Peri-Procedural Platelet Function and Platelet Inhibition in Percutaneous Coronary Intervention

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Pre-procedural platelet reactivity has been correlated with adverse ischemic events following percutaneous coronary intervention. Patients with high pre-percutaneous coronary intervention platelet reactivity demonstrate a differential response to standard doses of antiplatelet therapies and have higher residual post-treatment platelet reactivity. Peri-procedural platelet inhibition has been inversely correlated with the occurrence of adverse clinical outcomes, particularly myocardial infarction. Preliminary evidence supports the concept of a threshold for post-treatment platelet reactivity, and patients with less than 40% to 50% residual aggregation in response to 20-µmol/l adenosine diphosphate appear to have the best long-term clinical outcomes. Wide interindividual variability in response to either aspirin or clopidogrel has been demonstrated, and hyporesponsiveness to either agent has been associated with adverse clinical outcomes. Although the prevalence of either aspirin or clopidogrel resistance may be reduced by increasing the dose of medication, it cannot be eliminated, and interindividual variability in response persists. The advent of direct-acting antithrombin agents for peri-procedural anticoagulation coupled with novel antiplatelet therapies on the immediate horizon promise to enhance the safety and efficacy of peri-procedural adjunctive pharmacotherapy. (J Am Coll Cardiol Intv 2008;1:111–21) © 2008 by the American College of Cardiology Foundation

Arterial Injury, Platelet Activation, and the Coagulation Cascade

During either spontaneous or iatrogenic (percutaneous coronary intervention [PCI]) plaque rupture, the arterial endothelial barrier is denuded, and atherosclerotic material, connective tissue elements, and subendothelial matrix proteins (collagen, von Willebrand factor) are exposed to blood. Platelets adhere to collagen and von Willebrand factor via specific cell receptors (glycoprotein [GP] VI, GP Ia/IIa, GP Ib-IX) and become activated (1,2). Activated platelets degranulate and secrete agonists, chemotaxins, clotting factors, and vasoconstrictors that promote platelet aggregation, thrombin generation, and vasospasm. Following platelet activation, alpha granule contents (CD40L, CD62p, intracellular GP IIb/IIIa receptor pool, and so on) are exposed on the platelet membrane. Activated platelets stimulate cytokine release and tissue factor exposure (3–5).

The interactions of adenosine diphosphate (ADP) with platelet receptors, particularly P2Y12, and of TXA2 with thromboxane receptors play a central role in transforming the GP IIb/IIIa receptor to an activated state. The subsequent binding of fibrinogen and von Willebrand factor to activated GP IIb/IIIa receptors facilitates irreversible platelet aggregation and clot stabilization (6). Despite therapy with aspirin and unfractionated heparin...
Patients with unstable coronary syndromes have increased platelet surface receptor (CD62p, GP IIb/IIIa) expression (18,19) and a diminished inhibitory response to a standard dose of tirofiban or clopidogrel (16,17). A similar differential response to clopidogrel has been observed in diabetic patients who also demonstrate baseline abnormalities in platelet size and function (20). Baseline platelet reactivity has also been directly correlated with angiographic and clinical restenosis following bare-metal stent deployment (21).

Procedural Platelet Inhibition

Data from randomized controlled clinical trials, which evaluated various classes of platelet inhibitor therapies, support the premise that the magnitude of peri-procedural platelet inhibition is inversely correlated with the occurrence of adverse clinical outcomes, especially peri-procedural myocardial infarction. In the GOLD (AU-Assessing Ul-
CLEAR PLATELETS 1B (Clopidogrel Loading with Eptifibatide to Arrest the Reactivity of Platelets 1B) trials (31,33), a higher level of platelet inhibition was achieved during PCI in patients treated with the combination of clopidogrel and eptifibatide compared with clopidogrel treatment alone and was associated with a greater reduction in markers of inflammation (high-sensitivity C-reactive protein; tumor necrosis factor-alpha) (33) as well as peri-procedural myocardial necrosis (creatine kinase-myocardial band, troponin I, myoglobin) (31). Likewise, in the TOP-STAR (Troponin in Planned PTCA/Stent Implantation with or without Administration of the Glycoprotein IIb/IIIa Receptor Antagonist Tirofiban) trial (34), the addition of tirofiban to patients pretreated with aspirin and clopidogrel prior to PCI reduced peri-procedural elevations in troponin T. All of these studies suggest that the addition of a GP IIb/IIIa inhibitor to dual oral antiplatelet therapy (aspirin plus thienopyridine) during PCI provides a higher level of peri-procedural platelet inhibition, which in turn is associated with a lower incidence of peri-procedural myocardial infarction (35).

Further confirmation of the “more is better” premise, as it pertains to the magnitude of peri-procedural platelet inhibition, is provided by the ISAR REACT II (Intracorony Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment II) trial (36), in which high-risk acute coronary syndrome patients were pretreated with aspirin and clopidogrel (600 mg) after coronary angiography but at least 2 h prior to PCI. At the time of PCI, patients were randomly assigned to treatment with either abciximab or placebo, and all patients received concomitant intravenous weight-adjusted UFH. By 30 days post-procedure, abciximab-treated patients enjoyed a 25% relative reduction in ischemic primary end point events (8.9% abciximab, 11.9% placebo; p = 0.03). In a pre-specified subgroup analysis stratified by baseline (pre-PCI) troponin levels (elevated in approximately one-half of all patients) those patients with elevated troponin levels had the greatest magnitude of benefit from abciximab therapy (p = 0.02), although those with a normal baseline troponin demonstrated little or no benefit. Of note, the major portion of abciximab benefit was observed in patients with elevated baseline troponin who were <70 years of age, although patients >70 years old demonstrated no evidence for abciximab benefit regardless of baseline troponin level (37). The lack of apparent abciximab benefit for lower-risk patients in ISAR REACT II is similar to the observation made in the precedent ISAR-REACT randomized, placebo-controlled trial of abciximab administration following an oral clopidogrel load (600 mg ≥2 h pre-PCI) in patients with stable angina where no difference in primary end point events (30 days) between randomly assigned treatments was seen (38).

In summary, these data support the following concepts: 1) high levels of peri-procedural platelet inhibition should be targeted particularly in high-risk patients; 2) incremental levels of platelet inhibition are associated with a combination of agents that block various pathways (COX-1, P2Y12, GP IIb/IIIa); and 3) higher levels of peri-procedural platelet inhibition are associated with better clinical outcomes.

**Post-Treatment Platelet Reactivity**

It has only been more recently appreciated that patients who demonstrate higher levels of post-PCI (and post-adjunctive pharmacotherapy) residual platelet reactivity to ADP have adverse clinical outcomes (39–42). For example, following primary PCI for ST-segment elevation myocardial infarction, those patients in the lowest quartile for inhibition of ADP-induced aggregation demonstrated more adverse ischemic events through the 6-month follow-up period (38). Similarly, following elective stent deployment, those patients with higher (>50%) residual ex vivo platelet aggregation in response to 20-μmol/l ADP had an increase in ischemic events (40–42). Indeed, patients who subsequently experienced stent thrombosis were clustered at or above the 75th percentile for residual ex vivo platelet reactivity to either 5- or 20-μmol/l ADP (41). Subsequent studies have confirmed the observation that despite oral clopidogrel loading (>300 mg) prior to or during PCI, patients with higher levels of post-procedural residual platelet aggregation incur a higher incidence of major adverse cardiovascular events including stent thrombosis (42,43). Recent data suggest that those patients at greatest risk for
subsequent stent thrombosis may be identified by low levels (<25th percentile) of post-procedural platelet inhibition using a point-of-care platelet function assay (Accumetrics Verify Now) (44). Interindividual variability in platelet inhibitory response occurs following both aspirin and clopidogrel treatments and has been correlated with adverse peri-procedural and late ischemic events. Furthermore, preliminary evidence supports the concept of a post-treatment “threshold” of platelet reactivity, which is associated with adverse ischemic events in long-term follow-up (45,46). These studies suggest the potential utility of measuring residual platelet aggregation post-PCI (pre-discharge) so that adjunctive pharmacotherapy at hospital discharge may be appropriately tailored for those patients at high risk for subsequent ischemic events.

**Variability in Response to Aspirin**

Aspirin specifically and irreversibly inhibits platelet COX-1 through acetylation of the amino acid serine at position 529, thereby blocking arachidonic acid access to the COX-1 catalytic site through steric hindrance (47). The antithrombotic effects of aspirin (in addition to COX-1 blockade) include antioxidant, anti-inflammatory, and antiatherosclerotic effects on endothelial cells and leukocytes (47). Aspirin is a comparatively weak inhibitor of platelet function, because other agonists such as ADP, collagen, or thrombin can still activate platelets, as measured by ex vivo tests in patients during aspirin treatment (48). The limitations of aspirin as an antithrombotic agent include its inability to inhibit platelet adhesion or secretion; the limited inhibition of platelet aggregation in response to ADP, thrombin, or collagen; and the persistence of platelet aggregation, platelet thrombus formation, and post-angioplasty cyclic flow variation in aspirin-treated patients (47,48). In addition, aspirin effects are highly variable between individuals and may be counteracted by high shear rates or circulating epinephrine levels.

Individual variability in aspirin response and resistance may be related to clinical or cellular factors as well as to genetic polymorphisms (49). Laboratory methods for assessing platelet responsiveness to aspirin can be categorized as either COX-1–specific or –nonspecific. The prevalence of aspirin “resistance” appears to vary by definition from <6% (in response to stimulation by arachidonic acid) to 29% (by PFA-100 assay) and by aspirin dosage from ~36% (<100 mg) to ~26% (~300 mg) (50–52). It has been proposed that aspirin resistance can be measured by a test that directly indicates persistent COX-1 activity (51). Thus, aspirin resistance is most specifically identified by either: 1) the detection of stable metabolites of thromboxane A2 (i.e., serum thromboxane B2 or urinary 11-dehydrothromboxane B2); or 2) arachidonic acid–induced aggregation. Although prior studies have suggested that aspirin doses >81 mg provide equivalent inhibition of COX-1 (reduction in TXB2 production); more recent data suggest a dose-dependent effect of aspirin on platelet function via non–COX-1–dependent pathways at or downstream from the collagen (GPVI) receptor (52). Aspirin doses of >162 mg were required to achieve optimal inhibition of collagen-induced platelet aggregation. Thus, the effect of aspirin on non–COX-1–mediated pathways may also influence its overall antithrombotic properties. However, aspirin doses above 100 mg/day have not been shown to provide greater clinical benefit than lower doses and may be associated with more frequent bleeding complications (53,54). Aspirin resistance measured by various assays (including both COX-1–specific and –nonspecific) has been correlated with both peri-PCI ischemic events (including stent thrombosis) as well as late (>1 year) adverse cardiovascular events (55,56). A major limitation of studies evaluating aspirin resistance has been the lack of serial platelet function measurements, as the degree of aspirin responsiveness can fluctuate over time and may be affected by dose. Finally, aspirin hyporesponsiveness may also be associated with poor responsiveness to the concomitant administration of clopidogrel, which suggests the presence of a more generalized “high platelet reactivity phenotype” that may be associated with an increased risk for ischemic events (57–59).

**Variability in Response to Clopidogrel**

The active metabolites of thienopyridines (ticlopidine, clopidogrel, prasugrel) irreversibly bind to ADP (P2Y12) receptors on the platelet, thus attenuating ADP-mediated GP IIb/IIIa receptor activation and platelet aggregation (60). The addition of ticlopidine or clopidogrel to aspirin and heparin has been demonstrated to further reduce the indicators of procedural platelet activation (serotonin release; P-selectin expression) and the correlates of thrombin generation (fragment 1.2, thrombin–antithrombin complexes) following PCI (8,61). These findings are consistent with the observation of synergistic interaction between aspirin and ticlopidine for inhibition of thrombosis and platelet procoagulant activity (61). Indeed, the combination of aspirin and ticlopidine has proven superior to aspirin alone or the combination of aspirin and warfarin in reducing ischemic events and hemorrhagic complications after elective stent deployment (62,63). The basis for therapeutic conversion to clopidogrel (from ticlopidine) was largely due to enhanced safety and tolerance (64). Clopidogrel is administered orally as a prodrug that requires conversion to active metabolites by hepatic cytochrome P450 isoenzymes. Clopidogrel “resistance,” as identified by either: 1) persistent P2Y12 signaling measured by loss of vasodilator-stimulated phosphoprotein phosphorylation after ADP stimulation using flow cytometry methods; or 2) ADP-induced platelet activation as measured by turbidimetric aggregation or flow cytometric
assays (46), has been observed in approximately 1 of out 4 (range 5% to 44%) individuals undergoing elective PCI (17,46). Differences in the prevalence of resistance between studies may be related to differences in clopidogrel dosing, differences in definition of resistance, laboratory methods, or the timing of blood sampling relative to clopidogrel administration (5,17,46). Clopidogrel response variability has multiple proposed etiologies that include variability in intestinal absorption, CYP3A4 enzymatic activity (due to genetic polymorphisms or drug–drug interactions) and P2Y_{12} receptor density (65–68). Platelet responsiveness to clopidogrel as measured by turbidimetric aggregometry or flow cytometry after ADP stimulation follows a normal, bell-shaped distribution (Fig. 2) (17). Following a 300-mg oral clopidogrel loading dose and 75 mg administered daily thereafter, “resistance” was observed in 31% and 15% of patients at 5 and 30 days post-PCI, respectively (17).

Studies have described an attenuated response to clopidogrel by either relative or absolute inhibition (absolute change in aggregation from baseline). Both early (<30 days) and late (30 days to 1 year) stent thrombosis or other major adverse cardiac events (MACE) have most often been correlated with post-treatment platelet reactivity (40–43) rather than with the degree of inhibition (39). Thus, either “on-treatment” or “post-treatment” residual platelet reactivity may be a better indicator of patient risk for post-stenting ischemic events because risk may be overestimated in nonresponsive patients who begin with low pre-treatment platelet reactivity (69). However, none of these studies have been definitive, and most are limited by small numbers of patients and an absence of serial platelet function measurements. In general, those patients who manifest laboratory resistance or high post-treatment platelet reactivity incur an increased incidence of MACE. In this context, the administration of larger (>300 mg) oral loading doses of clopidogrel has been demonstrated to accelerate the time course and enhance the magnitude of subsequent platelet inhibition as well as reduce platelet reactivity (70–72). Debate remains regarding the ability of 900 mg of clopidogrel to further augment platelet inhibition compared with 600 mg (70,71). Although some have demonstrated more rapid and complete platelet inhibition with the higher dose when measured in response to a more potent (20–μmol/l ADP) agonist, others have reported no appreciable differences in either measured platelet inhibition or clopidogrel metabolite concentrations, suggesting the potential for saturation in the ability to either absorb or convert the increased dose. Nevertheless, a 600-mg clopidogrel load is associated with a lower prevalence of early resistance (~8%) compared with a 300-mg load (~25% to 28%) (72). Furthermore, the administration of a 600-mg loading dose to individuals on chronic clopidogrel therapy (75 mg daily) also provided a substantial increment in peri-procedural (PCI) platelet inhibition when compared with no loading dose (73). Even following a 600-mg oral clopidogrel loading dose, from 2 to 8 h are required to achieve maximum platelet inhibitory effects, which remain widely variable (20% to 80%) on an individual basis (70,74). Finally, data in support of an incremental clinical benefit associated with increased clopidogrel loading dose (600 vs. 300 mg) are limited to a small (255 patients) randomized trial involving clopidogrel-naïve patients that demonstrated a relative reduction in peri-procedural myocardial infarction following the 600-mg dose (75). However, the ARMYDA-4 (Antiplatelet Therapy for Reduction of Myocardial Damage during Angioplasty) study demonstrated no additional clinical benefit following a 600-mg pre-PCI clopidogrel load in patients already receiving chronic clopidogrel therapy (76). More recently, data have been presented that incremental levels of platelet inhibition may be achieved by increasing the clopidogrel maintenance dose from 75 to 150 mg daily, particularly in those patients who manifest initial hyporesponsiveness (77,78). Whether or not incremental platelet inhibition by the 150-mg daily maintenance dose can be translated into clinical benefit (MACE reduction) without the occurrence of adverse bleeding events remains to be determined by larger, adequately powered clinical trials.

In addition to dosage increments to augment clopidogrel platelet inhibition, the concomitant administration of CYP3A4 enzyme inducers (rifampin, St. John’s wort) has been demonstrated to enhance platelet inhibition and to convert clopidogrel “hyporesponders” to “responders” (65,79,80). The clinical utility of adjunctive CYP3A4 enzyme induction in clopidogrel hyporesponders has not been demonstrated. Furthermore, the addition of a 3rd agent,
cilostazol, to patients already being treated with the combination of aspirin and a thienopyridine may confer incremental clinical benefit (reduction in MACE and stent thrombosis) without an increase in bleeding events (81). As previously noted, the prevalence of clopidogrel hyporesponsiveness appears to be increased among patients who are resistant to aspirin, suggesting the presence of a “high platelet reactivity phenotype” (57,58,82). Those patients who manifest an attenuated response to both agents may have the highest prevalence of peri-procedural (PCI) myocardial necrosis (82). Interestingly, patients who are resistant to clopidogrel are frequently responsive to ticlopidine and vice versa, which suggests that differences in liver metabolic pathways responsible for active metabolite generation exist (83).

### Peri-Procedural Anticoagulation and Platelet Reactivity

The traditional “gold standard” for peri-procedural anticoagulation involved the administration of weight-adjusted doses of UFH with peri-procedural monitoring of the activated clotting time and supplemental heparin administration to achieve targeted activated clotting time levels of >250 s (in the absence of concomitant platelet GP IIb/IIIa receptor blockade) or >200 s (in the presence of GP IIb/IIIa receptor inhibition) (84). Over the past decade, multiple limitations of UFH have been recognized. The limitations include its inability to bind either clot-bound thrombin or factor Xa within the platelet prothrombinase complex, susceptibility to inactivation by platelet factor 4, nonspecific cellular binding (which results in biphasic, saturation kinetics and, thus, a variable dose-dependent pharmacokinetic half-life), direct platelet activation and aggregation, as well as consumption of antithrombin III, which may contribute to the subsequent relative hypercoagulability (heparin “rebound”) following discontinuation of therapy (85).

The central role played by thrombin in triggering platelet activation and the ability of direct-acting antithrombin agents, such as bivalirudin to inactivate clot-bound thrombin has been more recently appreciated (86). Multiple randomized controlled clinical trials have demonstrated bivalirudin to be at least as effective and safer (fewer major bleeding events) than UFH when administered as anticoagulation for PCI (87,88). Some studies have suggested that bivalirudin contributes to peri-procedural platelet inhibition by blocking thrombin-mediated platelet activation. Although intravenous bivalirudin in combination with oral aspirin and clopidogrel therapy appears to provide safe and effective peri-procedural adjunctive pharmacotherapy for most clinically stable patients undergoing PCI, the time course and magnitude of antithrombotic effects achieved by this regimen may not be adequate for patients with high levels of pre-procedural platelet reactivity (acute coronary syndrome with positive biomarkers, diabetics, and so on) and who, in addition, may be clopidogrel hyporesponders. These patient subgroups may manifest a relative increase in peri-procedural ischemic events (enzymatic myocardial infarction; urgent repeat revascularization; acute [<24 h] stent thrombosis) in the absence of concomitant platelet GP IIb/IIIa receptor blockade. Indeed, higher levels of peri-procedural platelet inhibition are achieved by the combination of aspirin, clopidogrel, and GP IIIb/IIIa inhibition compared with aspirin and clopidogrel alone in the context of either UFH or bivalirudin anticoagulation (31,89,90).

### New Therapeutic Options

The limitations of currently available thienopyridines (ticlopidine, clopidogrel) include delayed onset of action, irreversibility, response variability among individual patients, and overall modest levels of platelet inhibition. Several novel P2Y12 receptor inhibitors (both thienopyridine and non-thienopyridine) are currently in clinical development and have pharmacologic properties that should overcome some, if not all, of these limitations.

### Prasugrel

Prasugrel (CS747) is a novel thienopyridine that is administered orally in an inactive state and must be metabolized by cytochrome-P450–dependent pathways to generate an active form that irreversibly binds to the P2Y12 receptor (91,92). Comparative (prasugrel vs. clopidogrel) studies suggest that prasugrel provides more rapid and more potent platelet inhibition with less interindividual variability in response (93,94). Indeed, the vast majority of clopidogrel nonresponders are responsive to prasugrel (95). In a randomized controlled trial comparing prasugrel and clopidogrel in patients undergoing PCI, the JUMBO-TIMI 26 (Joint Utilization of Medications to Block Platelets Optimally–Thrombolysis In Myocardial Infarction) trial, clinical target vessel thrombotic events (composite occurrence of stent thrombosis and urgent repeat target vessel revascularization) were reduced (0.6% vs. 2.4%, respectively) by prasugrel and noncoronary bypass-related bleeding events were similar (96). The TRITON-TIMI 38 (Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) trial compared treatment with clopidogrel (300-mg load, 75 mg daily) versus prasugrel (60-mg load, 10 mg daily) in 13,608 patients with acute coronary syndromes in whom PCI was planned (97,98). Prasugrel therapy was associated with a significant reduction in the primary efficacy end point of the trial (cardiovascular...
death, nonfatal myocardial infarction, or nonfatal stroke) from 12.1% (clopidogrel) to 9.9% (prasugrel; p < 0.001). Furthermore, significant reductions in urgent target vessel revascularization (by 34%), myocardial infarction (by 24%), and stent thrombosis (by 52%) were observed following prasugrel therapy. The greater efficacy of prasugrel, which accompanied the higher level of platelet inhibition achieved by this agent, was associated with an increased incidence of life-threatening (1.4% vs. 0.9%) and fatal (0.4% vs. 0.1%) bleeding events compared with clopidogrel. The observation of no net clinical benefit (composite of efficacy and safety end points) for prasugrel in patients ≥75 years of age or <60 kg weight should prompt efforts at dose modification in these subgroups. Patients with prior stroke or transient ischemic attacks demonstrated net clinical benefit from clopidogrel (vs. prasugrel) (98). Finally, in the PRINCIPLE-TIMI 44 (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis In Myocardial Infarction) trial, prasugrel (60-mg load; 10 mg daily) resulted in greater platelet inhibition than was observed following high-dose clopidogrel (600-mg load, 150 mg daily) in patients undergoing catheterization with planned PCI (99).

**AZD 6140**

The AZD 6140 is a novel cyclo-pentyl-triazolo pyrimidine nonthienopyridine agent that acts directly (requires no metabolic activation) and provides very rapid, reversible, and potent P2Y$_{12}$ receptor inhibition (91,100,101). The plasma half-life of AZD 6140 is approximately 12 h and thus requires twice-daily dose administration (101). In the DISPERSE-2 (Dose Confirmation Study Assessing anti-Platelet Effects of AZD6140 versus Clopidogrel in NSTEMI) randomized comparative trial of AZD 6140 versus clopidogrel in patients presenting with acute coronary syndromes, myocardial infarction was less frequent in patients receiving AZD 6140 and major or minor bleeding events were similar (102). In the platelet function substudy of DISPERSE-2, AZD 6140 provided a greater magnitude of platelet inhibition with less interindividual variability than was observed with clopidogrel (103).

**Cangrelor**

Cangrelor (formerly ARC 69931 MX) is a nonthienopyridine, parenterally administered, direct-acting P2Y$_{12}$ receptor antagonist that provides dose-dependent, reversible inhibition. At high doses, cangrelor achieves nearly 100% inhibition of ADP-induced aggregation with very limited interindividual variability in response (104,105). The plasma half-life of cangrelor is approximately 3.3 min, and platelet function returns to normal rapidly (~60 min) following termination of intravenous infusion (105). No differences in bleeding event rates were observed in a randomized comparison with placebo in patients undergoing PCI (106). The pharmacologic properties of rapid onset and offset may be particularly advantageous for use in patients presenting with acute coronary syndromes and high-risk predictors (positive biomarkers, ST-segment shift) in whom early angiography with revascularization is considered. Indeed, controversy surrounds the potential for clinical benefit provided by P2Y$_{12}$ receptor inhibitor pretreatment (clopidogrel) prior to PCI and the concern for bleeding associated with irreversible drug effect if surgical coronary revascularization is required based on coronary anatomic considerations. Cangrelor is currently undergoing clinical evaluation in the CHAMPION (Cangrelor versus standard tHerapy to Achieve optimal Management of Platelet InhibitiON PCI) trial (107).

**Protease-Activated Receptor (PAR)-1 Inhibition**

The PAR-1 is present on platelets, smooth muscle cells, monocytes/macrophages from human atheroma tissue, and at lesion sites following percutaneous interventions (108). There has been a great recent interest in the development of PAR-1 antagonists as potential antithrombotic agents. Oral PAR-1 antagonists may provide several advantages over thrombin inhibitors in specifically inhibiting the PAR-1 receptor and having no influence on the enzymatic effect of thrombin in the coagulation cascade, the generation of the fibrin network, or the stimulation of anticoagulant pathways (activation of protein C). These attributes make PAR-1 antagonism a unique antithrombotic target with potential limited bleeding side effects (108).

The SCH-530348 drug has been demonstrated to be a specific, potent, and reversible PAR-1 antagonist with a long half-life and no apparent effect on bleeding or clotting times or other receptor signaling pathways in platelets. In a recently completed randomized, double-blind, placebo-controlled, dose-ranging Phase 2 study (TRA-PCI [Thrombin Receptor Antagonist–Percutaneous Coronary Intervention] study), 1,030 patients undergoing coronary angiography and/or nonemergent PCI were treated with loading doses of 10, 20, or 40 mg of SCH-530348 together with aspirin, clopidogrel, and an antithrombotic agent (heparin or direct thrombin inhibitor) (109). Following PCI, maintenance doses of 0.5, 1, or 2.5 mg were administered for 60 days along with aspirin and clopidogrel. Treatment with SCH-530348 was not associated with a significant increase in the trial primary end point (TIMI major or minor bleeding), although slight reductions in the secondary end points of MACE (by 32%) and myocardial infarction (by 41%) were observed. In a substudy, SCH-530348 did not affect arachidonic acid-, ADP-, or collagen-induced platelet aggregation, but was associated with >80% inhibition of 15-mmol/l thrombin receptor-activating
peptide–induced platelet aggregation at both the 1- and 2.5-mg maintenance doses. The results from the TRA-PCI study have provided the rationale for 2 large-scale multinational, randomized, double-blind, placebo-controlled phase 3 studies (TRA 2P-TIMI 50 [Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Events–Thrombolysis In Myocardial Infarction] and TRA-ACS [Thrombin Receptor Antagonist in Acute Coronary Syndrome] trials).

Conclusions

The level of pre-procedural platelet reactivity correlates directly with both the level of post-procedural (and post-treatment) platelet reactivity as well as the incidence of peri-procedural adverse clinical outcomes (MACE). The intensity of peri-procedural platelet inhibition by adjunctive pharmacotherapies has been inversely correlated with the occurrence of peri-procedural MACE. These observations have validated the concept of targeting high levels of peri-procedural platelet inhibition during PCI. Recent data support a direct relationship between the post-PCI and post-pharmacotherapeutic treatment level of platelet reactivity and the subsequent occurrence of ischemic events, including both early and late stent thrombosis. In fact, preliminary evidence supports the concept of a threshold for platelet function that best correlates with subsequent patient outcomes. Finally, the relationship of bleeding events to specific levels of residual ADP-induced platelet aggregation is unknown. Considerable interindividual variability in platelet inhibitory response exists to currently available antiplatelet therapies. The prevalence of aspirin and/or clopidogrel resistance is dependent on the definitions employed (clinical events vs. pharmacodynamic testing) as well as the specific test methodology (type and strength of agonist, specific threshold definition of hyporesponsiveness). Although the prevalence of either aspirin or clopidogrel resistance may be reduced by increasing the dose of medication, it cannot be eliminated, and interindividual variability in response persists. Ongoing large-scale clinical trials will better define the relationship between ex vivo platelet inhibition by specific therapeutic agents and the degree of clinical benefit conferred by treatment. Hopefully, these studies will also help to script the appropriate therapeutic algorithm for response in those patients determined to be at high risk for adverse clinical events based on measurement of platelet reactivity. Finally, the advent of direct-acting antithrombin agents for peri-procedural anticoagulation coupled with novel antiplatelet therapies on the immediate horizon promise to enhance the safety and efficacy of peri-procedural adjunctive pharmacotherapy and to improve late clinical outcomes following PCI.

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