The Future of Antiplatelet Therapy: Optimizing Management in Patients with Acute Coronary Syndrome

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Summary: In the past few years, the antiplatelet armamentarium has been markedly enriched. With the intravenous platelet glycoprotein IIb/IIIa inhibitors and the new thienopyridine clopidogrel, the options for acute and chronic antiplatelet therapy have expanded. Future therapies will optimize the application of these agents. For example, in percutaneous coronary intervention, it appears that patients may benefit by loading with an adenosine diphosphate receptor blocker before the procedure and may well benefit indefinitely from continuation of this therapy. Patients with aspirin resistance or the PLA_2 single nucleotide polymorphism that is common in the population may derive particular benefit from dual antiplatelet therapy. Similarly, patients who present with unstable angina while receiving chronic aspirin therapy and those with involvement of more than one atherosclerotic bed deserve consideration for dual antiplatelet therapy. New applications will be facilitated by point-of-care testing for platelet biology and genotyping, pharmacogenomics, and protection from inflammation in patients with serologic evidence of elevated markers, such as C-reactive protein. Indeed, even with the recent explosion of relevant data and enriched therapeutic choices, we are just beginning to understand the optimal application of these therapies to the appropriate clinical indications and patient groups.

Key words: antiplatelet, thienopyridine, coronary intervention, pharmacogenomics, polymorphism, glycoprotein IIb/IIIa receptor

Introduction

Our understanding of the platelet has grown immensely since its existence was first reported by Giulio Bizzozzero in

1882.¹ Current treatment strategies for acute coronary syndromes now place great emphasis on controlling the platelet's prothrombotic and proinflammatory properties. Since the introduction of aspirin more than 100 years ago, many newer agents have been developed for treatment. In the past few years, the antiplatelet armamentarium has been markedly enriched. In addition, recent findings on the biology of platelet function and interaction promise development of a plethora of new agents and methods of treatment that should result in greatly improved management strategies. This paper will review the current antiplatelet agents, discuss their use and methods for assessing their function, and provide an overview of what the future holds for optimizing their use.

The Three Principal Pathways of Platelet Activation

Scientific investigation of platelet receptors has produced a wealth of knowledge on the structure and function of the three principal pathways of platelet agonism: the thromboxane A_2 , adenosine diphosphate (ADP), and thrombin pathways. Antagonists that block each of these pathways have been created.

Aspirin, discovered more than 100 years ago, effectively blocks the thromboxane A_2 pathway.² Considered a comparatively weaker agent for effectively blocking platelet aggregation, it nevertheless has figured prominently in management strategies. In a later section, studies describing patients with "aspirin resistance"—at least 10% of the population—will be discussed. Thus, the therapeutic implication is that for effective platelet control, combination antiplatelet therapy involving aspirin and an agent blocking another pathway may be superior to aspirin monotherapy.

The thienopyridines clopidogrel and ticlopidine effectively block the ADP receptor.^{3,4} Clopidogrel and ticlopidine inhibit ADP-induced platelet aggregation by acting on the adenylyl cyclase pathway of the receptor.⁵ Clopidogrel has a more rapid effect than ticlopidine and also a significantly improved safety profile.^{6–11} The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial studied patients with either recent ischemic stroke, recent myocardial infarction (MI), or symptomatic peripheral arterial disease. The CAPRIE trial found an 8.7% relative risk reduction favoring clopidogrel over aspirin for the combined endpoint of MI, stroke, or vascular death.¹² Of the triple endpoint, greatest benefit was seen in the reduction of fatal and nonfatal MI by 19%.¹³

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The use of dual-pathway antagonism, specifically for the thromboxane and ADP pathways, to improve clinical outcomes has also been investigated and offers promising results. Experimental research has provided insight into the mechanisms of dual antiplatelet therapy. A study by Harker *et al.* on the experimental baboon stent thrombosis model described the synergistic effect of aspirin and clopidogrel.¹⁴ After low-dose clopidogrel ($0.2\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) significantly decreased platelet and fibrin deposition and eliminated ADP-induced platelet aggregation, the addition of aspirin substantially reduced depositions on the stent (Fig. 1).¹⁴ Also, Makkar *et al.* showed that this combination was potent in a rabbit carotid artery model highlighting high shear stress.¹⁵ These studies demonstrated an effect beyond simple additivity, meeting the Berenbaum criteria for synergy.¹⁶ Another study by Herbert *et al.* of several experimental rabbit models also showed a synergistic effect of aspirin and clopidogrel.¹⁷

The synergistic benefits of dual-pathway inhibition have also been tested in several recent clinical trials.^{6,7,11} In a non-randomized registry of 2,369 consecutive patients at the Cleveland Clinic using dual antiplatelet therapy and undergoing coronary stenting procedures, we compared the ability of ticlopidine and aspirin ($n = 1,717$) versus clopidogrel and aspirin ($n = 652$) to reduce death or MI at 30 days.¹⁸ Low event rates for both therapeutic groups were observed. Furthermore, patients treated with clopidogrel and aspirin experienced a significant reduction in death and MI compared with patients treated with ticlopidine and aspirin ($p = 0.024$ and 0.023 , respectively). These results were independent of any significant differences in patient characteristics or angiographic parameters between the groups.¹⁸

The platelet thrombin receptor first described by Shaun Coughlin has since undergone intense investigation.^{19–22} Studies have shown that two specific subtypes of the receptor, protease-activated receptor PAR 1¹⁹ and PAR 4,^{20,21} must be blocked simultaneously to inhibit the platelet thrombin receptor completely.²² Currently, there is no single agent available for clinical use that performs this combined action; however, this area shows promise for future clinical applications.

FIG. 1 Effects of low-dose clopidogrel (Clop.) ($0.2\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) and aspirin (ASA) ($10\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) on stent thrombosis. Platelet and fibrin deposition are both significantly reduced by clopidogrel. The addition of aspirin provided substantial reduction of stent depositions. Reprinted from Ref. No. 14 with permission.

The Final Common Pathway

There is a large body of clinical evidence showing that intravenous agents blocking the glycoprotein (GP) IIb/IIIa receptor are consistently successful in preventing major thrombotic events and death after percutaneous coronary intervention or as therapy for unstable coronary syndromes (Fig. 2).^{23–32} Further evidence of the long-term benefit of GPIIb/IIIa blocking agents was demonstrated in the Evaluation of Platelet Inhibition with Stenting (EPISTENT) trial in which the outcomes of patients who had and had not received ticlopidine therapy prior to undergoing coronary stenting were compared. The study reported a 1% 1-year mortality rate in 794 patients treated with stent and abciximab compared with 2.4% in 809 patients treated with stent and placebo ($p = 0.037$), indicating a 57% reduction in 1-year mortality.³³ A third group in the EPISTENT was treated with balloon angioplasty plus abciximab and demonstrated a 2.1% 1-year mortality rate.³³ This and other studies³⁴ have provided encouraging preliminary information on the importance of pretreatment. The ongoing Clopidogrel Reduction of Events During Extended Observation (CREDO) trial is attempting to provide a definite assessment of the value of pretreatment and effects of long-term dual antiplatelet treatment for event reduction. The CREDO trial will analyze event reduction at 30 days and 1 year after stenting with short- and long-term use of clopidogrel in combination with aspirin compared with aspirin alone.

In contrast to IV GPIIb/IIIa inhibitors, the oral GPIIb/IIIa inhibitors have been consistently found to have no efficacy and to potentiate bleeding complications. A meta-analysis of data from studies of three major oral GPIIb/IIIa blocking agents, The Evaluation of Xemilofiban In Controlling Thrombotic

FIG. 2 Death or nonfatal myocardial infarction (MI) outcomes at 30 days in 10 randomized, placebo-controlled trials of glycoprotein (GP) IIb/IIIa blockers. Data and references from 23–32. Odds ratio (OR) shown on right, with 95% confidence interval (CI). The size of the box is proportional to total sample size. The frequency of death or nonfatal MI in columns 4 and 5. The overall benefit favoring GPIIb/IIIa blockers is highly significant ($RR = 0.79$, $CI\ 0.73-0.85$, $p < 10^{-9}$). Reprinted from Ref. No. 23 with permission.

Events (EXCITE) (xemilofiban), Optimal Angioplasty Versus Primary Stenting-Thrombolysis In Myocardial Infarction (OPUS-TIMI) 16 (orbofiban), and Sibrafiban versus aspirin to Yield Maximum Protection from ischemic Heart events post-acute cOroNary sYndromes (SYMPHONY) (sibrafiban),³⁵ involving almost 27,000 patients, failed to show a significant benefit compared with placebo, but instead demonstrated an overall 27% increase in mortality. One possible explanation for these negative results may be a prothrombotic effect described by Holmes *et al.*, in which P-selectin expression, a useful marker of platelet activation and hence thrombogenicity, was shown to be significantly increased in subjects receiving orbofiban compared with placebo and baseline measurements.³⁶ This is in contradistinction to the lowering effect on P-selectin expression with the dual antiplatelet therapy of ticlopidine and aspirin.³⁷ Another possible explanation for the GPIIb/IIIa's thrombogenicity was provided by Peter *et al.*³⁸ Summarizing results in their *ex vivo* model, they described a mechanism in which the GPIIb/IIIa receptor changes conformation after binding to abciximab. After dissociating from the molecule, the receptor's conformational state then allows fibrinogen to be bound, thus promoting an intrinsic activation.³⁸ The RGD molecules can directly induce myocyte apoptosis, but the clinical significance of this biologic effect is uncertain.

Point-of-Care Testing

The importance of understanding the relationships between the level of platelet inhibition and efficacy has been evaluated in The GOLD Study.³⁹ A cohort of 500 patients undergoing a percutaneous coronary intervention with elective intravenous GPIIb/IIIa inhibitors (abciximab, eptifibatide, or tirofiban) had platelet function monitored at baseline, and then 10 min, 1 h, 8 h, and 24 h following GPIIb/IIIa bolus using a point-of-care,

rapid platelet function assay. Adverse events were systematically monitored. Preliminary results showed that the level of inhibition was an important parameter in relation to death or MI.⁴⁰ A U-shaped distribution of major adverse coronary events (MACE) occurred based on the proportion of platelet inhibition. The lowest MACE rates occurred when platelets were blocked between 70 and 90% (0–7% event rate), while MACE rates were higher at levels < 70% (24% event rate) or > 90% (13% event rate) of platelet inhibition. These preliminary results demonstrate the potential importance of rapid assessment of platelet inhibition to optimize outcomes where IV GPIIb/IIIas are used.

Detecting activated platelets may guide in preventing the onset of inflammation processes that lead to arteriosclerotic lesions. Studies have shown that patients (on aspirin) with stable coronary artery disease and acute coronary syndromes (ACS) have elevated levels of P-selectin (Fig. 3).^{41,42} P-selectin is a component of the platelet alpha granule membrane which mediates the binding of platelets to leukocytes, and this component has been identified as an important contributor to the inflammatory process in neointimal vasculature.⁴³ Thus, it would be useful to detect P-selectin levels of patients with ACS via point-of-care testing. Another important platelet mediator of inflammation is CD40, which is a type I membrane protein and a member of the tumor necrosis factor receptor family of proteins. Platelet expression of CD40 leads to up-regulation of endothelial cells to express E-selectin, ICAM-1, and VCAM-1.⁴⁴ These molecules mediate the adhesion of neutrophils, and (minutes later) lymphocytes, on an inflamed vascular wall. What results is an increase in the inflammatory process due to platelet involvement, a process that only recently implicated the platelet in the atherosclerotic disease process.^{44,45} A recent study by Aukrust *et al.* demonstrated enhanced levels of the CD40 ligand in patients with angina, with particularly high levels observed in patients with unstable angina (Fig. 4).⁴⁶

FIG. 3 (A) Platelet surface P-selectin, monocyte-platelet aggregates, and neutrophil-platelet aggregates in control (white) and patients with stable coronary artery disease (CAD, gray). (B) Platelet reactivity to exogenous agonists, determined by surface expression of P-selectin. Both panels demonstrate significant P-selectin levels in patients with CAD compared with controls. ADP = adenosine diphosphate, TRAP = thrombin receptor activating peptide. Adapted from Ref. No. 41 with permission.

FIG. 4 (A) Release of sCD40L from anti-CD3/anti-CD28 stimulated T cells after being cultured for 2 days in control subjects, patients with stable angina pectoris (AP), and patients with unstable AP (n = 5 each group). (B) Serum levels of sCD40L in control subjects (19), stable AP patients (29) and unstable AP patients (26). Adapted from Ref. No. 46 with permission.

Pharmacogenomics

We are fast approaching the era when therapy may be more accurately guided with the aid of genomic testing such as testing for aspirin resistance. A recent study we conducted in cardiac patients who had taken 325 mg of aspirin for at least 7 days, and who received no other antiaggregant drugs, found 10% of all patients to be resistant to aspirin as determined by measures of platelet aggregation.⁴⁷ Similar findings have also been observed in patients with stroke receiving aspirin therapy.⁴⁸ It was recently shown that a single nucleotide polymorphism in the gene encoding the GPIIIa portion of the GPIIb/IIIa receptor was a risk factor for patients with ACS, possibly because of an altered sensitivity to aspirin therapy.⁴⁹ Walter *et al.* reported a five-fold increased risk in stent thrombosis in patients with the PI^{A2} polymorphism,⁵⁰ and Weiss *et al.* reported a 2.1 increased risk of MI in patients with ACS with the PI^{A2} polymorphism.⁵¹ The PI^{A2} polymorphism has also been associated with a greater risk of restenosis after coronary stent placement.⁵² Further studies have shown that this polymorphism could result in less inhibition of platelet aggregation in subjects on aspirin therapy versus subjects without the nucleotide polymorphism.⁵³ It is of interest that the PI^{A2} polymorphism was identified with increased fibrinogen binding when stimulated with ADP,⁵⁴ suggesting that dual antiplatelet coverage, involving the thienopyridines, ticlopidine, or clopidogrel may be more therapeutic in these subjects.^{55,56}

Conclusion

The new antiplatelet strategies of intravenous GPIIb/IIIa blocking agents and dual antiplatelet therapy have provided important advances in the prevention of coronary thrombotic events. Chronic dual antiplatelet therapy may prove most useful in patients at high risk, including those with poor left ventricular function, end-stage or inoperable coronary artery disease, or diffuse disease in more than one atherosclerotic bed. Bedside testing of platelet function may help to optimize anti-

platelet therapy in patients who have reduced responses to conventional antiplatelet therapy and may assist in identifying patients at high risk of developing thrombotic events. Genomic testing is a growing field that can identify patients with polymorphisms who are at high risk of thrombotic events, may be resistant to aspirin, or both. This growing area, combined with bedside platelet function testing, may allow antiplatelet therapy to be individually tailored to optimize management in patients with ischemic heart disease.

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