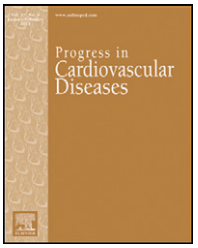
Available online at www.sciencedirect.com

ScienceDirect

www.onlinepcd.com



Novel Antiplatelet Agents: The Current State and What Is Coming Down the Pike

Francesco Franchi[a], *Fabiana Rollini*[a], *Yongwhi Park*[a,b], *Dominick J. Angiolillo*[a,*]

[a]*University of Florida College of Medicine–Jacksonville, Jacksonville, FL, USA*
[b]*Gyeongsang National University Hospital, Jinju, Korea*

ARTICLE INFO

Keywords:
Antiplatelet therapy
Acute coronary syndrome
Percutaneous coronary intervention
P2Y12 receptor
Thrombin receptor

ABSTRACT

Antiplatelet therapy is the cornerstone of treatment for patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI). Despite the use of dual antiplatelet therapy with aspirin and clopidogrel, a considerable number of patients still experience atherothrombotic events, which may be explained at least in part by inadequate platelet inhibition induced by this treatment regimen. This underscores the need for more potent antithrombotic strategies for the acute and long-term treatment of ischemic complications, especially in high-risk patients. These include novel generation $P2Y_{12}$ receptor antagonists, such as prasugrel, ticagrelor and cangrelor, or adjunctive antiplatelet agents targeting different pathways, such as the thrombin protease-activated receptors-1 receptor inhibitor vorapaxar. Moreover, since ischemic events accrue over time after an acute event, prolonging intensified antiplatelet therapy beyond 1-year has also been investigated. This manuscript provides an overview on the current status and future directions of antithrombotic therapies for the treatment of patients with ACS or treated with PCI, mainly focusing on novel agents.

Arterial thrombosis is the major determinant leading to acute coronary syndrome (ACS) and recurrent atherothrombotic events following percutaneous coronary intervention (PCI).[1,2] Adhesion, activation and aggregation of platelets at the site of vascular injury have a pivotal role in the formation of arterial thrombi and, therefore, antiplatelet therapy is the cornerstone of treatment of patients with ACS or undergoing PCI.[2,3] Multiple platelet signaling pathways are involved in this process, including thromboxane (TX) A2, adenosine diphosphate (ADP) and thrombin, which represent potential targets for antiplatelet agents (Fig 1).[2,3] Currently, four main classes of antiplatelet therapies are clinically available for oral and intravenous administration in patients with ACS or following PCI: 1) the cyclooxygenase (COX)-1 inhibitor aspirin (ASA); 2) the ADP $P2Y_{12}$ receptor antagonists clopidogrel, prasugrel, ticagrelor and cangrelor; 3) the glycoprotein IIb/IIIa inhibitors (GPIs) abciximab, eptifibatide and tirofiban; and 4) the thrombin protease-activated receptor (PAR)-1 inhibitor vorapaxar.[4–6] This manuscript provides an overview on the current status and future directions of antithrombotic therapies for the treatment of patients with ACS or treated with PCI, mainly focusing on novel drugs that have already been approved for clinical use.

Statement of Conflict of Interest: see page 276.

* Address reprint requests to Dominick J. Angiolillo, MD, PhD, Division of Cardiology, University of Florida College of Medicine–Jacksonville, ACC Building 5th floor, 655 West 8th Street, Jacksonville, FL 32209.
E-mail address: dominick.angiolillo@jax.ufl.edu (D.J. Angiolillo).

http://dx.doi.org/10.1016/j.pcad.2015.08.009
0033-0620/

Abbreviations and Acronyms

ACS = acute coronary syndrome

ADP = adenosine diphosphate

ASA = aspirin

ATP = adenosine triphosphate

CABG = coronary artery bypass graft

CAD = coronary artery disease

CYP = cytochrome P450

COX = cyclooxygenase

CV = cardiovascular

DAPT = dual antiplatelet therapy

DES = drug eluting stent

DM = diabetes mellitus

EMA = European Medicines Agency

FDA = Food and Drug Administration

GPI = glycoprotein IIb/IIIa inhibitor

GUSTO = global use of strategies to open occluded coronary arteries

HPR = high platelet reactivity

LD = loading dose

MACE = major adverse cardiovascular events

MD = maintenance dose

MI = myocardial infarction

NOAC = non-vitamin K antagonist oral anticoagulant

NSTE = non-ST-segment elevation

PAD = peripheral arterial disease

PAR = protease-activated receptor

PCI = percutaneous coronary intervention

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TIMI = thrombolysis in myocardial infarction

TP = thromboxane prostanoid

TRAP = thrombin receptor agonist peptide

TX = thromboxane

Oral antiplatelet therapy

ASA and clopidogrel

ASA exerts its effects by irreversibly blocking the enzyme COX-1, which is responsible for generation of TXA_2 from arachidonic acid, and inhibits platelet activation mediated by the TX and prostaglandin endoperoxide receptors.[7] Many clinical trials have demonstrated the efficacy of aspirin therapy in the reduction of major adverse cardiovascular events (MACE) in patients with different coronary artery disease (CAD) manifestations.[8] Consistent evidence also suggest that the benefit of ASA is achieved at low doses (75–100 mg daily), while higher dosing regimens mainly increase the risk of bleeding events, without improving ischemic outcomes.[2,9] However, the use of monotherapy with ASA is still associated with a high rate of recurrent ischemic events following an ACS or PCI.[8] This can be attributed to the fact that during COX-1 blockade other platelet activation pathways remain uninhibited, suggesting the need for adjunctive antiplatelet therapies, which had set the basis for the development of agents targeting the ADP $P2Y_{12}$ receptor.[2,3] Currently, dual antiplatelet therapy (DAPT) with a combination of ASA and a $P2Y_{12}$ receptor inhibitor represents the mainstay for the treatment and secondary prevention of ischemic recurrences in patients with ACS or treated with PCI.[2–6]

The second-generation thienopyridine clopidogrel is the most widely used $P2Y_{12}$ receptor antagonist and is the only agent of this class currently approved for patients with stable CAD treated with PCI.[5,6] Clopidogrel is a pro-drug that requires metabolic transformation in order to exert its antiplatelet effect (Table 1).[2,7] After intestinal absorption, approximately 85% of clopidogrel is hydrolyzed by carboxylase to an inactive metabolite. The remaining pro-drug is rapidly metabolized by hepatic cytochrome P450 (CYP) isoenzymes, mainly CYP2C19, in a 2-step oxidation process with the generation of a highly unstable active metabolite which irreversibly binds to the $P2Y_{12}$ receptor.[2,7] Several clinical trials have consistently shown the efficacy of DAPT with aspirin and clopidogrel in reducing the risk of acute and long-term atherothrombotic events in the setting of ACS and PCI.[10] Although in patients with stable CAD the combined used of DAPT along with newer and safer drug eluting stent (DES) platforms has led to an extremely low rate of ischemic complications,[11] a considerable number of patients with ACS still continue to experience recurrent thrombotic events.[2,10] This has been in part attributed to the high variability in response to clopidogrel.[12,13] In fact, approximately 30%–40% of patients have high platelet reactivity (HPR) while on-clopidogrel treatment, which has shown to be associated with an increased number of long-term atherothrombotic events, including stent thrombosis (ST).[12,13] Several factors have been associated with clopidogrel response variability, including clinical [i.e., poor absorption, drug–drug interactions, ACS, diabetes mellitus (DM), obesity, chronic kidney disease], genetic (i.e., CYP polymorphisms) and cellular (i.e., accelerated platelet turnover, reduced CYP metabolic activity, or up-regulation of $P2Y_{12}$ pathway) factors.[12] These observations emphasize the need for more potent antithrombotic agents, particularly for the treatment of patients with ACS. Although the addition of non-vitamin K antagonist oral anticoagulants (NOACs) to antiplatelet therapy has been tested in several clinical trials in patients with ACS, to date only low-dose rivaroxaban (2.5 mg b.i.d.) has shown to be effective in reducing ischemic events, at the expense of an increase in major bleeding.[14] A detailed description of the role of NOACs is beyond the scope of this manuscript and is described elsewhere.[15]

Prasugrel

Prasugrel (Effient®, Eli Lilly and Company, Indianapolis, IN) is an orally administered third-generation thienopyridine (Table 1). Similarly to clopidogrel, it requires an activation process through hepatic CYP isoenzymes which generate an active metabolite that irreversibly binds to the ADP $P2Y_{12}$ receptor.[2,7] Although the active metabolites of clopidogrel and prasugrel have the same *in vitro* affinity for the $P2Y_{12}$ receptor, prasugrel's single-step oxidation process is more efficient than clopidogrel's, leading to a 5-fold higher *in vivo* availability of the active metabolite.[2,7] These pharmacological properties translate into faster onset of action, enhanced platelet inhibition and lower interindividual variability in antiplatelet effect than clopidogrel.[2,7] In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by