PROSPECTS OF RIVAROXABAN USE 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 ischemic heart disease (IHD). The results of the most significant randomized clinical trials evaluating the efficacy and safety of dual antiplatelet therapy in the treatment of patients with chronic IHD are discussed. The use of rivaroxaban in addition to acetylsalicylic acid (ASA) to reduce the risk of cardiovascular events in patients with chronic IHD was substantiated.

Keywords: *chronic IHD, prognosis, efficacy and safety of therapy, antiaggregants, rivaroxaban*

АННОТАЦИЯ

Обзор посвящен анализу способов воздействия на гемостаз с целью улучшения прогноза пациентов с хронической ишемической болезнью сердца (ИБС). Обсуждаются результаты наиболее значимых рандомизированных клинических исследований по оценке эффективности и безопасности двойной антитромбоцитарной терапии в лечении пациентов с хронической ИБС. Обосновано использование ривароксабана в дополнение к ацетилсалициловой кислоте (АСК) для снижения риска сердечно-сосудистых событий у пациентов с хронической ИБС.

Ключевые слова: *хроническая ИБС, прогноз, эффективность и безопасность терапии, антиагреганты, ривароксабан.*

INTRODUCTION

It is well known that coronary heart disease (CHD) is one of the leading causes of death in the population of industrialized countries [1]. In the Russian Federation every second death from circulatory diseases is caused by CHD. Due to the establishment of a network of vascular centers and increased availability of

percutaneous coronary interventions (PCIs), the results of acute coronary syndrome (ACS) patients treatment have clearly improved in our country during the last decade. However, it is not so much the successful treatment of patients with already achieved cardiovascular events, as their effective prevention that matters for reducing mortality from circulatory diseases. Improving prognosis is considered as one of the main goals of treatment of patients with chronic CHD. Lifestyle changes, control of risk factors, patient education and evidence-based pharmacotherapy are recommended to reduce the risk of cardiovascular events in patients with chronic CHD. Since the main cause of cardiovascular events in patients with chronic CHD is atherothrombosis, medications affecting the blood- clotting system take the leading position among medications used to improve the prognosis in this disease.

DISCUSSION AND RESULTS

In recommendations of the European Society of Cardiology 2019. [2], low-dose ASA use is considered mandatory in patients who have undergone myocardial infarction (MI) or revascularization (recommendation class I, level of evidence A). In case of ASA intolerance, the use of clopidogrel is recommended (class of recommendation I, level of evidence B). In patients who have not undergone MI or revascularization but have imaging evidence of CHD, the use of ASA is not mandatory, but possible (grade of recommendation IIb, level of evidence C). The addition of a second antithrombotic agent to ASA for long-term secondary prevention should be considered in patients at high risk of ischemic events without a high risk of bleeding (recommendation class IIa, level of evidence A) and may be considered in patients at moderate risk of ischemic events without a high hemorrhagic risk (recommendation class IIb, level of evidence A). An indication of high coronary risk is considered to be multivessel coronary artery disease in combination with diabetes mellitus (DM) requiring drug therapy, a previous MI, peripheral artery 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. High hemorrhagic risk criteria include: previous intracerebral hemorrhage or ischemic stroke, other cranial cavity pathology in the history, recent gastrointestinal bleeding or anemia in the background of possible gastrointestinal bleeding, other gastrointestinal pathology at increased risk of bleeding, hepatic insufficiency, hemorrhagic diathesis or coagulopathy, extreme old age, CKD 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.

The use of dual antiplatelet therapy to improve the prognosis of patients with chronic CHD. The pathophysiological basis of MI, stroke and cardiovascular death in patients with CHD is intravascular thrombus formation. At the initial stage of thrombus formation after atherosclerotic plaque damage, platelet activation and aggregation occur, therefore, until recently, the attention of researchers was mainly focused on studying the effectiveness of antiplatelet agents, in particular dual antiplatelet therapy (DATT). DATT (ASA combined with P2Y12 receptor blocker) is successfully used for secondary prevention of CHD in ACS patients, regardless of the chosen treatment strategy, within 6-12 months after the index event in the absence of high bleeding risk [3, 4]. The hypothesis that DATT one year or more after MI, i.e., in the phase of stable CHD course, may reduce the risk of atherothrombosis has been tested in several studies. In a large study PEGASUS TIMI 54 [5] it was shown that the combination of ASA and ticagrelor compared to ASA alone provides a significant reduction in the risk of primary combined endpoint events (cardiovascular death, MI, stroke): from 9.04% in the ASA monotherapy group to 7.85% in the ticagrelor 90 mg twice daily combination therapy group (OR 0.75; 95% CI 0.75-0.96; p = 0.008) and to 7.77% in the ticagrelor 60 mg twice daily combination therapy group (OR 0.74; 95% CI 0.74-0.95; p = 0.004). However, DATT was accompanied by an increased incidence of major and other TIMI bleeding. Comparison of the incidence of atherothrombotic events and major bleeding in patients of the compared groups allowed to conclude that the combination of ASA and ticagrelor at a dose of 60 mg 2 times daily one year after MI in patients with high risk of atherothrombosis and low risk of hemorrhagic complications is reasonable. The results of this study were reflected in the guidelines for medical care of STEMI patients 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 CHD who have not suffered a near-term MI has proven effective only in patients undergoing elective PCI with coronary artery stenting. According to this indication, treatment with combination of ASA and P2Y12 receptor blocker is recommended within 12 months after the intervention in the absence of high risk of bleeding [6, 7]. DATT in patients with chronic CHD unrelated to PCI in the studies did not provide more reliable prevention of atherothrombotic events compared to the use of ASA alone. Thus, in CHARISMA study [8] in patients with chronic CHD, clopidogrel and ASA combination therapy compared to single-component treatment did not lead to improved prognosis, but was accompanied by an increase in the number of bleeding complications. Only in

patients with documented atherothrombotic complications in the history of DATT brought some additional benefit [9]. In the TRA2P-TIMI 50 study [10] it was shown that addition of vorapaxar, a PAR-1 receptor inhibitor, to standard ASA therapy in patients with atherosclerosis of peripheral arteries, MI or ischemic stroke in anamnesis led to decreased incidence of combined primary endpoint events (cardiovascular death, MI or stroke), but did not influence cardiovascular and overall mortality accompanied by significant increase of bleeding rate, including intracranial (1.0% vs 0.5%, $p<0.001$). Thus, in stable CHD, except for patients who underwent MI or elective PCI, the addition of a second antiplatelet drug to ASA does not provide a clinically significant reduction in the risk of individual cardiovascular events, but increases the risk of hemorrhagic complications.

Rationale for the use of rivaroxaban in the combination therapy of chronic CHD. Thrombin promotes transformation of fibrinogen into fibrin and induces platelet activation, i.e. it influences the two main mechanisms of arterial thrombus formation. Weakening of procoagulant action of thrombin for a long time is possible by using drugs intended for oral administration and providing either direct inhibition of thrombin (ximelagatran, dabigatran), or suppression of formation in the liver of vitamin K-dependent clotting factors (vitamin K antagonists), or selective direct inhibition of Ha clotting factor (rivaroxaban, apixaban, edoxaban, betriksaban). At the same time, it is obvious that adding anticoagulant to basic antiplatelet therapy will inevitably increase the hemorrhagic risk. Combined use of drugs affecting cellular and humoral part of hemostasis can be considered reasonable only in case of significant predominance of ischemic risk reduction in comparison with increased bleeding risk. 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 are registered for dabigatran, apixaban and edoxaban. In contrast to other direct oral anticoagulants, rivaroxaban has a proven ability to improve the prognosis of patients who underwent ACS. In ATLAS ACS 2-TIMI 51 trial [11] the drug was administered to patients with ACS in the doses of 2.5 mg 2 times a day and 5 mg 2 times a day after parenteral anticoagulant therapy against the background of antiaggregant therapy (in most patients - DATT ASA and clopidogrel). The average duration of follow- up of the patients included in this study was 13 months. Treatment with rivaroxaban significantly reduced the incidence of the primary endpoint events (cardiovascular death, MI, stroke) compared to placebo by 16% overall (OR 0.84; 95% CI 0.74-0.96; $p = 0.002$) and its components - cardiovascular

death (p = 0.04) and MI (p = 0.047), and the rate of stent thrombosis (p = 0.016). The incidence of major bleeding and hemorrhagic strokes increased during rivaroxaban therapy. At the same time, the groups of patients receiving rivaroxaban and placebo did not differ by the frequency of fatal intracranial bleeding. The dose of rivaroxaban 2.5 mg 2 times per day was sufficient to significantly reduce the incidence of primary endpoint, as well as cardiovascular and overall mortality compared to placebo. In patients receiving rivaroxaban at a dose of 2.5 mg 2 times a day, the incidence of major bleeding was not significantly, but less, and fatal bleeding was significantly less frequent than in the group of patients in whom rivaroxaban was administered at a dose of 5 mg 2 times a day. Current guidelines on the treatment of patients with MI and myocardial revascularization [3, 4, 6] state that low-dose rivaroxaban can be administered to ACS patients for up to two years to reduce the risk of ischemic events (class IIb recommendations, level of evidence B).

CONCLUSION

Thus, the addition of rivaroxaban at a dose of 2.5 mg 2 p/day to basic ASA therapy at a dose of 100 mg/day can significantly reduce the risk of cardiovascular events in a wide range of patients with chronic CHD. Positive effect of combination therapy is observed in patients with the presence or absence of cardiovascular events in the history and is not determined by the time elapsed since the last ischemic event. The increase in risk of bleeding caused by increasing influence on hemostasis is expressed in less degree, than decrease in risk of cardiovascular events. Moreover, with the increase of treatment duration of patients with combination of rivaroxaban and ASA, the risk of bleeding decreases, while the prophylactic effect of therapy does not weaken. The use of the combination of rivaroxaban and ASA in the studied doses for a long time can be considered as a real way to reduce mortality patients with chronic CHD, and given the medical and social significance of this disease - and mortality from circulatory diseases in general.

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