

Significance of antiplatelet therapy in emergency myocardial infarction treatment

Anna Komosa, Maciej Lesiak, Andrzej Siniawski, Tatiana Mularek-Kubzdela, Stefan Grajek

1st Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland

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Abstract

Antiplatelet drugs play a crucial role in the treatment of patients with myocardial infarction, particularly in association with percutaneous coronary intervention. Their main advantage is the reduction of adverse ischemic incidents and the major disadvantage is the increase in the frequency of hemorrhages. Thus, the choice of appropriate drug depends on the right risk assessment of the development of these complications in individual patients. The aim of this article is to provide an update of antiplatelet therapy in emergency myocardial infarction treatment. Currently, the most important role in the process of platelet inhibition is played by ADP P2Y₁₂ blockers: clopidogrel, prasugrel and ticagrelor. Clopidogrel and prasugrel belong to thienopyridines, and ticagrelor, a drug of irreversible action, is an analogue of adenosine triphosphate. By 2011 clopidogrel, alongside aspirin, had the highest recommendations of world cardiology associations for acute coronary syndrome treatment. The position on clopidogrel was changed following the publication of European Society of Cardiology guidelines for STEMI in 2012 which advocate the administration of acetylsalicylic acid (ASA) and ADP receptor blocker (in combination with ASA). It needs to be stressed that prasugrel and ticagrelor received class IB recommendation, while clopidogrel received only IC. However, the most recent studies aimed at introducing a new generation of antiplatelet drugs of high efficacy in prevention of ischemic incidents and of reversible action: cangrelor and elinogrel, which raise hopes for better prognosis for myocardial infarction patients.

Key words: antiplatelet therapy, platelets, P2Y₁₂, myocardial infarction, angioplasty.

Introduction

Myocardial infarction usually results from sudden occlusion of one of the coronary arteries caused by the damage of unstable atherosclerotic plaque (UAP). The plaque damage activates coagulation processes and the resulting thrombus closes the vessel. Primary coronary angioplasty is currently viewed as the most effective treatment for myocardial infarction; however, stenting of infarct-related artery (IRA) may lead to stent thrombosis and as a result to another infarction. The risk of early stent thrombosis in myocardial infarction patients with ST segment elevation (STEMI) is significantly higher than in elective surgery (3% vs. 0.3–0.4% respectively) [1]. Due to the fact that platelet activation plays a key role in this process, appropriate antiaggregation therapy is crucial.

The role of platelets in thrombosis in myocardial infarction

Platelet activation is performed in a specific and non-specific manner. Specific activation is related to direct

activation of platelets by substances released as a consequence of atherosclerotic plaque rupture. Non-specific platelet activation for aggregation is stimulated by hemodynamic disturbances leading to a decrease of the shear rate. A low shear rate results from the disturbed and non-effective blood flow in the vessel which activates platelets (decreased flow and/or turbulent flow).

The most commonly used antiplatelet drugs include GPIIb/IIIa glycoprotein receptor blockers (abciximab, tirofiban, eptifibatide), acetylsalicylic acid (ASA) and ADP P2Y₁₂ receptor blockers, such as clopidogrel, prasugrel and ticagrelor. Platelet activation requires the release of stimulating substances, such as thrombin, thromboxane A₂ and ADP. The combination of ADP and receptor P2Y₁₂ activates glycoprotein receptors IIb/IIIa resulting in platelet degranulation, thromboxane production and their subsequent aggregation and binding with fibrinogen. Inhibitors of GP IIb/IIIa hinder this process, allowing for infarct vessel patency even in the pre-operative period in approximately 1/3 of patients. It has been proved that

Corresponding author:

Anna Komosa MD, PhD, 1st Department of Cardiology, Poznan University of Medical Sciences, 1/2 Długa St, 60-848 Poznan, Poland, phone: +48 61 854 91 46, fax: +48 61 854 90 85, e-mail: komosa.ania@gmail.com

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pre-surgical combined treatment with ASA (250 mg *i.v.*), unfractionated heparin (5000 U *i.v.*) and IIb/IIIa blocker statistically significantly decreases 2-year mortality in STEMI by 6% [2]. It was observed that early administration of GP IIb/IIIa blockers also improved the coronary flow evaluated on the basis of the TIMI scale, as well as early treatment results in STEMI myocardial infarction patients in APEX-AMI examination [3]. Meta-analysis evaluating the application of IIb/IIIa blockers in STEMI showed their significant effectiveness in high-risk myocardial infarction patients (e.g. large necrosis, left ventricular dilation) [4]. The recently published INFUSE AMI study showed that abciximab administered locally into the developed thrombus using a special infusion catheter significantly decreased the range of infarction assessed by MRI [5].

Currently the most important role in the process of platelet inhibition is played by ADP P2Y₁₂ blockers. This group includes, among others, thienopyridines. The first one used in the treatment of acute coronary syndrome (ACS) was ticlopidine. Due to its numerous side effects it has been almost entirely superseded by clopidogrel.

Clopidogrel and prasugrel also belong to thienopyridines. Drugs from this group irreversibly modify the structure of the ADP platelet receptor P2Y₁₂, directly and specifically blocking ADP access, and inhibit GP IIb/IIIa complex activation. The third drug of a similar nature, but not a thienopyridine and exhibiting irreversible action, is ticagrelor.

Clopidogrel

Clopidogrel is a thienopyridine derivative of the second generation. The speed and degree to which the drug is absorbed (bioavailability) from its pharmacological form exceeds 50%. Clopidogrel binds to plasma proteins and tissues in 94–98% and its half-life is 7–8 h. The drug irreversibly modifies the structure of P2Y₁₂ platelet receptor by directly and specifically inhibiting the activation of GP IIb/IIIa complex. Its washout period remains throughout platelet lifetime (7–10 days). Only 60–70% of receptors exhibit sensitivity to clopidogrel and thus a standard dose does not lead to complete inhibition of all receptors, enabling about half of the thrombocytes to retain their aggregation activity. Efficacy of the drug depends not only on the dose but also on the time of therapy onset. The maximum antiplatelet effect is obtained within approx. 2–3 h after administration of a single loading dose of 600 mg and within approx. 3–7 days after application of 75 mg/day. Normal platelet functions are restored 5–7 days following drug discontinuation and are related to the restoration of a number of circulating cells [6]. The possible necessity to perform cardiac surgery definitely points to the drug's shortcoming. On the other hand, this may act as a protection against the consequences of omissions of even a few doses of the drug. In order to avoid the risk of significant bleeding elective

surgery (e.g. direct myocardial revascularization) should be performed within 5–7 days after the last dose of clopidogrel has been administered [7].

Clopidogrel is a prodrug, which in the stage of intestinal absorption undergoes hydrolysis to an intermediate metabolite – an ester by P-glycoprotein (ABCB1). This is followed by a two-phase process of hepatic oxidation with cytochrome (CYP) 450. Clopidogrel exhibits a thiol group conditioning its antiaggregation activity only in the second phase of oxidation. The most desired result of metabolism is the active form of drug inhibiting platelet aggregation, which constitutes only 15% of the drug. The remaining part (85%) is a non-active derivative of carbonic acid. The drug is eliminated by renal (50%) and fecal (46%) pathways [8].

Several studies have proved the effectiveness of clopidogrel. The CURE study analyzed a group of 12,562 patients with unstable angina pectoris or myocardial infarction without ST-segment elevation who were treated with clopidogrel – loading dose 300 mg and maintenance dose 75 mg daily combined with aspirin administration for 3 to 12 months. The result was a 20% decrease in risk of cardiovascular death, MI, and brain stroke in comparison with the patients treated only with aspirin [9]. A positive result of the therapy related mostly to the patients shortly after myocardial infarction without ST-segment elevation, interventionally treated (PCI-CURE study), which showed a 31% decrease in the frequency of cardiovascular death, MI, and brain stroke as compared to the group treated only with aspirin and placebo [10].

Also the COMMIT-CCS-2 study performed on a large group of patients (45,852 patients) with myocardial infarction and ST-segment elevation showed a lower risk of death, secondary myocardial infarction or brain stroke when treated with 75 mg clopidogrel and aspirin (22,961 patients) as compared to placebo and aspirin (22,891 patients). Four-week observation showed a proportional reduction in death rate, myocardial infarction and brain stroke (9.2% in clopidogrel group vs. 10.1% for placebo, $p = 0.002$). No statistically significant differences were found between the studied groups as for the side effects in terms of ischemic episodes requiring blood transfusion and intracranial bleeding (0.58% vs. 0.55%, $p = 0.59$) [11].

The CLARITY-TIMI 28 study, published in 2006, included 3491 STEMI myocardial infarction patients treated fibrinolytically who, apart from ASA and heparin, were administered either clopidogrel or placebo no longer than for the first 8 days. Administration of clopidogrel reduced by 21% the frequency of ischemic events: death, myocardial infarction or the need for another revascularization. This study showed that by adding clopidogrel to a standard fibrinolytic therapy the occurrence of the composite endpoint of death, myocardial infarction, and no patency of infarct-related artery after fibrinolytic therapy is reduced by 36% [12].

There have been numerous papers proving that an increase of a loading dose of clopidogrel specifically improves the antiaggregation result; the PERPAIR study focused on the dose change from 150 mg to 300 mg [13], and the ISAR-CHOICE study on the dose change from 300 mg to 600 mg. However, there was no evidence to support the increase of a loading dose to 900 mg, probably due to the fact that the maximal active drug form has been achieved [14]. The CLEAR-PLATELET study showed that administration of clopidogrel in a loading dose of 600 mg was related to an improved pharmacodynamic result when compared to a 300 mg dose [15].

The effects of an increased loading dose of clopidogrel (600 mg) were assessed in patients with acute coronary syndromes in the CURRENT-OASIS 7 study. It included over 17,000 patients with ACS and compared two manners of clopidogrel administration. The first one analyzed the administration of a loading dose of 600 mg, followed by 1-week administration of 150 mg and then 75 mg daily. The second, standard treatment, was related to the administration of a lower loading dose: 300 mg, followed by 75 mg administration for 30 days. This study also compared the administration of a higher loading dose of aspirin (300–325 mg) and a maintenance dose of 75–100 mg daily. It was proved that, contrary to the group treated with a standard dose of clopidogrel, the percutaneous coronary intervention (PCI)-treated group when administered a double dose of clopidogrel showed a reduction in primary endpoint (3.9% vs. 4.5%, $p = 0.039$) and reduction in stent thrombosis occurrence (0.7% vs. 1.3%, $p = 0.0001$). However, the administration of a lower or higher dose of aspirin was noted to be of no significance. Extensive ischemia was found to be more frequent after the administration of a double clopidogrel dose (1.6% vs. 1.1%, $p = 0.009$). No significant differences were found in relation to the dose of ASA (1.5% vs. 1.3%, $p = 0.20$) [16]. A significant problem relating to antiaggregation treatment is the increased risk of hemorrhagic complications. The CHARISMA study showed that the administration of double therapy, composed of aspirin and clopidogrel at daily doses of 75–162 and 75 mg respectively, significantly increases the risk of ischemic events in the period of approx. 250 days after the therapy onset [17].

By 2011 clopidogrel, alongside aspirin, had the highest recommendations of world cardiology associations (ESC/ACC/AHA) for ACS treatment. The position on clopidogrel was changed following the publication of the ESC (European Society of Cardiology) guidelines for STEMI in 2012, which advocate the administration of ASA and ADP receptor blocker (in combination with ASA): a) prasugrel – patients of age < 75, not taking clopidogrel before, who have not undergone a brain stroke or transient cerebral ischemia, b) ticagrelor, c) clopidogrel, if prasugrel and ticagrelor are unavailable or contraindicated [18]. It needs to be stressed that prasugrel and ticagrelor

received a class IB recommendation, while clopidogrel received only IC. The administration of antiaggregation drugs should be commenced as soon as possible before coronarography. It is admissible to administer a loading dose of ticagrelor to patients taking clopidogrel. In January 2013 “Circulation” published the latest guidelines of American associations (American College of Cardiology Foundation/American Heart Association) for STEMI, according to which clopidogrel, similarly to prasugrel and ticagrelor, received a class IB recommendation. Chronically, antiaggregation therapy with P2Y12 receptor inhibitors should be continued for 12 months at maintenance doses in the following manner: clopidogrel 75 mg, ticagrelor 90 mg (twice daily) or prasugrel 10 mg [19].

Low responsiveness to clopidogrel

Current available data show that 5–45% of patients display resistance to clopidogrel [20]. Low responsiveness to clopidogrel is caused by multiple factors such as the lack of appropriate cooperation between a patient and a doctor and premature drug discontinuation, individual differences in intestinal drug absorption (especially in obese, elderly and diabetic patients), the immunological state of a patient (injections), or, finally, interactions with other drugs (e.g. proton pump inhibitors). Specific factors include individual genetic conditioning affecting the velocity of drug transformation at several stages: oxidation by cytochrome (CYP) 450 enzymes (cytochrome genetic polymorphism), thrombin receptor activation (PAR-1) [21] and the presence of other enzymes participating in the process of clopidogrel bioactivation (PON-1) [22].

In 2010 Bonello *et al.* published the definition of resistance to clopidogrel [23], which was based on the absolute value of platelet reactivity cutoff during antiaggregation therapy for the commonly applied methods of platelet aggregation inhibition measurement. The term high on-treatment platelet reactivity (HTPR) was introduced, i.e. increased platelet reactivity despite antiaggregation treatment. Many papers have proved a significant influence of HTPR on adverse clinical incidents. The study by Breet *et al.* published in 2010 conducted on a group of 1069 elective PCI patients showed a marked increase in ischemic events during 1-year observation in patients with high platelet activity (HR: 2.0) [24]. Similarly, Sibbing *et al.* reported significantly more frequent stent thrombosis in a group of 1608 PCI patients with antiproliferative drug-eluting stents who were found to have increased platelet reactivity during clopidogrel treatment in a 30-day observation period (OR: 9.4) [25].

Clopidogrel metabolism

As mentioned before, clopidogrel is bioactivated in a two-step hepatic oxidation process, mainly by hepatic enzymes: CYP1A2, CYP3A4, CYP2B6 and CYP2C19 [26]. Mutations related to the allele coding the development

of these enzymes are responsible for lower responsiveness to clopidogrel. The patients who are carriers of such mutations are particularly prone to stent thrombosis, myocardial infarction or death. Genetic diversity of cytochrome (CYP) 450 enzymes is responsible for about 80% of incidents related to platelet aggregation disturbances [27]. Among several cytochrome (CYP) 450 enzymes CYP2C19 plays a particularly crucial role in the process of clopidogrel activation. There are 25 polymorphic varieties of CYP2C19, among which CYP2C19*2 and *3 are associated with impaired development of the active metabolite and, as a result, with decreased platelet inhibition. The healthy carriers of CYP2C19*2 allele showed decreased concentration of clopidogrel active metabolite in blood (by 34%) and lower aggregation inhibition as compared to the noncarriers, who did not have this allele mutation [28]. A recently published meta-analysis of 10 studies, by Hullot *et al.*, proved that CYP2C19 allele carriers are 30% more likely to develop major adverse cardiac incidents (MACE) as compared to noncarriers (9.7% vs. 7.8%; OR: 1.29, $p < 0.001$) [29].

Significance of genetic tests

There are many doubts relating to genetic tests used for detection of patients who are carriers of genes responsible for the impaired metabolism of antiaggregation drugs. It is estimated that as many as 30% of the white population are carriers of this defective gene variation, which results in an increased risk of adverse cardiovascular incidents. Despite the fact that it is theoretically possible to detect genetic variations predisposing to impaired response to antiaggregation therapy, so far there have been no available unequivocal data establishing how “genetic resistance” relates to clinical events in patients. Wide-scale implementation of genetic examinations with the aim of defining a variety of responses to antiplatelet drugs, in particular to clopidogrel, still remains a controversial issue. Ticagrelor is absorbed as an active substance, and genetic factors are not important for its activity [30]. Prasugrel, although it undergoes cytochrome transformation, depends on it to a lesser extent and the evaluation of its genetic distinctiveness also appears to be unnecessary here [31].

The Food and Drug Administration (FDA) in the United States has advocated including a warning in clopidogrel leaflets about its possible incomplete efficacy. Moreover, patients are informed about the possibility to have genetic tests performed at bedside, which may be helpful when choosing the appropriate drug and dose. Besides, genetic assessment may be useful for the treatment of STEMI patients. Currently available scientific data suggest that the authors who urge these tests to be implemented and propagated are right about perceiving them as a chance to improve the results of emergency myocardial infarction treatment [32]. However, genetic test op-

ponents point out that there is a lack of sufficient data of genetic conditioning responsible for clopidogrel metabolism as well as studies related to the influence of genes on treatment efficacy [33]. A Canadian study from 2010 performed on a group of 5059 acute coronary syndrome patients showed that antiaggregation efficacy of clopidogrel in the examined persons was not related to CYP2C19 genotype [34]. Thus, it seems necessary to perform further research and learn more about the factors responsible for lower responsiveness to clopidogrel. In 2011 the results of a meta-analysis of 32 major studies were published, which analyzed the effects of CYP2C19 polymorphism on platelet inhibition degree and clinical incidents in over 42,000 patients. It was shown that a lower level of active clopidogrel metabolite and increased platelet activity were present despite antiaggregation treatment in carriers of an allele of impaired clopidogrel metabolism. Despite the compelling number of included patients, no major influence of genotype on adverse coronary-vascular incidents was found [35]. So far it has been established that the consequences of genetic polymorphism, responsible for varied activity and thus for clinical efficacy of clopidogrel, are inconclusive and therefore further studies need to be conducted.

Another postulated mechanism of decreased sensitivity to clopidogrel is polymorphism of paraoxonase-1 (PON-1) responsible for clopidogrel bioactivation. Recent reviews have proved polymorphism Q192R of PON-1 to be a major determinant of clopidogrel activation [36]. The prospective research conducted on 1982 patients showed that homozygotes QQ192 responsible for PON-1 deficit caused statistically significantly lower clopidogrel activity. In order to conclusively define the influence of PON-1 on clopidogrel metabolism further studies are required [37].

Prasugrel

Prasugrel differs from clopidogrel in that it is activated in a single step in the liver. Active metabolite develops faster and thus more promptly reaches a higher concentration in the blood, which to a greater extent affects its speed and efficacy of action. Individual diversity of patients' sensitivity to prasugrel appears to be of no relevance. The TRITON-TIMI 38 study showed that the administration of prasugrel to ACS patients, including in those with ST-segment elevation, when compared with clopidogrel, is associated with a significant reduction in the primary endpoint – death due to cardiovascular reasons, myocardial infarction or brain stroke. It needs to be stressed here that prasugrel treatment showed greater efficacy in 30-day and 15-month period observations only in patients with anterior wall myocardial infarction: 9.5% vs. 6.5%, $p = 0.017$ and 12.4% vs. 10.0%, $p = 0.0221$ respectively. However, the subgroup including myocardial infarction patients treated with primary PCI ($n = 2438/69\%$) showed no statistically significant

differences relating to the frequency of primary end-point occurrence between clopidogrel and prasugrel treatment both in 30-day and 15-month period observations: 8.2% vs. 6.6%; HR: 0.80 (95% CI: 0.60–1.08), $p = 0.144$ and 11.6% vs. 10.2%, HR: 0.87 (95% CI: 0.68–1.11), $p = 0.2662$ respectively. These two subgroups also did not differ in terms of frequency of serious hemorrhagic events (according to TIMI). However, the brain stroke patients (3.8%) treated with prasugrel significantly more often showed intracranial hemorrhage (2.3% vs. 0.0%, $p = 0.02$). On the basis of the TRITON-TIMI 38 study a group of patients particularly prone to hemorrhagic complications was distinguished: patients who underwent brain stroke or temporary cerebral ischemia, patients over 75 years of age and with body weight below 60 kg [38]. The TRILOGY study which was published in October 2012 and focused on about 10,000 patients with myocardial infarction without ST-segment elevation treated conservatively did not confirm the advantage of prasugrel over clopidogrel in relation to occurrence of ischemic complications. A significant reduction in cardiovascular deaths – myocardial infarction and brain stroke – connected with prasugrel administration was observed in the group of patients below 75 years of age, in whom the conservative treatment was commenced after the performance of angiography tests (HR: 0.85; 95% CI: 0.72–1.00; $p = 0.04$). This study was conducted on a very large population of patients and proved the administration of maintenance prasugrel dose to be safe in patients who were initially treated with clopidogrel. Also, the reduced maintenance dose of prasugrel (5 mg) was found to be safe in patients aged > 75 with body weight below 60 kg – this group showed no increased risk of hemorrhagic complications [39]. Also in 2012 the results of the TRIPLET study were published, which tested the influence of antiaggregation drug change from clopidogrel to prasugrel on platelet aggregation inhibition and the occurrence of adverse clinical incidents. The study included 282 patients with acute coronary syndrome, who were randomized into 3 groups and who received respectively: 1) placebo loading dose followed by 60 mg prasugrel, 2) 600 mg clopidogrel followed by 60 mg prasugrel, 3) 600 mg clopidogrel followed by 30 mg prasugrel. No significant differences relating to platelet aggregation inhibition were noted with the use of the VerifyNow system in patients treated with prasugrel, irrespective of the previously administered clopidogrel loading dose. In the first and in the second group 3 cases of hemorrhagic complications were found while in the third group 6 such cases were observed, i.e. in patients treated with 600 mg clopidogrel loading dose followed by 30 mg prasugrel [40].

Ticagrelor

Ticagrelor is an analog of adenosine triphosphate that, unlike clopidogrel and prasugrel, is not a prodrug.

Thus, after administration it does not require metabolic activation by cytochrome (CYP) 450 – the issues of hepatic passage and interactions with other drugs are eliminated. The drug blocks platelet P2Y₁₂ receptor reversibly and its half-life is about 12 h. Its short period of action gives ticagrelor a potential advantage over thienopyridines in patients qualified for cardiac surgery. DISPERSE2, a comparative study of ticagrelor and clopidogrel, revealed no differences related to frequency of hemorrhagic complications [41]. Ticagrelor, when compared to clopidogrel, is characterized by reaching faster a potent concentration in serum (1.5–3 h) and low individual response diversities, and also faster platelet aggregation inhibition (2 h). The ONSET/OFFSET study performed on a group of 123 patients with stable coronary artery disease showed markedly faster and stronger platelet inhibition due to ticagrelor administration as compared to clopidogrel (600 mg followed by 75 mg within a day). Also, after discontinuation of ticagrelor platelets resumed their normal activity sooner than in the case of clopidogrel [42]. The PLATO study which randomized 18,624 patients with ACS, including 3203 patients who were primary PCI treated (STEMI PLATO), comparatively analyzed clopidogrel and ticagrelor. Clopidogrel was administered in a loading dose of 300 mg and maintenance dose of 75 mg while ticagrelor was administered in doses of 180 and 90 mg respectively at the onset of surgery. The study conducted on the STEMI PLATO subgroup, after 12 months, showed a significantly reduced risk of endpoints (deaths due to cardiovascular events, myocardial infarction or stroke) in patients treated with ticagrelor as compared to clopidogrel (11% vs. 9.3%, $p = 0.02$ respectively). The main reason for this difference was a decreased frequency of myocardial infarction occurrence (6.1% vs. 4.7%, $p = 0.01$). Also, a specific absolute reduction by 1.4% in the total number of deaths was found. No significant increase in the risk of serious hemorrhagic complications was observed according to the criteria applied by the authors (4.9% vs. 4.5%, $p = \text{NS}$), or according to TIMI (6.4% vs. 6.0%, $p = \text{NS}$) [43].

As proved in the currently available studies, the frequency of complications in the form of major bleeding according to the TIMI definition (Thrombolysis in Myocardial Infarction) varied and was 0.6% in COMMIT and 11.2% in PLATO. A significant percentage of hemorrhagic incidents found in the PLATO study, in the clopidogrel group, was observed in the subgroup treated with direct myocardial revascularization [44]. However, the group of patients treated with ticagrelor, who did not undergo CABG, was found to have statistically more major bleeding events when compared to the standard clopidogrel dose (2.8% vs. 2.2%, $p = 0.03$). The risk of brain stroke was low in both groups, yet greater in the ticagrelor treated group: 1.7% vs. 1.0%; HR: 1.63 (95% CI: 1.7–2.48, $p = 0.02$). In the last PLATO analysis conducted on 1152

(6%) patients who experienced brain stroke and transient cerebral ischemia, the frequency of bleeding in ticagrelor/clopidogrel groups showed no statistically significant difference: 14.6% vs. 14.9%, HR: 0.99 (95% CI: 0.71–1.37) [45]. Also, no major differences were observed relating to intracranial bleeding incidents (4.0 vs. 4.0) [46].

Due to the greater efficacy of prasugrel and ticagrelor in cardiovascular incidents prevention, a number of experts from the Polish Cardiac Society suggested a new model of antiplatelet therapy in STEMI (Model B), i.e. introduction of prasugrel or ticagrelor in the place of clopidogrel. This model is based on replacing a loading dose of clopidogrel (600 mg) administered pre-hospitally or on admission to the hemodynamic laboratory with the new antiplatelet drugs: prasugrel (loading dose 60 mg) or ticagrelor (loading dose 180 mg). The new drugs (prasugrel, ticagrelor) are to be administered on admission to the hemodynamic laboratory or after performance of the angiography test prior to the assessment of possible risk of bleeding complications [47].

New generation antiplatelet drugs

The new drugs cangrelor and elinogrel reversibly inhibit the P2Y₁₂ receptor. These drugs are metabolized in the liver and intestines where active metabolites are formed. They bind to the P2Y₁₂ platelet receptor, reversibly inhibiting platelet activity.

Cangrelor

Cangrelor is a non-thienopyridine, intravenously administered, reversible P2Y₁₂ receptor antagonist. The result of platelet inhibition is obtained about 30 min after the onset of infusion and within an hour of drug discontinuation platelets resume their normal activity [48]. However, some new data have appeared regarding competitive inhibition of the antiplatelet effect of thienopyridine metabolites after the administration of cangrelor. Two studies focusing on cangrelor – CHAMPION-PCI and CHAMPION-PLATFORM – were prematurely discontinued due to the lack of the expected positive results regarding reduction of the primary end-point (death, myocardial infarction, necessity to perform another revascularization due to ischemia within 48 h). However, an increased risk of major hemorrhages was observed (3.6% vs. 2.9%, OR: 1.26; 95% CI: 0.99 vs. 1.60; $p = 0.06$). The administration of cangrelor was associated with a decreased risk of stent thrombosis and death within the first 48 h. During the American College of Cardiology Congress in 2013 held in San Francisco, the most up-to-date results of the CHAMPION-PHOENIX study were presented. This is a large, multicenter clinical trial assessing the efficacy of cangrelor in PCI patients due to both stable CAD and other ACS. The study included 11,145 patients who were randomized for intravenous administration of cangrelor (study group, bolus 30 mg/kg + infusion 4 µg/kg/min

for 2–4 h) or for oral clopidogrel administration (control group, 300 mg or 600 mg loading dose + 75 mg maintenance dose). The composite primary endpoint was death, myocardial infarction, necessity for revascularization due to ischemia or acute stent thrombosis within 48 h after PCI. The primary endpoint was observed significantly less frequently in the cangrelor group: 4.7% vs. 5.9% ($p = 0.005$). This result was affected mainly by a smaller number of myocardial infarctions (3.8% vs. 4.7%, $p = 0.02$) and acute stent thrombosis (0.8% vs. 1.4%, $p = 0.005$). The noted differences were present during a 30-day observation period. A subgroup analysis proved the cangrelor activity result irrespective of PCI indication. Bleeding incidents were present equally often in the study group and in the control group (0.16% vs. 0.11%, $p = 0.44$) [49]. The positive result of this study will surely pave the way for the development of intravenous P2Y₁₂ receptor antagonists.

Elinogrel

Elinogrel directly inhibits the P2Y₁₂ receptor. It reversibly inhibits platelet aggregation and is available both in the oral and intravenous form. So far the performed studies have proved its stronger antiaggregation results as compared to clopidogrel, yet with certain higher inclinations for insignificant hemorrhagic complications. The drug is still undergoing clinical trials. In 2012 the results of the INNOVATE PCI study were published. The main aim of the study was to assess the safety, efficacy and tolerance of elinogrel in patients who underwent elective PCI. The part dealing with pharmacodynamics showed that the patients treated with elinogrel at the doses of 100 mg and 150 mg twice daily showed greater platelet inhibition as compared to the patients treated with clopidogrel, and the patients who received 150 mg presented stronger results of the drug. As for the hemorrhagic complications in patients who intravenously received elinogrel in the dose of 120 mg, researchers did not report more frequent major and minor bleedings within 24 h or before hospital discharge. More bleedings were observed in comparison to clopidogrel in the form of complications at the site of vascular access, which required medical intervention (elinogrel 47/408 (11.5%) vs. clopidogrel 13/208 (6.3%)). Moreover, more frequent hemorrhages requiring medical assistance were present within 24 h to 120 days in patients treated with elinogrel at the dose of 150 mg. It needs to be added that the research did not have appropriate statistical properties to assess ischemic endpoints [50]. The implications of these results require further studies in the third stage.

Conclusions

Antiplatelet drugs play a crucial role in the treatment of patients with myocardial infarction, particularly in association with percutaneous coronary intervention. Their

main advantage is the reduction of adverse ischemic incidents and the major disadvantage is the increase in the frequency of hemorrhages. Thus, the choice of appropriate drug depends on the right risk assessment of the development of these complications in individual patients.

The most recent studies aimed at introducing new drugs of high efficacy in prevention of ischemic incidents and simultaneously of reversible action raise hopes for better prognosis for myocardial infarction patients.

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