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The effect of rivaroxaban low doses on the stable angina of the II–III functional class clinical manifestations and the quality of life in patients with ischemic heart disease

Aim	To evaluate the effect of low-dose rivaroxaban on quality of life of patients and clinical manifestations of functional class (FC) II–III stable angina.
Material and methods	26 patients with ischemic heart disease (IHD) with FC II–III stable angina, who were newly prescribed rivaroxaban 2.5 mg twice a day in combination with acetylsalicylic acid 75–100 mg, were followed for 10 weeks. During the first (before the beginning of treatment) and the last weeks of study, patients kept diaries, in which they reported angina attacks and short-acting nitrate intake, filled in an angina questionnaire (SAQ), and underwent electrocardiogram (ECG) Holter monitoring (HM).
Results	The treatment was associated with decreases in the frequency of angina attacks (by 19.5%; p=0.027) and the number of taken short-acting nitrate pills (by 17.1%; p=0.021) and an improvement of quality of life according to stability scales (p=0.042). Data from ECG HM showed decreases in the number and duration of ischemic episodes (p≤0.05).
Conclusion	The treatment of IHD patients with rivaroxaban 2.5 mg twice a day in combination with acetylsalicylic acid 75–100 mg for 2 mos. was associated with decreased frequency of angina attacks, reduced requirement for short-acting nitrate, and with improvement of quality of life.

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Stable exertional angina is a common form of chronic coronary artery disease (CAD) associated with an increased risk of cardiovascular complications (mainly thrombosis) and death [1–3]. The prevention of acute cardiovascular events is thus the first and foremost task of treatment. Platelet aggregation inhibitors are commonly used for this purpose, especially acetylsalicylic acid (ASA) in combination with a second antiplatelet agent.

One recent noteworthy advance in cardiology is a new approach to antithrombotic therapy in which ASA is combined with low-dose Xa inhibitor rivaroxaban. The high therapeutic potential of this combination has been proven in large trials [4–6] and is captured by international and national guidelines [1, 2].

The results of the COMPASS trial [4] are especially illustrative. Combination therapy provided a 23% decrease in mortality and a 26% decrease in the risk of severe cardiovascular events, with a slight increase in the prevalence of bleeding (mostly mild and relatively rare, since the incidence of hemorrhagic complications is significantly lower than the incidence of ischemic complications).

As well as improving the prognosis, the second most important objective in treating patients with stable angina pectoris is to improve quality of life (QoL). This is difficult without relieving anginal pain and reducing the frequency and severity of attacks.

Rivaroxaban influences blood circulation through various mechanisms. In addition to inhibiting thrombin, anti-inflammatory, vascular, and antiplatelet effects were also established [7, 8]. This can potentially improve not only the prognosis but also patients' QoL. At the same time, the effects of small-dose rivaroxaban on the clinical manifestations of CAD were not sufficiently studied.

Aim

To assess the effect of low-dose rivaroxaban on patients' QoL and clinical manifestations of stable angina pectoris functional class (FC) II–III.

Material and Methods

An open-label prospective 10-week study including 26 patients with CAD and stable angina pectoris FC II–III were performed.

In week 1 of the study (control period), patients with CAD, stable angina pectoris FC II–III with indications for ASA in combination with low-dose rivaroxaban were included and signed the informed consent. According to the current clinical guidelines, those were individuals at high risk of thrombotic complications and low risk of bleeding [2]. For one week, each subject received his/her standard therapy and:

1) kept a self-monitoring diary to record angina attacks and the use of short-acting nitrates;
2) underwent Holter monitoring electrocardiogram (ECG);
3) completed a Seattle Angina Questionnaire (SAQ) once, in order to assess QoL and baseline angina severity.

From week 2, long-term administration of ASA 75–100 mg in combination with rivaroxaban 2.5 mg twice a day was initiated for all patients to prevent atherothrombotic events.

Within week 10, patients were asked once again: to keep the self-control diary; fill in the SAQ questionnaire; and undergo Holter ECG, in order to assess the number of myocardial ischemia episodes over time.

Inclusion criteria:

1) verified diagnosis of chronic CAD, and angina pectoris FC II–III (according to the Canadian Cardiovascular Society classification). The diagnosis was confirmed clinically and by history: the previous myocardial infarction (MI) and/or positive exercise tests, and/or detected stenotic lesions by coronary angiography, and/or history of revascularization (percutaneous coronary intervention or coronary artery bypass grafting);
2) the presence of indications for low-dose rivaroxaban following the clinical guidelines [2].

Exclusion criteria:

1) MI, stroke, revascularization within less than a year;
2) hospital admissions for decompensated chronic heart failure (CHF) within less than a year;
3) uncontrolled arterial hypertension (AH);
4) significant cognitive impairments which can affect the quality of keeping the diary and filling in the questionnaire;
5) contraindications to rivaroxaban according to the drug label.

All patients were treated as outpatients at the City Cardiology Dispensary of the City Clinical Hospital No. 5, Nizhny Novgorod, Russia, and signed informed consent to participate in the study.

A total of 26 patients with CAD, stable angina pectoris FC II–III were examined. The clinical characteristics are presented in Table 1.

All patients presented AH and CHF manifestations with preserved left ventricular ejection fraction (LVEF). The high risk of ischemic complications was confirmed by the presence of the following: postinfarction cardiosclerosis (50%); peripheral atherosclerosis (53.8%); a history of revascularization (65.4%); and diabetes mellitus type 2 (30.7%). At the same time, patients did not have any associated diseases which would significantly increase the risk of hemorrhagic complications.

Each patient had been undergoing long-term standard therapy, uncorrected for at least 3 months before and during the study (except for the administration of low-dose rivaroxaban). If the treatment had been corrected at the indicated period, the patient was excluded from the study. Antianginal agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, mineralocorticoid receptor antagonists, beta-blockers, etc., were used to treat cardiovascular pathologies. (see Table 1). All subjects took ASA before inclusion in the study.

All subjects answered the SAQ questions at inclusion (week 1) and at the end-of-study visit (week 10) [9–11]. The SAQ included five scales dedicated to various aspects of CAD: activity limitations; stability of angina attacks; frequency of angina attacks; treatment satisfaction; and attitudes to the disease [9]. Each scale ranges from 0 to 100, with higher scores corresponding to a better functional status.

Holter ECG was performed on an outpatient basis. Patients continued a normal daily routine at the beginning and at the end of the study. Episodes of ST-segment displacement were assessed. Ischemia was defined as ECG changes with horizontal or downsloping ST-segment depression ≥0.1 mV, with a gradual onset and end lasting at least 1 min. Each episode of ischemia was separated from the others by a 1 min interval, when the ST segment returned to baseline. In addition, rhythm disturbances were assessed, including the number of supraventricular and ventricular beats, as well as episodes of supraventricular and ventricular tachycardia. The main pacemaker was the sinus node in all patients. The circadian index was calculated to characterize the 24-hour (circadian) variability of the heart rate [12].

The data obtained was processed using the Statistica 8.0 software suite. The Wilcoxon test was used to compare quantitative indicators over time, and the McNemar method was used to compare the evolution of qualitative indicators. Mean and standard deviation were used to describe the samples. Qualitative characteristics are presented as a percentage. Differences were statistically significant, with p being less than 0.05.

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Results and Discussion

Comparative characteristics of the clinical indicators at the beginning and the end of the study are presented in Table 2. The average number of angina attacks per week decreased over time (by 19.5%; p=0.027), as reflected by the decrease in the number of short-acting nitrate tablets taken (by 17.1%; p=0.021). The findings suggest that low-dose rivaroxaban may help alleviate pain.

Maintaining QoL is of great importance for CAD patients. It inevitably decreases, even in a stable course of the disease. This is due to the limitations of daily activities, the negative impact of pain on physical and psychological status, and the need for constant medication. At the same time, the frequency and severity of anginal attacks are of crucial importance for all aspects of QoL.

The influence of the underlying disease on QoL over time is assessed using the five scores of the SAQ questionnaire in Table 2. According to the data presented, the use of low-dose rivaroxaban in patients with stable angina pectoris FC II–III was associated with a statistically significant improvement in QoL regarding stability (p=0.042) and the frequency of anginal attacks (p=0.015). Other aspects of QoL changed insignificantly within two months of follow-up.

Then we analyzed changes in the Holter ECG indicators. According to the data obtained, the percentage of patients with episodes of myocardial ischemia recorded by Holter ECG significantly decreased (2.2 times; p=0.046) during treatment, as well as the mean 24-hour duration of ischemic changes in the myocardium (1.5 times; p=0.037). Changes in ST-segment displacements concur with clinical data (reduced frequency and severity of angina attacks, improved QoL).

The combination of ASA and low-dose rivaroxaban showed a good safety profile. Five patients had adverse events, which were mild and transient. Changes in clinical data and Holter ECG indicators during the administration of rivaroxaban 2.5 mg twice a day in combination with ASA 75–100 mg, showed the high efficacy and safety of this combination in patients with stable angina pectoris FC II–I II.

The pathophysiological basis of anti-ischemic and other positive effects of rivaroxaban can be established by its

Table 1. Clinical and demographic characteristics of patients

Parameter	Value (n = 26)
Age, years	69.0 ± 7.11
Sex (male)	12 (46.2)
BMI, kg/m^2	27.8 ± 5.88
Angina pectoris	26 (100)
FC II	17 (65.4)
FC III	9 (34.6)
History of heart and blood vessel diseases	26 (100)
• Arterial hypertension	26 (100)
• CHF FC II-III	26 (100)
• Postinfarction cardiosclerosis	13 (50.0)
• Peripheral atherosclerosis	14 (53.8)
• History of revascularization	17 (65.4)
• Stenting	14 (53.8)
• CABG	4 (15.4)
Other diseases	
Diabetes mellitus type 2	8 (30.7)
History of cancer	5 (19.2)
Chronic kidney disease	2 (7.7)
GI disorders	2 (7.7)
COPD	3 (11.5)
LVEF, %	56.3 ± 7.15
Treatment	
ASA	26 (100)
Long-acting nitrates	9 (34.6)
Nicorandil	14 (53.8)
Beta-blockers	21 (80.7)
Statins	26 (100)
ACE inhibitors	13 (50)
ARBs	11 (42.3)
MCRA	10 (38.5)
Diuretics	11 (42.3)
Calcium antagonists	9 (34.6)
Amiodarone	3 (11.5)

The data is presented as the mean and standard deviation or the absolute number and percentage. BMI, body mass index; FC, functional class; CHF, chronic heart failure; CABG, coronary artery bypass grafting; GT, gastrointestinal tract; COPD, chronic obstructive pulmonary disease; LV, left ventricle; ASA, acetylsalicylic acid; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MCRA, mineralocorticoid receptor antagonist.

Table 2. Evolution of clinical indicators and quality of life throughout the study

Parameter	Week 1	Week 10	p
Number of angina attacks (per week)	4.1 ± 3.15	3.3 ± 3.42	0.027
Number of nitroglycerin tablets (per week)	3.5 ± 2.82	2.9 ± 2.95	0.021
Other complaints, n (%)			
• atypical chest pain	14 (53.8)	8 (30.8)	0.077
• palpitations, interruptions	7 (26.9)	7 (26.9)	–
• dyspnea	15 (57.7)	10 (38.5)	0.09
• headache	5 (19.2%)	6 (23.1)	0.48
• dyspepsia	3 (11.5)	5 (19.2)	0.47
Quality of life according to SAQ,%			
• limitation of activities	61.8±13.92	64.0±12.17	0.11
• stable angina	57.5±26.20	68.75±30.08	0.042
• frequency of angina attacks	68.7±23.68	78.8±27.29	0.015
• satisfaction with treatment	72.7±19.23	75.6±16.45	0.54
• attitude to the disease	65.8±16.16	68.3±18.11	0.23

additional mechanisms of action on the heart and blood vessels (other than those associated with thrombosis). The interactions between rivaroxaban and protease-activated receptors (PARs) have been actively studied in many recent research and experimental works. PARs are known to play an important role in the processes of vascular inflammation and atherogenesis; the development of ischemic damages in the myocardium; and the mechanisms of pathological cardiac remodeling [13, 14]. Xa factor and thrombin activate PARs stimulate some of the corresponding adverse cardiovascular effects. Xa inhibitor rivaroxaban appears to have the opposite effects as shown in several research studies. Rivaroxaban has been shown to reduce the area of atherosclerotic plaques [15, 16]; the expression of proinflammatory mediators in the myocardium [15]; fibrosis and pathological remodeling of the heart and blood vessels [8, 15, 17]; and some of its positive effects present even in low doses not affecting coagulation [17], They may also be associated with changes in PARs activity [15, 16].

The vascular effects of rivaroxaban are of interest. Its ability to suppress the formation of leukocyte-platelet aggregates [8, 18, 19] was confirmed experimentally during the 2-week monitoring after damage to vessels, leading to an improvement in blood viscosity and tissue circulation. Similar data was obtained when rivaroxaban was used in an experimental model of liver cirrhosis, contributing to reduced risk of microthrombosis, oxidative stress and improving endothelial function [20].

Moreover, a recent randomized clinical trial showed that a year-long treatment with rivaroxaban in patients with nonvalvular atrial fibrillation inhibited the growth of atherosclerotic plaques in the coronary arteries. It also slowed down the growth of a fibrous cap, and smaller volume when compared to warfarin [21]. The positive effects of rivaroxaban on the volume of atherosclerotic plaques in the coronary arteries may also partially contribute to its anti-ischemic effects.

Conclusion

Rivaroxaban 2.5 mg administered twice a day in combination with acetylsalicylic acid 75–100 mg for two months in patients with stable angina pectoris functional class I–III is associated with a decrease in the frequency of angina attacks, the need for short-acting nitrates, and better quality of life in patients with coronary artery disease.

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