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MINIREVIEWS

P2Y12-ADP receptor antagonists: Days of future and past

Marc Laine, Franck Paganelli, Laurent Bonello

Marc Laine, Franck Paganelli, Laurent Bonello, Cardiology Department, CHU NORD, Chemine des Bourrely, 13015 Marseille, France

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Correspondence to: Marc Laine, MD, Cardiology Department, CHU NORD, Chemine des Bourrely, AP-HM, 13015 Marseille, France. marc.laine@ap-hm.fr
Telephone: +33-4-91968858
Fax: +33-4-91968979

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Abstract

Antiplatelet therapy is the cornerstone of the therapeutic arsenal in coronary artery disease. Thanks to a better understanding in physiology, pharmacology and pharmacogenomics huge progress were made in the field of platelet reactivity inhibition thus allowing the expansion of percutaneous coronary intervention. Stent implantation requires the combination of two antiplatelet agents acting in a synergistic way. Asprin inhibit the cyclo-oxygenase pathway of platelet activation while clopidogrel is a P2Y12 adenosine diphosphate (ADP)-receptor antagonist. This dual antiplatelet therapy has dramatically improved the prognosis of stented patients. However, due to pharmacological limitations of clopidogrel (interindividual variability in its biological efficacy, slow onset of action, mild platelet reactivity inhibition) ischemic recurrences remained high following stent implantation especially in acute coronary syndrome patients. Thus, more potent P2Y12-ADP receptor inhibitors were developped including prasugrel, ticagrelor and more recently cangrelor to overcome these pitfalls. These new agents reduced the rate of thrombotic events in acute coronary syndrome patients at the cost of an increased bleeding risk. The abundance in antiplatelet agents allow us to tailor our strategy based on the thrombotic/bleeding profile of each patient. Recently, the ACCOAST trial cast a doubt on the benefit of pre treatment in non-ST segment elevation acute coronary syndrome. The aim of the present review is to summarize the results of the main studies dealing with antiplatelet therapy in stented/acute coronary syndromes patients.

Key words: Clopidogrel; Prasugrel; Ticagrelor; Acute coronary syndrome; Ticagrelor; Cangrelor

Core tip: Antiplatelet therapy in coronary artery disease has dramatically changed during the past few years. From ticlodipine to cangrelor, the present review summarizes the results of the main studies dealing with this hot topic of cardiology.

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INTRODUCTION

Allowing the expansion of percutaneous coronary intervention (PCI) and considered as the cornerstone of acute coronary syndromes (ACS) treatment, anti-platelet therapy is in large part responsible for the dramatic reduction of ischemic events observed in the past decades in ischemic heart disease patients. Indeed, dual anti-platelet therapy (DAPT) is mandatory to prevent both stent thrombosis and ischemic recurrences in stented patients. Over the past decade, from ticlodipine to clopidogrel and more recently prasugrel, ticagrelor or cangrelor, anti platelet therapy's efficacy has dramatically improved resulting in clinical benefit for our patients. This evolution is the typical example of therapeutics improvements obtained thanks to pharmacology, pharmacogenomics and clinical experience. The aim of the present review is to summarize the main results of currently available P2Y12-adenosine diphosphate (ADP) receptor antagonists.

PLATELET ACTIVATION PATHWAYS

Circulating in quiescent state, platelets can be activated through several pathways leading to the thrombus formation and growth. Following platelets' adhesion, cyclo-oxygenase 1 and 2 transform arachidonic acid into prostaglandin-H2 which is then converted in thromboxane A2 which has potent vasoconstrictor properties but also activates platelets through their TPα and TPβ receptors. Through this G-protein receptor, thromboxane A2 activates the Glycoprotein Ⅱb-Ⅲa (Gp Ⅱb-Ⅲa) receptor (final stage of platelet activation) that binds to fibrin and ensures platelets aggregation resulting in the formation of a thrombus. By inhibiting the cyclo-oxygenases, aspirin blocks the platelets' activation pathway mediated by thromboxane A2.

Another critical step of platelets' activation is mediated through ADP that is produced by red blood cells and activates platelets in an autocrine/paracrine way thanks to the P2Y1 and mainly P2Y12 receptors. The binding of ADP with its P2Y12-receptor results in a decrease of the intracellular concentration of cyclic AMP which, there again, leads to the Gp Ⅱb-Ⅲa receptor activation.

Approximately 70 agonists are involved in platelets' activation such as serotonin, thrombin, epinephrine or collagen. These other agents are not actually therapeutical targets in ischemic heart disease patients; therefore they will not be discussed in this review.

TICLODIPINE

Ticlodipine was the first commercially available P2Y12 ADP-receptor inhibitor. In the nineties, this thienopyridine has demonstrated its superiority in combination with aspirin over the gold standard therapy of that time that associated aspirin to oral anticoagulant therapy in stented patients. Schömig *et al*[1] in their study that randomized more than 500 patients demonstrated a 25% reduction in the rate of major adverse cardiovascular events (MACE) including stent thrombosis thanks to the DAPT. This benefit on ischemic events was also associated with a dramatic reduction in bleedings which are associated with poor outcome in stented patients[2].

In 1998, Leon *et al*[3] published a study that compared three anti-thrombotic regimens in stented patients: Aspirin alone, aspirin plus warfarin and aspirin in combination with ticlodipine. The primary endpoint combined death, revascularization of the target lesion, angiographically evident thrombosis and myocardial infarction at 30 d was observed in 3.6% of the aspirin group, 2.7% of the aspirin-warfarin group and 0.5% in the aspirin-ticlodipine group (P = 0.001 for the comparison of all three groups). Regarding hemorrhagic complications they occurred in respectively 1.8%, 6.2% and 5.5% of the patients (P = 0.001 for the comparison of all three groups)[3]. Bertrand *et al*[4] randomized approximately 500 stented patients to aspirin-ticlodipine or aspirin-anticoagulant therapy and unlike the previous described studies used bleedings or peripheral vascular complication as primary endpoint. Again, DAPT was superior to the former gold standard demonstrating a reduction in the primary endpoint 13.5% *vs* 21% (OR: 0.23; 95%CI: 0.05-0.91, P = 0.01). Further, DAPT reduced the rate of MACE (P = 0.01) and hospital stay (P = 0.0001) compared to the aspirin-anticoagulant therapy[4].

However, concerns were raised regarding the safety of ticlodipine. Indeed, serious hematological side effects of ticlodipine were highlighted in several studies, therefore an urgent need for a new P2Y12-inhibitor emerged.

CLOPIDOGREL

Like ticlodipine, clopidogrel belongs to the thienopyridine family. This pro-drug absorbed in the intestine required a two steps hepatic biotransformation to become active. About 85% of the absorbed clopidogrel is turned into SR26334 (an inactive metabolite) by carboxylase. The rest is metabolized by cytochrome P450 iso-enzymes in the liver. During the first step CYP2C19, CYP1A2 and CYP2B6 turn clopidogrel into 2-oxoclopidogrel which is then hydrolyzed by CYP2C19, CYP2C9 and CYP3A to become R130964, the active metabolite that irreversibly inhibits the P2Y12 ADP-receptor[5-7].

The CURE trial was the first large scale randomized study that compared the combination of aspirin-clopidogrel to aspirin alone in ACS patients. In this study that included more than 12000 patients, DAPT significantly reduced the rate of MACE (9.3% *vs* 11.4%; RR 0.80, 95%CI: 0.72-0.90, P < 0.001) at the cost of an increased in major bleedings (3.7% *vs* 2.7%; RR

1.38; $P = 0.001$)[8].

Further, the PCI CURE study randomized 2600 ACS patients treated with PCI to clopidogrel pre-treatment and long term therapy *vs* aspirin (and thienopyridine for 1 mo only following PCI). There again, clopidogrel pre-treatment and long term therapy reduced the rate of MACE by 30% (RR 0.70; 95%CI: 0.50-0.97, $P = 0.03$) without any increase in major bleedings. Consistently, clopidogrel use was associated with a lower rate of Gp Ⅱb-Ⅲa inhibitors use ($P = 0.001$)[9]. Based on these findings and on the fact that unlike ticlodipine clopidogrel is devoid of hematological side effects, DAPT combining aspirin and clopidogrel quickly became the gold standard in stented and/or ACS patients.

However, our patients are not equal before clopidogrel. Järemo *et al*[10] demonstrated in 2002 that a large inter-individual variability in response to clopidogrel exists. In fact, about 30%-40% of patients are hypo responders to clopidogrel[11]. Further, Barragan *et al*[12] correlated high on-treatment platelet reactivity (HTPR) with stent thrombosis, a finding that was later confirmed in numerous studies. Several factors may be responsible for high on-clopidogrel platelet reactivity; they can act alone or combined. Genetic polymorphism has been one of the first causes of HTPR investigated. Three independent genes have clearly been related to clopidogrel hypo responsiveness: CYP2C19 (*2), CYP3A4 and ABCB1[13-18]. Drug-drug interaction with proton pump inhibitor, but also calcium channel blocker or statin (even if the evidence level is lower for the two latest)[19,20]; clinical factors (diabetes mellitus, acute coronary syndrome and obesity) or biological factors (high platelet turnover, platelet receptors up-regulation) have also been incriminated[21-24].

Beside its inter-individual platelet reactivity, clopidogrel possesses other limitations including a slow onset of action (especially in the ACS setting) and it induced a mild platelet reactivity inhibition. Therefore, new drugs devoid of these disadvantages were developed: Prasugrel and ticagrelor.

PRASUGREL

Prasugrel is defined as a third generation thienopyridine that irreversibly inhibits platelets like clopidogrel through its P2Y12-ADP receptor. Prasugrel is also a pro-drug that requires hepatic bio-transformation to become active. Following absorption it is hydrolyzed into R-95913 (a thiolactone) by esterases[25]. Then CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6 turn it into R-138727, the active metabolite[26]. Interestingly, prasugrel active metabolite possesses similar efficacy than the active metabolite of clopidogrel suggesting that its higher potency is related to its simpler metabolism[27].

The PRINCIPLE-TIMI 44 study is a phase 2 trial that demonstrated a faster onset of action and a more potent platelet reactivity inhibition with prasugrel compared to clopidogrel in patients undergoing PCI[28].

The TRITON trial compared prasugrel to clopidogrel in 13608 ACS patients treated with PCI. This study demonstrated a 19% reduction of the primary endpoint composed of myocardial infarction, stroke, and cardiovascular deaths with prasugrel compared to clopidogrel (9.9% *vs* 12.1%; HR 0.81, 95%CI: 0.73-0.90, $P < 0.001$) at the cost of increased life-threatening bleedings (1.4% *vs* 0.9%, $P = 0.01$). Further analysis of this study revealed the lack of benefit of prasugrel in elderly (⩾ 75 years) or small weighted patients (< 60 kg) and a potential harm in patients with an history of stroke or transient ischemic attack history leading to a restriction of use in the first described populations and a contra-indication in the later[29].

It is important to keep in mind that prasugrel should only be administered in ACS patients treated with PCI, once the coronary anatomy is known, given the design of the TRITON trial that randomized patients after coronary angiography.

The TRILOGY ACS study randomized more than 7000 ACS patients medically managed (*i.e.*, without revascularization) to prasugrel or clopidogrel in this clinical setting. In this study, the rate of myocardial infarction, stroke or cardiovascular death (primary endpoint) was similar between both groups (prasugrel: 13.9%, clopidogrel: 16%; HR: 0.91, 95%CI: 0.79-1.05, $P = 0.21$). Therefore, prasugrel is not recommended in this situation[30].

More recently, the ACCOAST study compared in 4033 non-ST segment elevation ACS patients the impact of a 30 mg pre-treatment of prasugrel (a half loading-dose administered after randomization, complement being administered after PCI) to a full loading dose (60 mg) once the PCI is performed. No benefit was found to pre-treat the patient. The primary endpoint composed of myocardial infarction, stroke, death from cardiovascular causes, urgent revascularization, Gp Ⅱb/Ⅲa bailout was similar in the two groups (HR pre-treatment: 1.02, 95%CI: 0.84-1.25, $P = 0.81$) but the rate of TIMI major bleeding was higher in the pre-treatment group despite the half loading dose used before coronary angiography ($P = 0.006$)[31].

TICAGRELOR

Unlike clopidogrel or prasugrel, ticagrelor does not belong to the thienopyridine family but to the cyclopentyltriazolopyrimidine family. Divergences with previous drugs go further than this classification; indeed ticagrelor is not a pro-drug and reversibly inhibits P2Y12-ADP receptor. Ticagrelor's main active metabolite (namely AR-C124910) is formed by O-de-ethylation that depends on CYP3A4. This metabolite (also active) can reach 40% of the concentration of ticagrelor[32].

The phase 2 trial ONSET/OFFSET demonstrated the faster onset of action associated with a more potent platelet reactivity inhibition of ticagrelor compared to clopidogrel in stable patients[33].

The PLATO trial compared ticagrelor to clopidogrel in 18624 patients ACS patients and founded a significant

reduction of the rate of the primary endpoint (death from cardiovascular causes, myocardial infarction or stroke) in the ticagrelor group: 9.8% *vs* 11.7% (HR 0.84, 95%CI: 0.77-0.92, $P < 0.001$). Unlike prasugrel, ticagrelor reduced the rate of death from any causes ($P = 0.001$) compared to clopidogrel. Of note, the rate of death in the clopidogrel group of the PLATO trial was 5.9% while it was 3.2% in the clopidogrel group of the TRITON trial suggesting a lower risk population included in the latter study[29,34]. Interestingly, the benefit of ticagrelor was present whatever the method of revascularization used (PCI, CABG, none).

Concerning the safety, ticagrelor administration was associated with an increased risk of major bleedings not related to CABG ($P = 0.03$).

In the ATLANTIC study, investigators evaluated the efficacy of ticagrelor pre-treatment in 1862 STEMI patients compared to the administration of the loading dose in the cath lab. In this study, both strategies resulted in a similar efficacy[35].

CANGRELOR

Cangrelor is a non-thienopyridine intra-venous agent that reversibly inhibits P2Y12 ADP-receptor. Like ticagrelor, it does not require hepatic biotransformation to become active explaining its quick onset of action. Further, half-life of cangrelor is 3-6 min while platelets resume normal reactivity 30-60 min after discontinuation of the infusion[36]. Theoretically, cangrelor seems to be an interesting drug: A rapid onset of action, a potent platelet reactivity inhibition and a rapid reversible effect. However, despite these promising properties, the CHAMPION PCI and CHAMPION PLATFORM trials failed to demonstrate any benefit of cangrelor compared to clopidogrel in patients treated with PCI[37,38].

Later, the CHAMPION PHOENIX trial redefined periprocedural myocardial infarction and used an angiographic core lab. This study that once again compared cangrelor to clopidogrel in patients treated with PCI found a significant reduction in the rate of primary endpoint (death from any cause, myocardial infarction, ischemia driven revascularization, stent thrombosis at 48 h) in the cangrelor group (4.7% *vs* 5.9%, OR 0.79, 95%CI: 0.67-0.93, $P = 0.006$) without difference regarding severe bleedings[39].

Interestingly, the BRIDGE study confirmed a better platelet reactivity inhibition with cangrelor compared to placebo without significant difference in bleedings in ACS patients that discontinued thienopyridine before CABG[40].

Thanks to its pharmacological properties, cangrelor might be interesting in patients treated with P2Y12 inhibitors that require drug discontinuation before surgery or in unconscious patients admitted for ACS, unable to take orally administered anti platelet agents or in vomiting patients, a frequent setting during STEMI or in morphine treated patients.

CONCLUSION

Therapeutics has constantly improved over the last decades for the best of our patients. However, several debates remain regarding pre-treatment or optimal duration of DAPT in ACS patients emphasizing the importance of personalized treatment in stented patients.

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