Antiplatelet Therapy for Improving Post-PCI Outcomes: Interpreting Current Treatment Guidelines for Optimal Management of the Post-ACS Patient

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Abstract

Dual antiplatelet therapy with a thienopyridine in combination with aspirin for 1 to 6 months after stenting has been recommended by the manufacturers to reduce ischemic cardiovascular events and thrombosis after coronary stenting, whereas the current leading guidelines recommend dual antiplatelet therapy for 12 months following percutaneous coronary intervention in all patients not at high risk of bleeding. Despite the established benefits of dual antiplatelet therapy in acute coronary syndrome (ACS) patients, there are concerns regarding the risk of major bleeding. The risks, benefits, and complexity identified in these interventional trials are communicated in this article to enable well-informed therapeutic decisions. Thienopyridine nonresponsiveness and variability of response are emerging as significant concerns in ACS patients that may lead to poor long-term cardiovascular outcomes. Current research on thienopyridine responsiveness and evidence-based mechanisms for overcoming thienopyridine nonresponsiveness are discussed. In addition, adherence to dual antiplatelet therapy is critical but difficult to achieve, and a considerable proportion of patients (1 of 7) discontinue therapy before 30 days of drug-eluting stent implantation. It has been established that premature discontinuation of thienopyridine therapy is associated with a marked increase in the risk of stent thrombosis (and consequently myocardial infarction and/or death) and is the leading independent predictor of stent thrombosis in multivariate analyses. The factors related to premature cessation of thienopyridine therapy are listed with recommendations for minimizing the complications arising as a result of premature discontinuation.

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Dual antiplatelet therapy following percutaneous coronary intervention (PCI) has been used since 1994 after the first bare-metal stent (BMS) was approved. The first-generation thienopyridine, ticlopidine, was given in combination with aspirin before it was replaced with clopidogrel (second-generation thienopyridine) years later because of a much lower risk of hematologic adverse events with the latter.[1] In November 2007, a phase 3 trial comparing prasugrel (third-generation thienopyridine) with clopidogrel in post-PCI patients showed a potential advantage versus current dual antiplatelet therapy.[2]

Efficacy and Safety of Dual Antiplatelet Therapy

The goal of antiplatelet therapy in post-PCI patients is to maintain a balance between efficacy and bleeding outcomes. Since 1996, a number of large clinical trials have tested clopidogrel in various types of patients (Table 1).[3] There are 8 key trials showing benefit as secondary prevention after an acute coronary syndrome (ACS) with or without PCI.[4-11] Unfortunately the use of dual antiplatelet therapy stops with secondary prevention and shows no benefit for primary prevention of ACS.[12]

Despite ample evidence that dual antiplatelet therapy is beneficial, many patients continue to have recurrent atherothrombotic events (stent restenosis and thrombosis) post PCI. Approximately 10% of patients post PCI will reach an end point of myocardial infarction (MI), stroke, or cardiovascular death even with dual antiplatelet therapy.[2,5] Established factors that contribute to failure with dual antiplatelet therapy include lack of prescribing and noncompliance of medications.[13] In addition, small studies have suggested that clopidogrel has a large interpatient variability, delayed onset of action, and an unpredictable antiplatelet effect that may contribute to treatment failure.[14]

Prasugrel, a third-generation thienopyridine, has several characteristics that may lead to greater efficacy when compared with clopidogrel. Similar to other thienopyridines, prasugrel is a prodrug, which means it requires hepatic metabolism to convert it to an active form. Pharmacokinetic and pharmacodynamic studies have shown that prasugrel achieves a higher level of platelet inhibition, quicker onset of action, more efficient conversion of prasugrel to its

Table 1. Key Findings of Clopidogrel for ACS

Trial[a]	Duration	Risk Reduction	ARR, %	RRR, %	*P*
CAPRIE	1-3 y	Secondary prevention: MI, stroke, or vascular death after ACS	0.5	8.7	.043
CURE	12 mo	Secondary prevention: MI, stroke, or CV death after NSTEMI with medical management (no stent)	2.1	20	.001
CLARITY-TIMI 28	30 d	Secondary prevention: recurrent MI, recurrent ischemia, or CV death after STEMI with medical management (no stent)	2.5	20	.03
COMMIT	4 wk	Secondary prevention: death, re-infarction, or stroke after ACS with medical management (no stent)	0.9	9	.002
CREDO	1 y	Secondary prevention: death, MI, or stroke after ACS with PCI	3.0	27	.02
PCI-CLARITY	30 d	Secondary prevention: MI, stroke, or CV death after STEMI with fibrinolytics and PCI	2.6	46	.008
PCI-CURE	30 d	Secondary prevention: MI, CV death, or urgent revascularization after NSTEMI with PCI	1.9	30	.03
CHARISMA	28 mo	Primary prevention: MI, stroke, or CV death	0.5	7	.22
CAPRIE-like CHARISMA Cohort	28 mo	Secondary prevention: MI, stroke, or CV death after ACS	1.5	17	.01

ACS indicates acute coronary syndrome; ARR, absolute risk reduction; CAPRIE, Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CLARITY-TIMI, Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction Trial; CREDO, Clopidogrel for the Reduction of Events During Observation; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events; CV, cardiovascular; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RRR, relative risk reduction; STEMI, ST-segment elevation myocardial infarction.
[a]All the comparisons are between clopidogrel + aspirin and placebo + aspirin, except for CAPRIE, which compared clopidogrel and aspirin.

active metabolite, and a more predictable response of platelet inhibition when compared with clopidogrel.[15]

In a phase 3 trial, TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibitions with Prasugrel–Thrombolysis in Myocardial Infarction), 13,608 adults with moderate- to high-risk non–ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI) and planned PCI were randomized to receive treatment with a 60-mg loading dose of prasugrel and a 10-mg/day maintenance dose or a 300-mg loading dose of clopidogrel and a 75-mg/day maintenance dose for 6 to 15 months (all patients received aspirin dosed between 75 and 162 mg/day).[2] The primary end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke was significantly reduced in favor of prasugrel (9.9% vs 12.1%; hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.73-0.90; *P* <.001) (Table 2).[2] Of the 3 combined end points, only nonfatal MI was statistically significant favoring prasugrel versus clopidogrel (7.3% vs 9.5%; HR, 0.76; 95% CI, 0.67-0.85; *P* <.001). Several prespecified secondary analyses continue to show superior efficacy of prasugrel versus clopidogrel: urgent target vessel revascularization by the end of the follow-up period (2.5% vs 3.7%; HR, 0.66; 95% CI, 0.54-0.81; *P* <.001) and stent thrombosis (1.1% vs 2.4%; HR, 0.48; 95% CI, 0.36-0.64; *P* <.001). However, several major bleeding end points occurred in significantly more patients in the prasugrel group than in the clopidogrel group (Table 2).

Table 2. Key Efficacy and Bleeding End Points in the Overall Cohort of TRITON-TIMI 38

End Point	Prasugrel, %	Clopidogrel, %	Hazard Ratio for Prasugrel (95% CI)	*P*
Primary efficacy end point: death from cardiovascular causes, nonfatal MI, or nonfatal stroke	9.9	12.1	0.81 (0.73-0.90)	<.001
Primary safety end point: non–CABG-related TIMI major bleeding	2.4	1.8	1.32 (1.03-1.68)	.03
Selected secondary safety end points: spontaneous	1.6	1.1	1.51 (1.09-2.08)	.01
Life-threatening	1.4	0.9	1.52 (1.08-2.13)	.01
Bleeding requiring transfusion	4.0	3.0	1.34 (1.11-1.63)	<.001[a]
Fatal bleeding	0.4	0.1	4.19 (1.58-11.11)	.002
Net clinical benefit	12.2	13.9	0.87 (0.79-0.95)	.004

CABG indicates coronary artery bypass graft; CI, confidence interval; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TRITON-TIMI 38, Therapeutic Outcomes by Optimizing Platelet Inhibitions with Prasugrel–Thrombolysis in Myocardial Infarction.
[a]Transfusion was defined as any transfusion of whole blood or packed red cells.
Adapted from Wiviott SD, et al. *N Engl J Med.* 2007;357(20):2001-2015.

The TRITON-TIMI 38 investigators performed a series of post hoc exploratory analyses to identify patient subgroups that may not have benefited from prasugrel or who had net harm.[2] Patients with a history of stroke or transient ischemic attack (TIA) had net harm from prasugrel; they were more likely to meet the primary efficacy end point or have a nonfatal TIMI major bleed (23% vs 16%; HR, 1.54; 95% CI, 1.02-2.32; *P* = .04). Two groups were identified as receiving no net benefit from prasugrel versus clopidogrel: patients aged 75 years or older (HR, 0.99; 95% CI, 0.81-1.21; *P* = .92) and patients weighing less than 60 kg (HR, 1.03; 95% CI, 0.69-1.53; *P* = .89). When the efficacy rates were combined with the bleeding end points in a prespecified analysis of net clinical benefit, the findings still favored prasugrel (12.2% vs 13.9%; HR, 0.87; 95% CI, 0.79-0.95; *P* = .004) (Table 2). Overall, 46 patients is the number needed to treat with prasugrel to prevent 1 primary efficacy end point versus clopidogrel, whereas 167 patients would have to be treated with prasugrel to result in an excess TIMI major hemorrhage versus what would be expected with clopidogrel.

After the initial TRITON-TIMI 38 trial, several studies have continued to demonstrate the advantage of prasugrel versus clopidogrel.[16-18] Wiviott and colleagues reported prasugrel had statistically fewer events of stent thrombosis, irrespective of stent type (BMS or drug-eluting stent [DES]) and timing of stent thrombosis (early vs late).[16] In all 3 outcomes, prasugrel was statistically superior to clopidogrel. In a different subanalysis of TRITON-TIMI 38, Wiviott and colleagues assessed dual antiplatelet therapy in patients with diabetes mellitus.[17] Prasugrel was superior to clopidogrel in reducing primary efficacy outcomes in patients with diabetes mellitus without increasing the risk of bleeding (12.2% vs 17.0%; HR, 0.70; 95% CI, 0.58-0.85; *P* <.001).

Overcoming Thienopyridine Nonresponsiveness

Experience with dual antiplatelet therapy has shown that some patients do not exhibit the expected response, and recurrent events on aggressive therapy are common. According to Ferguson and colleagues, more than 10% of patients presenting with high-risk ACS treated with aspirin, clopidogrel, and a glycoprotein IIb/IIIa inhibitor ("triple antiplatelet therapy"), and antithrombin therapy (heparin or enoxaparin), still suffered a recurrent MI at 30 days.[19] Although there is no established definition or accepted method to test for thienopyridine resistance, clinical evidence suggests thienopyridine resistance occurs in approximately 5% of patients.[20] There is an accumulation of data

through ex vivo and small patient studies that suggest thienopyridine resistance leads to worse clinical outcomes.[21,22]

Two small studies examined clinical outcomes in the setting of clopidogrel resistance. Matetzky and colleagues evaluated the response of post-PCI patients receiving maintenance doses of clopidogrel. In the 6 months following enrollment, 13% of the patients had another cardiovascular event. Of these patients, 88% were considered clopidogrel resistant.[21] In another study, Gurbel and colleagues measured serum troponin levels after PCI. Patients who received a 600-mg loading dose of a glycoprotein IIb/IIIa inhibitor had lower serum troponin levels compared with less intensive antiplatelet therapy (300-mg clopidogrel loading dose with or without a glycoprotein IIb/IIIa inhibitor).[22] More recently, it has been demonstrated that patients with low responsiveness to clopidogrel who were given a glycoprotein IIb/IIIa inhibitor during PCI had lower rates of cardiovascular events within the first 30 days post PCI compared with low responders who were randomized to usual care with 600 mg of clopidogrel prior to PCI.[23] In addition, results of the PRINC (Plavix Response in Coronary Intervention) trial showed that higher loading and maintenance doses of clopidogrel produce more complete platelet inhibition and may benefit patients with a decreased ability to metabolize the drug or those with cytochrome P450 (CYP) 2C19 polymorphisms.[24,25]

Several mechanisms are theorized to contribute to the variable response to clopidogrel. Genetic polymorphisms, variability of CYP-3A4 activity, and increased systemic concentration of platelet activators (ie, adenosine diphosphate [ADP], nitrous oxide, thrombin levels) are thought to contribute to clopidogrel resistance.[26] Genetic polymorphisms could affect the response to clopidogrel through changes in the density and structure of the ADP receptor found on platelets. Since all thienopyridines are prodrugs, diminished CYP-3A4 activity results in less active drug.

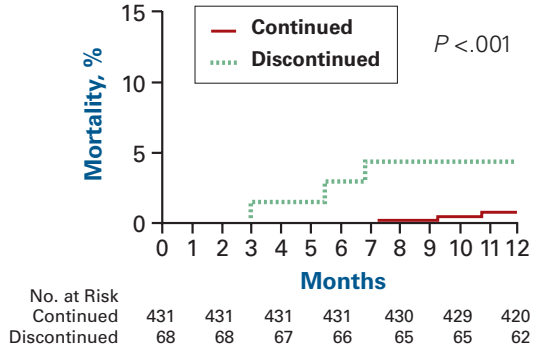
The pharmacokinetic profile of prasugrel might have a more predictable antiplatelet response and less risk of resistance. Brandt and colleagues were able to show in an ex vivo study in 60 patients that prasugrel had a more predictable inhibition of platelet aggregation after a 60-mg loading dose when compared with the same patients after a 300-mg loading dose of clopidogrel.[15]

Premature Discontinuation of Dual Antiplatelet Therapy

The introduction of DESs marked a significant advance in PCI by reducing restenosis compared with BMSs.[27] The risk of stent thrombosis continues to be problematic after stent placement, with an incidence rate of 1% to 2% in both DESs and BMSs.[28] The number one predictor of stent thrombosis after DES placement is premature discontinuation of thienopyridine therapy.[29,30]

According to the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions 2007 guideline update for PCI, all post-PCI stented patients receiving DESs should receive thienopyridine therapy for at least 12 months if not at high risk of bleeding.[31] An analysis of results from the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) study concluded that 1 in 7 patients (14%) inappropriately discontinue thienopyridine therapy within 30 days after DES placement.[13] Patients who discontinued therapy within 30 days were more likely to die during the next 11 months (7.5% vs 0.7%;

Figure. Kaplan-Meier Curves of Mortality From 1 to 12 Months After Myocardial Infarction Among Those Who Continued and Those Who Discontinued Thienopyridine Therapy at 1 Month After Myocardial Infarction[13]



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adjusted HR, 9.0; 95% CI, 1.3-60.6; P <.0001) (**Figure**). Not completing high school was the only factor that was independently associated with premature discontinuation of thienopyridine therapy (73% vs 89%; adjusted HR, 1.79; 95% CI, 1.01-3.01; P <.05). Other factors that trended toward association with premature discontinuation included: less likely to be married, affordability of medications, not referred to rehabilitation, no discharge medication instructions, and older age.

Medication nonadherence is an unrecognized risk factor for cardiovascular disease. The estimated yearly cost of medication nonadherence is $396 million to $792 million.[32] Clinicians should screen any adherence issues prior to stent placement and continue to stress medication compliance with dual antiplatelet therapy, especially within the setting of DESs. Services should be established to increase compliance for these patients. Evidence shows that adherence to antiplatelet use is much better in patients who receive pharmacist disease state management services versus traditional drug regimen review (88.2% vs 56.1%; P <.05).[33] Additional techniques that could increase adherence to dual antiplatelet therapy include utilizing students (eg, medical, pharmacy, nursing) to follow up via phone to ensure filling of prescriptions and compliance, identifying language barriers, developing a multidisciplinary PCI discharge team, involving managed care clinicians with follow-up communication, and expanding medication therapy management services.

Summary

Current dual antiplatelet therapy lowers the risk of atherothrombotic events, which ultimately improves survival, recurrent MI, and stroke. Unfortunately, even with appropriate dual antiplatelet therapy, there still is an established risk of thromboembolic complications post PCI. Prasugrel, a new thienopyridine, has been shown to be more efficacious versus clopidogrel in dual antiplatelet therapy post PCI, especially in patients with diabetes mellitus. Clinicians should be aware that the risk of major bleeding events is more likely to occur in patients receiving prasugrel, and that caution should be given to patients with a history of stroke, TIA, elderly (>75 years), or patients weighing less than 60 kg.

There is a collection of ex vivo and small in vivo studies that show that a subset of people maintained on clopidogrel do not exhibit the expected response, and that recurrent events are common despite aggressive therapy. Several mechanisms contribute to the reasoning behind clopidogrel resistance, whereas prasugrel might be able to avoid thienopyridine resistance because of its favorable pharmacokinetic profile.

Approximately 14% of patients inappropriately discontinue thienopyridine therapy after DES placement, which significantly increases their risk of mortality. Services must be established to increase and maintain thienopyridine compliance, which has been accomplished through pharmacist-driven disease state management services.

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