Review

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Antiplatelet Therapy in Acute Coronary Syndrome

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ABSTRACT Cardiovascular diseases are currently the most common causes of death worldwide, and most deaths from cardiovascular diseases are associated with coronary artery disease (CAD). CAD as a whole is a serious problem for the world's population, and acute coronary syndrome (ACS) is associated with high morbidity, mortality and a great financial burden on the health care system. This is an urgent situation in which diagnostic and treatment measures must be performed as soon as possible from the moment of onset of the disease. Diagnosis of ACS begins with a thorough clinical assessment of the patient's symptoms, electrocardiogram and blood troponin levels, as well as a history of the disease. Key components in the treatment of ACS include coronary revascularization when indicated and prompt initiation of adequate antiplatelet therapy. The presented literature review is devoted to the problems of adequate antiplatelet therapy in patients with ACS.

Keywords: acute coronary syndrome, STE-ACS, NSTE-ACS, thrombosis, antiplatelet therapy, dual antiplatelet therapy (DAPT), escalation, de-escalation

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ADP — adenosine diphosphate
GP — glycoprotein
DAPT — dual antiplatelet therapy
IHD — ischemic heart disease
MI — myocardial infarction
NSTE-ACS — non-ST-segment elevation acute coronary syndrome
STE-ACS — ST-segment elevation acute coronary syndrome
Ld — loading dose
UA — unstable angina
ACS — acute coronary syndrome
NSTEMI — non-ST-elevation myocardial infarction
STEMI — ST-segment elevation myocardial infarction
Md — maintenance dose

T ½ — half-life
VWF — von Willebrand factor
COX — cyclooxygenase
PCI — percutaneous coronary intervention
BARC — Bleeding Academic Research Consortium
CAD — cardiovascular disease
TXA2 — thromboxane A2
PAR-1 — protease-activated receptor-1
P2Y12 — chemoreceptor for adenosine diphosphate (ADP)

INTRODUCTION

Cardiovascular diseases are currently responsible for about one third of all deaths in the world. And among them ischemic heart disease (IHD), including acute coronary syndrome (ACS), occupies a leading position [1]. More than 500,000 new cases of ACS are registered annually in Russia, including more than 120,000 confirmed myocardial infarctions (MI) [2].

ACS is characterized by a combination of clinical symptoms associated with acute myocardial ischemia and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), and sudden cardiac death (SCD) [3]. Unstable angina pectoris and STEMI are closely related conditions: their pathophysiological origins and clinical manifestations are similar, but differ in severity [4]. The pathophysiological basis of NSTE-ACS is atherosclerotic plaque rupture accompanied by thrombus formation with partial occlusion of the arterial lumen [5, 6].

STE-ACS develops in case of acute complete or subtotal coronary occlusion. Most patients eventually develop ST-segment elevation myocardial infarction (STEMI) [7]. The main areas of treatment for those patients are: 1. Early reperfusion (percutaneous coronary intervention (PCI)) or, if it is impossible to perform timely PCI, fibrinolytic therapy; 2. Antiplatelet therapy; 3. Secondary prevention of atherothrombosis [8].

Over the past few years, clinical, anatomico-pathological observations and experimental studies have led to a better understanding of the pathogenesis of ACS. Research by Falk, Davies, and Thomas highlighted that plaque rupture and fissures in an atherosclerotic coronary artery play an important role in the ACS development [9]. The pathogenesis of IHD is a complex interaction between the endothelium, inflammatory cells (T and B lymphocytes, monocytes, macrophages) and blood thrombogenicity [10]. The usual anatomical substrates of ACS is coronary thrombosis after rupture or erosion of an inflamed atherosclerotic plaque, followed by partial or complete coronary occlusion and ischemia of the corresponding area of the myocardium. The degree of intracoronary thrombosis and distal embolization determines the clinical picture, ranging from UA without myocardial necrosis to NSTEMI and STEMI.

The starting point in the development of atherosclerosis is the infiltration of the intima and subendothelium with lipids and lipoproteins. As lipids accumulate in the core of the plaque, its size increases, and as a result the fibrous cap of the plaque becomes thinner due to the action of specific enzymes (elastases, metalloproteinases) and, under certain conditions (increased blood pressure, heavy exercise), ruptures. The rupture is accompanied by activation of the blood coagulation cascade, platelet aggregation with the formation of a thrombus that blocks the flow of blood in a blood vessel [11].

Platelets play a key role in blood clot formation in the lumen of the coronary artery. Thrombus formation consists of three main stages: platelet adhesion, activation and aggregation. The adhesion of platelets to the subendothelium occurs due to the interaction of the GPIb-IX-V complex located on the platelet surface and von Willebrand factor (VWF), as well as collagen accumulated at sites of vascular injury and platelet collagen receptors. After adhesion, numerous mediators and biologically active substances (thromboxane A2 (TXA2)), serotonin, adrenaline and thrombin) activate platelets and lead to a change in their shape, expression of pro-inflammatory molecules (soluble CD40 ligand and P-selectin) and platelet procoagulant activity. The last step in thrombus formation is the activation of the GP IIb / IIIa receptor in platelets. Activated GP IIb / IIIa receptors bind to soluble adhesive substrates, including fibrinogen and VWF, which results in platelet aggregation and thrombus formation. Vascular injury exposes subendothelial tissue factor, activates blood coagulation cascade leading to the formation of thrombin which is one of the most effective activators of platelets. During thrombus formation, thrombin converts fibrinogen into fibrin, which further activates platelets. Consequently, atherogenesis involves a complex interaction between the blood vessel wall, blood

corpuscles (predominantly, platelets), biologically active substances dissolved in the blood, and a local disturbance of blood flow (R. Virchow's triad) [12].

ANTIPLATELET DRUGS

The active participation of platelets in thrombus formation and the versatility of their functional activity determine the expediency of pharmacological influence on platelet hemostasis in patients with ACS both for therapeutic and prophylactic purposes. The antiplatelet drugs available today differ in the mechanism of action and the point of application to certain platelet receptors. These drugs include: (1) cyclooxygenase (COX) inhibitors - aspirin; (2) P2Y12 receptor blockers - ticlopidine, clopidogrel, prasugrel, ticagrelor and cangrelor; (3) glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors - abciximab, eptifibatide, tirofiban; and (4) a protease-activated receptor-1 (PAR-1) inhibitor - vorapaxar [13].

Aspirin administration has been the gold standard for the treatment and prevention of complications of cardiovascular disease for many years. Aspirin exerts its antiplatelet effect by irreversibly inhibiting the COX-1 enzyme via acetylation. This blocks the production of thromboxane A2 (TXA2), a platelet agonist, thereby reducing the likelihood of a blood clot formation. The drug is rapidly absorbed in the upper gastrointestinal tract [14]. In order to prevent stent thrombosis in patients after myocardial infarction, dual antiplatelet therapy is recommended for a year, followed by lifelong intake of aspirin, while patients with angina pectoris (stable or unstable) are prescribed aspirin monotherapy. Randomized clinical trials have shown that aspirin is an effective antithrombotic agent at doses ranging from 50 to 100 mg / day. There are no clinical trials showing the efficacy of high dose aspirin in reducing cardiovascular risk. The issue of minimizing the dose of the drug continues to be under active consideration [15].

Dual antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) is a standard treatment for ACS patients.

The first drug in this class was ticlopidine (thienopyridine), but its administration was largely discontinued due to frequent and severe side effects, including life-threatening bleeding, neutropenia, and thrombotic thrombocytopenic purpura [16]. P2Y12 inhibitors are classified according to their ability to bind to platelet receptors: thienopyridines (clopidogrel and prasugrel) and triazolopyridines (ticagrelor).

Clopidogrel is a second generation thienopyridine that irreversibly binds to the purinergic P2Y12 receptor inhibiting platelet activation and aggregation. It is safer than ticlopidine and provides a faster onset of action 2 hours after the loading dose. Clopidogrel is a prodrug that requires metabolic conversion to become antiplatelet effective. Approximately 85% of clopidogrel is hydrolyzed to an inactive metabolite by carboxylase in the intestine, the remaining approximately 15% is rapidly metabolized by hepatic cytochrome P450 (CYP) isoenzymes [17]. Randomized controlled trials have shown that clopidogrel alone is more effective than aspirin for the prevention of cardiovascular disease. And in combination with aspirin, clopidogrel significantly reduces mortality in patients with MI and improves outcomes in patients after PCI (pharmacokinetic parameters are shown in the Table) [18]. Despite the fact that clopidogrel is the most widely used antiplatelet drug, studies have shown that 5–44% of patients show poor responses to this medicine, which has led to development of new P2Y12 antagonists [19].

Ticagrelor is a cyclopentyltriazolopyrimidine that directly and reversibly inhibits the P2Y12 receptor. Ticagrelor is not a prodrug and does not require metabolic activation. The efficacy and safety of ticagrelor for patients with ACS was evaluated in the PLATO study. The study included patients with ACS who received both invasive and non-invasive treatment. Compared with clopidogrel, ticagrelor significantly reduced the overall mortality rate and the likelihood of developing AMI by 16%. Treatment with ticagrelor also significantly reduces the incidence of stent thrombosis [20]. Non-bleeding side effects of ticagrelor, such as a high incidence of dyspnea (15–22% of patients) and ventricular arrhythmias, as well as elevated creatinine and uric acid levels, are factors that limit its intake. It is important to note that ticagrelor did not have any effect on the objective lung function parameters: spirometry, total lung capacity, vital capacity, diffusing capacity and pulse oximetry [21]. Ticagrelor should not be used in patients with a high grade of atrioventricular block or sick sinus syndrome. No dose adjustment is required depending on age or body weight. It is recommended by the European Society of Cardiology that patients at high risk for MI should continue taking ticagrelor (60 mg 2 times a day) after a year of taking DAPT with 90 mg ticagrelor 2 times a day in order to prevent the risk of death from cardiovascular disease, myocardial infarction or stroke [22].

Table

Antiplatelet therapy in patients with acute coronary syndrome

Drugs	Method of administration, dosage regimen	Pharmacokinetics	Routes of drug administration	Drug interactions	Special remarks
Cyclooxygenase (COX) inhibitor - Aspirin	Ld: 150–300 mg orally or 75–250 mg intravenously, Md: 75–100 mg / day	T½ 3,5–4,5 h	Oral, sublingual, or intravenous	With P2Y12 inhibitors (prasugrel, ticagrelor, or clopidogrel)	
P2Y12 adenosine diphosphate (ADP)-receptor antagonists - Антагонисты рецептора аденозиндифосфата *P2Y*12 — ticlopidine, clopidogrel, prasugrel, ticagrelor, cangrelor	Clopidogrel - Ld: 600 mg orally, Md: 75 mg / day. Prasugrel- Ld: 60 mg orally, Md: 10 mg / day. Ticagrelor – Ld: 180 mg orally, Md: 90 mg 2 times / day	Clopidogrel - T½ 8 hours Prasugrel - T½ 7.4 hours Ticagrelor - T½ 7 and 8.5 hours	Oral		At the time of writing cangrelor is not registered for clinical use in the Russian Federation
GP IIb / IIIa inhibitors - abciximab, eptifibatide and tirofiban	Abciximab – bolus: 0.25 mg / kg, followed by: 0.125 mcg / kg / min (max 10 mcg / min) Eptifibatide - bolus: 180 mcg/kg followed by: 2.0 mcg/kg/min up to 18 hours Tirofiban – bolus: 25 mcg / kg, followed by: 0.15 mcg / kg / min	Abciximab: Initial T½ - 10 minutes, terminal T½ - 30 minutes. Eptifibatid :Plasma T1 / 2 - 2.5 hours Tirofiban: T½ - 2 hours	Intravenous		
Protease-activated receptor-1 (PAR-1) antagonist— Vorapaxar	Ld: 10, 20 and 40 mg, Md - 0.5, 1.0 and 2.5 mg / day	T½ 173–269 hours	Oral		Due to the high risk of bleeding, the III phase of the TRACER trial was prematurely terminated

Notes: Ld — loading dose, Md — maintenance dose, T½ — half-life

Prasugrel is a third generation thienopyridine. It is a prodrug that, after absorption in the intestine, requires one-step oxidation by cytochrome P450 isoenzymes to produce its active metabolite [23]. Prasugrel has a faster, stronger (increased platelet inhibition) and more predictable (lower interindividual variability) antiplatelet effect compared to clopidogrel. Prasugrel administration is indicated for patients undergoing percutaneous coronary intervention. The TRITON-TIMI trial showed that prasugrel significantly reduced the risk of cardiovascular death, nonfatal MI or nonfatal stroke compared with clopidogrel. The incidence of stent thrombosis is decreased by 52%, regardless of its type, and the need for urgent revascularization of the symptom-associated vessel decreased by 34%. However, along with this, the risk of developing massive bleeding increased. Prasugrel is contraindicated in patients with a history of stroke and / or transient ischemic attack, severe renal failure (stage C), with a high risk of bleeding, and it is not recommended to take the drug in patients weighing less than 60 kg and aged 75 years and older [24].

Cangrelor is a potent parenteral P2Y12 inhibitor approved by the FDA in 2015 for the reduction of ischemic events in PCI patients who have not received prior treatment with a P2Y12 antagonist. Bolus administration of cangrelor within two minutes develops a powerful antiplatelet effect and is characterized by a linear dose-dependent profile that leads to stable pharmacodynamic effects. A pooled analysis of the data from three studies showed that the use of cangrelor, on the one hand, is associated with a decreased risk of perioperative ischemic complications, but on the other hand, with an increased risk of bleeding. Cangrelor has been currently approved by US and European regulatory agencies for use in PCI patients, although it has not yet been recommended for clinical use by the National Institute for Health and Care Excellence (NICE) [25].

PARs are a family of G-protein-coupled seven transmembrane domain receptors. Four types of PARs are described. PAR-1 and PAR-4 are expressed in human platelets, PAR-1 plays a major role in platelet activation at low thrombin concentrations, while PAR-4 activation occurs only at high thrombin concentrations. Of all the PAR-1 antagonists, only vorapaxar has completed phase III clinical trials and is currently available for clinical use. However, in the TRACER study, vorapaxar did not reduce the risk of cardiovascular events, but significantly increased the risk of major bleeding [26].

The complex platelet glycoprotein (GP) IIb / IIIa is another pathway of platelet activation. This glycoprotein mediates platelet adhesion through binding to fibrinogen, thereby forming bridges between platelets. Subsequently, a hemostatic platelet plug develops, which increases in size with further platelet activation [27]. GP IIb/IIIa inhibitors block this pathway and thus reduce thrombus formation. Among the drugs of this class, abciximab (a fragment of a monoclonal antibody), tirofiban (a small nonpeptide molecule) and eptifibatide (a cyclic heptapeptide derived from rattlesnake venom) are used in clinical practice [28]. The use of GP IIb/IIIa inhibitors is advisable in case of extensive thrombosis, poor circulation or absent blood flow. However, the efficacy of GP IIb/IIIa inhibitors has not been proven in randomized clinical trials. Thus, there is no evidence to support the routine use of GP IIb / IIIa blockers during PCI. They have previously been used as key treatment strategies for acute MI. However, in recent years, the use of GP IIb / IIIa inhibitors has faded into the background in the treatment of patients with ACS compared to P2Y12 inhibitors. In addition, the presence of hemorrhagic complications also prevents their widespread use in clinical practice [29].

TRADITIONAL REGIMEN AND DURATION OF ANTIPLATELET THERAPY

DAPT with aspirin and a P2Y12 receptor antagonist is the method of choice for the prevention of atherothrombotic events both in patients with ACS and those undergoing endovascular intervention. DAPT reduces the risk of ischemic events such as (re) infarction and the risk of stent thrombosis in patients after PCI [30]. Current international guidelines recommend the use of prasugrel or ticagrelor in combination with aspirin as first-line therapy in patients with ACS [31]. In most cases, ticagrelor is preferred over clopidogrel, and prasugrel is preferred over clopidogrel in patients after PCI. On the other hand, clopidogrel is recommended for patients with systemic fibrinolysis. According to the most international recommendations, the duration of DAPT in patients with ACS is usually 12 months. This time period was selected based on the results of the CURE trial [32]. Nevertheless, the optimal duration of DAPT remains debatable. The research in this regard continues. Thus, long-term use of DAPT effectively prevents thrombotic and ischemic events, but significantly increases the risk of bleeding. Shorter DAPT significantly reduces the risk of bleeding, but the effect on mortality is controversial. Understanding which strategy is most clinically beneficial can play a role in the choice of treatment duration. Therefore, individualization of drug therapy can help in choosing the optimal strategy. In this connection, special scales have been developed for calculating individual risk when making decisions regarding the duration of DAPT. The PRECISE-DAPT risk calculator assigns scores based on patient age, creatinine clearance, hemoglobin, white blood cell count, and a history of spontaneous bleeding. Patients stratified by the PRECISE-DAPT and having a high score (score ⩾25) had a significant increased bleeding rate after a longer course of DAPT without any decrease in ischemic events. A low score (less than 25) indicates the possibility to safely extend DAPT duration, which is associated with a significant decrease in the incidence of thrombotic and ischemic events [33]. Using the DAPT score, you can decide whether to interrupt treatment after 12 months or to extend it up to 30 months after PCI [34].

MANAGEMENT OF ANTIPLATELET THERAPY

In recent years, approaches to managing the risks of ischemic and hemorrhagic events in patients with previous ACS episodes have been actively discussed. One of these approaches is to prescribe DAPT for a period of 1 year in order to reduce the risk of cardiovascular events in patients after MI or UA, regardless of the fact and method of revascularization. The changing of DAPT duration is allowed only if the patient has a high risk of bleeding (A HAS-BLED score of ⩾3, BARC scale of ⩾3, CRUSADE score of ⩾ 40, REACH score of ⩾ 9) [35]. Under certain clinical scenarios, the DAPT duration can be shortened (less than 12 months) or extended (more than 12 months), or modified (switched DAPT). These decisions depend on an individual clinical assessment, determined by the patient risk factors for bleeding and ischemic events, the occurrence of adverse events or decompensation of concomitant diseases, however, minor bleeding (nasal, from the gums) is not an indication for discontinuation of DAPT. In patients with NSTE-ACS and stent implantation who have a high risk of bleeding (eg, meeting PRECISE-DAPT ⩾25 or ARC-HBR criteria), discontinuation of P2Y12 inhibitor therapy should be considered after 3–6 months. In case of a very high risk of bleeding (BARC scale 3-5), a recent episode of bleeding (one month), or if there is a planned or urgent surgery in the near future, the possibility of taking aspirin and clopidogrel for 1 month should be considered [36, 37].

The clinical consequences of early discontinuation of DAPT in patients after ACS are obvious and are associated with the development of unfavorable cardiovascular outcomes. In turn, the significance of the transition from more potent P2Y12 inhibitors - ticagrelor and prasugrel - to clopidogrel and vice versa has

become the subject of active discussion only in recent years [38]. Modern clinical guidelines insist on the importance of maintaining DAPT for a year, and therefore the issue of individual selection, adjustment and switching between P2Y12 inhibitors has been actively discussed in the updated 2017 and 2020 guidelines.

Prasugrel and ticagrelor are characterized by enhanced pharmacodynamic effects compared to clopidogrel. Thus, switching between oral P2Y12 inhibitors may result in transition from a weaker drug to a stronger drug (eg, from clopidogrel to prasugrel or ticagrelor) or vice versa, from a stronger agent to a weaker agent (eg, from prasugrel or ticagrelor to clopidogrel). These modes of switching are defined as escalation and de-escalation of antiplatelet therapy [39]. Switching between prasugrel and ticagrelor is referred to as antiplatelet treatment change. The main problem with changing P2Y12 inhibitors is the risk of stent thrombosis in the event of inadequate platelet inhibition. Since thrombotic risk is highest during the first weeks after ACS or PCI, the timing of switching may be of therapeutic value. Accordingly, the transition time can be divided into phase segments: acute (less than 24 hours), early (1-30 days), late (30 days - 1 year) or very late (more than 1 year) [40]. The switching between drugs is carried out from the moment of taking the loading dose of the antiplatelet agent.

ANTIPLATELET DRUG REGIMENS

The reasons for changing an antiplatelet drug regimen can be very different: the development of massive bleeding, side effects of ticagrelor (shortness of breath), an indication for the addition of an anticoagulant (atrial fibrillation, left ventricular thrombosis), anemia, cost and availability of drugs, repeated MI in the hospital, young age, II-III grade obesity, concomitant pathologies (diabetes mellitus) [41]. In most cases, switching occurs in the operating room during or immediately after PCI.

Escalation (switching from clopidogrel to prasugrel or ticagrelor)

In the SWAP study conducted in patients receiving maintenance therapy with clopidogrel for ACS, transition from clopidogrel to prasugrel decreased platelet reactivity according to aggregometry data within 2 hours after taking 60 mg prasugrel loading dose followed by maintenance therapy of 10 mg for a week [42]. Escalation from clopidogrel to prasugrel or ticagrelor in the early, especially acute phase of treatment should occur with a loading dose of 60 mg prasugrel or 180 mg ticagrelor, respectively. The loading dose can be administered regardless of the time of the last clopidogrel dose. Thereafter, standard treatment regimens should be used: prasugrel 10 mg once a day or ticagrelor 90 mg 2 times a day. Studies that examined the transition from clopidogrel to prasugrel or ticagrelor consistently demonstrate that such escalation results in increased platelet inhibition, regardless of the clinical situation, as well as decreased platelet reactivity. Concerns about the increased risk of bleeding in case of prasugrel and ticagrelor administration remain the most important reasons for the escalation of antiplatelet therapy. Non-bleeding side effects such as shortness of breath are also a potential reason for discontinuing ticagrelor therapy [43].

De-escalation (switching from prasugrel or ticagrelor to clopidogrel)

Due to the difficulties in keeping some patients on DAPT with the use of novel antiplatelet drugs, it became necessary to switch therapy to clopidogrel. The TROPICAL-ACS trial examined the efficacy of the controlled reduction of antiplatelet therapy - one week of prasugrel followed by a change to clopidogrel during one week. Despite early de-escalation, there was no increased risk of cardiovascular death, MI, or stroke. The incidence of bleeding was not higher than in the group with long-term prasugrel intake. Thus, it was concluded that it is possible to obtain maximum benefit with minimally aggressive DAPT. The PRAGUE-18 study assessed the risk of complications and bleeding in patients switching to clopidogrel from prasugrel or ticagrelor after hospital discharge, and the researchers also noted a lower risk of cardiovascular complications compared with long-term use of novel antiplatelet drugs. The issue of de-escalation is especially important for patients with the need for simultaneous anticoagulant therapy (paroxysmal atrial fibrillation, left ventricular thrombosis). In the acute phase of de-escalation, 600 mg of Ld of clopidogrel is prudent and should be indicated during the next scheduled dose of P2Y12 inhibitor therapy (eg ~ 24 hours after the last dose of prasugrel). This strategy is convenient from a practical point of view, since it partially compensates for the effects of prasugrel and ticagrelor [44]. Clinical data show that the prevalence of nosocomial de-escalation is 5 to 14% [44]. The HOST-REDUCE-POLYTECH-ACS study shows that in patients after drug-eluting stent placement prasugrel dose reduction from 10 to 5 mg after 1 month of standard therapy significantly reduces incidence of major hemorrhage without adverse factors [45].

Change (switching between prasugrel and ticagrelor)

To date, there is limited information on the possibility of switching between the new generation P2Y12 inhibitors prasugrel and ticagrelor. Few studies show that switching rates between these agents range from 2% to 4%. Doctors may consider switching to prasugrel because it is administered only once a day, which may improve patient adherence to therapy. Another reason to consider switching from ticagrelor to prasugrel is shortness of breath associated with ticagrelor. The SWAP-3 study sought to assess the pharmacodynamic effects of switching from prasugrel to ticagrelor. The study showed that in patients who received prasugrel maintenance therapy switching to ticagrelor was associated with a temporary decrease in platelet reactivity, which might persist for several days after drug withdrawal. While switching from ticagrelor to prasugrel, a prasugrel loading dose of 60 mg should always be used 24 hours after the last ticagrelor administration, as this allows more time for ticagrelor and its metabolite to be cleared from the body and for new platelets to enter the systemic circulation [40, 43]. Switching between P2Y12 inhibitors after hospital discharge occurs in 5–8% of patients [46].

CONCLUSION

Platelet hemostasis is key in the pathogenesis of acute coronary syndrome, and antiplatelet therapy is the main direction of its pharmacological treatment. That said, dual antiplatelet therapy has become standard for those patients. The emergence of novel antiplatelet drugs has led to the formation of the concepts of escalation and de-escalation of antiplatelet therapy. These concepts certainly deserve due attention and further research.

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