

Antiplatelet Therapy in Patients with Coronary Heart Disease After Implantation of Drug Eluting Stents

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Abstract: The article touched upon issues related to dual antiplatelet therapy after DES stent implantation in patients with coronary artery disease.

Key words: coronary heart disease, dual antiplatelet therapy, percutaneous coronary intervention.

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The relevance of research. The leading cause of mortality in the world is cardiovascular pathology, despite the high level of development of cardiology in recent years (S.G. Johnson et al. 2007).

The use of intracoronary stents can improve the results of endovascular procedures (EVP), but does not solve the problem of restenosis in general, the main cause of which is the proliferation of smooth muscle cells. The creation of stents with various drug coatings (SLP) was a logical continuation of the search for effective ways to prevent restenosis. Basically, drugs with an inhibitory effect on the proliferation and migration of smooth muscle cells are used to cover stents. (Z.A. Aligishieva, D. G. Ioseliani 2008)

After performing percutaneous interventions on coronary arteries (PMSC) patients require the use of two-component antiplatelet therapy (DCAT), including aspirin and a derivative of thienopyridine. There was evidence of a higher effectiveness of such tactics compared with the use of oral anticoagulants (PAK) for the prevention of stent thrombosis (Maklakov A.E., Vishnevsky V.I. 2015).

The largest meta-analysis of the Antithrombotic Trialists' Collaboration, combining the results of 145 clinical studies, showed that the use of antithrombotic therapy in high-risk patients reduces the risk of cardiovascular complications by 25%. Particularly significant advantages of antiplatelet therapy are noted in patients who have undergone acute coronary syndrome (ACS), as well as in those who have had coronary artery surgery, primarily with the installation of a stent.

The purpose of research

To conduct a comparative evaluation of the effectiveness of various types of antiplatelet therapy on platelet aggregation activity in patients with coronary artery disease after implantation of DES stents.

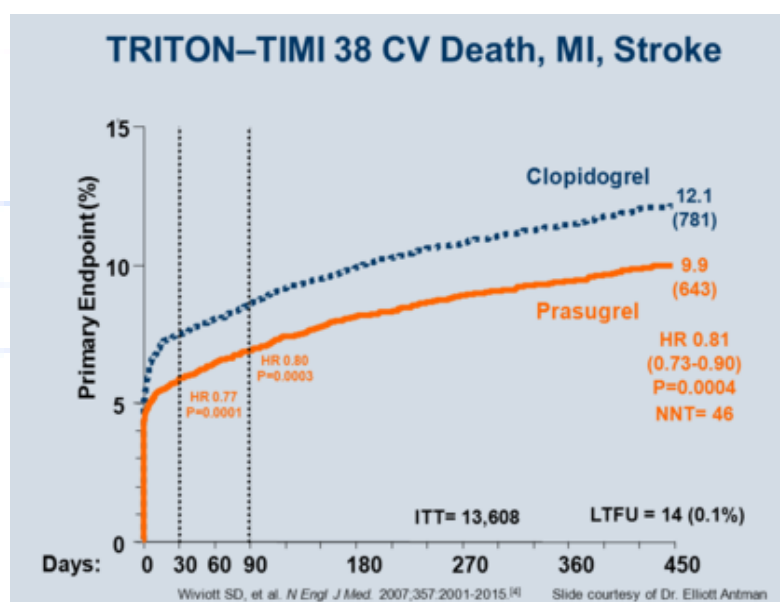
Double antiplatelet therapy using aspirin and a P2U12 receptor inhibitor is the basis of therapy for patients with acute coronary syndrome who are scheduled to undergo percutaneous coronary angioplasty. Clopidogrel is the most widely used inhibitor of P2U12 receptors[3]. ASA and clopidogrel – a number of large randomized trials have demonstrated that the use of such a combination is more effective than monotherapy with ASA, clopidogrel or any other antiplatelet reduces the risk of ischemic events with comparable safety (CURE, COMMIT/CCS-2, CREDO, CHARISMA, CLARITY-TIMI 28). Despite the clinical success of dual antiplatelet therapy using aspirin and clopidogrel, a significant number of patients develop recurrent cardiovascular complications. It should be noted that the body's response to clopidogrel, in various patients, depends on certain factors, such as: genetic polymorphism; taking drugs that disrupt the conversion of clopidogrel into its active metabolite. The variability of antiplatelet effects induced by clopidogrel proves its significant clinical effect, including an increased risk of atherothrombotic relapses (including stent thrombosis). The introduction of new P2U12 receptor inhibitors (in particular, prasugrel and ticagrelor), characterized by a more powerful and uniform inhibitory effect on platelets, allows doctors to consider these alternative drugs as an alternative to clopidogrel. Thus, understanding the strategies and consequences of switching from one antiplatelet therapy regimen to another is a key aspect of clinical practice.

Prasugrel is a thienopyridine of the third generation, which is registered as a drug for the prevention of thrombotic cardiovascular complications in patients with ACS who are scheduled for PCI [8]. According to the results of clinical studies, in healthy volunteers and in patients with stable angina pectoris, prasugrel has a faster effect compared to clopidogrel, also when taking prasugrel, a higher and persistent level of platelet inhibition is observed, less variability between patients, and an inadequate response is observed in fewer patients [2]. In the study TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel – Thrombolysis in Myocardial Infarction 38, a study to assess the improvement of clinical outcomes by optimizing platelet inhibition by prasugrel – thrombolysis in myocardial infarction 38) improved results of the effectiveness of prasugrel compared with clopidogrel were shown with respect to reducing the complex endpoint, which included deaths from cardiovascular causes, MI without fatal outcome or stroke without fatal outcome in patients with ACS of medium and high risk groups who were scheduled for PCI [1]. Similar results have been achieved in other studies (JUMBOTIMI 26 , PRINCIPLE TIMI-44). The described positive effect is mainly due to a decrease in the frequency of MI development. Prasugrel proved to be more effective in reducing the frequency of stent thrombosis, as in the early period (in the first 30 days) so in the late stages of treatment (up to 15 months) and a positive effect was recorded regardless of the type of stents. In addition, in patients with prasugrel therapy who survived after the first event, there was a decrease in the risk of recurrent myocardial ischemia, including with a fatal outcome, compared with clopidogrel [5]. However, in this study, when prescribing prasugrel, an increase in the risk of "large" bleeding, including fatal bleeding, was found compared with clopidogrel. S. D. Wiviott et al. the pharmacodynamic effects of prasugrel (Loading dose of 60 mg) were compared/Maintenance dose of 10 mg with clopidogrel in a high loading dose of 600 mg / maintenance dose of 150 mg in relation to laboratory parameters of platelet functions in 201 patients with coronary heart disease who were scheduled for PCI. All participants were included in a randomized double-blind cross-sectional phase II clinical trial [2]. Platelet inhibition was more pronounced when prescribing prasugrel in comparison with clopidogrel at all studied points during the phases of loading and maintenance therapy. The primary endpoint of efficacy (in the loading dose phase), which was IAT when stimulated with an ADP solution at a final concentration of 20 microns 6 hours after taking ND, was significantly higher in patients taking prasugrel at a dose of 60 mg, compared with patients receiving clopidogrel at a dose of 600 mg (74.8 and 31.8% accordingly)

According to the results of the TRITON-TIMI 38 study, the primary endpoint of efficacy occurred in 12.1% of patients treated with clopidogrel and in 9.9% of patients treated with prasugrel (prasugrel risk ratio relative to clopidogrel, 0.81; 95% confidence interval [CI], 0.73 to 0.90; $P < 0.001$). In the prasugrel group, there was a significant decrease in the frequency of myocardial infarction (9.7% for clopidogrel vs. 7.4% for prasugrel; $P < 0.001$), urgent (urgent) revascularization of the target vessel (3.7% vs. 2.5%; $P < 0.001$), and stent thrombosis (2.4% vs. 1.1%; $P < 0.001$). Major bleeding was observed in 2.4% of patients treated with prasugrel and in 1.8% of patients treated with clopidogrel (risk ratio 1.32; 95% CI, 1.03 to 1.68; $P = 0.03$). In addition, the frequency of life-threatening bleeding was higher in the prasugrel group (1.4% vs. 0.9%; $P = 0.01$), including non-fatal bleeding (1.1% vs. 0.9%; risk ratio, 1.25; $P = 0.23$) and bleeding resulting in death (fatal) (0.4% vs. 0.1%; $P = 0.002$).

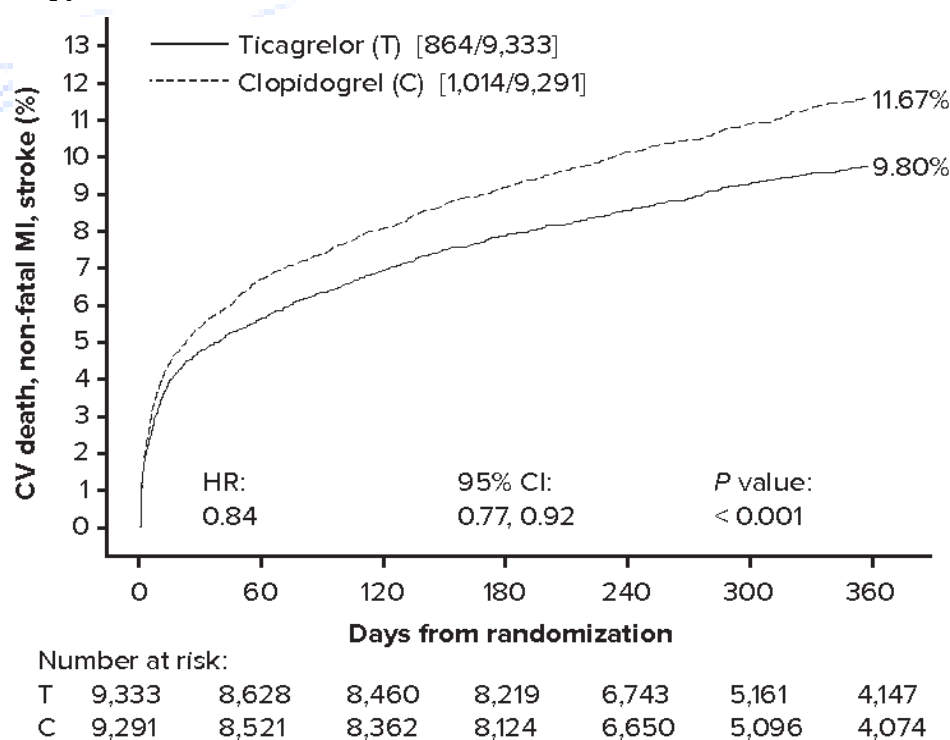
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Ticagrelor (non-thienopyridine reversible direct-acting P2Y₁₂ receptor antagonist for oral administration) The PLATO study (Platelet Inhibition and Patient Outcomes, platelet Inhibition and patient treatment Outcomes) is a multicenter, randomized, double-blind, two-placebo controlled trial, in which ticagrelor (180 mg ND followed by PD 90 mg 2 times a day) was compared with clopidogrel (300-600 mg ND followed by PD 75 mg/day) as a means of preventing vascular complications and deaths in 18,624 patients with stable angina pectoris, with or without ST segment elevation [6]. The primary endpoint represented a complex endpoint that included vascular complications, MI, or stroke. Overall, ticagrelor was more effective in reducing primary endpoint events compared to clopidogrel (9.8 and 11.7%, respectively; $p < 0.001$). The results of the PLATO study as a whole were confirmed in patients who were scheduled for PCA [1]. Since the design of the PLATO study provided the possibility of open use of clopidogrel before randomization, and 46% of patients from the ticagrelor group received clopidogrel in the open mode, the PLATO study in these patients practically represented the transition from clopidogrel to ticagrelor. This is how it differs from the TRITON

study, from which patients who received preliminary therapy with clopidogrel were excluded [2]. The transition from clopidogrel to ticagrelor in the PLATO study did not lead to any safety problems, while for the results of the safety assessment of the PLATO study as a whole, no significant differences were found between ticagrelor and clopidogrel in the overall frequency of "large" bleeding, according to their definition in this study (11.6 and 11.2%, respectively; $p=0.43$) and according to TIMI criteria (7.9 and 7.7%; $p=0.57$). Nevertheless, ticagrelor therapy was accompanied by a higher frequency of "large" bleeding not associated with CABG (4.5 and 3.8%, respectively; $p=0.03$) and a large number of cases of fatal intracranial bleeding (0.1 and 0.01%; $p=0.02$) compared with clopidogrel [7]. The antiplatelet activity of ticagrelor in patients previously treated with clopidogrel, stratified into 2 groups depending on the level of response to clopidogrel, was studied in the RESPONSE study (Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies, response to ticagrelor in patients with and without response to clopidogrel and the effect of switching therapy). During the 1st period of this cross-clinical trial, patients without a response to clopidogrel (identified by LTA assessment) and patients with a response were randomized to receive clopidogrel at a dose of 600 mg (ND) followed by 75 mg once a day and for ticagrelor therapy 180 mg (ND) followed by 90 mg 2 times a day for 14 days [7]. During the 2nd period, all patients who did not respond to the therapy were transferred to another drug. The primary endpoint of this analysis was an estimate of the proportion of patients without a response to clopidogrel who had a response to ticagrelor based on the results of an assessment of platelet aggregation 4 hours after taking the drug in an equilibrium state. Platelet aggregation decreased from 59% to 35% in all patients who switched from clopidogrel to ticagrelor ($p < 0.0001$). According to the results of the study, ticagrelor therapy compared with clopidogrel is associated with more pronounced inhibition of platelets in patients with and without response to clopidogrel, while the antiplatelet effects of ticagrelor are not affected by the patient's response status to clopidogrel. Ticagrelor therapy seems to overcome the lack of response to clopidogrel, and has similar efficacy when prescribed to patients with and without a response to treatment [5]. During therapy with clopidogrel, no events related to the development of bleeding were detected, while 1 "large" and 3 "small" bleeding was recorded against the background of ticagrelor therapy



Conclusions

Dual antiplatelet therapy with the appointment of thienopyridine and aspirin is the basis of therapy for patients with coronary heart disease after implantation of DES stents. But since therapy with the inclusion of clopidogrel is characterized by significant variability (it is influenced by the genetic polymorphism of CYP450 and drugs that inhibit the conversion of clopidogrel into its active metabolite), switching from clopidogrel to prasugrel or ticagrelor may be an effective and safe alternative for patients in whom further therapy with clopidogrel is impractical.

List of used literature

1. Wiviott S.D., Braunwald E., McCabe C.H., Montalescot G., Ruzyllo W., Gottlieb S., Neumann F.J., Ardissino D., De Servi S., Murphy S.A., Riesmeyer J., Weerakkody G., Gibson C.M., Antman E.M.; TRITON-TIMI 38 Investigators. N Engl J Med 2007; 357: 2001-2015.
2. Hughes S. TRITON-TIMI 38: What role for prasugrel in ACS www.theheart.org. November 5, 2007.
3. The effect of acetylsalicylic acid and clopidogrel on the structural and functional state of erythrocytes in acute coronary syndrome A.L. Alavi, R.A. Rakhimova, B.A. Alavi. Rational Pharmacotherapy in Cardiology 2009; No. 5.
4. Some aspects of the efficacy and safety of statins and antiplatelet agents in coronary heart disease after interventional intervention. BA Alavi, AH Abdullayev, NR Raimkulova, MM Karimov, LCD Uzokov, SHA Iskhakov.
5. Transition between antiplatelet therapy regimens. Alternatives to clopidogrel in patients with acute coronary syndrome who are scheduled for percutaneous coronary angioplasty: Sh.Azmun, D. Angiolillo 2014.
6. Kelly R.P., Close S.L., Farid N.A., Winters K.J., Shen L., Natanegara F. et al. 2012. Pharmacokinetics and pharmacodynamics of maintenance doses of prasugrel and clopidogrel in Chinese carriers of CYP2C19 variants. Br J Clin Pharmacol. 73
7. Mauri L., Kerejakes D. D., Ye R. V. et al. 2014. Twelve or 30 months of double antiplatelet therapy after drug-coated stents. N Engl J Med. 371
8. <http://www.escardio.org/guidelines>