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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# Antiplatelet Agents for the Treatment and Prevention of Coronary Atherothrombosis

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## ABSTRACT

Antiplatelet drugs provide first-line antithrombotic therapy for the management of acute ischemic syndromes (both coronary and cerebrovascular) and for the prevention of their recurrence. Their role in the primary prevention of atherothrombosis remains controversial because of the uncertain balance of the potential benefits and risks when combined with other preventive strategies. The aim of this consensus document is to review the evidence for the efficacy and safety of antiplatelet drugs, and to provide practicing cardiologists with an updated instrument to guide their choice of the most appropriate antiplatelet strategy for the individual patient presenting with different clinical manifestations of coronary atherothrombosis, in light of comorbidities and/or interventional procedures. (J Am Coll Cardiol 2017;70:1760–76) © 2017 by the American College of Cardiology Foundation.

Antiplatelet drugs have an established role in the management and prevention of coronary and cerebrovascular events associated with atherothrombosis, whereas their role in primary prevention of these events remains less clear. In this consensus document, the European Society of Cardiology Working Group on Thrombosis reviews the evidence for different antiplatelet drugs to provide

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clinicians with a guide to appropriate antiplatelet strategies.

## CLINICAL PHARMACOLOGY OF ANTIPLATELET DRUGS

Multiple pathways contribute to platelet activation and aggregation, and although pharmacological interference with these pathways reduces the risk of atherothrombotic complications, it is also associated with an increased risk of bleeding (**Figure 1**). It is important to emphasize that the thromboxane (TX) $A_2$-, adenosine diphosphate (ADP)-, and thrombin-activated pathways transduce independent signals of platelet activation and represent nonredundant targets for its pharmacological modulation. This is reflected by the additive nature of the effects of combined antiplatelet therapy, as discussed later.

**CYCLOOXYGENASE-1 INHIBITORS.** Aspirin irreversibly inactivates platelet cyclooxygenase (COX)-1 and suppresses $TXA_2$ generation by selectively acetylating a serine residue (Ser-529) close to the catalytic pocket of the enzyme (**Figure 2**) (1). Whereas a virtually complete and long-lasting inhibition of platelet COX-1 by low-dose aspirin is associated with reduced risk of atherothrombotic events (1), this is not achieved by most nonsteroidal anti-inflammatory drugs (NSAIDs), unmasking their COX-2–dependent cardiotoxicity (2). For more details, please see the Online Appendix.

**$P2Y_{12}$ INHIBITORS.** Oral inhibitors of the platelet ADP receptor, $P2Y_{12}$, include the thienopyridines (ticlopidine, clopidogrel, and prasugrel) and ticagrelor. Major characteristics of $P2Y_{12}$ inhibitors are summarized in **Table 1**. Thienopyridines are prodrugs, generating short-lived active metabolites (Online Figures 1A and 1B) that irreversibly inactivate the receptor and consequently inhibit ADP-induced platelet activation.

Ticagrelor is an adenosine triphosphate analogue. It directly and reversibly binds the $P2Y_{12}$ receptor, acting as an allosteric antagonist that noncompetitively prevents ADP-induced $P2Y_{12}$ activation (1).

When added to COX-1 suppression by low-dose aspirin, $P2Y_{12}$ blockade by clopidogrel produces an additional 10% to 20% relative risk reduction of major vascular events in high-risk patients (1). This relatively modest benefit may reflect the low degree of $P2Y_{12}$ inactivation achieved by clopidogrel in most patients. A faster and more complete $P2Y_{12}$ blockade by prasugrel or ticagrelor produced additional benefit versus clopidogrel in acute coronary syndromes (ACS) (3,4), supporting the clinical relevance of effectively targeting 2 nonredundant platelet signaling pathways. For more details please see the Online Appendix.

**PROTEASE-ACTIVATED RECEPTOR INHIBITORS.** At least 2 protease-activated receptors (PAR1 and PAR4) are present on human platelets, with PAR1 showing the highest affinity for thrombin. Vorapaxar competes with the tethered ligand of PAR1 generated by thrombin-catalyzed proteolysis, disrupting downstream signaling (1). Targeting this pathway in addition to aspirin and clopidogrel produced a nonsignificant reduction in major vascular events in ACS, associated with a disproportionate increase in bleeding (5). For more details, please see the Online Appendix.

**INTERINDIVIDUAL VARIABILITY IN DRUG RESPONSES.** At variance with drug resistance, interindividual variability in drug response is largely related to the mechanism(s) of drug absorption and biotransformation, and/or patient characteristics (6).

Clopidogrel has less than optimal pharmacokinetics: ~85% is inactivated by carboxylesterases before liver first pass; it is a substrate of the P-glycoprotein (P-gp) efflux transporter (also known as *ABCB1*) and is bio-activated by 2 sequential oxidative reactions involving several cytochrome P450 (CYP450) isozymes (1A2, 2B6, 2C9, 2C19, 3A4, and 3A5) (Online Figure 1A) with <10% systemic bioavailability. CYP2C19 and P-gp polymorphisms significantly affect the concentration of clopidogrel active metabolite and clinical efficacy, such that patients with the P-gp 3435 TT genotype and/or poor metabolizers (i.e., patients with any 2 loss-of-function CYP2C19 alleles) have a reduced drug efficacy and consequent poor clinical outcome (7–10). Interestingly, a recent trial in patients with symptomatic peripheral artery disease (PAD), which excluded poor metabolizers, showed superimposable efficacy and safety of clopidogrel and ticagrelor (11). The P-gp and CYP3A4, 2B6, 2C9, and 2C19 pathways account for clinically relevant drug-drug interactions with omeprazole, statins, and strong CYP3A4/P-gp inducers or inhibitors, which increase variability in response to clopidogrel, and likely affect its safety and efficacy (Online Figure 1A) (12). Prasugrel has simpler and more efficient pharmacokinetics than clopidogrel, resulting in less variability in drug response and no clinically relevant drug-drug interactions.

Ticagrelor has a half-life of 7 to 12 h and ~36% bioavailability (1). Ticagrelor is biotransformed by

### ABBREVIATIONS AND ACRONYMS

**ACS** = acute coronary syndromes

**CABG** = coronary artery bypass graft

**CAD** = coronary artery disease

**COX** = cyclooxygenase

**DAPT** = dual antiplatelet therapy

**ICH** = intracranial hemorrhage

**MI** = myocardial infarction

**OAC** = oral anticoagulation

**PAD** = peripheral artery disease

**PAR** = protease-activated receptor

**PCI** = percutaneous coronary intervention

**SAPT** = single antiplatelet therapy

**TX** = thromboxane