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Prospects For the Use of Rivaroxaban in the Treatment of Patients with Chronic Ischemic Heart Disease

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Abstract: The review is devoted to the analysis of ways to influence hemostasis in order to improve the prognosis of patients with chronic coronary heart disease (CHD). The results of the most significant randomized clinical trials evaluating the effectiveness and safety of dual antiplatelet therapy in the treatment of patients with chronic ischemic heart disease are discussed. The use of rivaroxaban in addition to acetylsalicylic acid (ASA) to reduce the risk of cardiovascular events in patients with chronic ischemic heart disease is justified.

Key words: chronic ischemic heart disease, prognosis, effectiveness and safety of therapy, antiplatelet agents, rivaroxaban.

It is well known that coronary heart disease (CHD) is one of the leading causes of death in industrialized countries [1]. In the Republic of Uzbekistan, every second death from diseases of the circulatory system is caused by ischemic heart disease. Thanks to the creation of a network of vascular centers and increased availability of percutaneous coronary interventions (PCI), the results of treatment of patients with acute coronary syndrome (ACS) in our country have clearly improved over the past decade. However, to reduce mortality from diseases of the circulatory system, it is important not so much the successful treatment of patients with already occurring cardiovascular events, but rather their effective prevention. Improving prognosis is considered one of the main goals of treatment for patients with chronic ischemic heart disease. To reduce the risk of cardiovascular events in patients with chronic CAD, lifestyle changes, risk factor control, patient education, and evidence-based pharmacotherapy are recommended. Since the main cause of cardiovascular events in patients with chronic ischemic heart disease is atherothrombosis, drugs that affect the blood coagulation system occupy a leading place among drugs used to improve the prognosis of this disease.

In the 2019 European Society of Cardiology guidelines [2], the use of low-dose ASA is considered mandatory in patients who have undergone myocardial infarction (MI) or revascularization (class of recommendation I, level of evidence A). In case of intolerance to ASA, the use of clopidogrel is recommended (grade I recommendation, level of evidence B). In patients who have not

undergone MI or revascularization, but have imaging signs of CAD, the use of ASA is not necessary, but possible (class of recommendation IIb, level of evidence C). The addition of a second antithrombotic drug to an ASA for long-term secondary prevention should be considered in patients at high risk of ischemic events without a high risk of bleeding (grade IIa, level of evidence A) and may be considered in patients with a moderate risk of ischemic events without a high risk of bleeding (grade IIb). , level of evidence A). A sign of high coronary risk is multivessel coronary heart disease in combination with diabetes mellitus (DM) requiring drug therapy, previous MI, peripheral arterial disease (PAD), chronic heart failure or chronic kidney disease (CKD) with glomerular filtration rate (GFR) 15-59 ml/min/1.73 m2. Each of the listed criteria separately is considered as a sign of moderate ischemic risk. Criteria for high bleeding risk include: previous intracerebral hemorrhage or ischemic stroke, history of other cranial pathology, recent gastrointestinal bleeding or anemia in the setting of possible gastrointestinal bleeding, other gastrointestinal pathology with an increased risk of bleeding, liver failure, hemorrhagic diathesis or coagulopathy, extreme old age, cirrhosis requiring dialysis therapy, or GFR less than 15 ml min/1.73 m2. Drugs that may be prescribed in addition to ASA include clopidogrel, ticagrelor, prasugrel and rivaroxaban.

Use of dual antiplatelet therapy to improve the prognosis of patients with chronic ischemic heart disease. The pathophysiological basis of MI, stroke and cardiovascular death in patients with coronary artery disease is the formation of an intravascular thrombus. At the initial stage of thrombus formation after damage to an atherosclerotic plaque, activation and aggregation of platelets occurs; therefore, until recently, the attention of researchers was mainly focused on studying the effectiveness of antiplatelet drugs, in particular dual antiplatelet therapy (DAPT). DAPT (ASA in combination with a P2Y12 receptor blocker) has been successfully used for secondary prevention of coronary artery disease in patients with SLE, regardless of the chosen treatment strategy, for 6-12 months after the index event in the absence of a high risk of bleeding [3, 4]. The hypothesis that DAPT a year or more after MI, i.e. in the stable phase of coronary artery disease, may reduce the risk of atherothrombosis, has been tested in several studies. In a large study, PEGASUSTIMI54 [5], it was shown that the combination of ASA and ticagrelor compared with ASA alone provides a significant reduction in the risk of primary combined endpoints (cardiovascular death, MI, stroke): from 9.04% in the ASA monotherapy group to 7.85% in the combination therapy group with ticagrelor 90 mg twice daily (RR 0.75; 95% CI 0.75-0.96; p = 0.008) and up to 7.77% in the combination therapy group with ticagrelor 60 mg twice daily (RR 0 .74; 95% CI 0.74-0.95; p= 0.004). However, DAPT was associated with an increased incidence of major and other TIMI bleeding. Comparison of the frequency of atherothrombotic events and major bleeding in patients of the compared groups allowed us to conclude that the combination of ASA and ticagrelor at a dose of 60 mg 2 times a day one year after MI in patients with a high risk of atherothrombosis and a low risk of hemorrhagic complications is advisable. The results of this study were reflected in recommendations for the provision of medical care to patients with AMI with and without ST-segment elevation [3, 4].

The use of two antiplatelet drugs with different mechanisms of action to improve the prognosis of patients with chronic coronary artery disease who have not suffered a MI in the near future was effective only in patients undergoing elective PCI with coronary artery stenting. For these indications, treatment with a combination of an ASA and a P2Y12 receptor blocker is recommended for 12 months after surgery, unless there is a high risk of bleeding [6, 7]. DAPT in patients with chronic CAD not associated with PCI in studies did not provide more reliable

prevention of atherothrombotic events compared with ASA alone. Thus, in the CHARISMA study [8] in patients with chronic ischemic heart disease, combination therapy with clopidogrel and ASA compared with single-component treatment did not lead to an improvement in prognosis, but was accompanied by an increase in the number of bleeding complications. Only in patients with a documented history of atherothrombotic complications did DAPT provide some additional benefit [9]. The TRA2P-TIMI50 trial [10] showed that the addition of vorapaxar, a PAR-1 receptor inhibitor, to standard ASA therapy in patients with a history of peripheral arterial atherosclerosis, myocardial infarction, or ischemic stroke resulted in a reduction in the incidence of the primary endpoint composite event (cardiovascular disease). vascular death, myocardial infarction or stroke), but did not affect cardiovascular and overall mortality, accompanied by a significant increase in the incidence of bleeding, including intracranial bleeding (1.0% vs. 0.5%, $p<0.001$). Thus, in stable CAD, with the exception of patients who have undergone MI or elective PCI, the addition of a second antiplatelet drug to an ASA does not provide a clinically significant reduction in the risk of individual cardiovascular events, but increases the risk of bleeding complications.

Rationale for the use of rivaroxaban in combination therapy of chronic ischemic heart disease. Thrombin promotes the conversion of fibrinogen into fibrin and causes platelet activation, that is, it affects the two main mechanisms of arterial thrombus formation. Weakening the procoagulant effect of thrombin for a long time is possible with the use of drugs intended for oral administration and providing either direct inhibition of thrombin (ximelagatran, dabigatran), or suppression of the formation of vitamin K-dependent coagulation factors in the liver (vitamin K antagonists), or selective direct inhibition of XA - clotting factor (rivaroxaban, apixaban, edoxaban, betrixaban). At the same time, it is obvious that adding an anticoagulant to the main antiplatelet therapy will inevitably increase the hemorrhagic risk. The combined use of drugs that affect the cellular and humoral components of hemostasis can be considered appropriate only in the case of a significant predominance of the reduction in ischemic risk compared to the increased risk of bleeding. Rivaroxaban is widely used in clinical practice for the prevention and treatment of venous thromboembolism, as well as for the prevention of ischemic strokes and thromboembolic complications in patients with atrial fibrillation. Similar indications have been reported for dabigatran, apixaban and edoxaban. Unlike other direct oral anticoagulants, rivaroxaban has a proven ability to improve the prognosis of patients undergoing CABG. In the ATLASACS2-TIMI51 study [11], the drug was prescribed to patients with ACS in doses of 2.5 mg 2 times a day and 5 mg 2 times a day after parenteral anticoagulant therapy against the background of antiplatelet therapy (in most patients, DAPT ASA and clopidogrel). The average duration of follow-up for patients included in this study was 13 months. Treatment with rivaroxaban significantly reduced the incidence of primary endpoint events (cardiovascular death, myocardial infarction, stroke) compared with placebo by 16% overall (RR 0.84; 95% CI 0.74-0.96; $p = 0.002$) and its components - cardiovascular death ($p = 0.04$) and MI ($p = 0.047$), as well as the frequency of stent thrombosis ($p = 0.016$). The incidence of major bleeding and hemorrhagic stroke increased during rivaroxaban therapy. At the same time, the groups of patients receiving rivaroxaban and placebo did not differ in the incidence of fatal intracranial bleeding. A dose of rivaroxaban 2.5 mg twice daily was sufficient to significantly reduce the incidence of the primary endpoint and cardiovascular and all-cause mortality compared with placebo. In patients receiving rivaroxaban 2.5 mg twice daily, the incidence of major bleeding was not significantly but lower, and fatal bleeding was significantly less common than in patients receiving rivaroxaban 5 mg twice daily. Current guidelines for the treatment of patients with MI and myocardial revascularization [3, 4, 6] state that low-dose

rivaroxaban can be prescribed to patients with ACS for up to two years to reduce the risk of ischemic events (class IIb recommendation, level of evidence B).

Conclusions. Thus, the addition of rivaroxaban at a dose of 2.5 mg 2 times / day to the basic therapy of ASA at a dose of 100 mg / day can significantly reduce the risk of cardiovascular events in a wide range of patients with chronic ischemic heart disease. The positive effect of combination therapy is observed in patients with or without a history of cardiovascular events and is not determined by the time elapsed since the last ischemic event. The increased risk of bleeding due to the increased effect on hemostasis is less pronounced than the reduced risk of cardiovascular events. Moreover, with increasing duration of treatment of patients with the combination of rivaroxaban and ASA, the risk of bleeding decreases, while the preventive effect of therapy does not weaken. The use of a combination of rivaroxaban and ASA in the studied doses for a long time can be considered as a real way to reduce mortality in patients with chronic ischemic heart disease, and given the medical and social significance of this disease, mortality from diseases of the circulatory system in general.

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