Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 56, No. 13, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.02.072

CLINICAL RESEARCH | Clinical Trial

Increased Platelet Inhibition After Switching From Maintenance Clopidogrel to Prasugrel in Patients With Acute Coronary Syndromes

Results of the SWAP (SWitching Anti Platelet) Study

Dominick J. Angiolillo, MD, PhD,* Jorge F. Saucedo, MD,† Roger DeRaad, MN,‡ Andrew L. Frelinger, PhD,§‖ Paul A. Gurbel, MD,¶ Timothy M. Costigan, PhD,# Joseph A. Jakubowski, PhD,# Clement K. Ojeh, PhD,# Mark B. Effron, MD,# for the SWAP Investigators

Jacksonville, Florida; Oklahoma City, Oklahoma; Rapid City, South Dakota; Worcester and Boston, Massachusetts; Baltimore, Maryland; and Indianapolis, Indiana

Objectives The objective was to evaluate the pharmacodynamic response of switching patients on maintenance phase clopidogrel therapy after an acute coronary syndrome (ACS) to prasugrel.

Background Prasugrel $P2Y_{12}$ receptor blockade is associated with greater pharmacodynamic platelet inhibition and reduction of ischemic complications compared with that of clopidogrel in ACS patients undergoing percutaneous coronary intervention. The pharmacodynamic effects of switching patients during maintenance phase clopidogrel therapy after an ACS event to prasugrel are unknown.

Methods The SWAP (SWitching Anti Platelet) study was a phase 2, multicenter, randomized, double-blind, double-dummy, active-control trial. After a run-in of daily open-label clopidogrel 75 mg with aspirin therapy for 10 to 14 days, patients were randomly assigned to 1 of the following 3 treatments: placebo loading dose (LD)/clopidogrel 75 mg maintenance dose (MD), placebo LD/prasugrel 10 mg MD, or prasugrel 60 mg LD/10 mg MD. Platelet function was evaluated at 2 h, 24 h, 7 days, and 14 days using light transmittance aggregometry, VerifyNow $P2Y_{12}$ assay, and vasodilator-stimulated phosphoprotein phosphorylation.

Results A total of 139 patients were randomized, of whom 100 were eligible for analysis. Maximum adenosine diphosphate-induced platelet aggregation (20 μM) by light transmittance aggregometry at 1 week (primary end point) was lower after prasugrel MD compared with clopidogrel MD (41.1% vs. 55.0%, $p < 0.0001$), and was also lower in the prasugrel LD+MD group compared with clopidogrel MD (41.0% vs. 55.0%, $p < 0.0001$). At 2 h, a prasugrel LD resulted in higher platelet inhibition compared with the other regimens. Similar results were found using light transmittance aggregometry with 5 μM adenosine diphosphate, VerifyNow $P2Y_{12}$, and vasodilator-stimulated phosphoprotein phosphorylation assays.

Conclusions For patients receiving maintenance clopidogrel therapy after an ACS event, switching from clopidogrel to prasugrel is associated with a further reduction in platelet function by 1 week using prasugrel MD or within 2 h with the administration of a prasugrel LD. (A Pharmacodynamic Comparison of Prasugrel [LY640315] Versus Clopidogrel in Subjects With Acute Coronary Syndrome Who Are Receiving Clopidogrel [SWAP]; NCT00356135) (J Am Coll Cardiol 2010;56:1017–23) © 2010 by the American College of Cardiology Foundation

From the *University of Florida College of Medicine, Jacksonville, Florida; †University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; ‡Black Hills Clinical Research Center, Rapid City, South Dakota; §University of Massachusetts Medical School, Worcester, Massachusetts; ‖Children's Hospital Boston, Boston, Massachusetts; ¶Sinai Center for Thrombosis Research, Baltimore, Maryland; and #Eli Lilly and Company or a subsidiary, Indianapolis, Indiana. The investigators and the centers participating in the SWAP study are listed in the Online Appendix. Financial support was provided by Daiichi Sankyo Inc. and by Eli Lilly and Company. Dr. Angiolillo reports receiving honoraria for lectures from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and Daiichi Sankyo; consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, The Medicines Company, Portola, Novartis, Medicure, Accumetrics, Arena Pharmaceuticals, and AstraZeneca; and research grants from GlaxoSmithKline, Otsuka, Eli Lilly, Daiichi Sankyo, The Medicines Company, Portola, Accumetrics, Schering-Plough, AstraZeneca, Eisai, and Johnson & Johnson. Dr. Saucedo reports grant and research support from The Medicines Company, AstraZeneca, Abbott Vascular, Bristol-Myers Squibb,

JACC Vol. 56, No. 13, 2010
September 21, 2010:1017–23

Abbreviations and Acronyms

ACS = acute coronary syndrome
ADP = adenosine diphosphate
LD = loading dose
LTA = light transmittance aggregometry
MD = maintenance dose
MPA = maximum platelet aggregation
PCI = percutaneous coronary intervention
PRU = $P2Y_{12}$ reaction units
VASP-P = vasodilator-stimulated phosphoprotein phosphorylation
VN = VerifyNow

Current guidelines recommend a combination of aspirin and a thienopyridine for the prevention of recurrent ischemic events in patients with acute coronary syndromes (ACS) and for patients undergoing percutaneous coronary intervention (PCI) (1). Variable antiplatelet response to clopidogrel has been reported, and patients with a reduced effect have an increased risk of ischemic complications (2). Prasugrel inhibits platelet activation through irreversible $P2Y_{12}$ receptor blockade by a mechanism similar to that of clopidogrel (3). Pharmacodynamic studies have shown that prasugrel exerts greater and more consistent platelet inhibition than clopidogrel even when used at high doses (4). In patients with ACS undergoing PCI, prasugrel resulted in lower recurrent atherothrombotic event rates but more major bleeding compared with clopidogrel (5). Nevertheless, there was a significant net clinical benefit, defined as the composite of efficacy and bleeding end points, with prasugrel. Further, patients randomly assigned to clopidogrel who survived their first event had a higher risk of recurrent events, including cardiovascular mortality, compared with prasugrel patients (6). Prasugrel is approved for the reduction of thrombotic cardiovascular events in patients with ACS managed with PCI. Therefore, switching these patients at high risk for recurrent cardiovascular events from clopidogrel to prasugrel may be a consideration, particularly if they respond poorly to clopidogrel by platelet function (2) or genomics testing (7), or are subject to reported drug–drug interactions that hamper the effectiveness of clopidogrel (8). However, the pharmacodynamic effects of changing from clopidogrel to prasugrel therapy in patients who had an ACS event are largely unknown.

Methods

Study design. The SWAP (SWitching Anti Platelet) study was a phase 2, multicenter, randomized, double-blind, double-dummy, active-control trial designed to evaluate the pharmacodynamic response in patients on maintenance dose (MD) clopidogrel therapy after an ACS event who were switched to prasugrel MD, with or without a prasugrel loading dose (LD). Patients were eligible for the study if they were between 18 and 75 years of age, 30 to 330 days after an ACS event, and treated with daily aspirin and clopidogrel. Patients were excluded in the presence of any of the following: cardiogenic shock, refractory ventricular arrhythmias, congestive heart failure (class III and IV), or left main coronary artery stent; had a planned PCI or coronary artery bypass graft surgery to occur during the study; or had undergone PCI or coronary artery bypass graft surgery within 30 days of study entry. Patients were also excluded if they were at high risk of bleeding, including a history of ischemic or hemorrhagic stroke, intracranial neoplasm, arteriovenous malformation or aneurysm, a history of transient ischemic attack, or a body weight <60 kg.

The study design is illustrated in Figure 1. Patients received a run-in of open-label 75 mg clopidogrel taken daily with their usual dose of aspirin for 10 to 14 days to assess compliance before randomization and to confirm a steady-state level of clopidogrel pharmacodynamic effects. Patients were then randomly assigned and switched 24 ± 2 h after the last dose of clopidogrel to 1 of 3 study arms: placebo LD/clopidogrel 75 mg MD (clopidogrel MD), placebo LD/prasugrel 10 mg MD (prasugrel MD), or 60 mg prasugrel LD/prasugrel 10 mg MD (prasugrel LD+MD). Clopidogrel (open-label and blinded study drug) was commercially available clopidogrel bisulfate (Plavix, 75 mg tablets, Bristol-Myers Squibb/Sanofi-Aventis, New York, New York). Prasugrel was administered as tablets containing 10 mg prasugrel (Eli Lilly and Company, Indianapolis, Indiana). The MD phase continued for 13 to 15 days. Aspirin was maintained using a dose at the discretion of the investigator (81 to 325 mg/day) and remained unchanged throughout the study.

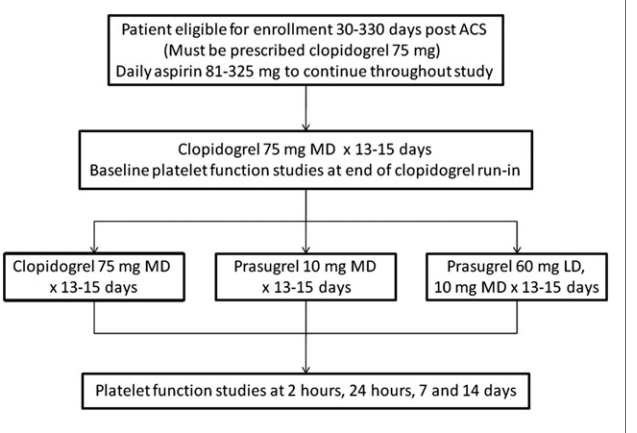

Figure 1 Study Design

ACS = acute coronary syndrome; LD = loading dose; MD = maintenance dose.

Medtronic, and Eli Lilly; and grant support, consulting fees, and honoraria from Schering-Plough. Dr. Frelinger reports grant and research support from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, and GLSynthesis; and consulting fees from Eli Lilly. Dr. Gurbel reports receiving honoraria for lectures from Sanofi-Aventis, AstraZeneca, Eli Lilly, Daiichi Sankyo, and Schering-Plough; consulting fees from Schering-Plough, AstraZeneca, Portola, Haemoscope, Sanofi, Pozen, and Bayer; and grant and research support from Schering-Plough, AstraZeneca, Portola, Haemoscope, and Bayer. Drs. Costigan, Jakubowski, Ojeh, and Effron are employees of and report equity ownership of or stock options in Eli Lilly. All other authors have reported that they have no relationships to disclose.

Manuscript received November 16, 2009; revised manuscript received February 5, 2010, accepted February 9, 2010.

Platelet function was tested at 6 time points: before study entry, 24 h after the last dose of clopidogrel from the run-in phase, 2 and 24 h after LD, and 1 and 2 weeks after randomization (approximately 24 h after the prior MD for the indicated day to avoid any potential interference in the assays). Platelet function measures included 1) maximum platelet aggregation (MPA) after stimulation with 5 and 20 μM adenosine diphosphate (ADP) using light transmittance aggregometry (LTA); 2) $P2Y_{12}$ reactivity index, determined by vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) using quantitative flow cytometry and commercially available labeled monoclonal antibodies (Biocytex, Marseille, France) at a central laboratory (Sinai Center for Thrombosis Research, Baltimore, Maryland); and 3) $P2Y_{12}$ reaction units (PRU) determined by VerifyNow $P2Y_{12}$ (VN-$P2Y_{12}$, Accumetrics, San Diego, California). Platelet function assessments were performed according to standard protocols and are described in detail elsewhere (9,10).

The protocol was approved by the institutional review boards at the individual sites and the study was conducted in accordance with regulatory standards and good clinical practice guidelines rooted in the Declaration of Helsinki. All patients provided written informed consent. The authors had full access to the data, take full responsibility for its integrity, and have agreed to the manuscript as written.

Study end points and statistical analyses. The primary end point was the comparison of mean MPA to 20 μM ADP at 1 week (7 to 9 days after randomization) of prasugrel MD to clopidogrel MD. This was performed by comparing the least square means of prasugrel MD group to clopidogrel MD group, obtained from an analysis of covariance model applied to the 3 randomized treatments groups. In this model, treatment and study site were fixed effects, and the latest MPA measurement before randomization (after 10 to 14 days of open-label clopidogrel 75 mg MD and aspirin) was a covariate. Similar comparisons were also performed for the other treatment comparisons (prasugrel LD+MD vs. clopidogrel MD; prasugrel LD+MD vs. prasugrel MD). A similar analysis was performed in which the 2 prasugrel groups were combined and compared with the clopidogrel MD group at day 7. The primary analysis population was the pharmacodynamic population: all randomized patients who had evaluable MPA at the 7-day visit, took at least 80% of their doses through week 1, and had the last dose of study drug the day before the blood draw for MPA. Additionally, MPA to 20 μM ADP was analyzed by a linear mixed effect model with treatment, categorical time point, and time-by-treatment interaction as fixed effects, subject as a random effect, and MPA before randomization as a covariate, with an unstructured covariance structure. Enrollment of as many as 150 patients to reach 120 patients completing the study was allowed. Secondary end points included functional assessments at all other time points by means of LTA as well as PRI and VN-$P2Y_{12}$ using similar statistical analyses.

Data related to safety and tolerability of switching patients from clopidogrel to prasugrel therapy were collected from patients who took at least 1 dose of randomized study drug. This information was assessed by evaluating vital signs, bleeding, and all reported adverse events. Bleeding was classified as minimal, minor, or major according to the TIMI (Thrombolysis In Myocardial Infarction) criteria (5). Treatment-emergent adverse events were summarized using the *Medical Dictionary for Regulatory Activities* (11) preferred term. For continuous characteristics, means of the treatment groups were compared using analysis of covariance. For categorical characteristics, percents were compared by chi-square tests. Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, North Carolina). Tests of treatment effects were conducted at 2-sided alpha level of 0.05 without adjustment for multiple comparisons.

Results

Patient population. From July 2006 through December 2008, 159 patients were enrolled (see Online Appendix for participating centers). Of these, 20 patients failed to complete the run-in phase. The safety population included a total of 139 randomized patients. A total of 128 patients completed the study, of whom 100 had evaluable data at both baseline and 7-day follow-up and made up the pharmacodynamic population to assess the primary end point. Figure 2 describes the patient disposition. Demographics and baseline characteristics for the pharmacodynamic population are summarized in Table 1, and show no significant differences among the 3 treatment groups.

Pharmacodynamic evaluations. After the run-in phase with open-label clopidogrel, MPA (20 μM ADP) was 53.8%, 60.2%, and 55.5% in the patients randomly allocated to clopidogrel MD, prasugrel MD, and prasugrel LD+MD treatment, respectively. The MPA (20 μM ADP) at day 7 after switching to study drug was significantly lower after prasugrel MD compared with clopidogrel MD (41.1% vs. 55.0%, $p < 0.0001$), as well as in the prasugrel LD+MD group compared with clopidogrel MD (41.0% vs. 55.0%, $p < 0.0001$) (Fig. 3A). As the MPA for each prasugrel group was essentially the same by day 7 after switching, the 2 groups were pooled, and the combined prasugrel group demonstrated a lower MPA compared with clopidogrel MD (41.1% vs. 55.0%, $p < 0.0001$). Reduced platelet aggregation was seen at 2 h after switching from open-label clopidogrel 75 mg to prasugrel LD+MD compared with either clopidogrel MD or prasugrel MD. This difference was sustained to 24 h. Additionally, there was a small but significant reduction in platelet aggregation at 2 h by both clopidogrel MD and prasugrel MD compared with their respective baselines. This reduction remained significant for prasugrel MD by 24 h but not for clopidogrel MD. By 7 days in the prasugrel LD+MD group, the MPA to MD

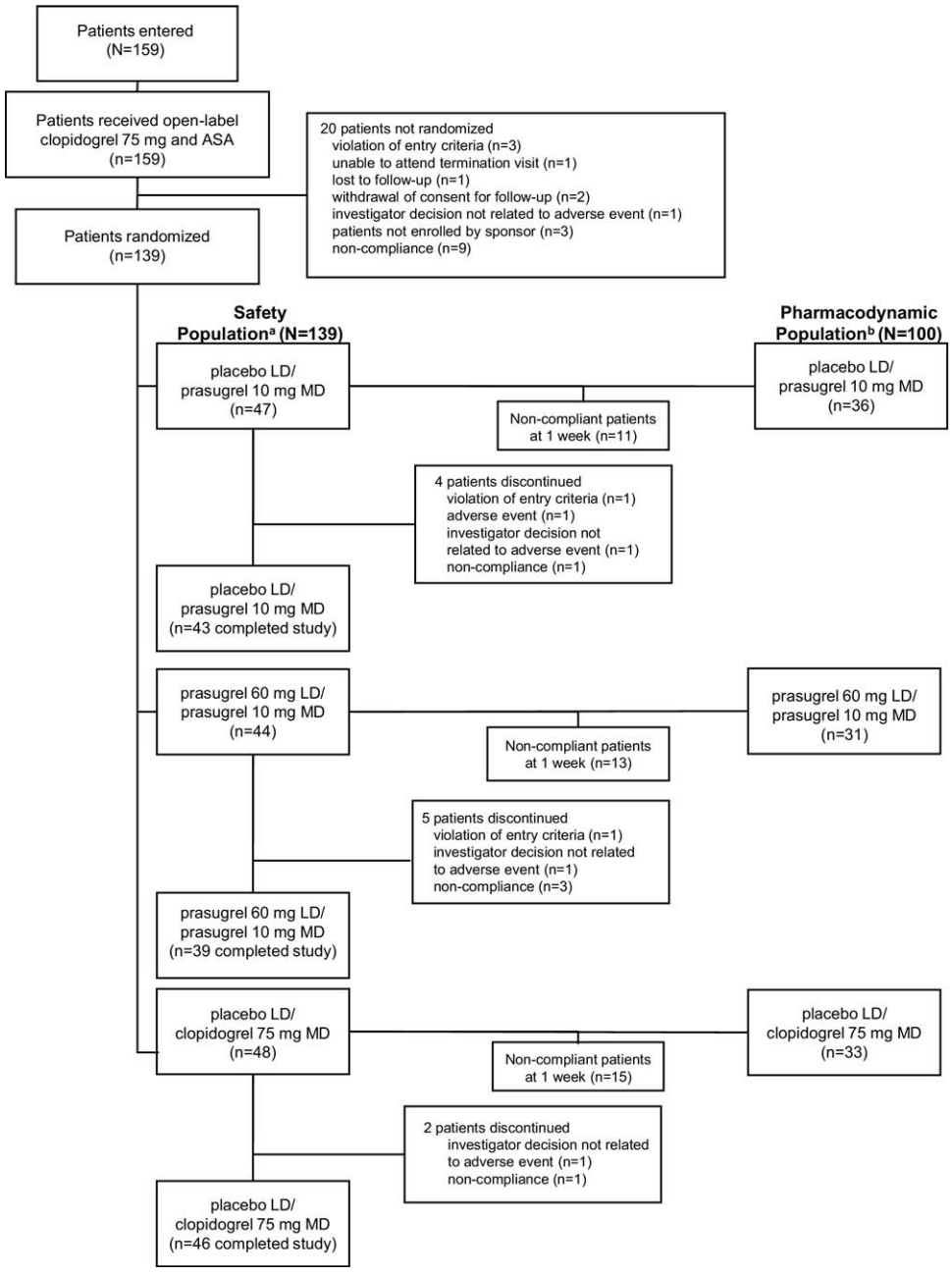

Figure 2 **Subject Disposition**

[a]Safety population: all randomized patients who took at least 1 dose of randomized study drug. [b]Pharmacodynamic population: all randomized patients who had evaluable maximum platelet aggregation (MPA) at the 7-day visit, took at least 80% of their doses through week 1, and had the last dose of study drug the day before the blood draw for MPA. ASA = acetyl salicylic acid (aspirin); LD = loading dose; MD = maintenance dose.

was higher than seen 24 h after the LD (40.6% vs. 27.4%). Greater decreases in MPA (20 μM ADP) in the prasugrel LD+MD compared with the clopidogrel MD were observed at all time points from 2 h to 14 days ($p < 0.0001$, all time points). Similar results were obtained using 5 μM ADP as the agonist (Fig. 3B). Switching from open-label clopidogrel 75 mg to prasugrel MD alone did not significantly alter the level of platelet aggregation compared with clopidogrel MD at 2 or 24 h compared with continued clopidogrel 75 mg MD (49.5% vs. 48.1% at 2 h and 52.3% vs. 53.8% at 24 h, respectively). Pharmacodynamic evaluations by the other platelet function assays (VASP-P and VN-P2Y$_{12}$) were consistent with the LTA observations (Figs. 4A and 4B).

Safety and tolerability. In the clopidogrel MD group, 52% of patients reported at least 1 adverse event whereas 36.2%

Table 1 Baseline Demographics and Clinical Characteristics

	Placebo LD, Clopidogrel 75 mg MD (n = 33)	Placebo LD, Prasugrel 10 mg MD (n = 36)	Prasugrel 60 mg LD, Prasugrel 10 mg MD (n = 31)	p Value
Age, yrs	57.1 ± 7.1	57.3 ± 7.9	57.0 ± 8.6	0.99
Male	63.6	77.8	67.7	0.43
Race				0.071*
Caucasian	60.6	83.3	83.9	
African	27.3	16.7	12.9	
Asian	0	0	0	
Other	12.1	0	3.2	
BMI, kg/m^2	33.1 ± 7.0	31.0 ± 6.5	31.1 ± 6.1	0.35
Risk factors/medical history				
Current smoker	21.2	41.7	25.8	0.15
Hypertension	81.8	80.6	81.8	0.95
Hypercholesterolemia	78.1	88.9	78.1	0.47
Diabetes mellitus	33.3	36.1	16.1	0.16
Prior MI	30.3	36.1	16.1	0.17
Prior TIA	3.0	2.8	3.2	1.00
Prior stroke	3.0	0	0	0.64
Prior PCI	42.4	44.4	32.3	0.58
Prior CABG	12.1	19.4	6.5	0.32
Qualifying ACS event				
Time from event to study entry, days	77.4 ± 47.3	102.2 ± 77.4	82.1 ± 71.0	0.26
Unstable angina/NSTEMI	60.6	63.9	61.3	0.97†
STEMI	39.4	36.1	38.7	
BMS (≥1) placed at time of event	39.4	30.6	41.9	0.61
DES (≥1) placed at time of event	45.4	52.8	58.1	0.59
Medical therapy				
Beta-blockers	90.9	94.4	93.6	0.89
Statins	81.8	88.9	83.9	0.73
Lipophilic	63.6	58.3	61.3	0.96
Nonlipophilic	18.2	33.3	25.8	0.36
Proton-pump inhibitors	36.4	16.7	25.8	0.18
Calcium-channel blockers	15.2	8.3	16.1	0.57

Values are mean ± SD or %. All patients were receiving aspirin (81 to 325 mg/day) and clopidogrel (75 mg/day). During the study, the majority of patients (at least 92.8% of all patients at each visit) received an 81 mg daily aspirin dose. The p values were determined using Fisher exact test or by analysis of variance. *Race by treatment comparison. †Acute coronary syndrome (ACS) event type by treatment comparison.

BMI = body mass index; BMS = bare-metal stent(s); CABG = coronary artery bypass graft surgery; DES = drug-eluting stent(s); LD = loading dose; MD = maintenance dose; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

of the prasugrel MD group and 25% of the prasugrel LD+MD group reported at least 1 adverse event (p = 0.027). The majority of events were mild or moderate in severity. There were no serious adverse events reported in either the clopidogrel MD group or prasugrel LD+MD group. A serious adverse event was reported in 3 patients in the prasugrel MD group, and included chest pain (n = 1), in-stent restenosis (n = 1), and syncope (n = 1). None of these events was considered related to the study drug and did not lead to treatment discontinuation. Bleeding by TIMI criteria was reported in 12.5% of the clopidogrel 75 mg MD group, 8.5% of the prasugrel 10 mg MD group, and 13.6% of the prasugrel LD+MD group. All bleeding events were minimal by TIMI criteria, and none needed medical or surgical intervention. No clinically significant findings were identified through the evaluation of clinical laboratory tests or vital signs, after switching from clopidogrel to prasugrel.

Discussion

The SWAP study is the first to assess the pharmacodynamics and tolerability of a prasugrel 10 mg MD administered immediately after clopidogrel 75 mg MD with or without a prasugrel LD to patients on maintenance clopidogrel therapy after an ACS event. In particular, the results of the SWAP study show that switching from 75 mg MD clopidogrel to 10 mg MD prasugrel, with or without an LD, in these patients results in significantly decreased platelet function 1 week later, as measured by multiple assays including LTA, VASP-P, and VN-P2Y$_{12}$. Additionally, switching to 10 mg prasugrel MD without an LD did not result in a loss of the existing platelet inhibition resulting from maintenance dose clopidogrel for the initial 24 h. Further, administration of a 60 mg prasugrel LD resulted in a rapid and marked decrease in platelet aggregation by 2 h. Finally, switching from clopidogrel to prasugrel was well

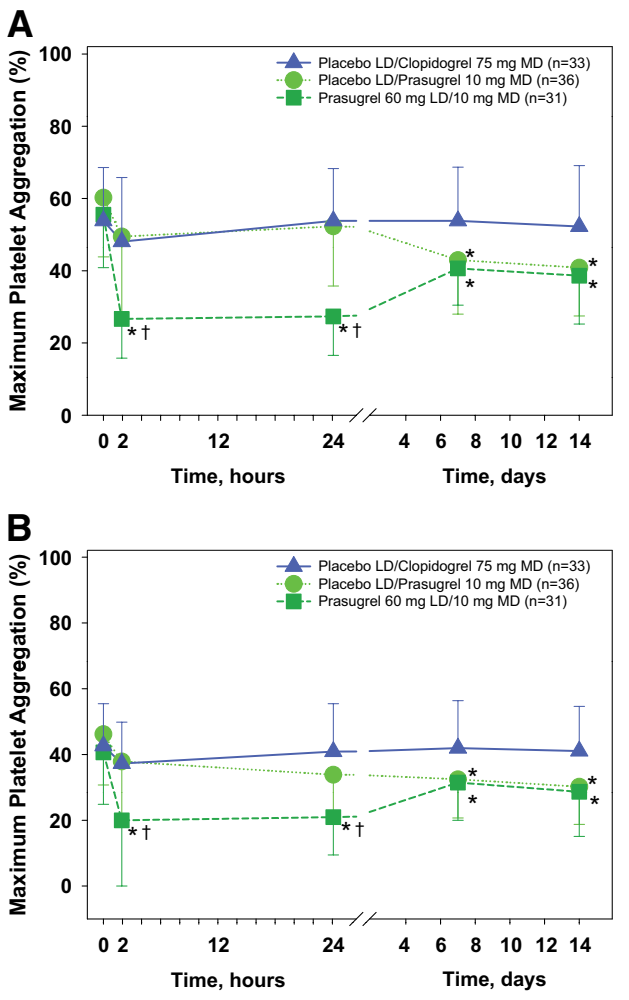

Figure 3 **Maximum Platelet Aggregation**

(A) Mean maximum platelet aggregation (MPA) to 20 μM adenosine diphosphate (ADP) ± SD. **(B)** Mean MPA to 5 μM ADP ± SD. Time 0 is baseline value obtained after 2-week open-label clopidogrel and before administration of first dose of study drug. *p < 0.0001 versus clopidogrel 75 mg maintenance dose (MD). †p < 0.0001 versus prasugrel 10 mg MD. **Blue triangles** indicate placebo loading dose (LD)/clopidogrel 75 mg MD (n = 33); **green circles** indicate placebo LD/prasugrel 10 mg MD (n = 36); and **green squares** indicate prasugrel 60 mg LD/10 mg MD (n = 31).

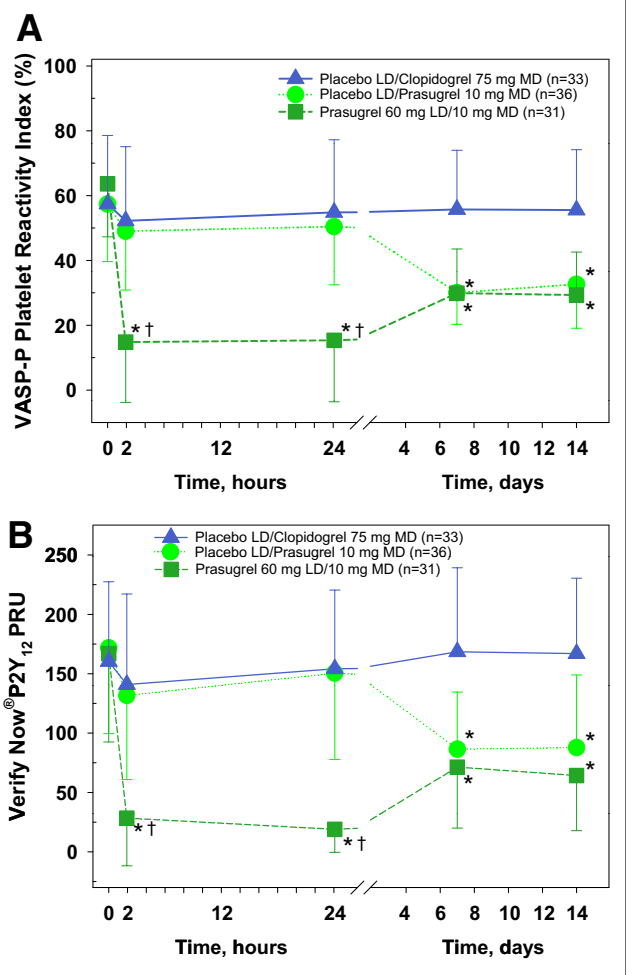

Figure 4 **Platelet Function Assays**

(A) Vasodilator-stimulated phosphoprotein phosphorylation (VASP-P). **(B)** VerifyNow (VN) $P2Y_{12}$. Results are presented as mean VASP-P platelet reactivity index (PRI)% ± SD **(A)** or mean VN-$P2Y_{12}$ reaction units (PRU) ± SD **(B)** at each time point. Time 0 is baseline value obtained after 2 weeks of open-label clopidogrel and before administration of first dose of study drug. *p < 0.0001 versus clopidogrel 75 mg maintenance dose (MD). †p <0.0001 versus prasugrel 10 mg MD. **Blue triangles** indicate placebo loading dose (LD)/clopidogrel 75 mg MD (n = 33); **green circles** indicate placebo LD/prasugrel 10 mg MD (n = 36); and **green squares** indicate prasugrel 60 mg LD/10 mg MD (n = 31).

tolerated without major safety events in this study. These findings provide pharmacodynamic insights to clinicians who may choose to switch from clopidogrel to prasugrel therapy.

The SWAP study results are consistent with a previous study of healthy volunteers in which switching directly from clopidogrel to prasugrel resulted in a significant reduction in platelet function and was well tolerated (12). Moreover, in a recent study involving ACS patients switching to a prasugrel 10 mg dose directly after treatment with a high clopidogrel LD (900 mg) and MD (150 mg) resulted in greater platelet inhibition without serious or life-threatening bleeding (13). The SWAP study supports that switching directly from clopidogrel to prasugrel provides additional platelet inhibition, which can be achieved more rapidly (within 2 h) if an LD of prasugrel is given. The pharmacodynamic effects are consistent with the higher levels of prasugrel active metabolite achieved after prasugrel administration compared with clopidogrel (3). These results are in contrast with those observed when switching from a direct-acting reversible $P2Y_{12}$ inhibitor to clopidogrel, which impeded platelet inhibitory effects of clopidogrel (14).

Lower levels of platelet function, reflecting greater platelet inhibition, have been associated with a lower risk of recurrent ischemic events (2). While prasugrel increases the

level of platelet inhibition compared with clopidogrel, there is no consensus agreement establishing specific levels of platelet function for optimal clinical efficacy or safety outcomes. Ongoing large-scale trials are evaluating the link between platelet function testing and patient outcomes and safety, as well as whether more intensive antiplatelet therapy directed by point-of-care testing using high-dose clopidogrel or prasugrel can improve clinical outcomes.

Study limitations. The SWAP study was a pharmacodynamic study and not sized to assess efficacy or safety. Therefore, this study was not designed to determine whether a reduction in cardiovascular thrombotic events would result when switching from clopidogrel to prasugrel. Additionally, although no serious bleeding was observed, no conclusions regarding the clinical results can be made. Ultimately, there was no evaluation of switching from prasugrel to clopidogrel.

Acknowledgments

The authors would like to thank Mark Antonino, BS (Sinai Center for Thrombosis Research, Baltimore, Maryland), for his excellent support in conducting the VASP-P assays for the SWAP study; Barbara Utterback (Eli Lilly and Company) for providing writing and project management support for the paper; Kristen Smith (Eli Lilly and Company) for providing editorial support; and Marjorie Zettler, PhD, MPH, and Baojin Zhu, PhD (Eli Lilly and Company) for providing additional medical and statistical review of the final manuscript.

Reprint requests and correspondence: Dr. Dominick J. Angiolillo, Cardiology Research, University of Florida Jacksonville, 655 West 8th Street, ACC 5th Floor, Jacksonville, Florida 32209. E-mail: dominick.angiolillo@jax.ufl.edu.

REFERENCES

1. Kushner FG, Hand M, Smith SC Jr., et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;54:2205–41.
2. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505–16.
3. Jakubowski JA, Winters KJ, Naganuma H, Wallentin L. Prasugrel: a novel thienopyridine antiplatelet agent. A review of preclinical and clinical studies and the mechanistic basis for its distinct antiplatelet profile. Cardiovasc Drug Rev 2007;25:357–74.
4. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. Circulation 2007;116:2923–32.
5. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
6. Murphy SA, Antman EM, Wiviott SD, et al. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. Eur Heart J 2008;29:2473–9.
7. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354–62.
8. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301:937–44.
9. Angiolillo DJ, Shoemaker SB, Desai B, et al. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. Circulation 2007;115:708–16.
10. Angiolillo DJ, Costa MA, Shoemaker SB, et al. Functional effects of high clopidogrel maintenance dosing in patients with inadequate platelet inhibition on standard dose treatment. Am J Cardiol 2008;101:440–5.
11. Medical Dictionary for Regulatory Activities (MedDRA), version 11.0. Chantilly, VA: Maintenance and Support Services Organization, April 2008.
12. Payne CD, Li YG, Brandt JT, et al. Switching directly to prasugrel from clopidogrel results in greater inhibition of platelet aggregation in aspirin-treated subjects. Platelets 2008;19:275–81.
13. Montalescot G, Sideris G, Cohen R, et al. Prasugrel compared with high-dose clopidogrel in acute coronary syndrome: the randomized, double-blind ACAPULCO study. Thromb Haemost 2010;103:213–23.
14. Steinhubl SR, Oh JJ, Oestreich JH, et al. Transitioning patients from cangrelor to clopidogrel: pharmacodynamic evidence of a competitive effect. Thromb Res 2008;121:527–34.

Key Words: acute coronary syndrome ■ clopidogrel ■ platelet ■ prasugrel.

APPENDIX

For a complete list of the investigators and centers participating in the SWAP study, please see the online version of this article.