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REVIEW OF A NEW ANTI-PLATELET AGENT: FOCUS ON PRASUGREL

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Acute coronary syndrome (ACS) generally refers to a group of clinical symptoms associated with acute myocardial ischemia.[1] ACS, which includes heart attacks and unstable angina, affects nearly 1.5 million people in the United States annually, many of whom are managed with percutaneous coronary intervention (PCI).[2] In 2009, an estimated 785,000 people in the United States will have a first heart attack and 470,000 will have a recurrent attack.[3]

Current therapy for patients presenting with acute myocardial ischemia include MONA (morphine, oxygen, nitroglycerin, aspirin).[4] Clopidogrel (Plavix®), a thienopyridine, can be used instead of or in addition to aspirin.[4] Prasugrel (Effient®) is a 3rd generation thienopyridine manufactured by Daiichi Sankyo and distributed by Eli Lilly in the United States. A direct competitor to clopidogrel, prasugrel was approved on July 10, 2009 for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS who are managed with PCI.[5] This article will review the safety and efficacy of prasugrel as an option for reducing cardiovascular events in patients with ACS managed with PCI.

PHARMACOLOGY

Prasugrel inhibits adenosine diphosphate (ADP) induced platelet aggregation.[6] Prasugrel, similar to clopidogrel, is an inactive prodrug which undergoes hepatic conversion to its active metabolite in a single rapid step process.[6,7] The active metabolite (R—138727) irreversibly binds and antagonizes the platelet P2Y12 receptor for the life of the platelet, thus preventing ADP binding.[8,9] With ADP unable to bind to the platelet, activation of glycoprotein IIb/IIIa (GIIb/IIIa) complex is impaired, ultimately reducing fibrinogen binding and platelet aggregation.[6,8]

PHARMACOKINETICS

Prasugrel is extensively (≥ 79%) and rapidly absorbed with peak plasma concentrations occurring 30 minutes after ingestion (Table 1). Following oral absorption, prasugrel is converted to its active metabolite via hydrolysis by intestinal carboxylesterases and subsequent oxidation by hepatic cytochrome P450 enzymes — primarily CYP3A4 and CYP2B6 and to a lesser extent CYP2C9 and CYP2C19.[6,7,9] The active metabolite is 98% bound to albumin and has an estimated volume of distribution of 44—68 L.[6,7] The active metabolite has an elimination half life of ~8 hours with clearance occurring via a secondary metabolism to two inactive compounds.[6,7] These inactive compounds are then excreted in the urine (70%) and feces (25%).[6,7] Repeated daily doses of 10 mg do not lead to accumulation of the active metabolite.[7]

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Table 1. Pharmacokinetic properties of prasugrel.[6]

PROPERTY	PRASUGREL
ONSET	15-30 mins
TIME TO PEAK CONCENTRATION	30 mins
TIME TO PEAK RESPONSE	2 hours
DURATION	5 days
BIOAVAILABILITY	79% (rapidly absorbed)
METABOLISM	Rapid & extensive via liver
EXCRETION	Renal (70%) & Feces (25%)
$T_{1/2}$	~ 8 hours

CLINICAL TRIALS

Clinical Efficacy & Safety Studies

Jernberg and colleagues conducted a randomized (with stratification), single-blind, parallel-group study in patients (n = 101) with CAD who were taking aspirin. Patients were male and female, between the ages of 40–75 years. The primary endpoint of the study was to characterize, in aspirin-treated subjects with stable CAD, the degree of inhibition of platelet aggregation (IPA) associated with four dosing regimens of prasugrel compared with the currently approved clopidogrel loading dose (LD) + maintenance dose (MD) regimen. Patients were randomly assigned to oral prasugrel 40/5, 40/7.5, 60/10 or 60/15 mg LD/MD or oral clopidogrel 300/75 mg LD/MD for 28 days. The investigators found that 4 hrs after dosing, with 20 mM ADP, both prasugrel 40 and 60 mg LDs achieved significantly higher mean IPA levels than clopidogrel 300 mg LD (60.6% and 68.4 vs. 30.0%, respectively; all P < 0.0001). Moreover, the prasugrel group contained lower a percentage (3% vs. 52%, P < 0.0001) of pharmacodynamic non-responders (defined as IPA, 20%) than clopidogrel. By day 28, prasugrel 10 and 15 mg MDs achieved consistently higher mean IPA than clopidogrel 75 mg (all P < 0.0001). At pre-MD on day 28, no non-responders were observed in the 10 and 15 mg prasugrel group, compared with 45% of subjects in the clopidogrel group (P = 0.0007). The study concluded that prasugrel (40–60 mg LD and 10–15 mg MD) achieves greater IPA and a lower proportion of pharmacodynamic non-responders compared with the approved clopidogrel dosing.[11]

The JUMBO-TIMI 26 was a phase II clinical trial that enrolled 904 patients undergoing elective or urgent PCI.[12] In this double-blind, dose-ranging safety trial, patients were randomly allocated to prasugrel or clopidogrel and monitored for 30 days for bleeding and clinical events. The primary endpoint was clinically significant (TIMI major plus minor) non–CABG-related bleeding events. Patients were treated with oral prasugrel 40/7.5, 60/10 or 60/15 mg LD/MD or oral clopidogrel 300/75 mg LD/ MD for 30 days. Hemorrhagic complications were infrequent, with no significant difference between treatment groups in the rate of significant bleeding (1.7% prasugrel versus 1.2% clopidogrel; hazard ratio, 1.42; 95% CI, 0.40, 5.08). No significant difference was observed between groups for the primary efficacy composite end point (30-day major adverse cardiac events) and several secondary end points, including myocardial infarction, recurrent ischemia, and clinical target vessel thrombosis. Prasugrel treatment was associated with a non-significant decrease in major adverse cardiac events (9.4 and 7.2% for clopidogrel and prasugrel, respectively), including death, stroke and myocardial infarction. The study was underpowered due to the lower than expected bleeding rates in both groups, but would set the stage for the larger, phase III TRITON-TIMI 38 trial.

Comparative Efficacy & Safety Studies

TRITON-TIMI 38, a phase III trial, compared prasugrel with clopidogrel in 13,608 patients with moderate-to-high-risk ACS and scheduled PCI.[12] Patients were studied for 6 to 15 months for the primary composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The key safety end point was major bleeding. Patients received oral prasugrel 60/10 mg LD/MD or oral clopidogrel 300/75 mg LD/MD for 12 months. The primary efficacy end point occurred in 12.1% of patients receiving clopidogrel vs. 9.9% of patients receiving prasugrel (hazard ratio for prasugrel vs. clopidogrel, 0.81; 95% confidence interval, 0.73 to 0.90; P<0.001). The investigators found significant reductions in favor of prasugrel in the rates of myocardial infarction (9.7% for clopidogrel vs. 7.4% for prasugrel; P<0.001), urgent target-vessel revascularization (3.7% vs. 2.5%; P<0.001), and stent thrombosis (2.4% vs. 1.1%; P<0.001). However, major bleeding occurred in 2.4% of patients receiving prasugrel vs. 1.8% of patients receiving clopidogrel (hazard ratio, 1.32; 95% CI, 1.03 to 1.68; P=0.03). In addition, the rate of life-threatening bleeding was greater in the prasugrel group (1.4% vs. 0.9%; P=0.01), including nonfatal bleeding (1.1% vs. 0.9%; hazard ratio, 1.25; P=0.23) and fatal bleeding (0.4% vs. 0.1%; P=0.002).[15] The increase in life-threatening bleeding prompted the FDA to include a box warning on prasugrel's label.

To date, no published studies address prasugrel's possible use for decreasing cardiovascular events (heart attack or stroke) in those without PCI (Table 2). TRILOGY ACS (TaRgeted platelet Inhibition to cLarify

Table 2. Summary of clinical trials of prasugrel.

STUDY	DESIGN	DOSE	RESULTS
Jernberg, et al.[11] (2006)	• Study in CAD patients (n=101) on ASA. • Randomized, single-blind, parallel-group. • History of CAD, aged 40–75 years. • Primary Endpoint: IPA with 4 dosing regimens of prasugrel vs. clopidogrel LD and MD.	• Prasugrel 40/5, 40/7.5, 60/10 or 60/15 mg LD/MD • Clopidogrel (300/75 mg LD/MD) for 28 days • *Ex vivo* ADP-induced MPA was serially assessed.	• 4 hrs after dosing, prasugrel LDs had significantly higher mean IPA levels vs. clopidogrel (60.6% and 68.4 vs. 30.0%; all P < 0.0001) • 4 hrs after dosing, fewer pharmacodynamic non-responders than clopidogrel (3 vs. 52%, P < 0.0001) • Prasugrel 10 and 15 mg MDs had higher mean IPA vs. clopidogrel 75 mg at day 28 (all P < 0.0001). • Day 28, no non-responders in the 10 and 15 mg prasugrel vs. 45% in the clopidogrel (P = 0.0007).
Wiviott, et al.[12] (2005)	• Phase II in patients (n = 904) undergoing PCI. • Randomized, dose-ranging, double-blind safety trial of prasugrel vs. clopidogrel. • Monitored 30 days for bleeding and clinical events. • Primary Endpoint: Clinically significant (TIMI major plus minor) non–CABG-related bleeding events in prasugrel vs. clopidogrel patients.	• Prasugrel 40/7.5, 60/10 or 60/15 mg LD/ MD • Clopidogrel 300/75 mg LD/ MD for approximately 30 days	• No significant difference between prasugrel or clopidogrel in the rate of significant bleeding (1.7% versus 1.2%; hazard ratio, 1.42; 95% CI, 0.40, 5.08). • Prasugrel group had lower incidences of primary efficacy composite end point (30-day major adverse cardiac events) and of the secondary end points myocardial infarction, recurrent ischemia, and clinical target vessel thrombosis.
Wiviott, et al.[13] (2007)	• Randomized, double-blind, phase II crossover study for planned PCI (n = 201) • Primary Endpoint: Loading-dose phase (prasugrel 60 mg vs. clopidogrel 600mg) was IPA with 20 µmol/L ADP at 6 hrs.	• Prasugrel 60/10 mg LD/MD or • Clopidogrel 600/150 mg LD/MD for 14 days.	• IPA at 6 hours was significantly higher in subjects receiving prasugrel (mean±SD, 74.8±13.0%) vs. clopidogrel (31.8±21.1%; *P*<0.0001). • MD phase, prasugrel was higher (61.3±17.8%) vs. clopidogrel (46.1±21.3%; *P*<0.0001).
Wallentin L, et al.[14] (2008)	• Phase II in patients (n = 110) with stable CAD, randomized to double-blind treatment with clopidogrel or prasugrel • Determined concentrations of prasugrel and clopidogrel active metabolites. • Primary Endpoint: Platelet aggregation reported as MPA and $P2Y_{12}$ function were assessed.	• Pretreated with aspirin (75 mg) then received either prasugrel 60/10 mg LD/MD or clopidogrel 600/75 mg LD/MD for 28 days.	• 2 h post-LD, mean MPA was 31% vs. 55%, and mean PRI 8.3% vs. 55.9% for prasugrel and clopidogrel, (*P* < 0.001). • MD on day 14 and 28, mean MPA was 42 vs. 54% and mean PRI was 25 vs. 51% (*P* < 0.001). • Peak level of the active metabolite and $P2Y_{12}$ inhibition occurred earlier and greater with prasugrel (*P* < 0.001). • Mean AUC of active metabolite was higher with prasugrel vs. clopidogrel post-LD (1.11 vs. 0.24) and post-MD (0.16 vs. 0.062).
Wiviott SD, et al.[15] (2007)	• Phase III to compare prasugrel with clopidogrel, in patients (n=13,608) with moderate-to-high-risk ACS with scheduled PCI. • Primary Endpoint: Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The key safety end point was major bleeding.	• Patients received prasugrel (60/10 mg LD/MD) or clopidogrel (300/75 mg LD/ MD) for approximately 12 months (range 6 to 15 months)	• Primary efficacy end point occurred in 12.1% in clopidogrel group vs. 9.9% in prasugrel group (hazard ratio for prasugrel vs. clopidogrel, 0.81; 95% confidence interval, 0.73 to 0.90; P<0.001). • Significant reductions in the prasugrel group in rates of MI (9.7% for clopidogrel vs. 7.4% for prasugrel; P<0.001), urgent target-vessel revascularization (3.7% vs. 2.5%; P<0.001), and stent thrombosis (2.4% vs. 1.1%; P<0.001). • Major bleeding in 2.4% of prasugrel group vs. 1.8% of clopidogrel group (hazard ratio, 1.32; 95% CI, 1.03 to 1.68; P=0.03). • Rate of life-threatening bleeding was 1.4% in prasugrel group vs. 0.9% in clopidogrel group (P=0.01).

IPA = Inhibition of Platelet Aggregation, LD = Loading Dose, MD= Maintenance Dose, TIMI = Thrombolysis In Myocardial Infarction, MPA = Maximal Platelet Aggregation.

Table 3.Bleeding episodes stratified by age and weight.[7,15]

	Major/Minor Bleeding		Fatal	
	Prasugrel (%)	*Clopidogrel (%)*	*Prasugrel (%)*	*Clopidogrel (%)*
Weight < 60kg (N=308 prasugrel, N=356 clopidogrel)	10.1	2.5	0	0.3
Weight ≥ 60kg (N=6373 prasugrel, N=6299 clopidogrel)	4.2	6.3	0.3	0.1
Age < 75 years (N=5850 prasugrel, N=5822 clopidogrel)	3.8	2.9	0.2	0.1
Age ≥ 75 years (N=891 prasugrel, N=894 clopidogrel)	9	6.9	1	0.1

the Optimal strateGy to medicallY manage Acute Coronary Syndromes) trial is an ongoing multi-center, double-blind, randomized controlled trial that will include approximately 10,000 patients at more than 800 hospitals in 35 countries to compare aspirin and prasugrel vs. aspirin and clopidogrel.[16,17] The primary outcome will be a reduction in risk of the composite endpoint of first occurrence of CV death, MI, or stroke.[17] TRILOGY-ACS is the first study to evaluate the clinical efficacy of prasugrel in medically managed patients with UA/NSTEMI. The expected completion date is October 2011.[17]

Safety Issues

Box Warning

The FDA has added a box warning for prasugrel due to an increased risk of significant, sometimes fatal, bleeding. Prasugrel is contraindicated in patients with active pathological bleeding or a history of transient ischemic attack or stroke.[7] The TRITON-TIMI 38 trial found that patients ≥ 75 years of age had an increased risk of major/minor and fatal bleeding compared with younger patients (Table 3).[7,15]

Prasugrel is also contraindicated in patients that undergo urgent coronary artery bypass graft surgery (CABG).[6,7] In TRITON-TIMI 38, patients who underwent CABG (n = 437) had a significantly higher rate of major and minor bleeding when treated with prasugrel (14%) compared with clopidogrel (4%).[9,15] When possible, discontinue prasugrel at least 7 days prior to any surgery. However, discontinuing prasugrel in the first few weeks of ACS puts the patient at risk for stent thrombosis, myocardial infarction, and death. Thus, within this time frame, bleeding should be managed without discontinuing prasugrel if possible.

In TRITON-TIMI 38, non-CABG related bleeding occurred more often in prasugrel-treated patients than those receiving clopidogrel (Table 4). However, non-bleeding adverse events generally occurred at a similar rate between the two treatment groups (Table 5).

Prasugrel is a substrate for CYP3A4, CYP2B6, CYP2C9, and CYP2C19 as well as a weak inhibitor of CYP2B6. Prasugrel is not expected to affect the pharmacokinetics of medications with CYP2B6 mediated metabolism. Prasugrel may be administered with medications that are inducers or inhibitors of the cytochrome P450 enzymes.[6,7] Concomitant treatment with ketoconazole, a CYP3A4 inhibitor, reduced the peak serum concentration of both prasugrel and clopidogrel active metabolites by ~50%. The area under the curve (AUC) of prasugrel and its IPA was not significantly changed, but the AUC of clopidogrel was significantly lower and its IPA was reduced 20%.[18]

Table 5. Bleeding events not related to CABG in TRITON-TIMI 38.[7]

Adverse Event	*Prasugrel (%) (N=6741)*	*Clopidogrel (%) (N=6716)*	P-value for comparison
TIMI Major or Minor bleeding	4.5	3.4	0.002
TIMI Major bleeding	2.2	1.7	0.029
Life-threatening	1.3	0.8	0.015
Fatal	0.3	0.1	
Symptomatic intracranial hemorrhage	0.3	0.3	
Requiring inotropes	0.3	0.1	
Requiring surgical intervention	0.3	0.3	
Requiring transfusion (≥4 units)	0.7	0.5	
TIMI Minor bleeding	2.4	1.9	0.022

Table 4. Non-hemorrhagic adverse events in TRITON -TIMI 38.[7]

Adverse Event	*Prasugrel* (%) (N=6741)	*Clopidogrel* (%) (N=6716)
Hypertension	7.5	7.1
Hypercholesterolemia	7.0	7.4
Headache	5.5	5.3
Back pain	5.0	4.5
Dyspnea	4.9	4.5
Nausea	4.6	4.3
Dizziness	4.1	4.6
Cough	3.9	4.1
Hypotension	3.9	3.8
Fatigue	3.7	4.8
Non-cardiac chest pain	3.1	3.5
Atrial fibrillation	2.9	3.1
Bradycardia	2.9	2.4
Leukopenia (< 4 x 109 WBC/L)	2.8	3.5
Rash	2.8	2.4
Pyrexia	2.7	2.2
Peripheral edema	2.7	3.0
Pain in extremity	2.6	2.6
Diarrhea	2.3	2.6

Dosing, Administration & Cost

The recommended dose for arterial thromboembolism prophylaxis in patients with ACS to be managed with PCI that are ≥ 60 kg and < 75 years of age is 60 mg PO as a loading dose, then 10 mg PO once daily.[6,7] The optimal duration of therapy is not known. Patients should take concomitant aspirin 75—325 mg/day. Antiplatelet therapy should be promptly administered in the management of ACS as many cardiovascular events occur within hours of initial presentation.

The manufacturer recommends a loading dose of 60 mg and a maintenance dose of 5 mg PO once daily for patients < 60 kg and <75 years of age, although this dose has not been prospectively studied for safety and efficacy.[6,9,10] Compared to heavier individuals, patients weighing < 60 kg have an increased exposure to the active metabolite and an increased risk of bleeding when given 10 mg PO once daily.[7] Prasugrel can be administered with or without food, but tablets should not be broken.[6,7] The cost of prasugrel approaches $200 monthly, regardless of strength (Table 6).

Table 6. Average retail cost of prasugrel per month.

Product	Average Price	Range
Effient® 5 mg	$192.25	$185.99-$200.25
Effient® 10 mg	$196.50	$189.99-$204

Summary

Antiplatelet medications reduce thrombotic cardiovascular events in patients with ACS undergoing PCI. Prasugrel has a significantly higher IPA than clopidogrel and produces fewer non-responders. However, prasugrel has a box warning (bleeding), is contraindicated in patients ≥75, and safety in patients < 60 kg remains unclear. At the time of this publication, the TRILOGY ACS trial is ongoing evaluating prasugel for reduction of stroke, myocardial infarction, and death in patients not undergoing PCI. The results of this trial should shed further light on the appropriate use of prasugrel in clinical practice.

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