.2)	21 (46.7)
• Newly diagnosed, n (%)	13 (15.5)	4 (8.9)
Smoking, n (%)	13 (15.5)	3 (6.7)
CKD, stage 3a-3b, n (%)	50 (59.5)	28 (62.2)
CKD, stage 4, n (%)	4 (4.8)	1 (2.2)
Concomitant diseases and past medical history, n (%)		
CHF	38 (45.2)	25 (55.6)
AH	82 (97.6)	44 (97.8)
DM	24 (28.6)	18 (40.0)
PICS	34 (40.5)	22 (48.9)
Peripheral atherosclerosis	22 (26.2)	16 (35.6)
Obesity	38 (45.2)	21 (46.7)
History of revascularization	22 (26.2)	17 (37.8)
Thromboembolic events	15 (17.9)	19 (42.2)
COPD	16 (19.0)	9 (20.0)
Active cancer	2 (2.4)	1 (2.2)
Erosive and ulcerative gastrointestinal diseases	6 (7.1)	6 (13.3)
Major bleeding*	7 (8.3)	7 (15.6)
Anemia at discharge	25 (29.8)	19 (42.2)

Unless otherwise indicated, the data is expressed as the mean and standard deviation (M±SD), the median and interquartile range (25th percentile; 75th percentile). * – bleeding that required intervention. PCI, percutaneous coronary intervention; MI, myocardial infarction; AF, atrial fibrillation; CKD, chronic kidney disease; CHF, chronic heart failure; AH, arterial hypertension; DM, diabetes mellitus; PICS, postinfarction cardiosclerosis; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal.

Figure 1. 12-month compliance with antiplatelet therapy



	1	2	3	4	5	6	7	8	9	10	11	12
Anticoagulant	100%	96%	96%	95%	94%	92%	88%	88%	88%	85%	84%	83%
Antiplatelet	100%	98%	97%	95%	95%	94%	91%	89%	89%	85%	80%	75%

4 (21.1%) patients discontinued antiplatelet therapy early. In the dual therapy group, 2 (7.7%) subjects stopped taking rivaroxaban, and 10 (38.5%) patients discontinued antiplatelet therapy.

Major bleeding, minor bleeding, and bleeding requiring intervention were reported in 19 (22.6%) patients with a history of PCI in the 12-month follow-up period. In the group of patients without a history of PCI, hemorrhagic complications were reported in 7 (15.6%) patients (Table 2).

The highest incidence of bleeding was reported during the first two administrations of combination therapy.

In the triple therapy group, the median incidence of hemorrhagic complications was 2. None of the bleeding cases was fatal. Major gastrointestinal and pulmonary bleedings were the most common (Table 3).

Factors of major, minor bleeding, and bleeding requiring intervention (TIMI) were assessed in all patients. The likelihood of bleeding increased 3.9 times (95% confidence interval (CI) 1.52–10.21) with age (≥75 years); 4.7 times (95% CI 1.24–17.58) in the case of severe acute heart failure (AHF; Killip 3–4) in hospital; 4.9 times (95% CI 1.42–16.59) in the case of gastrointestinal erosion and ulcers shown by gastroscopy; 7.2 times (95% CI 2.23–23.19) with a history of significant bleeding (requiring intervention); 3.8 times (95% CI 1.51–9.49) with mild anemia at discharge; and 6.1 times (95% CI 1.27–29.03) during combined ATT for 4 months; and decreased by 64% (95% CI 0.14–0.93) in obese patients (body mass index ≥30 kg/m^2).

Bleeding was not influenced by such factors as: gender; postinfarction cardiosclerosis; diabetes melli-

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Table 2. Primary endpoint

TIMI bleeding classification	Patients with a history of PCI, n=84	Patients without a history of PCI, n=45	Total, n=129
Major, n (%)	4 (4.8)	3 (6.7)	7 (5.4)
Minor, n (%)	7 (8.3)	1 (2.2)	8 (6.2)
Requiring intervention, n (%)	8 (9.5)	3 (6.7)	11 (8.5)
Major bleeding, minor bleeding, and bleeding requiring intervention, n (%)	19 (22.6)	7 (15.6)	26 (20.2)

PCI, percutaneous coronary intervention.

Table 3. Localization of bleeding

Localization / Terms of occurrence	Major bleeding	Major bleeding, minor bleeding, and bleeding requiring intervention
Gastrointestinal	3 (2.3)	8 (6.2)
Pulmonary	4 (3.1)	6 (4.7)
Urogenital	–	4 (3.1)
Nasal	–	4 (3.1)
After tooth extraction	–	1 (0.8)
Unknown location	–	3 (2.3)
Total	7 (5.4)	26 (20.2)

Table 4. Secondary endpoint

Parameter	Patients with a history of PCI, n=84	Patients without a history of PCI, n=45	Total, n=129
Composite endpoint	**14 (16.7)**	**10 (22.2)**	**24 (18.6)**
• Cardiovascular death	8 (9.5)	6 (13.3)	14 (10.9)
• Thromboembolic complications	2 (2.4)	–	2 (1.6)
• Nonfatal MI	5 (6.0)	8 (17.8)	13 (10.1)
• Stent thrombosis	2 (2.4)	–	2 (1.6)
All-cause mortality	8 (9.5)	8 (17.8)	16 (12.4)

PCI, percutaneous coronary intervention; MI, myocardial infarction.

tus; chronic obstructive pulmonary disease; peripheral arteriosclerosis; chronic heart failure; duration of triple therapy; and administration of rivaroxaban 20 mg.

In the multivariate analysis, the likelihood of hemorrhagic complications increased: 4.4 times (95% CI 1.52–12.66) with age ≥75 years; 4.8 times (95% CI 1.17–19.64) in severe AHF (Killip 3–4) in hospital; 6.6 times (95% CI 1.08–40.51) during combination ATT for 4 months; 6.2 times (95% CI 1.62–16.59) in the presence of gastrointestinal erosion and ulcers; and 7.2 times (95% CI 2.23–23.74) with a history of major bleeding.

Composite endpoint was achieved in 14 (16.7%) patients with a history of PCI during the 12-month follow-up period (Table 4).

8 (9.5%) patients died from cardiovascular events, 3 (37.5%) of whom had discontinued ATT. Cases of recurrent non-fatal MI were reported in 5 (6.0%) patients. Stent thrombosis was detected in 2 (2.4%) patients. Non-fatal thromboembolic events (CVA) occurred in 2 (2.4%) patients.

Composite endpoint was reported in 10 (22.2%) patients without a history of PCI. 6 (13.3%) patients died from cardiovascular events, 8 (17.8%) of whom had had recurrent non-fatal MI. No non-fatal thromboembolic complication was reported. There was one case of fatal pulmonary embolism (PE) due to the discontinuation of rivaroxaban.

Discussion

This study assessed the outcomes in patients with ACS and AF taking combination ATT with rivaroxaban and antiplatelet drug (s) during the 12 month follow-up period and also described predictors of bleeding.

The study included patients who were administered dual and triple therapy with rivaroxaban 20, 15, and 10 mg. The dose of 10 mg was indicated for CKD stages 3B (GFR 30–44 mL/min/1.73 m^2) and 4 (GFR 15–29 mL/min/1.73 m^2). According to the label, a reduced dose of rivaroxaban is recommended to be administered in combination with antiplatelet therapy in patients with AF after PCI. Our registry included 51 (60.7%) patients with a history of PCI receiving such doses. Low-dose rivaroxaban (10 mg) is not indicated in the case of patients without a history of PCI. In our study, 29 (64.4%) patients without a history of PCI received full doses of rivaroxaban.

Antiplatelet therapy and rivaroxaban were discontinued early by 32 (24.8%) and 22 (17.1%) patients, respectively. There were no differences in treatment compliance in the dual and triple therapy groups. The number of patients compliant with anticoagulant therapy was similar to the ANTEI trial, in which 80% of patients continued taking an anticoagulant in 12 months [15]. Patient compliance with treatment was better in our study than in the Russian register RECORD 3, in which the ATT combination was continued by less than 50% of

patients [16]. The reasons for drug discontinuation were not analyzed since it was not the objective of this study. However, most patients stopped taking drugs without discussing the matter with a physician and in the absence of indications for discontinuation. Poor compliance with ATT is indicative of a lack of awareness of patients about the possibility of thromboembolic and recurrent ischemic events.

Major, minor bleeding, and bleeding requiring intervention (TIMI) were reported in 26 (20.2%) cases during the 12-month follow-up period. None of the bleeding cases was fatal. Most of the bleeding cases occurred in the first two months of ATT. This is comparable with the data of the COMPASS and ATLAS ACS-TIMI 46 RCTs [17, 18]. Bleeding was reported in 19 (22.6%) patients with a history of PCI.

Direct comparison of the data obtained on outcomes in our study with the PIONEER AF-PCI RCT is impossible since only 40% of patients in the RCT had ACS. Also higher doses of rivaroxaban were administered, patients were older, had a higher risk of thromboembolic complications (CHA_2DS_2VASc) and more concomitant diseases in this study. The PIONEER AF-PCI trial compared triple therapy (vitamin K antagonists, thienopyridine, and acetylsalicylic acid for 1 to 6 months) with dual therapy (rivaroxaban 15 mg and P2Y-12 receptor inhibitor. Rivaroxaban 10 mg was administered to patients with GFR 30–49 mL/min/1.73 m^2). In the PIONEER AF-PCI trial, the incidence of hemorrhagic complications in patients with ACS was 15.5% in the rivaroxaban 15 mg/thienopyridine group, and 23.7% in the warfarin group (p=0,009).

In a comparison of our register and the RCT, the incidence of hemorrhagic complications did not exceed the rate of bleeding in the warfarin group, despite the use of rivaroxaban in the triple therapy in 80% of patients and full dose (20 and 15 mg) in 40% of cases. This data confirms that rivaroxaban is safer than warfarin regardless of the type of ATT and drug doses.

The following predictors influencing the development of hemorrhagic complications were identified: age ≥75 years; severe AHF at hospitalization; gastrointestinal erosion and ulcers; history of major bleeding; and administration of antiplatelet therapy for 4 months.

After discharge, 14 (10.9%) patients died from cardiovascular events during the follow-up period. According to the RECORD 3 register, post-discharge mortality was 8.4% in ACS patients, and 15.3% in patients with AF, which is slightly higher than our results [19]. In our study, recurrent MI was reported in 13 (10.1%) patients, and stent thrombosis was rare – in 2 (2.4%) cases. Nonfatal thromboembolic complications included only 2 (1.6%) CVA events. One patient died of pulmonary embolism. In all cases, anticoagulation was discontinued before the development of a thromboembolic complication.

Composite endpoint events were reported in 24 (18.6%) patients. The data obtained is comparable to the results of the RECORD 3 register, in which the frequency of the composite endpoint was 13.8% in the ACS group and 24.4% in the AF group [19]. Composite endpoint was reported in 14 (16.7%) patients with a history of PCI. In the PIONEER AF-PCI trial, the incidence of cardiovascular events in patients with ACS was 8.2% in the group of dual therapy with rivaroxaban and 5.9% in the group of triple therapy with warfarin. In our study, the higher incidence of ischemic complications may be due to differences in the patient populations. All patients had ACS, there were more patients older than 75, and more patients presented serious comorbidities.

Limitations

This study is limited by the fact that only two vascular centers participate in the registry, the uneven numbers of patients in the groups, and small sample.

Conclusion

The lack of compliance with antithrombotic therapy was identified. Every fourth patient discontinued antiplatelet therapy early, while every fifth patient stopped taking an anticoagulant.

The study observed a high incidence of bleeding complications, with more events of minor bleeding and bleeding requiring intervention. None of the bleeding events led to a fatal outcome. The incidence of hemorrhagic complications was higher in our study than compared to the rivaroxaban group in the PIONEER AF-PCI trial. However, it did not exceed the incidence of bleeding in the warfarin group in the PIONEER AF-PCI trial. This confirms that rivaroxaban is safer than warfarin irrespective of the type of antithrombotic therapy and drug doses.

The fixed incidence of recurrent ischemic events characterized by high mortality is more problematic than hemorrhagic complications of the combination antithrombotic therapy, thus confirming that it is feasible to use a more aggressive antithrombotic strategy in patients at high risk.

The difference between the data obtained and the PIONEER AF-PCI trial may be due to differences in

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the patient populations (all patients had acute coronary syndrome, more patients older than 75 years, higher comorbidity), and the lack of compliance with drug therapy.

No conflict of interest is reported.

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