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Risk factors and outcomes of gastrointestinal bleeding in patients with stable coronary artery disease: data from the observational registry of long-term antithrombotic therapy REGATTA-1

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Aim. To optimize the upper gastrointestinal bleeding (UGIB) risk scale in patients with chronic coronary artery disease (CAD) receiving long-term antiplatelet therapy.

Material and methods. The UGIB risk scale was developed based on the prospective REGistry of long-term AnTithrombotic TherApy-1 REGATTA-1 (ClinicalTrials.gov Identifier: NCT04347200). The registry includes 934 patients with stable CAD (men, 78,6%; median age, 61±10,7 years), 76% of whom were included after elective percutaneous coronary interventions and received dual antiplatelet therapy for 6-12 months. After a UGIB episode, patients were prescribed proton pump inhibitors. The 2015 European Society of Cardiology (ESC) scale was used for assessing the UGIB risk. In addition, we evaluated the ultrasound data on atherosclerotic burden (abdominal aorta and peripheral arteries).

Results. The median follow-up was 2,5 years [1,1-14,7 years]. The incidence of UGIB was 1,9 cases per 100 patient/years. Recurrent UGIB episodes and thrombosis was recorded in 13,7% and 31,4%, respectively. Based on the results of a multivariate logistic regression, a novel scale for assessing the UGIB risk (REGATTA) has been developed. In accordance with the odds ratio, points were assigned for each independent risk factor (RF): age ≥80 years — 3 points, prior gastric erosion, peptic ulcer disease or UGIB — 3 points for each RF, anticoagulation therapy — 4 points, non-steroidal anti-inflammatory drug therapy — 2 points. The atherosclerotic burden (peripheral atherosclerosis and/or abdominal aortic aneurysm; 2 points) and heart failure (in most cases after a myocardial infarction; 2 points) were marked as a new independent predictor. The cutoff value (≥4 points) was determined, reflecting the high UGIB risk (sensitivity, 80,4%; specificity, 84,5%). The REGATTA scale was more powerful than the traditional 2015 ESC scale: AUC of 0,88, (95% confidence interval, 0,86-0,9) vs AUC of 0,79, (95% confidence interval, 0,76-0,82) (p=0,04).

Conclusion. The identified UGIB predictors (atherosclerotic burden and heart failure) and the developed REGATTA scale made it possible to improve the prognosis and prevention of UGIB in patients with stable CAD receiving long-term antiplatelet therapy.

Keywords: coronary artery disease, antiplatelet therapy, gastrointestinal bleeding, percutaneous coronary intervention, proton pump inhibitors, peripheral atherosclerosis.

Trial ID: ClinicalTrials NCT04347200.

Relationships and Activities: none.

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Upper gastrointestinal bleeding from the tract (UGIB) is one of the most common complications of antithrombotic therapy associated with high mortality [1]. Adequate score for assessing the bleeding risk in patients with coronary artery disease (CAD) would make it possible to select candidates for primary UGIB prevention (primarily by using proton pump inhibitors (PPIs)), to plan active monitoring of such patients (complete blood count, fecal occult blood test, esophagogastroduodenoscopy (EGD)). In addition, the high risk of UGIB may be the basis for a more careful choice of antithrombotic therapy.

There are two approaches to UGIB risk stratification in patients with CAD. The first one predicts the likelihood of any bleeding and takes into account general risk factors (RF) characterizing the severity of patient's condition as a whole (PRECISE-DAPT [2] and ARC-HBR [3] scores). The second approach [4] by the European Society of Gastrointestinal Endoscopy (2015), which was recommended for patients with CAD by the European Society of Cardiology (ESC), involves taking into account age and medications (steroids, non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants), as well as local RFs characterizing the mucous membrane. We assume that combining various RFs into a single model can enhance the prognostic value of known scores and allow careful predicting UGIB.

The aim was to optimize the UGIB risk scale in patients with chronic CAD receiving long-term antiplatelet therapy.

Material and methods

To create a UGIB risk scale and assess its predictive value, a cohort of patients with stable CAD was used, included in the single-center prospective register of long-term antithrombotic therapy REGATA [5], created on the basis of the National Medical Research Center of Cardiology (Figure 1). Within this study, patients included in the period from 2003 to 2019 was analyzed.

The study was performed in accordance with standards of Good Clinical Practice and Declaration of Helsinki. The study protocol was approved by the local ethics committee. All patients signed written informed consent.

Inclusion and exclusion criteria have been detailed in our previous publications [5]. Briefly, the study included patients with stable CAD (most of them after elective percutaneous coronary interventions (PCI)) who have no contraindications to standard antithrombotic therapy.

Study progress. In addition to the standard examination, screening for concomitant peripheral atherosclerosis was performed, including ankle-brachial index (ABI) test, Doppler ultrasound of extracranial arteries, abdominal aorta and its branches (and/or contrast-enhanced abdominal multislice computed tomography if indicated). In the presence of intermittent claudication and/or a decrease in ABI <0,9, lower limp artery ultrasound was performed. To define the "peripheral atherosclerosis", generally accepted criteria were used [4]. Attention was also paid to prior gastric erosions and ulcer, verified by EGD.

The scale recommended by ESC in 2015 was chosen for assessing the UGIB risk [4]. For all patients, the UGIB risk was stratified according to this scale, which, however, had a number of limitations. Thus, *H. pylori* infection was assessed by the decision of an attending physician. Due to insufficient data, this parameter was not included in further statistical processing. For the same reason, the presence of gastroesophageal reflux disease was not taken into account. Also, for a large number of patients, no reliable information was obtained regarding the alcohol consumption. Therefore, this symptom was also not analyzed.

The planned duration of prospective follow-up was more than 2 years. Follow-up visits were carried out 6 and 12 months after inclusion, then — every 12 months. If necessary, unscheduled visits were carried out due to CAD progression. Telephone contacts were made every 3 months.

End points. The primary endpoint was overt UGIB (verified by EGD or typical symptoms — melena, vomiting blood, or a combination thereof). Bleeding counts met BARC class 2-5.

The following adverse events were also recorded: death (with an indication of cause), myocardial infarction, unstable angina requiring hospitalization, ischemic stroke, transient ischemic attack, peripheral arterial thrombosis.

Medication therapy. All patients received standard treatment according to the current Russian Society of Cardiology and ESC guidelines on CAD and myocardial revascularization [4]. All patients were prescribed with aspirin 75-100 mg a day. After PCI, patients also received clopidogrel for 6-12 months. The adherence to treatment with antiplatelet agents, statins and other drugs that affect the cardiovascular prognosis was monitored. At the discretion of an attending physician, preventive therapy with PPIs was prescribed, appointment of which was assessed using medical records. Patients who underwent UGIB after being included in the registry were additionally observed by a gastroenterologist. Mandatory prescription of PPIs and assessing adherence to treatment was envisaged. If indicated, additional EGD and eradication therapy for *H. pylori* were performed.

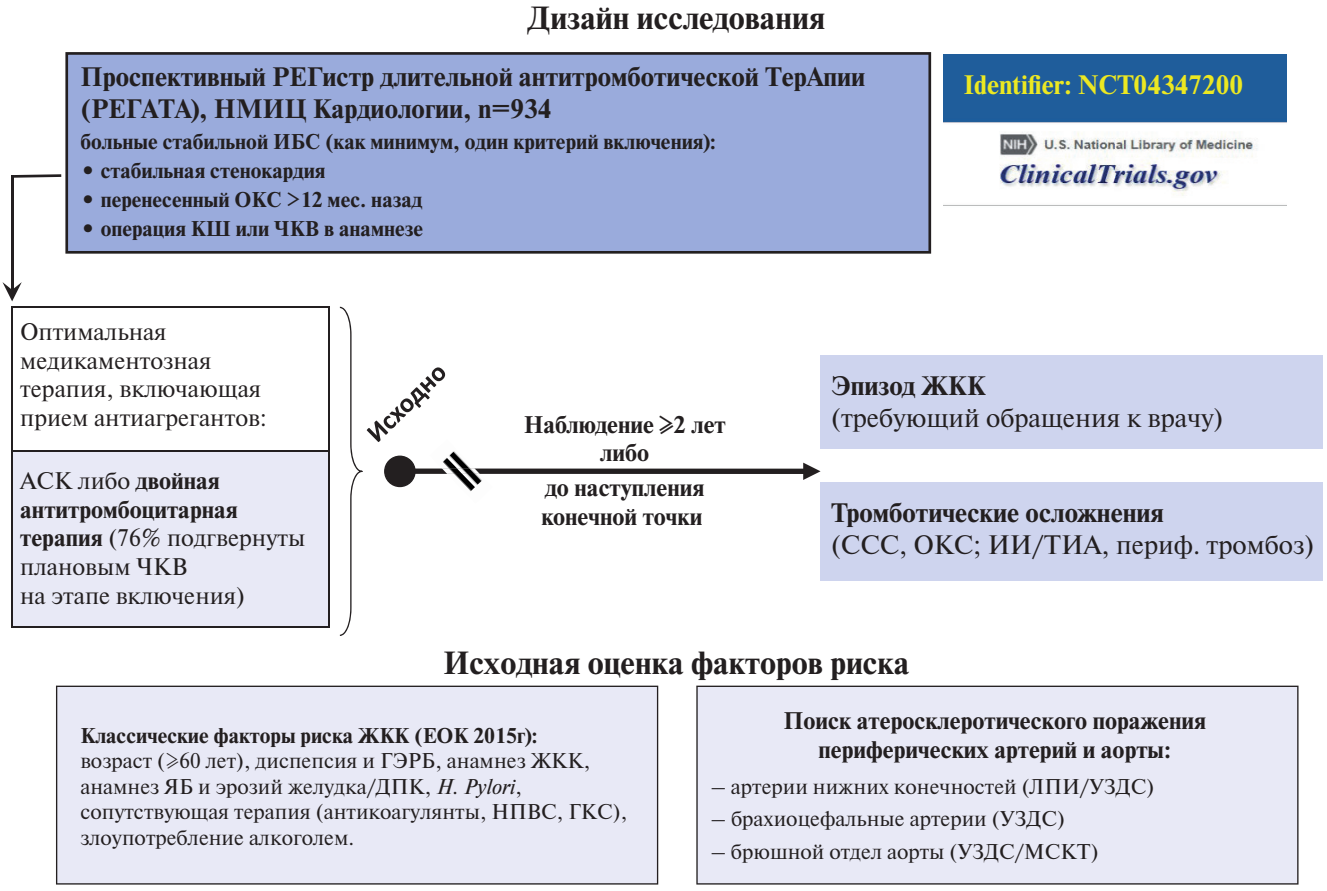


Figure 1. Study design.
Abbreviations: ASA — acetylsalicylic acid, GCSs — glucocorticosteroids, GERD — gastroesophageal reflux disease, ESC — European Society of Cardiology, UGIB — upper gastrointestinal bleeding, CAD — coronary artery disease, ABI — ankle-brachial index, MSCT — multislice computed tomography, NSAIDs — non-steroidal anti-inflammatory drugs, ACS — acute coronary syndrome, CVD — cardiovascular death, TIA — transient ischemic attack, PCI — percutaneous coronary intervention.

Statistical processing and risk scale development. Statistical processing was carried out using the Statistica 10.0, SPSS 20 and MedCalc 18.11 software packages. Univariate and multivariate regression was used to identify potential RFs of UGIB. Parameters with a significant odds ratio (OR) (95% confidence interval (CI) of which did not include one) were selected by multiple logistic regression model. Based on the OR values obtained in multiple logistic regression, the identified independent predictors of UGIB were assigned scores characterizing the contribution of each factor to the total bleeding risk. Taking into account the relatively small sample size and follow-up period, the characteristics of patients (for example, initially, patients receiving anticoagulants, NSAIDs, steroids were practically not included), number of assigned scores for RFs that are rare in our sample was adjusted in accordance with literature data covering more representative cohorts.

To assess the predictive value of scale, we used the ROC analysis with determining area under the curve (ROC curve). As a cutoff point for score determining the high UGIB risk, the value with closest sensitivity and specificity was chosen.

To assess the adequacy of cut-off point, the incidence of UGIB for subgroups of patients allocated in accordance with score was compared with the incidence of UGIB, which we theoretically calculated, which was considered as high. The calculation was based on the following data:

1) Academic Research Consortium experts proposed a cut-off point of 4% per year as a high-risk criterion for all major bleeding (BARC 3-5) after PCI [3];

2) among all such bleedings, the proportion of UGIB is ~60% [6],

3) among all gastrointestinal bleeding, more than half (64,4%) falls on the upper gastrointestinal tract [7].

Thus, the cutoff line of high risk for major UGIB is 4% × 0,6 × 0,64 = 1,536%.

This calculation takes into account only major bleeding. It is known that 3 cases of major gastrointestinal bleeding (BARC 3-5) account for 1 additional BARC 2 bleeding [8]. Due to the above, the cutoff point of high risk for major and clinically

Table 1

Prevalence of gastrointestinal bleeding RFs in patients with stable CAD, depending on bleeding within the follow-up period

Total, n (%)	All patients, n=934	Patients with gastrointestinal bleeding within follow-up, n=51	Patients without gastrointestinal bleeding within follow-up, n=883	P_{1-2}
Sex				
Male	723 (78,6%)	42 (78,1%)	681 (77,9%)	0,386
Female	211 (21,4%)	9 (21,9%)	202 (22,5%)	
Age				
<70 years	762 (81,6%)	32 (58,8%)	730 (82,7%)	<0,001
70-79 years	152 (16,3%)	12 (23,5%)	140 (15,9%)	0,149
⩾80 years	20 (2,1%)	7 (13,7%)	13 (1,5%)	<0,001
Clinical risk factors:				
• BMI >30 kg/m^2	544 (58,2%)	36 (70,6%)	375 (57,5%)	0,073
• Diabetes	190 (20,3%)	11 (21,6%)	179 (20,3%)	0,823
• Stage ⩾3a chronic kidney disease	97 (10,4%)	12 (23,5%)	85 (9,6%)	0,002
• Prior MI	538 (57,6%)	29 (56,9%)	509 (57,6%)	0,701
• PCI within 12 months prior to inclusion	707 (75,7%)	25 (49,0%)	682 (60,2%)	<0,001
• HF*	73 (7,8%)	17 (33,3%)	56 (6,3%)	<0,001
• Prior ischemic stroke + TIA	72 (7,7%)	5 (9,8%)	67 (7,6%)	0,564
• Peripheral arterial atherosclerosis	176 (18,8%)	18 (35,3%)	158 (17,9%)	0,012
• Abdominal aortic aneurysm	22 (2,4%)	10 (19,6%)	12 (1,4%)	<0,001
Condition of the upper gastrointestinal tract:				
• Prior mucosal erosion	238 (25,5%)	29 (56,9%)	209 (23,7%)	<0,001
• Prior mucosal ulcer	164 (17,6%)	23 (45,1%)	141 (16,0%)	<0,001
• Erosion exacerbation after PCI	138 (14,8%)	11 (21,6%)	127 (14,4%)	0,162
• Prior gastrointestinal bleeding	6 (0,64%)	6 (11,8%)	0	<0,001
Drug therapy:				
• NSAIDs	4 (0,43%)	4 (7,8%)	0	<0,001
• Anticoagulation (dual or triple therapy)	48 (5,1%)	12 (23,5%)	36 (4,1%)	<0,001
• PPIs	264 (28,3%)	51 (100%)	213 (54,1%)	<0,001

Note: * — in 90% of patients with HF developed after MI.

Abbreviations: MI — myocardial infarction, BMI — body mass index, PPIs — proton pump inhibitors, NSAIDs — non-steroidal anti-inflammatory drugs, TIA — transient ischemic attack, HF — heart failure, PCI — percutaneous coronary intervention.

relevant UGIB was increased by a third and amounted to 2,06%. Thus, >2 events per 100 people per year was chosen as a criterion for the high UGIB risk (BARC 2-5).

Comparison of the predictive value of developed scale with 2015 ESC scale [4] was carried out by comparing the corresponding areas under the ROC curves.

Differences were considered significant at p<0,05.

Results

Initial characteristics of patients. In total, the study included 934 patients with stable CAD (median age, 61 years [53-68 years]; men, 78,6%) (Table 1). At the enrollment, 687 patients (76%) underwent elective PCI, and therefore received dual antiplatelet therapy (DAPT) for 6-12 months. We have described in detail the clinical and demographic characteristics of patients, classical UGIB RFs, the prevalence of peripheral atherosclerosis and abdominal aortic aneurysm in the studied cohort previously [5].

Upper gastrointestinal bleeding. The median follow-up was 2,5 years [1,1-14,7 years]. Major and clinically relevant UGIB (BARC ⩾2) was recorded with a frequency of 1,9 cases per 100 people per year (Figure 2). It should be emphasized that most of UGIB occurred in the first 2 months from treatment initiation (median duration before UGIB development was 71 days [13-212]). Most of the bleeding (62,8%) was verified by EGD; the rest were diagnosed retrospectively by typical clinical picture.

Table 2

Gastrointestinal bleeding risk assessment scale REGATA: RFs and their relative contribution to gastrointestinal bleeding risk

Risk factors	Score	OR [95% CI]	p
Age:			
— 70-79 years old	1*	1,2 [0,5-2,9]	0,616
— ⩾80 years old	3	4,8 [1,2-18,7]	0,024
Abdominal aortic aneurysm and/or peripheral atherosclerosis	2	3,4 [1,7-6,9]	0,0005
Heart failure	2	4,4 [1,9-10,3]	0,0007
Prior gastric/duodenal erosion	3	5,6 [2,7-11,3]	0,000002
Prior gastric/duodenal ulcer	3	4,9 [2,4-10,1]	0,00002
Prior gastrointestinal bleeding	3*	2,2 [1,5-35,7]	<0,0001
NSAIDs	3	8,16 [3,4-124,7]	<0,0001
Anticoagulant therapy (including in combination with antiplatelet agents)	4	164,8 [15,5-1755,6]	0,00002

Notes: * — assigned score is corrected in accordance with literature data. Risk factors that are absent in the 2015 ESC scale are marked in color.

Abbreviations: CI — confidence interval, NSAIDs — non-steroidal anti-inflammatory drugs, OR — odds ratio.

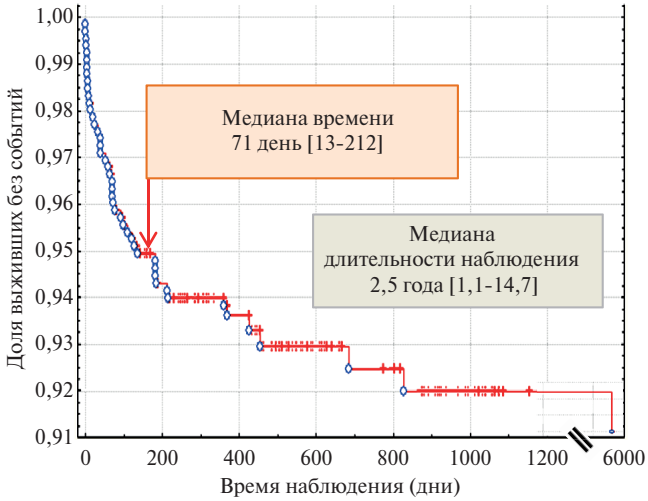
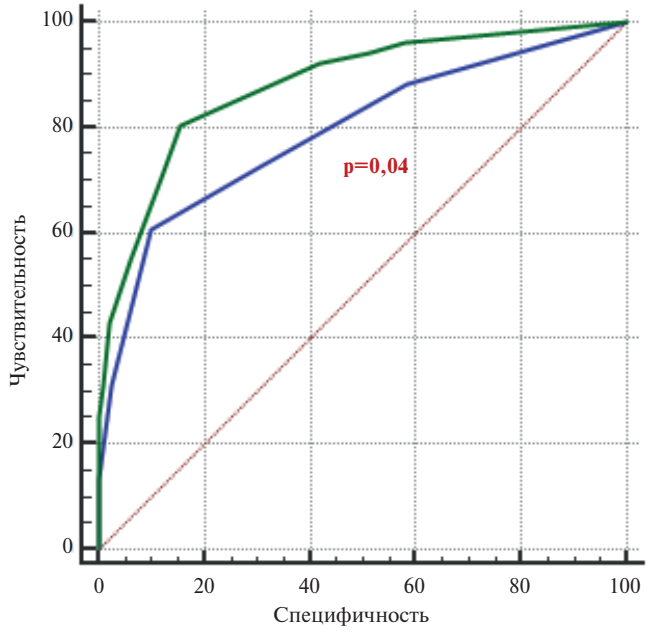


Figure 2. Cumulative incidence of upper gastrointestinal bleeding in patients with stable CAD (Kaplan-Meier curve).

All patients with further gastrointestinal bleeding have information in their medical records about PPI appointment, but adherence to therapy is not known. After an episode of bleeding, the patients were followed up by a gastroenterologist. A set of measures was carried out aimed at the secondary gastrointestinal bleeding prevention, including long-term PPI therapy and correction of modifiable RFs (withdrawal of NSAIDs, alcohol, eradication of *H. pylori* if indicated, etc.). Against the background of such events, the incidence of recurrent gastrointestinal bleeding was only 13,7%.

To identify gastrointestinal bleeding predictors, in addition to conventional RFs, other indicators were analyzed, reflecting renal function, atherothrombosis, prior vascular events and heart failure



	Отрезное значение	Чувствительность	Специфичность
Шкала ЕОК 2015г	⩾2 баллов	72,6%	69,3%
Шкала Регата	⩾4 баллов	80,4%	84,5%

Figure 3. Comparison of the predictive value of gastrointestinal bleeding risk scales REGATA and 2015 ESC using ROC analysis.
Abbreviations: CI — Confidence Interval, ESC — European Society of Cardiology.

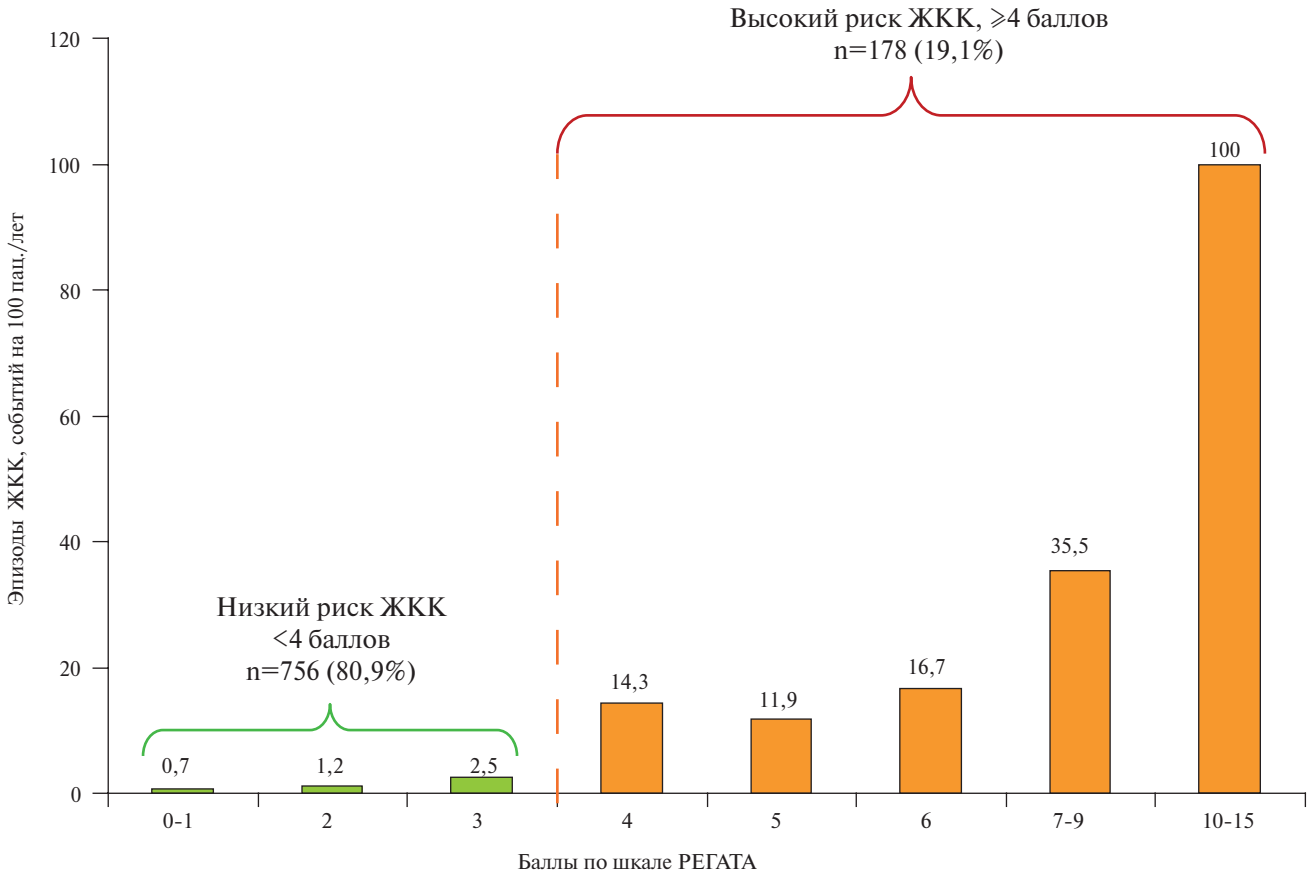


Figure 4. Gastrointestinal bleeding rate depending on score on the REGATA scale.
Abbreviation: UGIB — upper gastrointestinal bleeding.

as the final stage of cardiovascular continuum (Table 1). We have identified a symptom that most fully reflects the atherosclerosis extent — presence of peripheral atherosclerosis and/or abdominal aortic aneurysm. Age as one of the leading RFs of gastrointestinal bleeding was analyzed by groups (<70 years old, 70-79 years old, and ⩾80 years old); the criteria for dividing patients into groups by age were borrowed from large-scale observational studies carried out in 2017-2019 [1, 9]). Since dyspepsia as a term does not have clear criteria, and EGD confirmation of gastroesophageal reflux disease in actual clinical practice is often difficult, these RFs were not taken into account in further analysis.

According to multivariate analysis (Table 2), the already known factors were independent UGIB predictors in our cohort of patients with stable CAD: history of peptic ulcer disease or upper gastrointestinal erosions, age over 80 years, prior gastrointestinal bleeding, as well as NSAID and anticoagulant therapy. We also found that the risk of gastrointestinal bleeding increased in patients with advanced atherosclerosis (peripheral atherosclerosis and/or abdominal aortic aneurysm), as well as in patients with heart failure.

Risk stratification scale for UGIB in patients with stable CAD REGATA. Based on the results obtained, we have developed a novel risk stratification scale for UGIB in patients with stable CAD — REGATA (Table 2). Based on the OR values obtained by multivariate analysis, each of the RFs we found was assigned a certain score: factors with OR <1,5 were assigned 1 point, 1,5⩽ OR <4,5 — 2 points, 4,5⩽ OR <10 — 3 points, ⩾10 — 4 points. For signs that are rare in these patients (prior gastrointestinal bleeding), as well as for the age of 70-79 years, the score was adjusted in accordance with literature data (first of all, we relied on similar indicators in the 2015 ESC scale [5]).

We compared the predictive value of REGATA and 2015 ESC scales (Figure 3). It was found that the area under the curve (ROC AUC) for REGATA scale was larger than in 2015 ESC scale. The ROC AUC was 0,88 (95% CI, 0,86-0,9) and 0,79 (95% CI, 0,76-0,82), respectively (p=0,04). For REGATA scale, the optimal cut-off point, which determines the high bleeding risk, was a score of 4. With such a cut-off point, the sensitivity and specificity were 80,4% and 84,5%, respectively.

All patients were divided into 8 groups in accordance with score on the REGATA scale. For

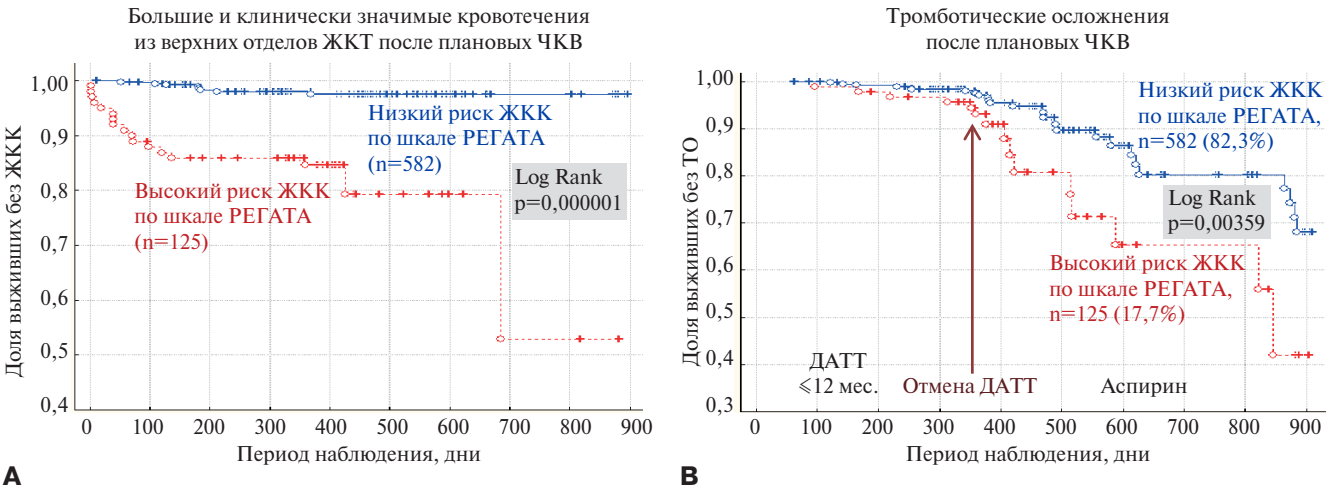


Figure 5. Survival without upper gastrointestinal bleeding (**A**) and thrombotic events (**B**) in the high and low risk groups according to the REGATA scale (Kaplan-Meier curves).
Abbreviations: DAPT — dual antiplatelet therapy, UGIB — bleeding from the upper gastrointestinal tract, TE — thrombotic events, PCI — percutaneous coronary intervention.

each group, the incidence of gastrointestinal bleeding was estimated (Figure 4). The incidence of gastrointestinal bleeding in patients with score of 3 (highest score in the low-risk category) was 2,5 cases per 100 patients per year. This indicator was very close to the theoretically calculated value of 2% per year, which is an additional criterion for the high predictive value of the scale we developed. In 19,1% of patients, the risk of gastrointestinal bleeding was defined as high on the REGATA scale.

Logistic regression showed that the incidence of gastrointestinal bleeding in the subgroup of patients with high REGATA risk (⩾4) was significantly higher than in patients with low risk (1-3): 23% vs 1,3% (p=0,000001).

Predictive value of the REGATA scale in patients after elective PCI. Three quarters of patients at the inclusion stage received DAPT after elective PCI. We analyzed the outcomes in this subgroup separately.

The REGATA scale demonstrated good predictive value of gastrointestinal bleeding in this subgroup of patients as well (Figure 5 A). In addition, patients with a high gastrointestinal bleeding risk were also characterized by a high risk of thrombotic events (TEs) (Figure 5 B). At the same time, the incidence of TEs for the entire follow-up period was higher than gastrointestinal bleeding. It is important that the divergence of survival curves without TEs began at the start of second year after PCI — after the planned cancellation of DAPT.

Prognosis of CAD patients who underwent gastrointestinal bleeding during prospective follow-up. The analysis of outcomes in patients after gastrointestinal bleeding showed that the incidence of recurrent bleeding in this subgroup was 13,7%, while the incidence of TEs in them was twice as high — 31,4%.

The likely reason for the increase in TEs after gastrointestinal bleeding was the complete cancellation or decrease in the intensity of antiplatelet therapy. Among 51 patients who underwent gastrointestinal bleeding, 7 died in the next week, 5 died within a year from causes not related to thrombosis and bleeding, 39 patients survived after the first bleeding episode. Antiplatelet therapy was resumed in full by 30 people, and 9 patients reduced or completely canceled antiplatelet agents. It should be emphasized that among 9 people who reduced or canceled antiplatelet drugs, the frequency of thrombotic events subsequently was almost 2 times higher — 55,6% vs 26,7% in those who continued antiplatelet therapy. However, the small sample size did not allow us to assess the reliability of revealed differences.

Discussion

Gastrointestinal bleeding occupies a leading position in pattern of hemorrhagic events in patients receiving antiplatelet drugs. The prognosis of patients with various manifestations of atherothrombosis after such bleeding is considered unfavorable: 1-year mortality after any clinically relevant episode of gastrointestinal bleeding is 20-25% [1, 5].

The existing approach to assessing the likelihood of gastrointestinal bleeding is based solely on the opinion of experts who have combined the generally recognized RFs [4] into a common scale that has not undergone any validation. The high risk of gastrointestinal bleeding, determined in accordance with this scale, is a formal indication for PPI ap-

pointment. Nevertheless, it has not yet been possible to convincingly demonstrate the feasibility of this method of prevention. All of the above determines the need for well-organized observational studies and registers aimed both at assessing the predictive value of this scale and at finding new RFs. In our work, we chose just such an approach, which made it possible to integrate already known and new factors into a unified prognostic model.

The stratification was changed in relation to one of the key RFs, which is age. According to our data, the previously accepted division of patients into groups over and under 65 years of age is not optimal: a significant increase in gastrointestinal bleeding risk was noted in older people (Table 2), which was logically reflected in REGATA scale. A similar change in risk stratification with an emphasis on older age groups has been proposed in recent years by other authors [1, 6].

There were certain limitations that did not allow adequately validating the gastrointestinal bleeding risk scale proposed by the ESC in 2015 in relation to patients from the REGATA register. Our cohort of patients was characterized by a relatively low rate of using NSAIDs and anticoagulants. In addition, the register did not include persons who required corticosteroid therapy. It was also difficult to qualify the alcohol abuse. Routine screening for reflux disease and *H. pylori* infection has not been performed.

Another problem was recording the dyspepsia symptoms. There are no clear criteria for dyspepsia, which determines the well-known subjectivity when calculating gastrointestinal bleeding risk score. We, in turn, drew attention to another, more objective criterion associated with certain dyspepsia symptoms, namely, with gastrointestinal erosions. It is known that such a lesion is characteristic of *H. pylori* infection [10], which logically explains the significance of detected RF in relation to bleeding.

The presence of erosion may indicate impaired reparative processes, including due to gastrointestinal mucosa ischemia. In this regard, it seems logical to emphasize the importance of the discovered RFs characterizing the atherothrombosis burden, namely, the involvement of peripheral arteries and abdominal aorta, as well as heart failure, which developed in most cases after MI (Table 1). The relationship between widespread atherosclerotic lesions and the development of gastrointestinal bleeding has been demonstrated by other authors [11]. For obvious reasons, no work analyzed the state of arteries directly supplying the upper gastrointestinal tract. Nevertheless, given the systemic nature of atherothrombotic process, it is logical to assume ischemia in this vascular system, both due to anatomical flow obstruction and due to distal embolism by damaged plaques and thrombi, the source of which is most likely the abdominal aorta.

Taking into account novel RFs, reflecting the prevalence and severity of atherothrombotic process, allowed us to improve the prognosis of gastrointestinal bleeding. The sensitivity and specificity of REGATA scale developed by us was significantly higher than the ESC risk score.

Thrombosis and bleeding RFs are closely related [12]. One of these common RFs was atherothrombosis burden, which determines the need for long-term therapy, optimally including a second antithrombotic agent in addition to aspirin [13].

We have previously shown [5] that the outcomes of patients after gastrointestinal bleeding are determined by the high TE rate, while the incidence of recurrent bleeding was significantly less. An analysis of a cohort of patients undergoing elective PCI and receiving initial therapy with two antiplatelet agents (Figure 5) demonstrated an increase in TE rate in the group with a high risk of gastrointestinal bleeding, which corresponded to the timing of DAPT withdrawal. Thus, our results suggest that net clinical benefit in these patients is determined by the risk of thrombosis rather than bleeding. The data obtained in large-scale registers [12] also indicate that in most patients with many RFs of TEs, the risk of cardiovascular events significantly exceeds the likelihood of bleeding. From all of the above, an important practical conclusion follows that the bleeding risk is not a reason for routine withdrawal of antithrombotic therapy, which is prescribed due to high risk of ischemic events.

This provision may apply to the most vulnerable category of patients — those with prior gastrointestinal bleeding. There is reason to believe that treatment (at least one antiplatelet agent) is preferable to maintain, if there is adequate endoscopic hemostasis [14]. Our research has also demonstrated the benefits of this approach. Taking into account all the possible limitations associated with the small number of groups, the lack of data on factors influencing the choice of antithrombotic drugs by physicians, etc., it should be stated that TE rate is lower in the case of resuming the previous antiplatelet therapy a week after gastrointestinal bleeding.

The safety of antithrombotic therapy can be maintained only if there is an active search and correction of all modifiable factors that increase the bleeding risk, as well as preventive administration of PPIs. Compliance with these rules allowed us to ensure low recurrence rate in patients with bleeding. The specifics of observational study did not allow us to carry out the same measures in all patients included in registry.

An active search for a potential source of bleeding could be discussed as an additional preventive measure. We showed that the largest number of gastrointestinal bleeding developed in the coming months from the initiation/intensification of treatment. Antithrombotic therapy is a kind of stress test that reveals the silent initial pathology of the gastrointestinal mucosa [15]. Thus, it is prudent to provide for endoscopic screening or, at least, fecal occult blood test, if there are any concerns about the safety of prescribed therapy.

Conclusion

As a result, we discovered novel predictors and developed a scale for assessing the gastrointestinal bleeding risk in patients with CAD receiving long-term antiplatelet therapy. The relationship with gastrointestinal bleeding was demonstrated for RFs characterizing the atherothrombosis burden, namely, peripheral artery and abdominal aorta involvement, as well as heart failure due to myocardial infarction. A high risk of gastrointestinal bleeding should not be a routine reason for refusal from antithrombotic therapy. The proposed modification is designed to facilitate the implementation of measures (PPI prescription, EGD screening, *H. pylori* eradication) aimed at preventing gastrointestinal bleeding in patients with various clinical manifestations of atherothrombosis.

Relationships and Activities: none.

References

1. Sehested TSG, Carlson N, Hansen PW, et al. Reduced risk of gastrointestinal bleeding associated with proton pump inhibitor therapy in patients treated with dual antiplatelet therapy after myocardial infarction. European Heart Journal. 2019;40(24):1963-70. doi:10.1093/eurheartj/ehz104.
2. Costa F, van Klaveren D, James S, et al. PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017;389:1025-34. doi:10.1016/S0140-6736(17)30397-5.
3. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. Eur Heart J. 2019;40(31):2632-53. doi:10.1093/eurheartj/ehz372.
4. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European Heart Journal. 2016;37(3):267-315. doi:10.1093/eurheartj/ehv320.
5. Shakhmatova OO, Komarov AL, Korobkova VV, et al. Upper gastrointestinal bleeding in patients with stable coronary artery disease (registry of antithrombotic therapy "REGATTA" results). Terapevticheskii arkhiv. 2020;92(9):30-8. (In Russ.) doi:10.26442/00403660.2020.09.000699.
6. Généreux P, Giustino G, Witzenbichler B, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. J Am Coll Cardiol. 2015;66(9):1036-45. doi:10.1016/j.jacc.2015.06.1323.
7. Shaukat A, Waheed S, Alexander E, et al. Etiology of gastrointestinal bleeding in patients on dual antiplatelet therapy. J Dig Dis. 2018;19:66-73. doi:10.1111/1751-2980.12575.
8. Koskinas KC, Räber L, Zanchin T, et al. Clinical impact of gastrointestinal bleeding in patients undergoing percutaneous coronary interventions. Circ Cardiovasc Interv. 2015;8(5):e002053. doi:10.1161/CIRCINTERVENTIONS.114.002053.
9. Jensen BES, Hansen JM, Larsen KS, et al. Randomized clinical trial: the impact of gastrointestinal gastrointestinal risk factor screening and prophylactic proton pump inhibitor therapy in patients receiving dual antiplatelet therapy. Eur J Gastroenterol Hepatol. 2017;29(10):1118-25. doi:10.1097/meg.0000000000000934.
10. Crowe SE. Helicobacter pylori Infection. N Engl J Med. 2019;380(12):1158-65. doi:10.1056/NEJMcp1710945.
11. Jolobe OMP. The Association of Peptic Ulcer Disease and Abdominal Aortic Aneurysm. The American Journal of Medicine. 2019;132(9):e724. doi:10.1016/j.amjmed.2019.03.047.
12. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295(2):180-9. doi:10.1001/jama.295.2.180.
13. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal. 2020;41(3):407-77. doi:10.1093/eurheartj/ehz425.
14. Sung JJ, Lau JY, Ching JY, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann Intern Med. 2010;152(1):1-9. doi:10.7326/0003-4819-152-1-201001050-00179.
15. Clemens A, Strack A, Noack H, et al. Anticoagulant-related gastrointestinal bleeding–could this facilitate early detection of benign or malignant gastrointestinal lesions? Annals of Medicine. 2014;46:672-8. doi:10.3109/07853890.2014.952327.