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NONSTATIN DRUGS (W BORDEN, SECTION EDITOR)

Novel Antiplatelet Therapies

Luke Kim · Konstantinos Charitakis · Rajesh V. Swaminathan · Dmitriy N. Feldman

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Abstract Advances in antiplatelet therapy have significantly improved outcomes in patients with ischemic heart disease. Thienopyridines remain a cornerstone of therapy along with aspirin. Recently, concerns have been raised about the use of clopidogrel due to its pharmacokinetic and pharmacogenetic interpatient variability. A third-generation thienopyridine, prasugrel, overcomes some of these problems by improving inhibition of platelet aggregation, but increasing the risk of peri-procedural bleeding. Other novel antiplatelet agents, such as ticagrelor, have shown improved efficacy in recent trials and require further investigations. The field of pharmacotherapy continues to rapidly evolve as newer agents, such as thrombin receptor antagonists, along with older agents, such as cilostazol and glycoprotein IIb/IIIa inhibitors, are being explored.

Keywords Antiplatelet · Thienopyridines · Thrombin receptor antagonists · Aspirin · GP IIb/IIIa inhibitors · Ticagrelor · Cilostazol

Introduction

Coronary artery disease (CAD) remains one of the leading causes of death in the United States and has become an increasing problem worldwide [1, 2]. Over the past few decades, advances in medical therapy have significantly improved outcomes in patients with ischemic heart disease. Antiplatelet agents have become a standard therapy in patients with established CAD [3, 4]. Advances in antiplatelet and antithrombotic therapies have significantly reduced ischemic complications in patients undergoing percutaneous coronary intervention (PCI) as well as in conservatively medically managed patients [5, 6]. Many trials from the past few years have revolutionized the field of pharmacotherapy, and antiplatelet therapies can now be tailored to individuals depending on the clinical scenario. This article reviews the updated literature on traditional antiplatelet therapies and discusses the emerging role of novel agents in an era of pharmacogenetics and personalized medicine.

L. Kim · K. Charitakis · R. V. Swaminathan · D. N. Feldman (✉)
Greenberg Division of Cardiology, New York Presbyterian Hospital, Weill Cornell Medical College,
520 East 70th Street, Starr-434 Pavilion,
New York, NY 10021, USA
e-mail: dnf9001@med.cornell.edu

Traditional Antiplatelet Therapies

Aspirin has become a foundation for treatment of CAD based on extensive data demonstrating its protective effect. Aspirin causes an irreversible inactivation of the cyclooxygenase-1 (COX-1) enzyme that is required for prostaglandin and thromboxane synthesis, which in turn diminishes platelet aggregation. One of the earlier trials enrolling male patients in the VA Cooperative Study demonstrated that there was a 51% reduction in the incidence of death or acute myocardial infarction (MI) in those who received aspirin for unstable angina (UA) [7]. Numerous subsequent trials have reproduced a similar finding, further providing irrefutable evidence that aspirin use is associated with a significant reduction in the combined endpoint of death and MI [8–11]. It has been postulated that higher doses of aspirin can inhibit endothelial cell synthesis of prostacyclin, which is responsible for vasodilation and inhibition of platelet aggregation. Howev-

er, clinical relevance of this dose-dependent mechanism has never been demonstrated. Even in the more recent Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS 7) trial, a higher dose of aspirin (300–325 mg) failed to demonstrate improved efficacy post-PCI in comparison to a low dose of aspirin (75–100 mg) [12].

With the development of thienopyridines, a combination of aspirin and thienopyridines has become a standard regimen in patients with ischemic heart disease. Thienopyridines block the adenosine diphosphate (ADP) receptors on platelets, therefore decreasing platelet activation and aggregation. Due to the unfavorable side effect profile of ticlopidine, clopidogrel has become the preferred thienopyridine [13]. Numerous trials have demonstrated the benefit of clopidogrel in a wide spectrum of CAD. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, clopidogrel significantly reduced the combined endpoint of ischemic stroke, MI, and vascular death in patients with atherosclerotic disease [14]. The role of clopidogrel was further evaluated in acute settings in numerous studies including the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, which studied the role of clopidogrel in non–ST-elevation acute coronary syndrome (ACS). This trial demonstrated a 20% reduction in the combined endpoint of cardiovascular death, MI, or stroke in the group receiving clopidogrel and aspirin in comparison to aspirin alone (9.3% vs 11.4%) [15]. In patients undergoing PCI, the Clopidogrel for Reduction of Events During Observation (CREDO) trial demonstrated an improved outcome with 26.9% reduction in the combined risk of death, MI, or stroke (8.5% vs 11.5%) when clopidogrel was continued for up to 1 year [16]. More importantly, clopidogrel pretreatment at least 3 h prior to PCI reduced the combined risk of death, MI, or urgent target vessel revascularization by 38.6% at 28 days.

Although the use of clopidogrel in non–ST-elevation MI gained widespread acceptance, several trials helped to establish its role in patients presenting with an ST-elevation MI (STEMI). The Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial revealed that clopidogrel therapy as an adjunctive therapy to thrombolytics and aspirin reduced the composite endpoint of cardiovascular mortality, recurrent MI, and recurrent ischemia by 20% in STEMI patients [17]. Furthermore, there was an improved patency rate of the infarct-related artery without any significant increase in major bleeding. Another landmark trial, the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Chinese Cardiac Study-2 (COMMIT/CCS-2), further validated the benefit of clopidogrel in STEMI patients by demonstrating the reduction in the combined rate of death, reinfarction, and stroke by 9% (9.3% vs 10.1%) without a significant increase in bleeding rates [18].

After numerous trials demonstrated a clear benefit of clopidogrel in all patients undergoing PCI, several trials attempted to identify the appropriate timing and dose of clopidogrel prior to PCI. The Antiplatelet Therapy for Reduction of Myocardial Damage during Angioplasty Study (ARMYDA-2) compared a 600-mg versus 300-mg clopidogrel load given 6 h prior to PCI [19]. At 30 days, there was a significant reduction in composite endpoint of death, MI, or target vessel revascularization (4% vs 12%) in the 600-mg group compared to the 300-mg group. However, a higher dose (900 mg) of clopidogrel in the Intracoronary Stenting and Antithrombotic Regimen-Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect trial (ISAR-CHOICE) was associated with an increase in bleeding rates without any additional anti-ischemic benefit [20]. Recently, the CURRENT-OASIS 7 trial demonstrated a reduction in combined endpoints of death, MI and stroke (3.9% vs 4.5%) in a subgroup of patients with ACS undergoing PCI who received a double-dose of clopidogrel (150 mg) for 1 week in comparison to a routine 75-mg dose [12, 21].

Controversy with Older-Generation Thienopyridines

Despite a benefit in the overall population with ischemic heart disease, recent studies have raised concerns about the effectiveness of clopidogrel when used concurrently with other drugs involved with the cytochrome p450 metabolism. Clopidogrel is a prodrug, with 85% of medication being hydrolyzed to an inactive carboxylic acid derivative [22]. Therefore, only a small portion of the drug is transformed to the active metabolite via the p450-dependent system, mainly by CYP 3A4/5 and CYP 2C19. Drugs affecting the CYP 3A4/5 and CYP 2C19 may potentially affect clopidogrel metabolism, and thus its clinical efficacy. Proton pump inhibitors (PPIs) have been recently implicated in the drug-drug interaction with clopidogrel. There have been a number of pharmacokinetic reports of reduced clopidogrel efficacy in association with PPIs [23]. Specifically, omeprazole, metabolized mostly via CYP 2C19, is associated with decreased platelet inhibition and a higher clopidogrel "nonresponder" rate [24–26]. However, several studies have shown lack of such association with other PPIs, such as pantoprazole or esomeprazole [27, 28]. Unfortunately, the only randomized clinical trial, the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT), was terminated prior to its completion [29]. However, this trial did not demonstrate any increase in cardiovascular events when omeprazole was used concomitantly with clopidogrel [29]. Certainly, numerous categories of drugs have potential drug-

drug interaction via the p450 system, and further studies are necessary to clarify the controversy surrounding this issue.

In addition to the drug-induced changes in p450 metabolism system, there has been increasing awareness and interest in genetic variation in CYP isoenzymes affecting the clopidogrel efficacy. Pharmacogenetics has been implicated as an important contributor to interpatient variability in response to thienopyridine therapy [30, 31]. CYP 2C19 polymorphisms have recently been linked with decreased platelet inhibition to clopidogrel and increased cardiovascular events [32–34, 35•]. These loss-of-function CYP 2C19C polymorphisms lead to decreased active clopidogrel metabolite, resulting in less platelet inhibition. More than one loss-of-function allele appears to lead to a more profound reduction in platelet inhibition. In addition, studies have suggested variable frequency of these polymorphisms in different ethnic groups, with greater number of clopidogrel "nonresponders" in certain ethnic groups, such as Asians [36]. These findings were compelling enough to have the US Food and Drug Administration add a warning to physicians in regard to use of clopidogrel in patients with these polymorphisms. Other polymorphisms in the *ABCD1* gene, which is implicated in intestinal absorption, have also been described as a contributing factor that affects response to clopidogrel [35•]. Certainly, further studies are needed in order to define the role of genotype variability on clopidogrel responsiveness.

With reports of clopidogrel "nonresponsiveness" in about 30% of patients, there has been an increasing interest in direct measurement of platelet inhibition [37]. Numerous methods exist for laboratory testing of platelet inhibition. Light transmittance aggregometry (LTA) is considered the "gold standard" measurement of platelet aggregation, which analyzes percent inhibition by measuring the amount of transmitted light through a vial of platelet plasma before and after the addition of ADP, which induces platelet aggregation. This test is very labor intensive and thus limits its routine use for guiding clinical care. Other tests for platelet inhibition include flow cytometry, platelet function analyzer (PFA-100), vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay, and the VerifyNow P2Y12 assay (Dynamic Medical, Blaricum, The Netherlands) [38]. The bedside VerifyNow P2Y12 assay measures the aggregation of platelets to fibrinogen-coated beads, and has been used as a point-of-care platelet function assay to determine if tailoring antiplatelet therapy can improve patient outcomes. This was recently evaluated in the multicenter trial, Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety (GRAVITAS) trial, which tailored clopidogrel dose in patients undergoing PCI with drug-eluting stents with inadequate platelet inhibition [39••]. However, the trial failed to demonstrate improved outcomes with tailored high-dose (150 mg) clopidogrel therapy. Despite these findings, there is more awareness and interest in identifying the appropriate choice and dosing of antiplatelet therapy in patients with CAD, especially in those undergoing PCI for ACS.

Third-Generation Thienopyridines

With the recent findings of variable responsiveness to clopidogrel, a newer generation of thienopyridines was met with great interest. Prasugrel, a third-generation thienopyridine, has been shown to generate an active metabolite more efficiently, leading to higher levels of platelet inhibition. The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial compared prasugrel (60-mg loading dose followed by 10-mg maintenance dose) to a higher dose of clopidogrel (600-mg loading dose followed by 150-mg maintenance dose) in patients undergoing elective PCI [40]. This trial demonstrated that prasugrel achieved superior platelet inhibition in comparison to high-dose of clopidogrel.

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, 13,608 patients with moderate-risk and high-risk ACS undergoing PCI were randomized to prasugrel (60-mg loading dose followed by 10-mg maintenance dose) or clopidogrel (300-mg loading dose followed by 75-mg maintenance dose) [41]. This study demonstrated that prasugrel reduced the composite endpoint of death, nonfatal MI, and nonfatal stroke by 20% in comparison to clopidogrel (9.9% vs 12.1%). In addition, the rate of stent thrombosis was significantly reduced with prasugrel (1.1% vs 2.4%). However, the rate of major hemorrhage was increased by 32% in the prasugrel group compared to the clopidogrel group. Subgroup analyses have identified those patients who were at high risk of bleeding with prasugrel. These risk factors included age ≥75 years, history of stroke or transient ischemic attack, and body weight <60 kg. Therefore, prasugrel is an effective antiplatelet agent, particularly for those patients who are poor metabolizers of clopidogrel or have high platelet reactivity while taking clopidogrel. Importantly, risk/benefit evaluation of bleeding/anti-ischemic risk should take place prior to initiating prasugrel peri-procedurally in patients with ACS.

Glycoprotein IIb/IIIa Inhibitors

Despite the advances in development of thienopyridines, the addition of glycoprotein (GP) IIb/IIIa inhibitors to thienopyridines has shown a clear benefit in high-risk

patients with ischemic heart disease. GP IIb/IIIa inhibitors prevent fibrinogen from cross-linking with platelets and prevent platelet aggregation by occupying the receptor. Tirofiban, a nonpeptide molecule, successfully reduced mortality (2.3% vs 3.6%) in the Platelet Receptor Inhibition in Ischemic Syndrome Management Study (PRISM) for non-ST-elevation ACS [42]. Eptifibatide, a synthetic, non-immunogenic heptapeptide that mimics the Arg-Gly-Asp amino acid sequence by which fibrinogen binds to the GP IIb/IIIa receptor, was also evaluated in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy trial (PURSUIT) [43]. The addition of eptifibatide reduced the combined endpoint of death and nonfatal MI by 1.5% (14.2% vs 15.7%) with the benefit persisting through 30 days. Abciximab, a Fab fragment of a monoclonal antibody directed at the GP IIb/IIIa receptor, has been studied extensively in several trials as well. The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina trial (CAPTURE) demonstrated a reduction in the combined endpoint of death, MI, and revascularization at 30 days (11.3% vs 15.9%) in patients with unstable angina undergoing PCI. Furthermore, the Evaluation of c7E3 for Prevention of Ischemic Complications (EPIC) trial showed an improvement in long-term outcomes as long as 3 years after PCI in patients with non–ST-elevation ACS receiving abciximab [44].

Given the benefit of peri-procedural clopidogrel, recent trials investigated the role of GP IIb/IIIa agents in conjunction with thienopyridines. In the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) trial, 2,022 patients undergoing PCI secondary to non-ST-elevation ACS were randomized to abciximab versus placebo along with aspirin, heparin, and pretreatment with 600 mg of clopidogrel [45]. By 30 days, there was a 25% reduction in ischemic events in the abciximab group (8.9% vs 11.9%), with the subset of patients with elevated troponin I benefiting the most. Therefore, patients presenting with ACS with high-risk features should be considered for GP IIb/IIIa inhibitors in addition to clopidogrel, especially if they are being considered for an invasive strategy. However, further studies are necessary to delineate the benefit of GP IIb/IIIa inhibitors with the development of novel oral antiplatelet agents as well as novel antithrombotic agents, such as bivalirudin.

Novel Antiplatelet Agents

Although prasugrel demonstrated improved efficacy as a more potent thienopyridine, the increased bleeding risk limits its utility in certain subsets of patients. Ticagrelor, a novel ADP P2Y12 antagonist, has shown encouraging results in recent studies [46]. Ticagrelor is rapidly absorbed in the gastrointestinal tract, and hepatic activation does not impact its metabolism as opposed to thienopyridines. Ticagrelor, a reversible, direct-acting ADP receptor P2Y12 antagonist, has a binding site different from traditional thienopyridines [47]. In the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor (loading dose of 180 mg and maintenance dose of 90 mg twice daily) was compared to clopidogrel (loading dose of 300 mg and maintenance dose of 75 mg daily) in 18,624 patients presenting with ACS [48•]. By 1 year, there was a significant reduction in the composite endpoint of death, MI, or stroke (9.8% vs 11.7%) in the ticagrelor group versus the clopidogrel group. Furthermore, the rate of major bleeding was not increased in the ticagrelor group (11.6% vs 11.2%) in comparison to the clopidogrel group. There was a higher rate of non–coronary artery bypass surgery (CABG)-related bleeding and a trend toward a higher rate of intracranial bleeding, but the rate of intracranial bleeding was very low (0.3%) in the study. Another important finding in the study was a 1.4% absolute reduction in mortality. This mortality benefit will need to be further confirmed in future studies. One of the important aspects of ticagrelor is its reversible nature and relatively short half-life, which may prevent significant delays (5–7 days with thienopyridines) when urgent CABG surgery is needed.

With the delayed onset of action of clopidogrel and concerns for stent thrombosis, there has been growing interest in rapid-onset ADP receptor antagonists. Cangrelor is an intravenous adenosine triphosphate analogue that reversibly inhibits the ADP P2Y12 receptor [49]. In contrast to oral thienopyridines, cangrelor is an active drug without the need for metabolic conversion. Two trials have studied the role of cangrelor in patients undergoing PCI. In the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PLATFORM trial, cangrelor was compared to placebo in 5,362 patients undergoing PCI [49]. Cangrelor was not superior in reducing the composite endpoints of death, MI, or ischemia-driven revascularization at 48 h. Although there was a small decrease in secondary endpoints of stent thrombosis in the cangrelor group (0.2% vs 0.6%), such benefit was not observed in the CHAMPION PCI trial when patients were pre-loaded with clopidogrel prior to revascularization [50]. In addition, there was a trend toward a higher rate of major bleeding in both trials. Therefore, cangrelor did not appear to demonstrate additive benefit in patients undergoing PCI and preloaded timely with clopidogrel.

Elinogrel, a reversible ADP P2Y12 antagonist, is one of the latest antiplatelet agents being examined in the management of ischemic heart disease. Elinogrel, available orally and parenterally, does not require metabolic activation and has a fast onset of action. Initial data from the Early Rapid Reversal of platelet thrombosis with intrave-

nous Elinogrel before PCI to optimize reperfusion in acute Myocardial Infarction (ERASE MI) pilot trial, has shown promising data in terms of its safety profile including bleeding risk in acute MI [51]. Recently, the results from the phase 2 study of the Intravenous and Oral administration of elinogrel, a selective and reversible P2Y12-receptor inhibitor, versus clopidogrel to evaluate Tolerability and Efficacy in nonurgent Percutaneous Coronary Interventions patients (INNOVATE-PCI) trial, demonstrated greater platelet inhibition with elinogrel without a significant increase in major bleeding risks [52]. A large phase 3 clinical trial will be needed to examine the role of elinogrel in improving ischemic outcomes after PCI.

Recently, thrombin has been explored as another target for platelet inhibition. Thrombin activates platelets via protease-activated receptor 1. Vorapaxar is a thrombin receptor antagonist currently being investigated. Data from early studies did not show increased bleeding in patients undergoing PCI when vorapaxar was added to dual antiplatelet therapy [53]. Currently ongoing large- scale trials will further assess the safety and efficacy of vorapaxar [54]. Atopaxar is another thrombin receptor antagonist and preliminary data appear promising in terms of its safety profile [55, 56].

Other Antiplatelet Agents

Cilostazol is a reversible inhibitor of phosphodiesterase III, resulting in increased cAMP levels. Increase in cAMP, in turn, leads to arterial vasodilatation and inhibition of platelet aggregation [57]. Cilostazol has been traditionally used to treat claudication in peripheral arterial disease, but recent studies have demonstrated an antiplatelet role of cilostazol in patients undergoing PCI [58]. Retrospective data have suggested that triple therapy with cilostazol plus traditional antiplatelet agents (aspirin and clopidogrel) is associated with a reduction in stent thrombosis post-PCI. Furthermore, a recent meta-analysis demonstrated that the addition of cilostazol to traditional dual-antiplatelet therapy may be associated with a significant reduction in angiographic restenosis and target lesion revascularization [58]. However, a recent randomized trial assessing the efficacy of cilostazol in patients undergoing PCI with drug-eluting stents did not demonstrate any significant reduction in composite adverse cardiovascular events despite a greater reduction in platelet reactivity [59]. The role of cilostazol post-PCI needs further evaluation in large randomized clinical trials.

Conclusions

There have been remarkable advances in antiplatelet pharmacotherapy in the past decade. As the importance of platelet inhibition as well as individual variation in platelet function and pharmacokinetics has gained widespread recognition, more efforts have been made to identify appropriate agents and dosing of antiplatelet agents. The development of the novel antiplatelet agents may help to reduce adverse cardiovascular events in patients with ischemic heart disease while keeping the bleeding risk to a minimum. Over the next several years, clinicians will be equipped with various combinations of antiplatelet therapies that could be personalized to patients depending on their individual characteristics and clinical presentation.

Disclosure

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