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LEADING ARTICLE

Continuous combined multicomponent antithrombotic therapy of patients with coronary heart disease: the benefits and risks

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Resume

Meta-analysis of the results, obtained in the long-term controlled studies, showed that treatment with aspirin or clopidogrel compared with placebo reduces significantly the risk of overall mortality, non-fatal myocardial infarction, stroke and vascular death by 25%. Combinatory therapy of aspirin and clopidogrel for patients with acute myocardial infarction did not affect overall mortality, and only the frequency of the combined endpoint decreased by 20% ($p < 0.001$) (non-fatal myocardial infarction, stroke, revascularization of the heart and cardiovascular death). Attempts to evaluate in numerous studies the possibility of increasing the effectiveness of long-term antithrombotic therapy in patients after acute coronary syndrome, by increasing the dose of antiaggregant or simply uncontrolled increase in the number of antithrombotic drugs — two antiaggregants in combination with one of the new oral anticoagulants, — showed no significant improvement in the treatment results. Because the frequency of the primary endpoint — overall mortality — did not change. Some reduction in the combined endpoint — a secondary point on its value — accompanied by a significant increase in the risk of bleeding, which is associated with an increased risk of death. The same results were obtained in the study PEGASUS (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) in patients with documented chronic coronary heart disease (CHD) (myocardial infarction). The finding data suggests that the uncontrolled increase in the dose of drugs and combinations thereof has no effect on overall mortality. One of the new trends in finding a solution to increase the therapy efficacy, without increasing the risk of bleeding, may be an individual choice of the drug, based on an assessment of the extent of its effect on platelet aggregation. Today, many studies have shown an interconnection between high residual platelet reactivity and mortality of patients with CHD. Based on these data, there have been proposed target levels of the platelet reactivity reducing by therapy with aspirin and clopidogrel, which allow the selection of an effective drug for each patient. This article devoted to the study of this issue.

Key words

Atherotrombosis, antithrombotic therapy, platelet aggregation, antiaggregants

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In studies for the prevention of the atherothrombotic etiology diseases, despite the increase of gastrointestinal bleeding in 1–2 times, the presence of benefits of aspirin therapy is proven, which is demonstrated by a significant reduction in overall mortality [1]. The latest index makes it possible to assess the effectiveness of drug therapy or other interventions adequately. All other endpoints are of secondary importance for the patient, especially the so-called combined endpoints.

In addition to aspirin in low doses, up to 100 mg/day, another group of antiaggregants is also used for the prevention of these diseases — inhibitors of R2U12 platelet receptors (clopidogrel, tikagrelol, prasugrel). The results of the data meta-analysis from long-term controlled studies, compared with placebo, have shown that treatment with aspirin or clopidogrel reduces the risk of overall mortality, cardiovascular death and the risk of non-fatal myocardial infarction, stroke by 25 %. When analyzed separately, the greatest risk reduction was observed against myocardial infarction — 1/3, stroke — 1/4, and death — only 1/6 [2]. A moderate reduction in the risk of diseases, which caused by atherothrombosis, is associated in particular with the presence of high residual platelet reactivity in many patients during antiplatelet therapy. To improve its effectiveness, attempts were made to use higher doses of aspirin and clopidogrel (up to 1500 mg and 150 mg respectively). The results showed that during prolonged antiplatelet therapy, higher doses only increase the risk of bleeding. In order to improve the efficiency of antiplatelet therapy, a combination of two antiplatelet agents is used, as well as attempts to accede one of the new oral anticoagulants to them.

A positive result of the first study, using the combination of aspirin and clopidogrel in patients with acute myocardial infarction, was defined only by evaluating the combined endpoint, which included nonfatal myocardial infarction, stroke, revascularization of the heart and cardiovascular death, the frequency of which turned out to be 20 % lower (p <0.001) [3]. Later on, there have been many studies, which included patients with acute coronary syndrome (ACS), patients with implanted stents in the coronary arteries, for which a double or multicomponent antithrombotic therapy was carried out, the results of which were evaluated using meta-analysis. As the main criterion of benefit, the independent authors used indicator of overall mortality. Other indicators — secondary for the patient combined points, on which there were based the findings of the authors who conducted the study, were compared with the risk of serious complications, particularly the risk of major bleeding that required to fill the loss of blood, or have caused death or disability of the patient. In one of the first meta-analyzes of data, obtained from > 35 thousand patients [4], there was no difference in overall mortality (p = 0.6) with a group of patients, who received a single antiplatelet (aspirin or clopidogrel). However, there was a significant (by 1.5–3 times) increase in the number of major bleeding (p <0.001) and a small (only by 9 %) reduction in the number of large cardiovascular events — myocardial infarction, stroke. In another meta-analysis [5], obtained in the treatment of ACS patients (n = 31 286) using dual antiplatelet therapy in combination with one of the new oral anticoagulants (antagonists of Xa factor, inhibitor of thrombin receptors), reduction in total mortality were also absent. The benefits of moderate decrease in risk of stent thrombosis is not higher than the risk of major bleeding. The number of major bleeding increased high significantly (p <0.001) in the triple antiplatelet therapy compared to the control group.

The results of the meta-analysis were confirmed in another meta-analysis [6], which included data obtained at 25 643 patients with ACS on a three component antithrombotic therapy — a combination of two antiplatelet agents and one antagonist of factor Xa or inhibitor of thrombin receptors, in comparison with the results of treatment with two antiaggregants. Triple antithrombotic therapy, compared with standard dual antiplatelet therapy, had no effect on overall mortality (p = 0.86), although the frequency of reinfarction decreased slightly (p = 0.02). However, the number of major bleeding increased dramatically, in 3 times, particularly intracranial (p <0.001). This indicates that the damage from the triple antithrombotic therapy outweigh the benefits.

We analyzed data collected from 30,866 patients with ACS, for whom to a dual antiplatelet therapy we joined one of the new oral anticoagulants (apixaban, rivaroxaban, direksaban, dabigatran), but only after 7–14 days from the onset of disease. In all studies, such therapy was accompanied by some reduction in the incidence only of the combined endpoint, but increased risk of major bleeding significantly (in 2 or more times) [7].

Thus, the attempts to increase the effectiveness of long-term antithrombotic therapy in patients with ACS, by increasing the dose of antiplatelet or simply

uncontrolled increase in the number of antithrombotic drugs, have not provided significant improvement in the results of treatment, and in particular the frequency of the primary endpoint — overall mortality. Some reduction in the combined endpoint (secondary point of its value) was accompanied by a significant increase in the risk of bleeding. Therefore, the results of the data meta-analysis, which was carried out by independent experts, point on the expediency of finding other ways to improve the long-term treatment of patients with different forms of coronary heart disease (CHD) with the help of antithrombotic drugs.

One of possible options in finding a solution to increase the therapy efficacy without increasing the risk of bleeding may be an individual choice of the drug, based on the extent assessment of its effect on platelet aggregation, particularly among patients with CHD who are in stable condition, including endured ACS. Today, many studies have shown an interconnection between high residual platelet reactivity (RPR), on the therapy, and mortality of patients with CHD [8–10]. Based on these data, target levels of reducing a platelet reactivity have been proposed, while on therapy with aspirin, clopidogrel [11]. Comparative evaluation of information content of methods for determining the aggregation platelet reactivity [12] showed that among the 5 studied methods only 3 methods are optical aggregometry; VerifyNow, Platelet works provided an opportunity to identify patients with high risk of endpoints. When using optical aggregometry, effective decrease of platelet reactivity level was suggested as < 46 %, and when using the VerifyNow — less than 208 units. Platelet aggregation during the treatment, which was higher than mentioned parameters, is defined as the high RPR, which indicates a lack of effectiveness of the antiplatelet. The incidence of high RPR in the data analysis, obtained in many studies including > 12 thousand patients under the supervision, differed sharply — from 6 % to 79 %.

Therefore to assess the possibility of individual choice of the drug, in this study, platelet aggregation reactivity was evaluated in the same patients on different preparations, with a help of laser optical aggregometry and determining the content of the thromboxane B2 in urine [13]. Reduction of metabolite of thromboxane A2 in urine, when determining antiaggregation activity of aspirin, indicates an inhibition of the synthesis of endogenous inducer of platelet aggregation in patient's blood, which further confirmed the results obtained by optical aggregometry.

To assess the reproducibility of results obtained using both methods, for patients in a control period, platelet aggregation was determined twice at an interval of 1 week, without altering the therapy. The differences in these indicators were inaccurate, that allowed to consider the used methods as useful for assessing the results of therapy during dynamic monitoring of patients. Comparative evaluation of two dosage forms of aspirin (resorbable in the mouth and absorbed in the intestine) demonstrated greater efficacy of the drug, resorbable in the mouth. The difference of obtained data is probably explained due to less influence on platelet aggregation by aspirin metabolites, which formed during the first passage of blood through the liver after its absorption in the intestine; which was manifested especially clearly in determining the concentration of thromboxane B2 in the urine. Comparative evaluation of antiplatelet activity of trombo ASS and clopidogrel showed that the enteric form of aspirin affects the platelet aggregation less. The target level of its reduction was achieved during taking trombo ASS only for 28 % of patients, while on therapy with clopidogrel — for 63 % of patients. Average value of RPR, in this group of patients, was also significantly reduced by treatment with clopidogrel (43 %) compared with aspirin (56 %). The presence of high RPR on the aspirin therapy indicates that its enteric form is not sufficiently effective for the majority of patients (72 %). For many of these patients, clopidogrel therapy provide a reducing of platelet aggregation reactivity to the target level. Among all patients only for 12 % of them on clopidogrel and aspirin therapy, the achieving of the target RPR level was not indicated, i.e. there was a resistance to the action of studied antiplatelet.

In March 2015, the results of study PEGASUS-TIMI 54 were published (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin), in which 21,162 patients were taken under the supervision, taking an aspirin in 1–3 years after suffering myocardial infarction [14].

All patients were divided into 3 groups: a) in the first group tikagrelol was attached to aspirin therapy at a dose of 90 mg 2 times a day; b) in the second group — tikagrelol was 60 mg also 2 times a day; c) in the third group patients received a placebo with aspirin. The median duration of observation was 33 months. The results of therapy: all-cause mortality on tikagrelol therapy did not differ from mortality in group on placebo therapy (in combination with aspi-

rin). In the first group 326 patients died (5.15 %), in the second group — 289 patients died (4.69 %), in the third group — also 326 patients died (15.16 %), differences are unreliable (p = 0.14). Similar with studies involving patients with ACS, in this study, a decrease in the risk of combined endpoint was also noted: cardiovascular death, myocardial infarction and stroke. The absence of reducing overall mortality on the tikagrelol therapy, with decreasing cardiovascular mortality, is probably due to available significant increase (at > 2 times) in the number of major bleeding on dual antiplatelet therapy. It is known that among the survivors with this complication, mortality increases significantly.

Thus, the high RPR is recorded in 72 % and 37 % of patients with chronic CHD, on monotherapy with the enteric aspirin form or clopidogrel respectively. The oral form (absorption in the mouth) of normal aspirin is favorably than enteric form, taking into account not only its pharmacy-economic evaluation. Disaggregation activity of clopidogrel is significantly higher than the aspirin enteric form activity. Patients, in whom aspirin or clopidogrel monotherapy does not provide reducing RPR to the target level, had resistance to the antiplatelet action. Therefore, for these patients prolonged antiplatelet therapy may be carried out using new oral anticoagulants, in particular by means of rivaroxaban. This recommendation is based on data, obtained in the study ATLAS-2 TIMI 51 (Acute Coronary Syndrome Thrombolysis in Myocardial Infarction) [15], in which the efficacy and safety of double and triple antithrombotic therapy were also compared in patients with ACS (n = 15 526).

To the standard therapy with aspirin and clopidogrel, 2.5 mg of rivaroxaban or 5 mg of placebo was added 2 times a day. The incidence of the combined endpoint decreased on triple antithrombotic therapy. However, overall mortality decreased at the expense of cardiovascular only on rivaroxaban therapy at a dose 2.5 mg — 2.9 % and 4.5 % respectively (p = 0.002). At the same time, the incidence of major bleeding increased > 3 times, including intracranial bleeding, especially at a dose 5 mg of rivaroxaban (p <0.001). The reduction of overall mortality in patients, who were on the rivaroxaban therapy at a small dose, may be a justification for the use of this dose for patients with resistance to antiplatelet action; which of course requires a confirmation in additional studies.

Efficacy and safety of the long-term combined multicomponent antithrombotic therapy are not so obvious for all patients without the current control; because it is useful in some patients, and it harms in approximately the same number of patients.

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