Modern aspects of the application of antiplatelet and hypolipidemic therapy in ischemic heart disease after coronary artery stenting

1. **Saydalev Rustam Saydalievich**

2. **Toychiyev Shohruh**

3. **Abdulloh Rohina**

Tashkent Medical Academy, Tashkent, Uzbekistan[1,2,3]

Annotation: *In this article it will be discussed actual issues and modern problems of the ischemic disease of the heart, antiplatelet therapy, its effects, hypolipidemic therapy, indications, counter indications, potential side effects as well as, successful management strategies after percutaneous coronary intervention following with drug eluted stents.*

Key words: Ischemic disease; Antiplatelet therapy; Hypolipidemic therapy; Stenting.

1.Introduction

Cardiovascular diseases (CVD) are one of the most important medical and social problems of our time and they occupy almost two-thirds of the causes of death and almost half of the causes of disability in the population [1], which leads to significant social economic losses [2], shortening the duration and reducing the quality of life [3]. According to experts, in the next 15 years, more than 23 million people will die from them in the world every year [1]. Understanding the causes of these diseases, as well as expanding opportunities in the field of their prevention, diagnosis and treatment, is one of the key priorities of today's cardiology.

In this case, coronary heart disease (IHD) - atherosclerosis of the vessels of the heart makes up the lion's share of CVD [4,5]. Ischemic Heart Disease [IHD] and its complications are the leading causes of death, despite significant progress in the control of risk factors (RF) and treatment, including the widespread use of surgical and endovascular methods of revascularization [6,7,8]. All the forces of modern medicine and fundamental sciences are thrown into "extinguishing this fire" in the form of diseases of the heart and blood vessels [9]. Leading RFs: high blood pressure, tobacco smoking, alcohol consumption, high blood cholesterol (CS), overweight, low consumption of fruits and vegetables, and a sedentary lifestyle determine almost 60% of all causes of CVD [10]. The strategic goals in the treatment

of IHD patients are to prevent premature death, prevent progression and achieve partial regression of coronary artery atherosclerosis (CA) [11], reduce the number of complications and exacerbations of the disease, and the frequency and duration of hospitalization [12]. Secondary prevention of coronary artery disease includes drug and non-drug components [13]. For this, drugs are used, the effectiveness of which has been proven by the results of large international studies. Timely diagnosis and prevention can dramatically reduce the risk of CVD and increase a person's life expectancy by 10-15 years [14]. In recent years, the features of the development and course of ischemic heart disease, in particular, its acute forms, in various groups of patients, depending on gender, age, comorbid and other signs, have been actively studied [15,16,17]. The success of the treatment of coronary artery disease is largely determined by the maintenance of adequate coronary blood flow, including by performing Percutaneous Coronary Interventions (PCI), Stenting of the Coronary Arteries (SCA) [18]. Local changes in the vascular intima (rupture of an atherosclerotic plaque or a crack in the capsule covering it, less often hemorrhage into the plaque), as well as an increase in the activity of the coagulation system and a decrease in the activity of the anticoagulant system, contribute to the onset of coronary thrombosis [19].

When a plaque is damaged, collagen fibers are exposed, adhesion and aggregation of platelets occurs at the site of damage, the release of platelet coagulation factors and the activation of plasma coagulation factors [20]. A blood clot is formed that closes the lumen of the artery. CA thrombosis, as a rule, is combined with its spasm. The resulting acute occlusion of the coronary artery causes myocardial ischemia, a sharp painful attack and, if reperfusion does not occur, necrosis of this part of the myocardium. Atherosclerotic and thrombotic processes are closely interrelated and therefore are currently united by the term "atherothrombosis". The process of atherothrombosis starts at the moment of rupture of the fibrous wall of an atherosclerotic plaque or its erosion [21]. Platelets are the first to react to plaque rupture. The adhesion of platelets to the damaged endothelium leads to their further aggregation, local vasospasm, the development of dynamic stenosis leading to hypoxia and ischemia of the organ [22]. Platelet aggregation is the starting point of the processes that culminate in the formation of a thrombus in resistive vessels [23]. The rupture of an unstable atherosclerotic plaque, adhesion and aggregation of blood cells, the inclusion of plasma coagulation factors in the process and the formation of a thrombus are a single pathway for the development of cardiovascular catastrophes [24]. The end points of the latter are acute myocardial infarction, ischemic stroke, critical ischemia of the lower extremities, the development of chronic heart failure, i.e., conditions that determine the main indicators of mortality and disability worldwide. In this regard, antiplatelet therapy plays an important role, both in primary and, to an even greater extent, in secondary prevention [25]. The maintenance of positive results after SCA depends on the prevention of subsequent thrombotic complications [26]. Stent thrombosis is a life-threatening complication that can develop acutely, subacutely and in the long term after stent implantation [27]. More often it develops with insufficient suppression of platelet aggregation [28]. Platelet activation and aggregation play a key role in the development of ischemic events in acute coronary syndrome and during PCI.In this regard, patients are prescribed antiplatelet therapy, including acetylsalicylic acid (ASA) and clopidogrel [29]. ASA blocks cyclooxygenase-1 of platelets, disrupting the synthesis of thromboxane A2 in them. Thus, ASA irreversibly suppresses platelet aggregation induced by collagen, ADP, and thrombin. The mechanism of the antiplatelet effect of clopidogrel is associated with the suppression of ADP-induced platelet aggregation by irreversible binding to the P2Y12 membrane protein receptor.

However, in some patients, such antiplatelet therapy may not be effective [30]. The reason for this is individual drug sensitivity. Modern medical treatment of ischemic heart disease, in addition to taking antianginal and anti-ischemic drugs, should include the use of antithrombotic (antiplatelet) [31], lipid-lowering (statins) [32], antihypertensive and metabolic agents.A successfully performed PCI does not eliminate the cause of ischemic heart disease - atherosclerosis, but only levels the pathophysiological effect of a hemodynamically significant atherosclerotic plaque [33]. The atherosclerotic process can progress both in the stented or balloon, and in other segments of the coronary bed. In addition, implantation of a foreign body - a stent can give rise to an iatrogenic disease - stent thrombosis, which can develop in the long term. In this situation, it is necessary to strictly observe all measures of secondary prevention of coronary artery disease, for which a decrease in the risk of developing coronary and cerebral complications, cardiovascular mortality in patients after PCI has been proven [34].

The course of the disease and the prognosis of patients who have undergone SCA largely depend on the completeness of compliance with the standards of drug therapy, primarily antiplatelet therapy [35]. According to the recommendations, patients who received stents need to receive Dual Anti Platelet Therapy (DAPT) for at least 12 months. However, there are research results indicating that longer use of the combination of ASA and clopidogrel improves the prognosis. At the same time, the cancellation of DAPT or one of the drugs in the early period is associated with the most unfavorable course.

Unfortunately, the implementation of treatment standards does not always fully exclude the possibility of complications, which is largely due to the unfavorable background on which the disease proceeds: multiple risk factors, mutations of genes responsible for the regulation of lipid metabolism, thrombus formation factors [36]. The consequence of this is insufficient control of platelet aggregation, which ultimately contributes to stent thrombosis - one of the main causes of complications in patients undergoing SCA.

The most important direction of drug treatment of patients with coronary artery disease is the use of drugs that lower blood lipids [37]. The main agents that reduce the levels of cholesterol and cholesterol of low density lipoproteins (LDL-

C) in blood plasma are cholesterol synthesis inhibitors – statins [37]. The most important goal of lipid profile correction is to reduce LDL-C levels [38]. Statins not only reduce the level of atherogenic lipids, but also the risk of PCI complications and have a beneficial effect on the course of the disease.

Unfortunately, in some patients, ischemic events recur on the background of DAPT. In many clinical studies, the heterogeneity of the platelet suppression response to the use of DAPT has been demonstrated.

Purpose

The study aimed to evaluate the effectiveness of antiplatelet and lipid-lowering therapy in patients with ischemic heart disease after coronary artery stenting based on the analysis of clinical and laboratory parameters.

2.Material and methods

The study included 30 patients with coronary artery disease after coronary artery stenting with DES stents (26 men and 4 women), who received antiplatelet agents (ASA and clopidogrel), rosuvastatin, 10-20 mg / day, according to current recommendations. Sixteen (12 men and 4 women) out of 30 patients were with metabolic syndrome (MS) and arterial hypertension (AH), who received appropriate therapy. Initially and after 3 months, Total Cholesterol (TC), LDL- C, HDL-C, triglycerides

(TG), C-reactive protein (CRP), the activity of the enzymes alanine and aspartate aminotransferase (ALT and AST), the content of total bilirubin (OB) were determined in the patients' blood Conducted

electrocardiography (ECG), if necessary ECG with exercise, echocardiography (ECHOKG) with an assessment of the parameters of the structural and functional state of the left ventricle (LV), dopplerography (Samsung medison "AccuvixV20").

3.Results and discussion

Before stenting, an increase in the functional activity of platelets, the content of total cholesterol, LDL-C, TG, and a decrease in HD-C was revealed. Initial lipid parameters: total cholesterol –6.9 mmol / l; CSLPNP –3.6; CSHDL -1.1; TG –

2.3 mmol / L and CRP –7.5 mg / L. In IHD patients with MS and AH, the CRP content averaged 16.4 ± 1.2 mg / l. The study of the lipid spectrum in these patients revealed higher total cholesterol levels-7.2 ± 0.6; TG-2.5 ± 0.2; LDL-C - 3.7

± 0.26 mmol / L and a lower content of HDL-C level: 1.2 ± 0.1 in patients with MS and AH and 1.15 ± 0.14 mmol / L in patients without MS and AH. Total cholesterol and LDL cholesterol after three months of therapy decreased by 30 and 36%. Changes in the level of antiatherogenic HDL-C were not so pronounced (an increase of about 8%), but a 38% decrease in the TG content was revealed. One of the factors of inflammation, CRP, was 35% higher than normal. The high level of CRP indicated the instability of the atherosclerotic plaque. In almost all patients at baseline, the degree of platelet aggregation was increased (on average by 20%). In the absence of a loading dose, the antiplatelet effect of the drugs on the 5th day of administration was moderately expressed. In 11 (37%) patients, normalization of all aggregation parameters was observed. In the rest, despite a decrease in some cases, it remained elevated. After 2 months of treatment, it returned to normal in 24 (80%) patients, and in 5 (17%) patients, increased aggregation parameters remained. It should be noted that in 4 out of 5 patients, spontaneous aggregation disappeared, while ADP-induced aggregation decreased significantly. Three months later, favorable changes in the indicators of platelet aggregation were achieved (the degree and rate of aggregation, an indicator of the presence of disaggregation).

A favorable hypolipidemic effect of statin was revealed, which manifested itself in the normalization of the lipid spectrum. Before stenting, despite an almost normal ejection fraction (EF) with preserved LV systolic function, most parameters of transmitral blood flow differed from the norm, and impaired LV diastolic function was determined. Three months later, an increase in LVEF was observed, which averaged 61.5%. The rate of early LV filling (peak E) before stenting and after 3 months was 0.67 and 0.76 m / s, the rate of diastolic filling during left atrial systole (peak A) was

0.77 and 0.7 m / s. sec, the ratio of speed characteristics (E / A) - 0.87 and 1.08; LV isovolumic relaxation time - 139 and

142.5 ms; the slowdown time of the early filling speed is 208 and 208 ms. Before stenting, most parameters of the transmitral blood flow differed from the norm, and impaired LV diastolic function was determined. Painless myocardial ischemia in patients with LV hypertrophy was more common than in the examined patients without altered LV geometry. The pleiotropic properties of statins were noted already in the first months of treatment. The beneficial effect of statins on the studied clinical, instrumental and laboratory parameters once again indicates their effect on the pathogenetic links of ischemic heart disease, which is especially important in the treatment of such patients with concomitant MS and AH. Modern ideas about the pathogenesis of ischemic heart disease indicate the need for a differentiated approach to the treatment of patients with this pathology, taking into account the possible

components of MS. No adverse effect of the tested drugs on the activity of ALT, AST and the content of OB was revealed. Antiplatelet agents were well tolerated and did not cause hypocoagulation. When used together, the lipid-lowering efficacy of rosuvastatin, as well as the antiplatelet effect of ASA and clopidogrel, remained at a sufficient level. The combination of these drugs did not lead to the development of liver disorders, which was confirmed by ALT, AST and OB.

Against the background of drug therapy, changes in the indicators of platelet aggregation were achieved. The degree of platelet aggregation in patients without MS and AH was lower than in patients with these comorbid conditions [39]. The rate of platelet aggregation was also higher in patients with MS and AH [40]. The time of aggregation, as well as the indicator of the presence of disaggregation, were lower among patients without MS and AH. No side effects and drug resistance were identified.

The causes of resistance to ASA and clopidogrel are heterogeneous and multicomponent: clinical (weight, age, dose reduction or premature drug withdrawal, poor absorption, drug effects, diabetes) and cellular (accelerated platelet pool formation, decreased metabolic activity, dysregulation of P2Y12 or P2Y1 receptors , impaired P2Y1 activation, insufficient suppression of catechol-induced platelet activation) [41]. The ineffectiveness of antiplatelet therapy may not be the only mechanism of ischemic events associated with antiplatelet therapy [42]. This suggests the importance of laboratory confirmation of clinical resistance [43]. Clinical studies have shown that titration of clopidogrel dose based on platelet function results improves clinical outcome in patients undergoing PCI [44]. The use of two drugs with different mechanisms of antiplatelet action can increase the effectiveness of antiplatelet therapy and, accordingly, reduce the risk of thrombosis. Important points are the achievement of the target blood pressure level, a decrease in the level of blood lipids, and in patients with diabetes mellitus - the achievement of compensation for carbohydrate metabolism. A specific feature of secondary prophylaxis after PCI is the administration of DAPT in adequate doses and the required duration. Unfortunately, according to research data, patient adherence to drug therapy that affects the prognosis after PCI remains insufficient.

4.Conclusion

Thus, the personalized selection of doses of lipid-lowering and, especially, antiplatelet drugs, taking into account the individual characteristics of patients and pharmacogenetics, increases the effectiveness of treatment, prevents the development of restenosis and other complications. This minimizes the side effects of drugs and the development of resistance to them.

Compliance with ethical standards

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