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Prediction-Determining Outcomes and Their Predictors in Atrial Fibrillation Patients Receiving Multicomponent Antithrombotic Therapy in Real Clinical Practice

Aim — Searching for clinical, angiographic, and biochemical predictors of cardiovascular complications (CVC) and hemorrhagic complications in patients with atrial fibrillation (AF) receiving a multicomponent antithrombotic therapy (MAT) for an elective percutaneous coronary intervention (PCI). Patients with ischemic heart disease (IHD) and AF who require MAT for PCI are at a high risk of thrombotic complications (stroke, systemic embolism, coronary events) and hemorrhage. This warrants searching for new risk factors determining prediction of the outcome.

Materials and methods — This study included 207 patients (146 males aged 70.1±8.3 years) with IHD and AF who received direct oral anticoagulants (DOAC) as a part of their MAT therapy. Median duration of the follow-up was 12 [8.0; 12.0] months. The efficacy endpoint was a sum of CVCs combining cardiovascular death, ischemic stroke, venous thromboembolic complications, acute coronary syndrome (ACS), and requirement for an unscheduled PCI. «Coronary events», including ACS and requirement for an unscheduled PCI were analyzed separately. The safety endpoint was BARC type 2–5 bleeding. Upon admission, biomarkers (growth-differentiation factor 15 (GDF-15), D-dimer, thrombin-activated fibrinolysis inhibitor (TAFI), and plasminogen activator inhibitor-1 (PAI-1)) were measured for all patients. Searching for prognostically significant indexes was performed with the Cox proportional hazards regression.

Results — Incidence of all CVCs was 16.4%. Independent predictors of CVC included the DOAC treatment at a reduced dose (odds ratio (OR) 2.5 at 95% confidence interval (CI) 1.02–6.15; p=0.0454), GDF-15 >1191 pg/ml (OR 3.76 at 95% CI, 1.26–11.18; p=0.0172), PAI-1 >13.2 U/ml (OR 2.67 at 95% CI, 1.13–6,26; p=0.0245). Incidence of coronary complications was 9.2%. Independent predictors of coronary complications included a SYNTAX index >26.5 (OR 4.5 at 95% CI, 1.45–13.60; p=0.0090), PCI for chronic coronary occlusion (OR 3.21 at 95% CI, 1.10–9.33; p=0.0326), a GDF-15 >1191 pg/ml (OR 4.70 at 95% CI, 1.32–16.81; p=0.0172). Incidence of BARC type 2–5 bleeding was 26.1%. The only independent predictor for hemorrhage complications was the total PRECISE-DAPT score >30 (OR 3.22; 95% CI, 1.89–5.51; p<0.0001).

Conclusion — Three independent predictors of CVC were identified for patients with IHD and AF treated with MAT following an elective PCI: treatment with a reduced dose of DOAC, GDF-15 >1191 pg/ml, and PAI-1>13.2 U/ml. Independent predictors of coronary complications included a SYNTAX index >26.5, PCI for chronic coronary occlusion, and GDF-15 >1191 pg/ml. The factor associated with a risk of bleeding was the total PRECISE-DAPT score >30.

Keywords — Direct oral anticoagulants; multicomponent antithrombotic therapy; atrial fibrillation; percutaneous coronary interventions; cardiovascular complications; hemorrhage; biomarkers; GDF-15, plasminogen activator inhibitor-1; PRECISE-DAPT

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Patients with coronary artery disease (CAD) and atrial fibrillation (AF) treated with multiple antithrombotic therapy (MAT) for percutaneous coronary intervention (PCI) are at a high risk of stroke, systemic embolism, and coronary complications. We have previously determined that patients in need of MAT have many comorbidities which increase the risk of cardiovascular complications (CVCs) and bleeding

[1, 2]. The risk of bleeding is known to increase 2–3 times during MAT [3]. When treating patients with AF after a scheduled PCI, maintaining a balance between MAT efficacy and safety is one of the main targets.

The main challenges of the administration of multiple antithrombotic agents lie in the composition and duration of the antithrombotic therapy. With regards to the composition of MAT, clopidogrel should be used as a P2Y12 receptor blocker in most patients [4–9]. Given the benefits of direct oral anticoagulants (DOACs) over vitamin K antagonists in terms of efficacy and safety, it is recommended that this class of anticoagulants be chosen for MAT if there are no contraindications [5–10]. The dosage of DOACs within MAT remains a sensitive issue. According to our real-practice data [1, 2], lower doses of DOACs in MAT do not reduce the number of bleedings, yet increase the number of ischemic complications. The duration of acetylsalicylic acid (ASA) administration as part of triple antithrombotic therapy (TAT), and the possibility of using dual antithrombotic therapy (DAT) immediately after the PCI, are the main issues currently under discussion in terms of the MAT model.

There is a clear need to find new predictors to refine MAT composition and duration. The existing CVC and bleeding risk scores include mainly clinical and angiographic variables. Thus, new biochemical and coagulation markers including growth differentiation factor-15 (GDF-15) associated with cell aging, inflammatory responses, oxidative damage, and predictor outcomes in patients with cardiovascular diseases [11–15] are of undoubtedly great interest. They are important in the evaluation of laboratory findings to stratify the risk of thrombotic complications and bleedings in patients treated with multiple antithrombotic agents.

The aim of the study was to establish clinical, angiographic, and biochemical predictors of CVCs and hemorrhagic complications in patients with AF treated with MAT for scheduled PCI.

Material and Methods

The study included 207 patients with CAD and AF who had undergone scheduled PCI and were followed up in the Department of Clinical Implications of Atherothrombosis within the REGATTA-2 register (ClinicalTrials.gov number NCT04347187) between 2014 and 2019.

The inclusion criteria was a successful PCI in a patient with AF and indications for anticoagulant therapy. The exclusion criteria were contraindications to anticoagulant and antiplatelet therapy and an episode of acute coronary syndrome (ACS) less than one month previously.

Before inclusion in the study, all patients signed an informed consent form outlining the study's nature and methods.

Median follow-up period was 12 [8.0; 12.0] months.

The follow-up included a telephone survey (once every 1–3 months) and scheduled visits to the clinic once every six months. The outcome analysis was undertaken by telephone survey or during the visit to the clinic. All patients took DOACs as a part of MAT, clopidogrel 75 mg/day and/or ASA 75–100 mg/day. Antithrombotic, hypotensive, antiarrhythmic, antianginal, hypolipidemic, and hypoglycemic treatments were adjusted at scheduled visits, if necessary.

Our study is a part of the REGATTA-2 register and reflects the clinical practice run at the A. L. Myasnikov Institute of Cardiology. The study included neither a comparison of the safety and efficacy of physician-prescribed TAT or DAT nor a comparison of different durations of TAT.

Given that the composition and duration of the MAT could be subject to change over a period of five years, the authors found it possible to analyze the outcomes of patients with AF after PCI, included in the REGATTA-2 register between 2014 and 2019. These variables were compared in 57 patients included in the REGATTA-2 register between 2014–2017 and 150 patients registered between 2017–2019. The analysis showed that the DAT and TAT rates were the same in the analysis groups (DAT 15.8 and 13.3%, respectively, p=0.66; TAT 84.2 and 86.7%, respectively, p=0.66). The median TAT duration was 2.0 [1.0; 6.0] months in 2014–2017 and 1.0 [1.0; 5.0] month (r=0.10) in 2018–2019. This in general terms corresponded with expert guidelines on a best possible MAT strategy in patients with AF after PCI.

The choice of DOACs, dosages, and the composition of antithrombotic therapy (clopidogrel or ASA + clopidogrel) was subject to the physician's discretion. TAT was prescribed to 86% of patients.

If a patient with multiple coronary lesions needed several consecutive PCIs (staged PCI), it was not considered an endpoint since a quota covered only a single-vessel PCI. However, it caused an increase in the duration of MAT.

In order to fulfill the objective, we analyzed the coronary angiograms according to the SYNTAX algorithm, with the exception of angiograms of patients who had previously undergone coronary artery bypass grafting (CABG). A SYNTAX II index combining clinical and angiographic risk factors (RFs) was then calculated.

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The risk of ischemic stroke (IS) and systemic embolism was assessed using the CHA_2DS_2 VASc score. The Charlson index was used to estimate the patient's comorbidity burden. The risk of bleeding was stratified using the HAS-BLED and PRECISE-DAPT scores.

Clinical characteristics of patients

A total of 207 patients (146 male and 61 female) were included in the study. The mean age was 70.1±8.3 years. The clinical characteristics are presented in Table 1. The patients included had a high risk of stroke and systemic embolism (CHA_2DS_2 VASc 5 [4; 6]), a high risk of bleeding (HAS-BLED 4 [3; 3]), and many comorbidities (Charlson Index 7 [5; 9]). The median SYNTAX index was 15 [9; 22]. At the time of inclusion, 32.9% of patients had been previously treated with MAT, and 30.4% of patients received anticoagulant therapy for the first time. Immediately after the scheduled PCI, TAT was prescribed to 86% of patients and DAT to 14%. DOACs rivaroxaban, apixaban, and dabigatran were prescribed to 122 (58.9%), 53 (25,6%), and 32 (15,5%) patients, respectively. The physicians chose lower doses of DOACs (rivaroxaban 15 mg once a day, apixaban 2.5 mg twice a day, dabigatran 110 mg twice a day) in 49.3% of cases.

Upon inclusion, venous blood samples were collected from 150 patients, in order to determine growth factors and differentiate GDF-15, as well as the components of the hemostasis system, such as D-dimer, plasminogen activator inhibitor type 1 (PAI-1), and thrombin-activated fibrinolysis inhibitor (TAFI). Plasma samples were not collected from 57 patients because they were included in the REGATTA-2 register on Days 7 to 30 after PCI.

GDF-15 was defined by means of an enzyme-linked immunosorbent assay (ELISA) using a GDF-15/MIC-1 Human ELISA reagent kit. The calibration range was 22–4,480 IU/mL. PAI-1 was defined by the ELISA method using a PAI-1 Actibind kit. The calibration range was 1.5–30 IU/mL. Diagnostics Stago reagents were used to determine D-dimer and TAFI levels. D-dimer was defined by ELISA using an Asserachrom D–Di reagent kit. The calibration range was 50–2,000 IU/mL. TAFI was determined by a photometric method using an STA Stachrom TAFI reagent kit and an STA Compact analyzer. The calibration range was 5–195% of normal. A 100% content of donor blood in plasma was accepted as normal.

The primary endpoint of efficacy was defined as the sum of outcomes that included cardiovascular death, IS, venous thromboembolism (VTE), ACS, and the need for urgent coronary revascularization.

Table 1. Clinical characteristics of patients included in the study (n=207)

Parameter	Value
Male/female, n (%)	146/61 (70.5/29.5)
Age, years	70.0 [64.0; 77.0]
Hypertension, n (%)	200 (96.6)
History of myocardial infarction, n (%)	103 (49.8)
CHF, n (%)	145 (70.1)
CHF with LVEF<50%, n (%)	56 (27.1)
Diabetes mellitus, n (%)	70 (33.8)
History of ischemic stroke, n (%)	44 (21.3)
GFR (CKD EPI) mL/min/1.73 m2	73.1 [57.3; 86.8]
GFR (CKD-EPI) <60 mL/min/1.73 m^2, n (%)	56 (27.1)
Chronic kidney disease, n (%)	62 (30.0)
Smoking, n (%)	84 (40.6)
Peripheral arterial disease*, n (%)	96 (46.4)
History of hemorrhagic complications, n (%)	41 (19.8)
History of gastric/duodenal ulcer, n (%)	43 (20.8)
History of erosive gastritis, n (%)	68 (32.9)
Anticoagulant-naive patients, n (%)	63 (30.4)
History of TAT/DAT, n (%)	68 (32.9)
TAT, n (%)	178 (86.0)
DAT immediately after PCI, n (%)	29 (14.0)
Lower doses of DOACs, n (%)	102 (49.3)
Dabigatran, n (%)	32 (15.5)
Rivaroxaban, n (%)	122 (58.9)
Apixaban, n (%)	53 (25.6)
CHA_2DS_2-VASc, score	5.0 [4.0; 6.0]
Charlson index	7.0 [5.0; 9.0]
HAS-BLED, score	3.0 [3.0; 4.0]
HAS-DAPT, score	21.0 [15.0; 31.0]
History of CABG, n (%)	22 (10.6)
History of PCI, n (%)	64 (30.9)
SYNTAX index	15.0 [9.0; 22.0]
SYNTAX II index	34.8 [27.9; 43.9]
Staged PCI**, n (%)	43 (20.8)
Number of drugs prescribed at discharge	8 (7.0; 10.0)
Occasional use of NSAIDs, n (%)	42 (20.3)
Use of PPIs, n (%)	134 (64.7)

The data is expressed as the median and the interquartile range (Me [25%; 75%]) unless otherwise specified. Hereinafter: CHF, chronic heart failure; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; TAT, triple antithrombotic therapy; DAT, dual antithrombotic therapy; DOACs, direct oral anticoagulants; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors. *, ≥50% atherosclerotic lesion of the brachiocephalic arteries and the arteries of the lower extremities, aneurysm of the abdominal aorta, revascularization of a peripheral vascular system; **, sequential scheduled PCI of multiple coronary arteries.

The secondary endpoint of efficacy was the sum of ACS and urgent PCI due to exacerbation/recurrence of angina pectoris or onset of ACS. This endpoint was named «coronary events» (CEs).

The safety endpoint was BARC type 2–5 hemorrhagic complications [16] which combined bleedings requiring medical attention and additional examination, with a decrease in hemoglobin by 3 g/dL requiring intervention and blood transfusion; and bleedings complicating coronary artery bypass grafting and fatal bleedings.

The independent ethics committee of the Russian National Cardiology Research Center approved the study.

The data were processed using Statistica 10.0 and MedCalc 10.0. The non-parametric quantitative variables were estimated using the median and the interquartile range (Me [25%; 75%]). The chi-square test and the Student's t-test were used to evaluate the significance of intergroup differences. ROC analysis was performed, and cut-off values were defined, in order to find an optimal value predicting the risk of the onset of the endpoints. The cut-off values for the variables of interest were selected based on maximum sensitivity and specificity values. Multiple binary logistic regression models were used to assess the predictive power of variables. The Cox proportional hazards regression was used to model survival and identify significantly predictive variables. The direct stepwise variable selection was used to build the model. The model produced an output variable as odds ratio (OR) and the 95% confidence interval (CI). The differences were statistically significant at $p < 0.05$.

Results

Bleeding in patients with AF who received MAT after the scheduled PCI and the variables associated with the risk of bleeding

Massive and clinically significant bleeding (BARC 2–5) was reported in 54 (26.1%) patients during the follow-up period. Clinically significant and heavy bleedings (BARC) are set out in Table 2.

During TAT (178 patients), 34 events of massive and clinically significant bleeding (62.7% of the total reported events of massive and clinically significant bleeding) occurred before the withdrawal of one antiplatelet drug. TAT median duration before the onset of the first severe and clinically significant bleeding was 31 [17; 150] days, and the total median duration of TAT was 61 [31; 153] days.

Gastrointestinal bleeding was the most frequent hemorrhagic complication (n=25, 46.3%). Of these five events were in the upper gastrointestinal tract and 20 events in the lower gastrointestinal tract. The rate of nasal bleeding, including events requiring tamponade, was 31%. Hematuria was 11%, scleral hemorrhages 6%, subcutaneous hematoma 4%, and mouth bleeding 2%.

The clinical characteristics of patients with (n=54) and without hemorrhagic complications (n=153) are presented in Table 3.

As shown in Table 3, patients who suffered massive and clinically significant bleeding were significantly more likely to have a history of hemorrhagic complications, chronic kidney disease (CKD), and higher bleeding risk scores.

There was no correlation of bleeding with the GDF-15 levels and the TAFI and PAI-1 coagulation variables.

We subsequently compared the predictive power of the HAS-BLED and PRECISE-DAPT blood risk scores using the ROC analysis. The predictive power of the PRECISE-DAPT score was comparable to that of the HAS-BLED score ($z=0.715$; $p=0.4743$). The cut-off points for the PRECISE-DAPT and HAS-BLED scores which were significantly predictive for BARC 3–4 bleeding risk, were >30 and >3, respectively (Figure 1).

All the clinical variables that were of relevance for massive and clinically significant bleeding in the multivariate regression analysis (history of hemorrhagic complications and CKD) and the total scores of PRECISE-DAPT >30 and HAS-BLED >3 were included in the Cox proportional hazard model. The only independent predictor of massive and clinically significant bleeding was a total PRECISE-DAPT score of more than 30 (OR 3.22, 95% CI 1.89–5.51). Predictive power of the multivariate hazard model: $\chi^2=17.38$; $p<0.0001$.

CVCs in patients with AF after scheduled PCI and variables associated with risk of bleeding

During the follow-up period, CVCs, including cardiovascular death, IS, ACS, VTE, and the need for urgent coronary revascularization were reported in 34 (16.4%) patients. The most common complication was the need for an urgent PCI (n=17). Cardiovascular death was reported in 10 patients. One case was a ruptured

Table 2. Characteristics of massive and clinically significant bleedings according to the BARC score

Type of bleeding	Value
BARC 2	49 (90.7%)
BARC 3	5 (9.3%)
BARC 4	0
BARC 5	0
Total	**54 (100%)**

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Table 3. Comparative characteristics of patients depending on the presence of massive or clinically significant hemorrhage in the follow-up period (n=207)

Parameter	Patients with hemorrhagic complications (n=54)	Patients without hemorrhagic complications (n=153)	p
Clinical performance			
Male/female, n (%)	33/21 (61.1/38.9)	113/40 (73.9/26.1)	0.0848
Age, years	70.0 [66.0; 77.0]	71.0 [64.0; 76.0]	0.1978
Age >65 years, n (%)	26 (48.2)	55 (36.0)	0.1442
TAT, years (%)	47 (87.0)	131 (85.6)	1.0000
DAT immediately after PCI, n (%)	7 (13.0)	22 (14.4)	1.0000
Anticoagulant-naive patients, n (%)	21 (38.9)	42 (27.5)	0.1709
History of hemorrhagic complications, n (%)	18 (33.3)	23 (15.0)	0.0019
Staged PCI, n (%)	13 (24.1)	30 (19.6)	0.5587
Lower doses of DOACs, n (%)	28 (51.9)	74 (48.4)	0.3889
Use of PPIs, n (%)	39 (72.2)	95 (62.1)	0.1904
BMI <27 kg/m2, n (%)	8 (22.2)	37 (21.6)	1.0000
CHF, n (%)	38 (70.4)	107 (69.9)	1.0000
CHF with LVEF<50%, n (%)	11 (20.4)	45 (29.4)	0.2157
Diabetes mellitus, n (%)	20 (37.0)	50 (32.7)	0.6167
History of ischemic stroke, n (%)	13 (24.1)	31 (20.3)	0.5654
GFR (CKD-EPI)<60 mL/min/1.73 m^2, n (%)	21 (38.9)	33 (21.6)	0.0185
Chronic kidney disease, n (%)	25 (46.3)	37 (24.2)	0.0032
Intermittent claudication, n (%)	7 (13.0)	21 (13.7)	1.0000
History of gastric/duodenal ulcer, n (%)	15 (27.8)	28 (18.3)	0.1717
History of erosive gastritis, n (%)	19 (35.2)	49 (32.0)	0.7367
CHA_2DS_2-VASc, score	5.0 [4.0; 6.0]	5.0 [3.5; 6.0]	0.1395
Charlson index	7.0 [5.0; 9.0]	7.0 [5.0; 8.0]	0.1529
SYNTAX index	14.0 [8.0; 21.0]	16.0 [9.0; 22.0]	0.4450
SYNTAX II index	34.4 [26.2; 45.5]	34.8 [29.6; 43.7]	0.9067
Bleeding risk assessment scores			
HAS-BLED, score	4.0 [3.0; 4.0]	3.0 [3.0; 4.0]	0.0002
HAS-DAPT, score	30.0 [20.0; 41.0]	20.0 [14.0; 27.0]	0.0001
Biochemical variables			
GDF-15, pg/mL	1186.0 [987.0; 1792.0]	1287.0 [947.0; 1769.0]	0.9038
PAI-1, U/mL	9.9 [6.2; 16.3]	10.2 [6.4; 17.1]	0.9276
TAFI, %	97.0 [78.0; 101.0]	91.0 [77.0; 108.0]	0.7177

The data is expressed as the median and the interquartile range (Me [25%; 75%]), unless otherwise specified. TAT, triple antithrombotic therapy; PCI, percutaneous coronary intervention; DAT, dual antithrombotic therapy; DOACs, direct oral anticoagulants; PPIs, proton pump inhibitors; BMI, body mass index; CHF, chronic heart failure; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; GDF-15, growth differentiation factor 15; PAI-1, plasminogen activator inhibitor type 1; TAFI, thrombin-activated fibrinolysis inhibitor.

aneurysm of the abdominal aorta. Three patients died of progressive heart failure. Two patients suffered fatal pulmonary embolism. Four cases involved fatal IS, while three patients suffered non-fatal IS during the follow-up period. Two patients developed non-fatal myocardial infarction. One patient had deep vein thrombosis of the lower extremities, while one patient developed renal artery stent thrombosis.

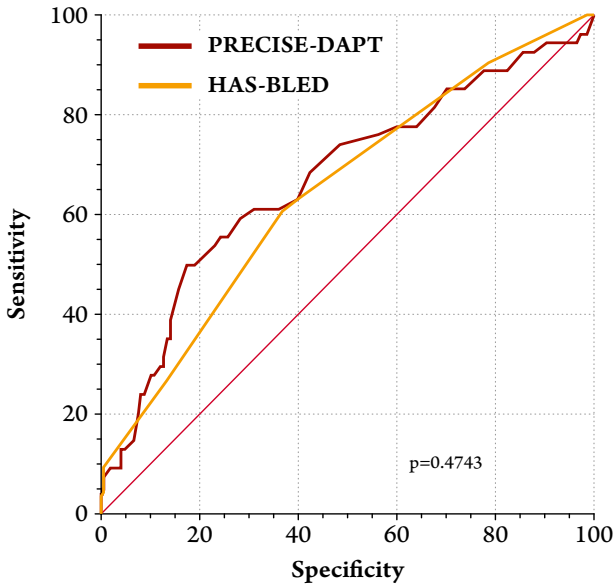
The clinical characteristics of patients with (n=34) and without CVCs (n=173) are presented in Table 4.

Univariate analysis found that patients who had suffered CVCs were more likely to receive DOACs at lower doses compared to patients without CVCs. They were also more likely to undergo staged and multiple stenting and endovascular interventions in chronic coronary occlusions, and had higher values of the SYNTAX index and biochemical variables GDF-15 and PAI-1.

According to the ROC-analysis, the values of GDF-15 >1191 pg/mL and PAI-1 >13.2 U/mL, and SYNTAX >26.5 increase the probability of CVCs (Figure 2).

The Cox proportional hazard model included variables confirmed by multivariate regression analysis to be predictive of the development of CVCs, including

Figure 1. Comparison of the predictive powers of the HAS-BLED and PRECISE-DAPT scores (%)



Parameter	AUC	95% CI	p	Related criteria
PRECISE-DAPT	0.671	0.601–0.735	0.0002	>30
HAS-BLED	0.646	0.576–0.712	0.0003	>3

clinical RFs (staged PCIs, lower doses of DOACs); biochemical markers (GDF-15 >1191 pg/mL and PAI-1 >13.2 U/mL); angiographic variables (SYNTAX >26.5 and endovascular intervention for chronic coronary occlusions).

The independent predictors of CVCs were lower doses of DOACs (OR 2.5, 95% CI 1.02–6.15; p=0.0454), GDF-15 >1191 pg/mL (OR 3.76, 95% CI 1.26–11.18; p=0.0172), PAI-1 >13.2 U/mL (OR 2.67, 95% CI 1.13–6.26; p=0.0245). Predictive power of the multivariate hazard model: χ^2=17.64; p=0.0005.

Predictors of coronary complications (secondary efficacy endpoint) in patients with AF receiving MAT after scheduled PCI

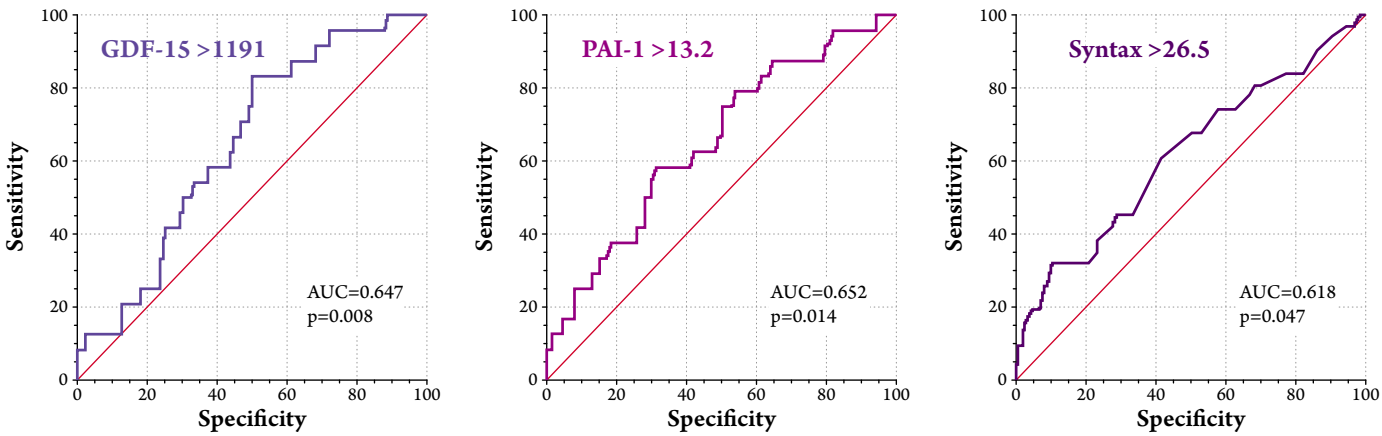
Given the relevance of finding new risk factors for CEs in patients with AF in need of MAT, and the univariate and ROC analysis findings on the role of the variables associated with the PCI, it was found necessary to search for predictors of the secondary efficacy endpoint defined as a total outcome: ACS and urgent PCIs due to the exacerbation/recurrence of angina pectoris or the onset of ACS.

During the follow-up period, 19 CEs were reported. Of these 2 cases were ACS, and 17 cases were urgent PCIs. The clinical characteristics of patients with (n=19) and without CEs (n=188) are presented in Table 5.

According to the univariate analysis, patients who suffered CEs had higher values of SYNTAX and GDF-15. They received more frequent gastro-protective therapy with proton pump inhibitors (PPIs) and underwent more frequent multiple stenting and interventions for chronic coronary occlusions.

All variables which proved to be predictive of the development of CEs, according to the multivariate regression analysis (SYNTAX >26.5; GDF-15 >1191 pg/mL; the use of PPIs, and endovascular intervention for chronic coronary occlusion), were included in the Cox proportional hazard model.

Figure 2. Diagnostic significance of biomarkers (GDF-15, PAI-1) and SYNTAX index in terms of the onset of cardiovascular complications (%)



Sensitivity	83,3
Specificity	50,0

Sensitivity	58,3
Specificity	68,5

Sensitivity	32,3
Specificity	89,7

GDF-15, growth differentiation factor 15; PAI-1, plasminogen activator inhibitor type 1.

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Table 4. Comparative characteristics of patients depending on the presence of cardiovascular complications in the follow-up period (n=207)

Parameter	Patients with CVCs (n=34)	Patients without CVCs (n=173)	p
Clinical performance			
Male/female, n (%)	27/7 (79.4/20.6)	119/54 (68.8/31.2)	0.3032
Age, years	71.5 [64.0; 76.0]	70.0 [64.0; 77.0]	0.5599
Smoking, n (%)	15 (44.1)	69 (39.9)	0.7040
TAT, n (%)	30 (88.2)	148 (85.6)	0.7932
DAT immediately after PCI, n (%)	5 (14.7)	26 (15.0)	0.7932
Anticoagulant-naive patients, n (%)	10 (29.4)	53 (30.6)	1.0000
Lower doses of DOACs, n (%)	24 (70.6)	78 (45.1)	0.0082
BMI <27 kg/m^2, n (%)	8 (23.5)	37 (21.4)	0.8209
History of ischemic stroke, n (%)	9 (26.5)	35 (20.2)	0.4112
CHF with LVEF<50%, n (%)	13 (38.2)	43 (24.9)	0.1385
Peripheral atherosclerosis, n (%)	17 (50.0)	79 (45.7)	0.8490
Intermittent claudication, n (%)	4 (11.8)	24 (13.9)	1.0000
Chronic kidney disease, n (%)	9 (26.5)	53 (30.6)	0.6873
History of gastric/duodenal ulcer, n (%)	5 (14.7)	38 (22.0)	0.4878
History of erosive gastritis, n (%)	12 (35.3)	56 (32.4)	0.8419
Diabetes mellitus, n (%)	11 (32.4)	58 (33.5)	1.0000
CHA_2DS_2-VASc, score	5.0 [4.0; 6.0]	5.0 [4.0; 6.0]	0.6311
Charlson index	7.0 [6.0; 9.0]	7.0 [5.0; 9.0]	0.4073
Charlson index ≥7, n (%)	22 (64.7)	86 (49.7)	0.1338
CHA_2DS_2 VASc ≥5, n (%)	20 (58.8)	88 (50.9)	0.4550
CHA_2DS_2 VASc ≥6, n (%)	13 (38.2)	53 (30.6)	0.4229
History of CABG, n (%)	2 (5.9)	20 (11.6)	0.5417
History of PCI, n (%)	11 (32.4)	53 (30.6)	0.8412
Staged PCI, n (%)	13 (38.2)	30 (17.3)	0.0101
Occasional use of NSAIDs, n (%)	24 (70.6)	110 (63.6)	0.5565
Use of PPIs, n (%)	5 (14.7)	37 (21.4)	0.4869
Angiographic variables			
Extended stenting*, n (%)	15 (44.1)	50 (28.9)	0.1051
Multiple stenting**, n (%)	13 (38.2)	31 (17.9)	0.0119
Endovascular intervention for chronic coronary occlusion, n (%)	8 (23.5)	13 (7.5)	0.0099
SYNTAX index	17.0 [11.0; 29.0]	15.0 [9.0; 21.0]	0.0113
SYNTAX II index	36.8 [31.2; 46.9]	34.5 [26.6; 43.2]	0.6510
Diffuse multi-vessel coronary disease, n (%)	13 (38.2)	50 (28.9)	0.3103
Hemodynamically significant lesion of LCA or proximal LAD, n (%)	13 (38.2)	61 (35.3)	0.8451
Biochemical variables			
GDF-15, pg/mL	1501.5 [1210.0; 1968.0]	1198.5 [899.0; 1733.0]	0.0140
PAI-1, U/mL	14.6 [9.5; 24.9]	9.8 [6.0; 16.4]	0.0044
D-dimer, ng/mL	521.0 [387.5; 755.0]	500.0 [285.0; 831.5]	0.6010

The data is expressed as the median and the interquartile range (Me [25%; 75%]), unless otherwise specified.
*, the total length of implanted stents>60 mm; **, simultaneous implantation of three or more stents. CVCs, cardiovascular complications; TAT, triple antithrombotic therapy; DAT, dual antithrombotic therapy; PCI, percutaneous coronary intervention; DOACs, direct oral anticoagulants; BMI, body mass index; CHF, chronic heart failure; LVEF, left ventricular ejection fraction; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; LAD, left anterior descending artery; LCA, left coronary artery; GDF-15, growth differentiation factor 15; PAI-1, plasminogen activator inhibitor type 1.

Table 5. Comparative characteristics of patients depending on the presence of coronary complications in the follow-up period (n=207)

Parameter	Patients with CEs (n=19)	Patients without CEs (n=188)	p
Baseline patient characteristics			
Male/female, n (%)	14/5 (73.7/26.3)	132/56 (70.2/29.8)	1.0000
Age, years	70.0 [65.0; 76.0]	70.0 [64.0; 77.0]	0.9955
Smoking, n (%)	7 (36.8)	77 (41.0)	0.8099
BMI <27 kg/m^2, n (%)	3 (15.8)	42 (22.3)	0.7705
History of myocardial infarction, n (%)	12 (63.2)	91 (48.4)	0.2391
CHF with LVEF<50%, n (%)	6 (31.6)	50 (26.6)	0.5993
Peripheral atherosclerosis, n (%)	11 (57.9)	85 (45.2)	0.3392
Chronic kidney disease, n (%)	7 (36.8)	55 (29.3)	0.5995
History of gastric/duodenal ulcer, n (%)	4 (21.1)	39 (20.7)	1.0000
History of erosive gastritis, n (%)	7 (36.8)	61 (32.3)	0.7984
Diabetes mellitus, n (%)	8 (42.1)	62 (33.0)	0.4512
CHA_2DS_2-VASc, score	5.0 [4.0; 6.0]	5.0 [4.0; 6.0]	0.3001
Charlson index	8.0 [7.0; 9.0]	6.5 [5.0; 9.0]	0.1384
Charlson index ≥7, n (%)	14 (73.7)	94 (50.0)	0.0563
Hemodynamically significant lesion of LCA or proximal LAD, n (%)	10 (52.6)	64 (34.0)	0.1328
Hemodynamically significant lesion of LCA, n (%)	2 (10.5)	18 (9.6)	1.0000
Hemodynamically significant lesion of proximal LAD, n (%)	10 (52.6)	60 (31.9)	0.0789
SYNTAX index	17.0 [13.0; 29.0]	15.0 [9.0; 21.0]	0.0714
SYNTAX>26.5	6 (33.3)	20 (12.1)	0.0251
SYNTAX II index	36.9 [31.6; 46.9]	34.6 [26.8; 43.2]	0.2096
GDF-15> 1191 pg/mL	14 (82.4)	69 (51.9)	0.0198
PAI-1>13.2 U/mL	9 (52.9)	44 (33.6)	0.1770
Treatment			
TAT, n (%)	17 (89.5)	161 (85.6)	1.0000
DAT immediately after PCI, n (%)	2 (10.5)	27 (14.4)	1.0000
Use of PPIs, n (%)	17 (89.4)	117 (62.2)	0.0125
Staged PCI, n (%)	7 (36.8)	36 (19.2)	0.0799
Extended stenting, n (%)	9 (47.4)	56 (29.8)	0.1260
Multiple stenting, n (%)	8 (42.1)	36 (19.2)	0.0346
Endovascular intervention for chronic coronary occlusion, n (%)	6 (31.6)	15 (8.0)	0.0060

The data is expressed as the median and the interquartile range (Me [25%; 75%]), unless otherwise specified. CEs, coronary events; BMI, body mass index; CHF, chronic heart failure; LVEF, left ventricular ejection fraction; LCA, left coronary artery; LAD, left anterior descending artery; GDF-15, growth differentiation factor 15; PAI-1, plasminogen activator inhibitor type 1; TAT, triple antithrombotic therapy; DAT, dual antithrombotic therapy; PCI, percutaneous coronary intervention; PPIs, proton pump inhibitors.

The independent predictors of CEs were GDF-15>1191 pg/mL (OR 4.70, 95% CI 1.32–16.81; p=0.0172), SYNTAX>26.5 (OR 4.5, 95% CI 1.45–13.69; p=0.0090), endovascular intervention for chronic coronary occlusion (OR 3.21, 95% CI 1.10–9.33; p=0.0326). Predictive power of the multivariate hazard model: χ^2=16.61; p=0.0009.

Discussion

The aim of the study was to find predictors of cardiovascular and hemorrhagic complications in patients with CAD and AF receiving MAT after the scheduled PCI.

Patients in need of MAT are highly comorbid. They are at a high risk of stroke, systemic embolism (CHA_2DS_2 VASc 5 [4; 6]), and bleeding (HAS-BLED 3 [3; 4]). They also have many comorbidities (Charlson index 7 [5; 9]). CAD requiring PCI leads to increased risks, including risks of CEs. In our study, the median follow-up period was 12 [8.0; 12.0] months. CVCs were reported in 16.4% of patients during this time. The median TAT duration was 61 [31; 153] days. TAT median duration before the first massive or clinically significant hemorrhage was 31 [17; 150] days. The incidence of massive and clinically significant bleedings (26.1%) was even higher than that of CVCs. Massive

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ВКЛЮЧЕН В ЖНВЛП[2] И ОНЛС[3]

КРАТКАЯ ИНСТРУКЦИЯ ПО МЕДИЦИНСКОМУ ПРИМЕНЕНИЮ ЛЕКАРСТВЕННОГО ПРЕПАРАТА ФОРСИГА®; РЕГИСТРАЦИОННЫЙ НОМЕР: ЛП-002596 **ТОРГОВОЕ НАЗВАНИЕ:** ФОРСИГА (FORXIGA)®. **МЕЖДУНАРОДНОЕ НЕПАТЕНТОВАННОЕ НАЗВАНИЕ:** ДАПАГЛИФЛОЗИН. **ЛЕКАРСТВЕННАЯ ФОРМА:** таблетки, покрытые плёночной оболочкой. **ПОКАЗАНИЯ К ПРИМЕНЕНИЮ: САХАРНЫЙ ДИАБЕТ 2 ТИПА** у взрослых пациентов в дополнение к диете и физическим упражнениям для улучшения гликемического контроля в качестве: монотерапии, когда применение метформина невозможно ввиду непереносимости; комбинированной терапии с метформином, производными сульфонилмочевины (в том числе, в комбинации с метформином), тиазолидиндионами, ингибиторами дипептидилпептидазы 4 (ДПП-4) (в том числе, в комбинации с метформином); агонистом рецепторов глюкагоноподобного полипептида-1 (ГПП-1) эксенатидом пролонгированного действия в комбинации с метформином; препаратами инсулина (в том числе, в комбинации с одним или двумя гипогликемическими препаратами для перорального применения) при отсутствии адекватного гликемического контроля на данной терапии; стартовой комбинированной терапии с метформином, при целесообразности данной терапии. Сахарный диабет 2 типа у взрослых пациентов с установленным диагнозом сердечно-сосудистого заболевания или двумя и более факторами сердечно-сосудистого риска (возраст у мужчин ≥ 55 лет или ≥ 60 лет у женщин и наличие не менее одного фактора риска: дислипидемия, артериальная гипертензия, курение) для снижения риска госпитализации по поводу сердечной недостаточности. **СЕРДЕЧНАЯ НЕДОСТАТОЧНОСТЬ (II-IV функциональный класс по классификации NYHA) со сниженной фракцией выброса у взрослых пациентов для снижения риска сердечно-сосудистой смерти и госпитализации по поводу сердечной недостаточности. ПРОТИВОПОКАЗАНИЯ:** повышенная индивидуальная чувствительность к любому компоненту препарата; сахарный диабет 1-го типа; диабетический кетоацидоз; нарушение функции почек при расчетной СКФ (рСКФ) стабильно менее 45 мл/мин/1,73 м², включая нарушение функции почек тяжелой степени и терминальную стадию почечной недостаточности, при применении по показанию «сахарный диабет 2 типа»; нарушение функции почек тяжелой степени и терминальная стадия почечной недостаточности (рСКФ < 30 мл/мин/1,73 м²), при применении по показанию «сердечная недостаточность» (в связи с ограниченным опытом применения в клинических исследованиях); наследственная непереносимость лактозы, дефицит лактазы или глюкозо-галактозная мальабсорбция; беременность и период грудного вскармливания; детский возраст до 18 лет (безопасность и эффективность не изучены). **С ОСТОРОЖНОСТЬЮ:** печеночная недостаточность тяжелой степени, инфекции мочевыделительной системы, повышенное значение гематокрита. **ПРИМЕНЕНИЕ В ПЕРИОД БЕРЕМЕННОСТИ И ГРУДНОГО ВСКАРМЛИВАНИЯ** В связи с тем, что применение дапаглифлозина в период беременности не изучено, препарат противопоказан в период беременности. В случае диагностирования беременности терапия дапаглифлозином должна быть прекращена. Неизвестно, проникает ли дапаглифлозин и/или его неактивные метаболиты в грудное молоко. Нельзя исключить риск для новорожденных/младенцев. Дапаглифлозин противопоказан в период грудного вскармливания. **СПОСОБ ПРИМЕНЕНИЯ И ДОЗЫ:** Внутрь, независимо от приёма пищи, не разжевывая. Сахарный диабет 2 типа. Монотерапия: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки. Комбинированная терапия: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки в комбинации с метформином, производными сульфонилмочевины (в том числе, в комбинации с метформином), тиазолидиндионами, ингибиторами ДПП-4 (в том числе, в комбинации с метформином); агонистом рецепторов ГПП-1 – эксенатидом пролонгированного действия, в комбинации с метформином; препаратами инсулина (в том числе, в комбинации с одним или двумя гипогликемическими препаратами для перорального применения). С целью снижения риска гипогликемии при совместном назначении препарата Форсига с препаратами инсулина или препаратами, повышающими секрецию инсулина (например, с производным сульфонилмочевины), может потребоваться снижение дозы препаратов инсулина или препаратов, повышающих секрецию инсулина. Стартовая комбинированная терапия с метформином: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки, доза метформина – 500 мг один раз в сутки. В случае неадекватного гликемического контроля дозу метформина следует увеличить. СД2 у взрослых пациентов с установленным диагнозом сердечно-сосудистого заболевания или двумя и более факторами сердечно-сосудистого риска для снижения риска госпитализации по поводу сердечной недостаточности: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки. **Сердечная недостаточность: рекомендуемая доза препарата Форсига составляет 10 мг один раз в сутки. ПОБОЧНОЕ ДЕЙСТВИЕ.** Краткий обзор профиля безопасности. В клинических исследованиях СД2 более 15000 пациентов получали терапию дапаглифлозином. Первичная оценка безопасности и переносимости проводилась в заранее запланированном анализе объединенных данных 13 краткосрочных (до 24 недель) плацебо-контролируемых исследований, в которых 2360 пациентов принимали дапаглифлозин в дозе 10 мг и 2295 пациентов получали плацебо. В исследовании дапаглифлозина в отношении сердечно-сосудистых исходов при СД2 (DECLARE) 8574 пациента получали дапаглифлозин 10 мг и 8569 получали плацебо (медиана воздействия 48 месяцев). В общей сложности экспозиция дапаглифлозина составила 30623 пациенто-лет. В исследовании дапаглифлозина в отношении сердечно-сосудистых исходов у пациентов с сердечной недостаточностью со сниженной фракцией выброса (DAPA-HF) 2368 пациентов получали дапаглифлозин 10 мг и 2368 получали плацебо (медиана воздействия 18 месяцев). Популяция включала пациентов с СД2 и без него, и пациентов с рСКФ ≥ 30 мл/мин/1,73 м². Профиль безопасности дапаглифлозина в исследованиях был в целом схожим по изучаемым показаниям. Тяжелую гипогликемию и диабетический кетоацидоз отмечали только у пациентов с сахарным диабетом. Ниже представлены НР, отмечавшиеся в плацебо-контролируемых клинических исследованиях и при пострегистрационном применении. Ни одна из них не зависела от дозы препарата. НР классифицированы по частоте и классу систем и органов. Частота НР представлена в виде следующей градации: очень часто (≥1/10), часто (≥1/100, <1/10), нечасто (≥1/1000, <1/100), редко (≥1/10000, <1/1000), очень редко (<1/10000) и неуточненной частоты (невозможно оценить по полученным данным). Инфекционные и паразитарные заболевания: часто – вульвовагинит, баланит и связанные с ними генитальные инфекции, инфекция мочевыводящих путей; нечасто – вульвовагинальный зуд, грибковые инфекционные заболевания; очень редко – некротизирующий фасциит промежности (гангрена Фурнье). Нарушения со стороны обмена веществ и питания: очень часто – гипогликемия (при применении в комбинации с производным сульфонилмочевины или инсулином); нечасто – снижение ОЦК, жажда; редко – диабетический кетоацидоз (при применении при СД2). Нарушения со стороны нервной системы: часто – головокружение. Нарушения со стороны желудочно-кишечного тракта: нечасто – запор, сухость во рту. Нарушения со стороны кожи и подкожных тканей: часто – сыпь; очень редко – ангионевротический отек. Нарушения со стороны костно-мышечной системы и соединительной ткани: часто – боль в спине. Нарушения со стороны почек и мочевыводящих путей: часто – дизурия, полиурия; нечасто – никтурия. Лабораторные и инструментальные данные: часто – дислипидемия, повышение значения гематокрита, снижение почечного клиренса креатинина на начальном этапе терапии; нечасто – повышение концентрации мочевины в крови, повышение концентрации креатинина в крови на начальном этапе терапии.

Ссылка на полную инструкцию: Инструкция по медицинскому применению лекарственного препарата Форсига ® (таблетки, покрытые пленочной оболочкой, 5 мг, 10 мг). Регистрационное удостоверение ЛП-002596 от 21.08.2014

ХСНнФВ – хроническая сердечная недостаточность со сниженной фракцией выброса; СС – сердечно-сосудистый; СН – сердечная недостаточность.
* Включая неотложные обращения по причине СН. # Снижение относительного риска сердечно-сосудистой смерти и смерти от всех причин в группе дапаглифлозина по сравнению с плацебо в исследовании DAPA HF.
1. Инструкция по медицинскому применению лекарственного препарата Форсига® (таблетки, покрытые пленочной оболочкой, 5 мг, 10 мг). Регистрационное удостоверение № ЛП 002596 от 21.08.2014.
2. Перечень жизненно необходимых и важнейших лекарственных препаратов для медицинского применения 3. Перечень лекарств для обеспечения отдельных категорий граждан. 4. McMurray JJV et al., N Engl J Med. 2019;381(21):1995–2008.

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and clinically significant gastrointestinal bleedings (upper and lower gastrointestinal tract) were the most commonly reported complications during MAT (consisting of three components in 86% of cases). This is consistent with large registers and our previous studies [2, 17–19].

There is no specialized score for assessing the risk of bleeding in patients on MAT. There are different scores for assessing the risk of bleeding in patients with a history of ACS and/or PCI. One of the latest is the PRECISE-DAPT score that combines five clinical and laboratory variables (age, creatinine clearance, hemoglobin and leukocyte levels, history of bleeding); it is designed to optimize the duration of DAT. PRECISE-DAPT has been validated in the cohort of patients with a history PCI who participated in the PLATO trial and those enrolled in the BernPCI registry [20].

One of the advantages of this score is that creatinine clearance is estimated as a continuous variable; something which allows mild to moderate CKD to be taken into account. Creatinine clearance is well-known to be associated with hemorrhagic complications [21–23]. The evaluation of kidney function is especially relevant during the use of DOACs given some degree of renal excretion (80% dabigatran, 35% rivaroxban, 25% apixaban). According to several small trials, the predictive power of PRECISE-DAPT was no less than that of HAD-BLED in patients with AF taking DAT or TAT [24, 25]. This is consistent with our findings. According to our data, the only independent predictor of massive and clinically significant bleeding was a PRECISE-DAPT score of more than 30.

The effects of GDF-15 on mortality and incidence of stroke in patients with AF have been studied in ARISTOTLE, RE-LY, ENGAGE AF-TIMI 48 studies [13, 14, 26, 27]. Increased levels of GDF-15 were found to be associated with the onset of IS and systemic embolism, as well as with the presence of a clot in the left atrial appendage and increased plasma euglobulin clot lysis time in patients with AF [14, 27–29]. However, GDF-15 was not predictive in the multivariate model which also included two other variables (NT-proBNP and troponin T) in the onset of stroke [14, 27]. Only seven strokes were reported in the patients examined during the follow-up period. This is why we did not assess the relationship between GDF-15 and the risk of stroke. However, we were able to determine the predictive power of GDF-15 >1191 pg/mL for the development of all CVCs and CEs in particular, consistent with [13] the predictive power of GDF-15, NT-proBNP, and troponin T for the mortality of patients with AF, included in the ARISTOTLE and RE-LY studies. It is also consistent with data on the relationship of cytokine GDF-15 with cardiovascular and all-cause mortality in patients with CAD [15].

PAI-1 of at least 13.2 U/mL was another variable predictive of CVCs. The findings of small trials and several meta-analyses show a relationship between the increased plasma levels of PAI-1 and CEs, death, diabetes mellitus, IS, and increased plasma euglobulin clot lysis time in patients with AF [30–34]. The power of PAI-1 to predict CVCs may reflect the atherothrombosis burden in our patients.

According to our data, the use of lower doses of DOACs in MAT was the third independent predictor of CVCs. As mentioned earlier, our study reflects clinical practice in the A. L. Myasnikov Institute of Cardiology. Thus, a DOAC and dosing were chosen at the physician's discretion. In our study, the unreasonable use of lower doses of DOACs observed in 50% of cases and biomarkers were independent predictors of all CVCs.

Our findings are consistent with registers and small trials which have shown that the rate of the off-label use in clinical practice of lower doses of DOACs is as high as 40% [35–43]. However, several trials [35, 42–44] and our study [1, 2] have shown that off-label doses of DOACs do not improve safety or reduce the efficacy of treatment by increasing the incidence of thrombotic complications. The apparent reason for using lower doses of DOACs is the physician's concern about possible bleeding, especially during MAT.

However, the risks of bleeding and ischemic complications in patients with AF are correlated [45]. This is shown by the fact that lower doses of DOACs are significantly associated with a high risk of VTE [1, 37, 40, 44]. Non-compliance with the dosing criteria with no anticoagulation control poses a risk of low anticoagulant levels in blood [46]. Thus, the unreasonable use of lower doses of DOACs to prevent cardioembolic strokes is not justified.

The choice of the correct dose of DOACs for MAT has been broadly discussed for some time. Until 2019, experts of various communities had recommended that DOACs as part of MAT should be prescribed in lower doses. It was first advised to use full doses of DOACs in patients with AS after PCI in the 2019 Guidelines of the European Society of Cardiology (ECS) [9].

In our study, TAT median duration before the first massive/clinically significant hemorrhage was 31 days. This is consistent with ESC expert opinion that TAT should be limited to 1 month in most patients with an acceptable risk of bleeding [4, 6, 8]. At the same time, the 2019 ECS Guidelines on Chronic Coronary Syndrome deem it possible to limit TAT to 1 week, in the case of

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uncomplicated PCI and a low risk of stent thrombosis [9]. However, the efficacy of such treatment in patients at high risk of thrombotic (coronary) complications is questionable. In the AUGUSTUS study, a clear trend towards an increased incidence of CEs was observed in patients who took ASA for six days or less after PCI [47]. According to expert opinion, the difference might have been more significant, if more patients were included in the study [48]. Thus, it is essential to identify patients at high risk of CEs. Experts defined numerous signs of high risk of CEs [7]. According to our data, three variables determine the risk of CEs in patients with AF who underwent the scheduled PCIs. It is currently unknown whether it is possible to modify GDF-15 which reflects stress-induced cytokine activation. The two other predictors (intervention for coronary occlusion and SYNTAX >26.5) reflect the state of the coronary system and do not support performing the PCI in patients with similar characteristics. However, if the PCI is performed in such patients, it should be single-stage, since staged PCIs negatively affects the prediction of CVCs, including as a result of the increased duration of TAT.

Our study was limited by a small number of observations and the efficacy endpoint combining cardiovascular death, IS, VTEs, ACS, and the need for urgent coronary revascularization.

Conclusion

In real-world clinical practice, patients with stable coronary artery disease and atrial fibrillation, who have undergone percutaneous coronary intervention and require multiple antithrombotic therapy, are characterized by high risks of stroke, bleeding, and multiple comorbidities. Half (49.3% in our study) of such patients receive unreasonably low doses of direct oral anticoagulants within multiple antithrombotic therapy. The median duration of triple antithrombotic therapy (direct oral anticoagulants + acetylsalicylic acid + clopidogrel) prior to the first massive or clinically significant hemorrhage is 31 days. The incidence of massive and clinically significant (predictive) bleeding during the one-year follow-up period is 26%, which exceeds the incidence of thrombosis-associated complications (16%). It has been shown that a total PRECISE-DAPT score of more than 30 is the factor associated with the risk of bleeding. Three new independent predictors of cardiovascular complications have been identified. These include: the use of lower doses of direct oral anticoagulants; the levels of growth differentiation factor 15 >1191 pg/mL; and the content of plasminogen activator inhibitor type 1 >13.2 U/mL. SYNTAX >26.5, percutaneous coronary intervention for chronic coronary occlusion, and growth differentiation factor 15 >1191 pg/mL are the independent predictors of coronary complications, including the need for urgent revascularization due to the development of the acute coronary syndrome and/or the exacerbation/recurrence of angina pectoris.

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