ANTIPLATELET THERAPY IN ST ELEVATION MYOCARDIAL INFARCTION

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Abstract. Antiplatelet therapy in ST elevation myocardial infarction represents the cornerstone of adjuvant pharmacological measures in order to increase the patency of infarct related artery and to obtain myocardial reperfusion. Additionally, there is the most important available treatment for maintaining the results of primary percutaneous coronary interventions and preventing the stent thrombosis. The widespread research in the field resulted in the last few years in the development of new molecules that have solid clinical evidence. Aspirin remains the unchallenged partner of the new antiplatelet agents, being recommended in all patients with acute coronary syndrome with ST segment elevation, regardless of the therapeutic approach chosen. Clopidogrel was surpassed in the clinical trials by the new antiplatelet drugs (ticagrelor and prasugrel) but it should be noted that none of this more potent agents should be used in patients with previous stroke or in patients with moderate to severe liver. The optimal duration of dual antiplatelet treatment and reduction of bleeding risk remain challenging issues, where decision should be individualized.

Key words: Antiplatelet therapy, ST elevation myocardial infarction, aspirin, clopidogrel, prasugrel, ticagrelor

Introduction

Both acute coronary thrombosis and thrombus dissolution are multifactorial mechanisms where a complex interaction occurs between platelet activity, coagulation system and local rheological conditions. Irrespective of the reperfusion therapy type, adjuvant treatment is essential in order to increase the success rate of maintaining vessel patency and achieving efficient myocardial tissue reperfusion. Antiplatelet therapy has a key role in adjuvant treatment due to the platelet released mediators and consecutive activation and further aggregation phenomena which lies beneath the failure of reperfusion. The ideal antiplatelet agent should encompass the following main characteristics: (1) to have a rapid onset of action, (2) to be available for intravenous administration, (3) to achieve complete platelet inhibition, (4) to have an entirely reversible effect, (5) to come up with a low bleeding risk. Despite the extensive progress that was attained in the field of antiplatelet therapy in the last decade, we are far from consensus both in the choice of the drug or the combination between agents and also in prescribing recommendations and duration of treatment. Our paper will make a brief review of the old story of antiplatelet therapy where new actors have started to play as main characters.

Aspirin

Aspirin is the cornerstone of antiplatelet therapy. It was first synthesized in 1898 by Hoffman and marketed in 1899 for its anti-inflammatory and antipyretic effects. Aspirin began to be used as an antiplatelet agent 70 years later when the ability to extend bleeding time was discovered. In the past 50 years, aspirin has been extensively studied and used due to its low cost and proven efficacy on multiple trials. In 1988 the FDA approved the use of Aspirin for acute myocardial infarction and secondary prevention of ischemic heart disease and ischemic stroke, recommending a dose of 300 mg or 325 mg aspirin for the achievement of the antiaggregant effect[1]. More than twenty years ago, Swedish Angina Pectoris Aspirin Trial (SAPAT), demonstrated that the daily addition of 75 mg aspirin to sotalol treatment reduced the incidence of first myocardial infarction in patients with symptoms of stable angina pectoris[2]. A decade later, the results of a meta-analysis of 287 studies that compared different regimens of antiplatelet therapy with the control group, supported and outlined the protective effect of aspirin in patients with acute myocardial infarction. Also, the results have indicated that doses of 75-150 mg of aspirin are affective for maintenance therapy and mentioned the possible need for a loading dose higher than 150 mg[3]. Compelling evidence of the benefit of this drug for patients with STEMI is found also
within the results of the Second International Study of Infarct Survival (ISIS-2), in which the benefits of aspirin and streptokinase were seen to be additive[4,5]. Currently, the 2012 European Society of Cardiology Guideline for the Management of Acute Myocardial Infarction in Patients Presenting with ST- Segment Elevation recommends the use of aspirin in all patients with acute coronary syndrome with ST segment elevation, regardless of the therapeutic approach chosen (invasive treatment, fibrinolytic therapy or conservative treatment (Table I)[4].

- With primary PCI it is recommended to use as soon as possible a loading dose of 150–300 mg orally or of 80–150 mg i.V. If oral ingestion is not possible.
- For the non-reperfused patients should be given a starting dose of 150–500 mg orally.
- With fibrinolytic therapy is indicated a starting dose of 150–500 mg orally or i.v. Dose of 250 mg if oral ingestion is not possible[4].

\textit{In all the three listed above strategies a maintenance dose of 75–100 mg/day of aspirin is recommended.}

Table I. Recommended doses of aspirin

Aspirin has the disadvantage of limited action to the cyclooxygenase pathway of platelet aggregation, which implies an incomplete effect on other platelet activation pathways[6]. Thus, aspirin is unable to prevent thrombin-induced platelet aggregation and it inhibits only partly the ADP-dependent aggregation mechanism. Therefore, regardless of the therapeutic approach chosen (invasive treatment, fibrinolytic therapy or conservative treatment) the recommended antiplatelet therapy for patients with STEMI consists in associating aspirin with an adenosine diphosphate (ADP) receptor blocker.

P2Y12 receptor inhibitors

Regarding the ADP-mediated platelet activation, ADP interferes with the aggregation process by using the two G-protein-coupled receptors P2Y1 and P2Y12. By binding to these receptors, mainly being used the P2Y12 receptor it activates the glycoprotein IIB/IIIa[7]. This leads to the initiation of the platelet degranulation process, production of thromboxane and platelet aggregation[7, 8].

Thienopyridines (Ticlopidine, Clopidogrel, Prasugrel)

Thienopyridines are a class of antiaggregant drugs whose mechanism of action involves the inhibition of the above mentioned P2Y12 receptor. They act indirectly by requiring prior biotransformation in the liver via the cytochrome P450[9] and are causing irreversible inhibition of the mentioned receptors. This is an important feature for the clinical practice because the platelet function will be resumed only after thrombocytes replacement with new ones and after removal from the circulatory system of active metabolites[10]. Therefore, in patients that might require urgent surgery, reversible P2Y12 receptor antagonists are preferable, considering that they have the advantage of a faster offset of antiplatelet effect. Given these pharmacokinetic characteristics and the trial data, the current recommendations regarding the withholding ADP inhibitors for surgery, in stabilized patients are detailed in Table II[4].

Table II. Withholding ADP inhibitors for surgery

- Ticlopidine - First Generation Thienopyridine. Ticlopidine, a first generation thienopyridine, has currently no indication of use in the medical management of STEMI. The main reasons are the hematological adverse effects (i.e. neutropenia), the slow onset of action, the high costs and the existing far superior alternatives. Ticlopidine had nevertheless an important role since it led to the dual antiplatelet treatment concept after being noticed the additional antiplatelet effect in association with aspirin[11].

- Clopidogrel - Second Generation Thienopyridine. Clopidogrel is a second-generation thienopyridine. It is a derivative of ticlopidine, being 6 times more potent than its predecessor and also more rapidly absorbed and metabolized[12]. Regarding the evidence of effectiveness in STEMI therapy, in CLARITY-TIMI 28 TRIAL[13], which enrolled 3491 subjects, adding clopidogrel 300 mg loading dose followed by 75 mg daily (vs. placebo) to standard fibrinolytic treatment and aspirin resulted at 30 days in a 20% reduction of odds to composite endpoint of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization without an increase in the rate of major bleeding or intracranial hemorrhage. It has been proven in many studies the effectiveness of clopidogrel in both acute and long term management of patients with STEMI, while the topic regarding the optimal dose of antiplatelet therapy is still under debate based mainly on pharmacogenomic findings.

Clopidogrel was found to have an inter-individual variability in antiplatelet effect, its intestinal absorption and metabolic activation in the liver being both affected by genetic polymorphisms[14]. The loss of function for alleles of the CYP2C19 gene produces a decreased response to clopidogrel[15], the affected individuals being exposed to an increased risk of death, myocardial infarction and stroke especially those undergoing stenting[16,17]. In 2011, FDA issued a warning for clopidogrel pointing out that poor metabolizers treated with clopidogrel at standard recommended doses exhibit higher cardiovascular event rates following ACS than patients with normal CYP2C19 function. The same warning recommended
considering alternative treatment or treatment strategy in individuals identified with this genotype[18]. This is why higher doses of Clopidogrel have been studied, the CURRENT-OASIS 7 TRIAL showing a 14% reduction in major adverse cardiovascular events for patients with acute coronary syndromes and intended early PCI who received a 600 mg loading dose followed by 150 mg daily in the first week and afterwards 75 mg daily[19]. Another reason for studying higher dosage of Clopidogrel is that at higher dose, the antiplatelet function is not only more potent, but also the effect emerges more rapidly, important feature for emergency situations like STEMI. In connection with this, there have been conducted studies with even higher doses of Clopidogrel in STEMI (i.e. 900 mg in Load and Go trial) publication of results being currently expected. The 2012 European Society of Cardiology Guideline for the Management of Acute Myocardial Infarction in Patients Presenting with ST - segment Elevation recommends the use of clopidogrel with primary PCI when prasugrel or ticagrelor are either not available or contraindicated (I C). However, when referring to antiplatelet co-therapies with fibrinolytic therapy or for patients treated without reperfusion therapy, the only antiplatelet drug recommended (I A) is clopidogrel.

Figure 1. Currently recommended dosage

Although, clopidogrel was surpassed in the latest trials by the new antiplatelet drugs (prasugrel and ticagrelor)[20, 21], it is notable that none of the more potent agents mentioned above should be used in patients with previous stroke or in patients with moderate to severe liver disease and clopidogrel should be given instead[19]. Concerning the optimal time interval between clopidogrel administration and PCI, based on his pharmacokinetic characteristics, clopidogrel should be administered as early as possible before PCI and not at the time when PCI is performed. The current guideline recommends the strategy of dual antiplatelet therapy after STEMI for up to 12 months following primary PCI or fibrinolysis and for at least 1 up to 12 months for patients who have not undergone reperfusion. The strict minimum of dual therapy duration is of 1 month for patients receiving RMS and 6 months for patients receiving DES, class IIb guideline indication[4].

**Prasugrel** - Third Generation Thienopyridine. Prasugrel, just as its predecessors, ticlopidine and clopidogrel, inhibits the platelet aggregation by blocking in an irreversible way the P2Y12 ADP receptor. It is also a prodrug; however it has a greater bioavailability than clopidogrel and the metabolism of prasugrel differs from that of clopidogrel which is converted into its active metabolite in a proportion of 15% and requires two metabolic steps CYP dependent for activation[22]. Prasugrel is more efficiently converted into its active metabolite and it requires a single pass through the hepatic CYP step, explaining its faster onset of action[22]. Laboratory testing of prasugrel shows a more potent antiaggregant effect and a lower incidence of inter-patient variability in antiplatelet response, compared with clopidogrel [23, 24]. It should be noted that the polymorphic CYP450 enzyme is involved in the metabolism of both clopidogrel and prasugrel, explaining the variability in response to this drugs[9].

The higher potency of prasugrel is supported by data from clinical trials. According to PRINCIPLE-TIMI 44 study, the loading dose of prasugrel (60 mg) achieves greater platelet inhibition than clopidogrel (the standard dose of 600mg) and the superiority is observed also for the maintenance dose[20]. In TRITON TIMI 38, referring to the subgroup of STEMI subjects treated with primary PCI, the end point of CV disease, non-fatal MI and non-fatal stroke was significantly reduced after 30 days of treatment with prasugrel compared with clopidogrel (6.5 vs. 9.5%; p=0.002)[25]. The benefit of prasugrel over clopidogrel persisted through 15 months and regarding the non CABG-related bleeding risk there was no significant increase in this subset of patients[25]. The recommended dose of prasugrel is 60 mg orally loading dose and a 10 mg maintenance dose, class I level of evidence B, being mentioned that its use is not recommended for patients aged ≥75 years or with less than 60kg body weight[4]. If used in these patients mentioned above, a reduced maintenance dose of 5mg should be considered (Tabel III).

**Table III. Advantages of Prasugrel over Clopidogrel [4]**

- Faster onset of efficient antiplatelet effect (30 minutes with prasugrel 60 mg compared with 1-2 hours for 600 mg clopidogrel)
- More potent antiaggregant effect
- Dual antiplatelet therapy with a combination of aspirin and prasugrel or ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI

**Non-Thienopyridines (Ticagrelor, Cangrelor, Elinogrel)**

The non-thienopyridine derivatives act directly on P2Y12 receptor, without requiring prior biotransformation in the liver and determine reversible platelet inhibition by changing the conformation of the mentioned ADP receptor[10].

**Ticagrelor** - Ticagrelor is a potent antiaggregant drug. It was approved to be used for acute coronary syndromes in 2011, both in Europe and in United States. It has the advantage of a faster onset of action (reaching the maximum platelet inhibition at
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2 hours after administration, with a significant effect observed at 30 minutes[26], being valuable in the setting of urgent PCI. Because of its short half-life time it requires a twice daily administration. The most significant pharmacologic data come from the ONSET/OFFSET study (randomized double-blind assessment the ONSET and OFFSET of the antiplatelet effects of Ticagrelor versus Clopidogrel in patients) that demonstrated the markedly greater and faster antiplatelet effect of 180 mg Ticagrelor as compared with 600 mg loading dose of Clopidogrel which remains sustained during maintenance therapy and the significantly faster offset effect of Ticagrelor[26]. PLATO trial (platelet inhibition and patient outcomes) validated the clinical superiority of ticagrelor, patients with STEMI planned for primary PCI randomized to Ticagrelor as compared to Clopidogrel having a consistent (18%) reduction in all-cause mortality[21]. It has been noted also a 15% reduction in reaching the primary end point of MI, stroke or vascular death with Ticagrelor vs. Clopidogrel. There was no difference with respect to the rate of fatal bleeding or life-threatening bleeding, but there was an increase in non-CABG TIMI major bleeding[21]. It should be noted that Ticagrelor has a new spectrum of side effects including transient dyspnea at the onset of therapy and bradycardia. The current guideline recommends the use of Ticagrelor for patients with STEMI in the setting of primary percutaneous coronary intervention. There is a class I, level B indication, and the doses regimen consists in a loading dose of 180 mg orally and a maintenance dose of 90 mg bid[4].

Cangrelor - Cangrelor is an intravenous P2Y12 receptor blocker with very rapid onset of action, and short plasma half time. Just like ticagrelor, it does not require metabolic transformation[27]. In terms of its utility in the treatment of STEMI, CHAMPION-PCI trial compared cangrelor to clopidogrel but the results were not as expected. Although higher levels of thrombocyte inhibition were achieved with cangrelor, there was no superiority of cangrelor regarding the primary composite end-point and in addition it was associated with a higher rate of bleeding[28]. However, a recently published study – THE CHAMPION PHOENIX trial, that enrolled approximately 11,000 patients undergoing PCI, brought compelling evidence of superiority of cangrelor over clopidogrel. The contradictory results have been explained by a pharmacologic mechanism of competition between cangrelor and clopidogrel for the P2Y12 receptors. There has been noted a reduced receptor binding capacity of clopidogrel in the presence of cangrelor resulting in a diminished thienopyridine mediated inhibition[29]. This is why the two mentioned trials differ in the timing of antiaggregant therapy: both cangrelor and clopidogrel were given 30 minutes before PCI in CHAMPION-PCI versus cangrelor at the start of PCI and clopidogrel after PCI in CHAMPION-PHOENIX. The recent BRIDGE trial (bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery), brought data that i.v. cangrelor could represent an effective bridging therapy to surgery for patients taking clopidogrel and scheduled for surgery. The preliminary results support the hypothesis that cangrelor can safely provide consistent P2Y12 receptor inhibition during prolonged infusion in patients who must wait for cardiac surgery after thienopyridine discontinuation and also there were no significant differences in CABG-related bleeding with cangrelor compared with the placebo group[30]. At the moment, Cangrelor is not available on the market, but it might be a valuable drug in the future, both for STEMI treatment and for bridging therapy for CABG.

Elinogrel - Elinogrel is also a non-thienopyridine drug. Unlike the other antiplatelet drugs, elinogrel can be administrated both orally and intravenously. There have been performed in vitro tests studying the effect of adding elinogrel in blood samples collected from patients who underwent PCI, treated also with clopidogrel. It was observed an effect of potentiation of the antiplatelet effect of the two drugs and an inhibition of clot formation[31]. Phase I and II studies have demonstrated tolerability, strong antiplatelet effect with rapid onset of action and reversible effect in less than 24 hours, for both intravenous and orally Elinogrel[32]. Regarding its usefulness in the treatment of STEMI, the evidence currently available derive from a small study, The ERASE MI (the early rapid reversal of platelet thrombosis with intravenous PRT060128 before PCI to optimize reperfusion in acute MI). Elinogrel was tested as a unique i.v. bolus before PCI in association with clopidogrel, the standard dose of loading and maintenance. The results did not point toward a benefit of adding Elinogrel, no differences in serious adverse events being observed between the studied groups[33]. Further studies are needed to further assess elinogrel usefulness in the setting of primary PCI.

Thrombin Inhibitors

Thrombin is a key enzyme of the coagulation process. It is involved in fibrinogen to fibrin conversion and it interferes with platelet activation. Its mechanism of action entails the PAR cellular receptors (protease...
despite the solid pharmacological and clinical data risk should dominate the clinical judgment. So, combined evaluation of both ischemic and bleeding the concept of global risk assessment – meaning the
Clinical practice discussions
alternative to the standard therapy.
its effectiveness in the treatment of acute coronary
Phase II studies, adding atopaxap on top of standard antiplatelet therapy (Aspirin and Clopidogrel). Vorapaxap addition caused a statistically insignificant reduction in ischemic events with the price of an increased rate of bleeding events. TRA 2P-TIMI 50 trial - The Thrombin-Receptor Antagonist in the Secondary Prevention of Atherothrombotic Ischemic Events, is a study that evaluated the efficacy and safety of this drug as long therapy in patients with established atherosclerosis. It enrolled over 26,000 patients with a history of myocardial infarction, ischemic stroke and peripheral artery disease, registering a significant decrease in ischemic events with the same drawback of increasing bleeding events, especially in the group of patients with a history stroke, the elderly and those with low body mass index[36]. To conclude, Vorapaxap is effective in reducing recurrent ischemic events mainly in the group of patients with a history of myocardial infarction, but significantly raises the rate of bleeding, especially in the group of patients with increased bleeding risk (older age, lower body weight). In terms of its usefulness in the treatment of acute phase STEMI clinical studies are needed to assess the effectiveness and safety in the treatment of this pathology.

Atopaxap - Atopaxap is a new antiplatelet agent that acts by antagonizing PAR-1 receptors. In extensive Phase II studies, adding atopaxap on top of standard antiplatelet therapy in patients with acute coronary syndrome was well tolerated, with no statistically significant increase in major bleeding events[37]. Further phase III studies are needed to determine its effectiveness in the treatment of acute coronary syndromes and possible future use as additional or alternative to the standard therapy.

Clinical practice discussions
In the field of treating the patients with STEMI the concept of global risk assessment – meaning the combined evaluation of both ischemic and bleeding risk should dominate the clinical judgment. So, despite the solid pharmacological and clinical data that demonstrated the superiority of ticagrelor and prasugrel as compared to clopidogrel, favoring the use of these new antiplatelet agents, the recommendation is far from being a universal one.

For the time being, this indication is made for a well-defined segment from the wide population with atherosclerotic vascular disease who usually needs single or dual antiplatelet therapy: those who suffer a STEMI and are treated with primary PCI, and do not have a history of hemorrhagic stroke or a moderate-to-severe form of liver disease. Moreover, prasugrel should not be given to those patients with any history of stroke (including ischemic stroke and transient ischemic attack) or with increased bleeding risk – the elderly (age ≥75years) and those with low body weight. Also, it should be noted that there are no data to support the use of ticagrelor or prasugrel as adjunctive treatment of thrombolysis.

Gastrointestinal bleeding remains one of the most feared complications of DAPT that should be addressed in practice by prescribing a proton-pump inhibitor (PPI) for the entire length of the time interval the patient receives DAPT. There were conflicting data regarding the pharmacokinetic interaction of clopidogrel with omeprazole and esomeprazole that inhibits CYP2C19 activity reducing clopidogrel activation, but there are no such interactions between ticagrelor or prasugrel and any of the PPI family members. Concerning the patients with chronic kidney disease (CKD) there is no need for dose adjustment for none of the antiplatelet agents that are currently in use but the data on the patients with end stage CKD or on dialysis are limited or absent[4].

Regarding the patients on dual antiplatelet therapy that need CABG surgery both clopidogrel and prasugrel are associated with an increased mortality through hemorrhagic events if the operation is performed less than 5 days prior discontinuation. The data on ticagrelor are in some way confusing due to the fact that despite similar bleeding rates with those registered in patients receiving clopidogrel and prasugrel, there was a remarkable reduction to a half in mortality rates for the patients receiving ticagrelor. The difference in mortality is explained by the differences in the time intervals between the day of stopping DAPT and the day CABG was performed – for instance, the analysis of the subgroup of those who stopped the second antiplatelet agent one to four days before CABG indicated that total mortality was 3.4% vs 15.5% (HR 0.21; p<0.01 for interaction) in the ticagrelor-treated patients as compared with those treated with clopidogrel[39]. Despite these encouraging data the guideline recommendation is more prudent and quite imprecise stating that ticagrelor should be stopped 3 – 5 days prior to CABG surgery, leaving the important and stringent choice of when to operate with the best risk-ratio profile on clinical judgment.

Conclusions
It should be stated that aspirin remains the unchallenged partner of the new antiplatelet agents, being recommended in all patients with acute coronary
syndrome with ST segment elevation, regardless of the therapeutic approach chosen (invasive treatment, fibrinolytic therapy or conservative treatment). There is only one possible exception to this statement – the circumstance where patients also need long term oral anticoagulation, the “triple therapy” being associated with a high bleeding risk that increases over time. This exception was the answer of the WOEST trial (What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting) where 573 patients on oral anticoagulation who underwent PCI were assigned clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy), those who did not receive aspirin having significantly lower bleeding events without an increase in thrombotic events[38]. The recent PRODIGY trial[39] that concluded that optimal duration of dual antiplatelet treatment might be stent specific is supporting our answer to the question which is aspirin’s best partner in platelet inhibition and how long this partnership should go: we consider there is no definite answer and probably will not be, because the profile of the patient and the type of coronary stent will further individualize this decision.

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