

# Pharmacodynamics and Pharmacokinetics of Single Doses of Prasugrel 30 mg and Clopidogrel 300 mg in Healthy Chinese and White Volunteers: An Open-Label Trial

David S. Small, PhD<sup>1</sup>; Christopher D. Payne, MS<sup>2</sup>; Prajakti Kothare, PhD<sup>1</sup>; Eunice Yuen, BPharm<sup>2</sup>; Fanni Natanegara, PhD<sup>1</sup>; Mei Teng Loh, PhD<sup>3</sup>; Joseph A. Jakubowski, PhD<sup>1</sup>; D. Richard Lachno, DPhil<sup>2</sup>; Ying G. Li, MS<sup>1</sup>; Kenneth J. Winters, MD<sup>1</sup>; Nagy A. Farid, PhD<sup>1</sup>; Lan Ni, PhD<sup>1</sup>; Daniel E. Salazar, PhD<sup>4</sup>; Molly Tomlin, MS<sup>1</sup>; and Ronan Kelly, MD, DPhil<sup>3</sup>

<sup>1</sup>Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana; <sup>2</sup>Lilly Research Laboratories, Eli Lilly and Company, Windlesham, Surrey, United Kingdom; <sup>3</sup>Lilly-NUS Centre for Clinical Pharmacology, Singapore; <sup>4</sup>Daiichi Sankyo, Inc., Parsippany, New Jersey

## ABSTRACT

**Background:** Prasugrel is an oral antiplatelet agent approved for the reduction of atherothrombotic cardiovascular events in patients presenting with acute coronary syndrome and undergoing percutaneous coronary intervention. Although the approved loading dose is 60 mg, earlier studies of prasugrel suggested that active-metabolite exposure and pharmacodynamic response may be higher in Asian subjects than in white subjects.

**Objectives:** This study compared the pharmacodynamic response to a single 30-mg dose of prasugrel in healthy Chinese and white subjects and the response to a single 30-mg dose of prasugrel and a single 300-mg dose of clopidogrel in healthy Chinese subjects. The pharmacokinetics and tolerability of both drugs were also assessed.

**Methods:** This was an open-label, single-dose study conducted in Singapore. Chinese subjects were randomly allocated to receive prasugrel 30 mg or clopidogrel 300 mg; after a 14-day washout period, they received the alternative drug. White subjects received only prasugrel 30 mg. Blood samples for pharmacodynamic assessments were collected before dosing and at 0.5, 1, 2, 4, and 24 hours after dosing. Three methods were used to measure inhibition of platelet aggregation (IPA)—traditional light transmission aggregometry (LTA), the VerifyNow P2Y12 (VN-P2Y12) assay, and a vasodilator-stimulated phosphoprotein (VASP) phosphorylation flow cytometry assay—and their results were compared. Blood samples for pharmacokinetic assessments were collected at 0.25, 0.5, 1, 1.5, 2,

4, 8, 12, and 24 hours after dosing. Concentrations of the active metabolite of prasugrel were measured using a validated LC-MS/MS method.

**Results:** The study enrolled 18 Chinese subjects and 14 white subjects. Chinese subjects had a mean (SD) age of 31 (10) years and a mean body weight of 65.2 (8.9) kg; 83% were male. The corresponding values for white subjects were 30 (10) years, 77.2 (12.4) kg, and 86%. Thirty of the 32 enrolled subjects completed the study. Two Chinese men were withdrawn from the study, one due to a low platelet-rich plasma count after receipt of prasugrel 30 mg and the other due to mild, intermittent rectal bleeding after bowel movements that began ~2 days after receipt of clopidogrel 300 mg. The mean IPA with prasugrel was significantly higher in Chinese than in white subjects at 0.5, 1, and 2 hours after dosing ( $P < 0.05$ ), but not at 4 or 24 hours. In Chinese subjects, mean maximal IPA (87%) occurred 1 hour after prasugrel dosing; in white subjects, mean maximal IPA (78%) occurred 2 hours after prasugrel dosing. In Chinese subjects, the mean IPA was significantly higher at all time points after administration of prasugrel 30 mg than after administration of clopidogrel 300 mg ( $P <$

Data in this paper were presented in part at the 109th Annual Congress of the American Society for Clinical Pharmacology and Therapeutics, April 2–5, 2008, Orlando, Florida, and the Angioplasty Summit–TCT Asia Pacific, April 23–25, 2008, Seoul, Korea.

Accepted for publication January 29, 2010.

doi:10.1016/j.clinthera.2010.02.015

0149-2918/\$ - see front matter

© 2010 Excerpta Medica Inc. All rights reserved.

0.001). After administration of clopidogrel 300 mg in Chinese subjects, mean maximal IPA (58%) occurred at 4 hours. The VN-P2Y12 and VASP phosphorylation assays yielded results comparable to those obtained by LTA. Mean exposure to prasugrel's active metabolite was higher in Chinese than in white subjects (geometric least squares mean ratio for  $AUC_{0-t} = 1.47$  (90% CI, 1.24–1.73). Both drugs were well tolerated.

**Conclusions:** In this study, platelet inhibition was significantly higher in Chinese than in white subjects up to 2 hours after a single 30-mg dose of prasugrel. Platelet inhibition was significantly higher in Chinese subjects at all time points after a 30-mg dose of prasugrel than after a 300-mg dose of clopidogrel. Both treatments were generally well tolerated. (*Clin Ther*. 2010;32:365–379) © 2010 Excerpta Medica Inc.

**Key words:** prasugrel, clopidogrel, East Asian population, platelet aggregation.

## INTRODUCTION

Prasugrel, a thienopyridine prodrug, is an oral antiplatelet agent approved in the United States, the European Union, and several other countries for the reduction of atherothrombotic cardiovascular events in patients presenting with acute coronary syndrome and undergoing percutaneous coronary intervention. Prasugrel is metabolized to an active metabolite (Pras-AM) that binds irreversibly to the P2Y12 class of platelet purinergic receptors, thus inhibiting platelet reactivity to adenosine diphosphate (ADP) for the remainder of the life of the platelet.<sup>1</sup>

Prasugrel's pharmacokinetics have been reported to be comparable in healthy subjects and patients with cardiovascular disease. After a 60-mg loading dose of prasugrel, Pras-AM appears quickly in plasma, with concentrations peaking at ~30 minutes and then declining biphasically, with a terminal elimination half-life of ~7.4 hours.<sup>2</sup> The apparent CL of Pras-AM is 149 L/hour, and the apparent  $V_d$  is 66.4 L.<sup>3</sup>

Several studies have reported greater, more rapid, and more consistent platelet inhibition with prasugrel than with clopidogrel in healthy subjects and in patients with stable coronary artery disease.<sup>4–7</sup> The more extensive platelet inhibition produced by prasugrel is associated with a clinical benefit. Specifically, in the 13,608 patients in TRITON-TIMI 38 (Trial to

Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38), a prasugrel regimen consisting of a 60-mg loading dose and maintenance doses of 10 mg/d plus aspirin ( $n = 6813$ ) was associated with a 19% reduction in the composite rate of cardiovascular death, myocardial infarction, and stroke compared with the approved clopidogrel regimen of a 300-mg loading dose and maintenance doses of 75 mg/d plus aspirin ( $n = 6813$ ) (9.9% vs 12.1%, respectively; hazard ratio [HR] = 0.81; 95% CI, 0.73–0.90;  $P < 0.001$ ).<sup>8</sup> However, the benefit of prasugrel relative to clopidogrel was accompanied by a higher risk for major bleeding (2.4% vs 1.8%, respectively; HR = 1.32; 95% CI, 1.03–1.68;  $P = 0.03$ ).

The pharmacokinetics of and pharmacodynamic response to clopidogrel have already been well characterized in white subjects.<sup>4</sup> Although most studies of prasugrel have enrolled mainly white subjects, one prospectively designed study compared prasugrel's pharmacokinetics, pharmacodynamics, and tolerability in healthy Chinese, Japanese, Korean, and white subjects.<sup>9</sup> That study found that even after normalization by body weight, Pras-AM exposure was ~30% higher in each group of Asian subjects compared with white subjects after a 60-mg prasugrel loading dose and maintenance doses of 5 or 10 mg/d (90% CI, 12%–51%). Platelet inhibition was 8.63 percentage points higher in Asian subjects than in white subjects at 24 hours after the loading dose (90% CI, 1.91–15.30) and 9.09 percentage points higher at 4 hours after a maintenance dose (90% CI, 2.36–15.80). The results of this study prompted the present investigation of the pharmacokinetics and pharmacodynamic response to a lower prasugrel loading dose in Chinese subjects.

The primary objective of the present study was to compare the effects of a prasugrel 30-mg loading dose on inhibition of platelet aggregation (IPA) in healthy Chinese and white subjects. Secondary objectives were to compare exposure to Pras-AM in Chinese and white subjects after a prasugrel 30-mg dose and to compare the effects on IPA of a prasugrel 30-mg dose and a clopidogrel 300-mg dose in Chinese subjects. The study also assessed the pharmacokinetics of clopidogrel after a 300-mg dose in Chinese subjects, and compared various methods of assessing platelet aggregation.

## SUBJECTS AND METHODS

### Subjects

Eligible subjects were healthy men and women aged 21 to 60 years. They were required to have values within the following ranges at screening: a body mass index (BMI) of 18.5 to 29.9 kg/m<sup>2</sup>, a baseline maximal platelet aggregation (MPA) response to 20 μM ADP of ≥60%, and normal results on clinical laboratory tests (including a complete blood count and tests of renal function, hepatic function, and coagulation) and urinalysis. Clinical laboratory tests were conducted at the National University Hospital Referral Laboratory, Singapore, which is fully accredited by the College of American Pathologists, and urinalysis was performed at the investigative site using urine test strips. Female subjects of childbearing potential were required to have a negative pregnancy test at study entry and had to agree to use a reliable method of birth control throughout the study. Key exclusion criteria included the presence of disorders that had the potential to alter the absorption, metabolism, or elimination of the study drugs or that could constitute a risk to the subject when taking the study drugs. No prescription or over-the-counter medications were permitted within 14 days before administration of

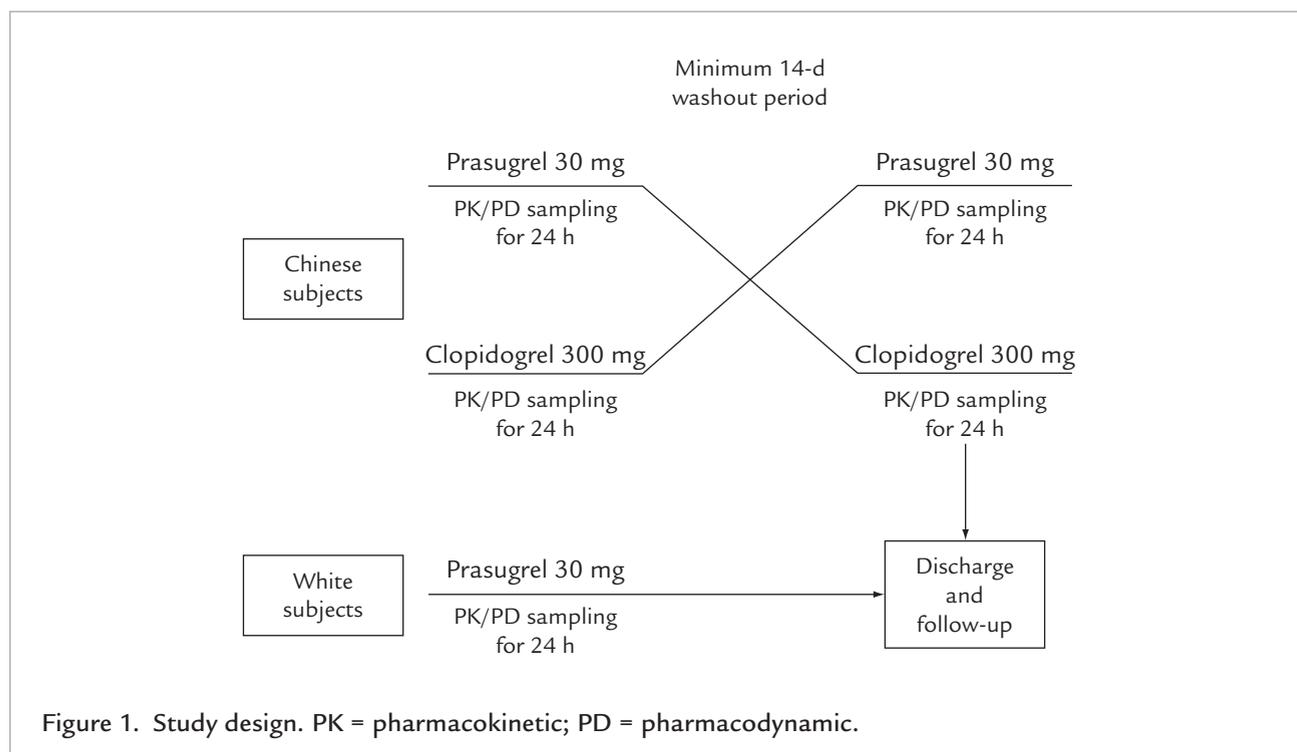
study drug. NSAIDs and aspirin were not to be used within 21 days before administration of study drug.

### Study Design and Procedures

This open-label study of prasugrel and clopidogrel (study code H7T-FW-TACF) in Chinese and white subjects was conducted at the Lilly-NUS Centre for Clinical Pharmacology in Singapore from September 2006 to February 2007. The randomization sequence was prepared by the statistician before the study. Chinese subjects were randomly allocated to receive a single dose of either prasugrel 30 mg or clopidogrel 300 mg; after a 14-day washout period, they received a single dose of the alternative drug (Figure 1). White subjects received only a single dose of prasugrel 30 mg. Prasugrel was administered as three 10-mg tablets of the hydrochloride salt (supplied by Eli Lilly and Company) and clopidogrel\* was administered as four 75-mg tablets (purchased from a commercial source).

Subjects were admitted to the clinical research unit the night before dosing. They observed an overnight

\*Trademark: Plavix® (Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, New Jersey).



fast, and no fluid was allowed from 1 hour before dosing. All doses were administered with 200 mL of water with the subject in an upright position. Subjects remained in the clinical research unit until 24 hours after dosing. They were monitored continuously throughout the study period.

The study protocol was approved by the National Healthcare Group Domain-Specific Review Board of Singapore. Subjects provided written informed consent. The study was conducted in accordance with applicable laws and regulations, with good clinical practices, and with the ethical principles originating in the Declaration of Helsinki.

### Pharmacodynamic Assessments

Blood samples for pharmacodynamic assessments were collected by direct venipuncture before dosing and at 0.5, 1, 2, 4, and 24 hours after dosing. Platelet aggregation was assessed by 3 methods—traditional light transmission aggregometry (LTA), the *VerifyNow* P2Y12 (VN-P2Y12) assay (AccuMetrics, San Diego, California), and the vasodilator-stimulated phosphoprotein (VASP) phosphorylation flow cytometry assay. Use of these methods for the evaluation of the pharmacodynamic effects of clopidogrel and prasugrel has been described previously.<sup>10–12</sup>

### Light Transmission Aggregometry

Venous blood samples of ~13.5 mL (3 tubes of 4.5 mL each) were obtained and processed at room temperature within 2 to 4 hours after sampling. Platelet aggregation in response to 5 and 20  $\mu$ M ADP (Bio/Data Corporation, Singapore) was measured in platelet-rich plasma using a PAP-4 optical aggregometer (Bio/Data Corporation) with temperature maintained at 37°C. Because the pattern of results was similar for 5 and 20  $\mu$ M ADP, this report focuses on the 20- $\mu$ M ADP data. Platelet-rich plasma was adjusted to ~250,000 cells/ $\mu$ L using autologous platelet-poor plasma.

The MPA was recorded, and the IPA to 20  $\mu$ M ADP (the primary pharmacodynamic parameter) was calculated using the following equation:

$$IPA_t = ([MPA_0 - MPA_t]/MPA_0) \times 100\%$$

where  $IPA_t$  represents the IPA at time  $t$ ,  $MPA_t$  represents the MPA at time  $t$ , and  $MPA_0$  represents the

MPA value at baseline. A lower MPA or higher IPA signified greater antiplatelet effect.

### VN-P2Y12 Assay

Blood samples of ~2 mL each were collected into citrate tubes and processed on the VN-P2Y12 system within 2 to 4 hours after sampling, in accordance with the manufacturer's recommendations. Data were obtained directly from the VN-P2Y12 device and were recorded as P2Y12 reaction units (PRU) and device-reported percent inhibition of PRU. A higher percent inhibition signified greater antiplatelet effect.

### VASP Phosphorylation Assay

Blood samples of ~2 mL each were collected into citrate tubes and tested within 48 hours of sampling. VASP phosphorylation was assessed by whole-blood flow cytometry using a Platelet VASP-FCM kit (BioCytex, Marseille, France). The VASP results were reported as the platelet reactivity index (PRI), which was calculated from the corrected mean fluorescence intensity (cMFI) after stimulation of platelets with prostaglandin  $E_1$  ( $PGE_1$ ) or  $PGE_1$  + ADP as follows:

$$PRI = (1 - [cMFI_{PGE_1 + ADP}/cMFI_{PGE_1}]) \times 100\%$$

A lower PRI signified greater antiplatelet effect.

### Ex Vivo Addition of Pras-AM

At study entry or before administration of study drug in either period, blood samples were collected for an ex vivo assessment of inhibition of ADP-induced platelet aggregation over a range of concentrations of Pras-AM. This assessment was conducted to investigate whether any differences in pharmacodynamics found in vivo could be attributed to an ethnic difference in platelet function.

Blood samples of ~27 mL were collected into citrate tubes. Aliquots were incubated for 30 minutes at 37°C with 0-, 0.3-, 1-, 3-, and 10- $\mu$ M concentrations of Pras-AM (Daiichi Sankyo Company, Ltd., Tokyo, Japan). These concentrations were chosen to include the range of Pras-AM  $C_{max}$  values reported in clinical studies in white and East Asian subjects: 1.3 to 1.7  $\mu$ M after a 60-mg loading dose and 0.16 to 0.20  $\mu$ M during 10-mg maintenance dosing.<sup>9,13–17</sup> The platelet aggregation response to 20  $\mu$ M ADP was measured after incubation.

### Pharmacokinetic Assessments

Blood samples of 4 mL each were collected via an indwelling catheter into tubes containing EDTA and 2-bromo-3'-methoxyacetophenone reagent at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, and 24 hours after dosing. The samples were reacted with 25  $\mu$ L of 500 mM 3'-methoxyphenacyl bromide in acetonitrile within 30 seconds of collection to derivatize and thus stabilize Pras-AM or the active metabolite of clopidogrel (Clop-AM). Plasma was separated by centrifugation at 1500g to 2000g for 10 to 15 minutes at 2°C to 8°C. The separated plasma samples were stored at approximately -70°C in labeled polypropylene tubes until analyzed by a validated HPLC-MS/MS method.<sup>18,19</sup> The lower limit of quantitation (LLOQ) was 0.5 ng/mL for both active metabolites. For Pras-AM, the accuracy (relative error) and precision (%CV) of the assay were within 20% at the LLOQ and within 15% at higher concentrations.<sup>18</sup> For Clop-AM, the intra-assay and inter-assay accuracy and precision were within 12% and 6%, respectively, over the range from 0.5 to 250 ng/mL.<sup>19</sup>

The primary pharmacokinetic parameter was the  $AUC_{0-t}$ . After a prasugrel 60-mg loading dose, the  $AUC_{0-t}$  of Pras-AM encompasses >95% of the total AUC and therefore closely approximates the total AUC.<sup>3,9</sup> Previous experience has consistently suggested that the terminal phase of Pras-AM cannot be estimated well at doses <60 mg; therefore, the  $AUC_{0-t}$  of Pras-AM was assumed to approximate total exposure after the prasugrel 30-mg loading dose.  $C_{max}$  and  $T_{max}$  were determined from the data.

### Tolerability

Data on adverse events (both observed and spontaneously reported) and their resolution were recorded throughout the study. An *adverse event* was defined as any untoward medical event associated with the use of a drug, whether considered related to that drug or not.

Safety assessments performed at the screening visit included physical examination, measurement of vital signs, funduscopic examination and examination for petechiae, and a 12-lead ECG. Vital signs were measured and physical examinations were performed before dosing, before discharge from the study site, and at the follow-up visit, which took place within 14 days after the last administration of study drug. Funduscopic examination and examination for

petechiae were also conducted at the follow-up visit. Additional medical assessments could be performed at the discretion of the study investigator.

### Statistical Analysis

A sample size of 14 subjects in each ethnic group was calculated to provide  $\geq 80\%$  probability of detecting a mean difference in IPA of 15 percentage points between groups at any time point on a 2-sided test at a 0.10 level of significance. For IPA, a total SD of 15 percentage points was estimated for both ethnic groups.

A mixed-effects ANCOVA model was used to compare mean IPA values for prasugrel between Chinese and white subjects at each time point, with baseline MPA as a continuous covariate. Ethnic group, time, and ethnic group by time were included in the model as fixed effects, and subject and subject by time were used as random effects. The least squares mean (LSM) and 2-sided 90% CI for the mean IPA in each ethnic group and the mean difference in IPA between ethnic groups were estimated at each time point.

Similar methods were used to compare mean IPA values between prasugrel and clopidogrel at each time point in Chinese subjects. A mixed-effects ANCOVA model was used, with baseline MPA values as a continuous covariate and treatment, time, and treatment by time as fixed effects. Subject, subject by treatment, and subject by time were fitted as random effects. The LS mean and 2-sided 90% CI for the mean IPA in each treatment group and the mean difference in IPA between treatment groups were estimated at each time point.

For the experiment involving the ex vivo addition of Pras-AM, descriptive statistics were generated to describe the IPA at each concentration of Pras-AM in each ethnic group.

For the pharmacokinetic analyses, parameter estimates were log transformed. A linear mixed-effects model, with ethnic group as a fixed effect and subject as a random effect, was used to compare the pharmacokinetic parameters of prasugrel between Chinese and white subjects. In addition, a linear mixed-effect model with ethnic group as a fixed effect, subject as a random effect, and weight as a covariate was used to compare pharmacokinetic parameters between the 2 ethnic groups. Geometric LSMs, geometric LSM ratios, and the corresponding 2-sided 90% CIs for the ratios were estimated for both models. The  $T_{max}$  was

compared between ethnic groups using the nonparametric Wilcoxon rank sum test. Pharmacokinetic parameter estimates of Clop-AM in Chinese subjects were summarized using descriptive statistics.

SAS version 8 (SAS Institute Inc., Cary, North Carolina) was used to analyze demographic characteristics, laboratory parameters, pharmacodynamic measures, and adverse events. Pharmacokinetic parameter estimates for Pras-AM and Clop-AM were calculated by noncompartmental methods using WinNonlin Enterprise version 5.0.1 (Pharsight Corporation, Mountain View, California).

## RESULTS

### Subjects

The study enrolled 18 Chinese subjects (15 men, 3 women) and 14 white subjects (12 men, 2 women). The mean (SD) age of Chinese subjects was 31 (10) years, their mean body weight was 65.2 (8.9) kg, and their BMI was 23.1 (2.2) kg/m<sup>2</sup>. The corresponding values for white subjects were 30 (10) years, 77.2 (12.4) kg, and 23.4 (2.9) kg/m<sup>2</sup>.

Thirty of the 32 subjects completed the study. One Chinese man was withdrawn by the investigator due to a low platelet-rich plasma count measured in a sample collected before dosing; this subject had already received prasugrel 30 mg at the time of withdrawal. Another Chinese man with a history of hemorrhoids was withdrawn due to mild, intermittent rectal bleeding after bowel movements that began ~2 days after receipt of clopidogrel 300 mg and resolved 18 days after treatment. The investigator considered this event possibly related to study drug.

### Pharmacodynamics

#### Light Transmission Aggregometry

As measured by LTA, the mean baseline MPA to 20  $\mu$ M ADP was significantly higher in white subjects than in Chinese subjects (80% vs 71%, respectively;  $P = 0.047$ ). However, this was accounted for by the inclusion of baseline MPA in the statistical model.

After a single 30-mg dose of prasugrel, the mean IPA to 20  $\mu$ M ADP was numerically higher in Chinese than in white subjects from 0.5 to 24 hours after dosing; however, the mean differences were statistically significant only at 0.5, 1, and 2 hours after dosing ( $P < 0.05$ ) (Figure 2). The mean IPA was near maximal by 1 hour after dosing in Chinese subjects (87%) and

by 2 hours after dosing in white subjects (78%). In Chinese subjects, the mean IPA to 20  $\mu$ M ADP was significantly higher after a prasugrel 30-mg dose than after a clopidogrel 300-mg dose at all time points ( $P < 0.001$ ). The mean IPA after a clopidogrel 300-mg dose continued to increase up to 4 hours after dosing before reaching a peak of 58%.

#### VN-P2Y12 Assay

On the VN-P2Y12 assay, the mean percent inhibition after a 30-mg dose of prasugrel was significantly higher in Chinese subjects than in white subjects at 0.5 and 1 hour after dosing (0.5 hour: 53% vs 28%, respectively; 1 hour: 95% vs 65%; both,  $P < 0.01$ ) (Figure 3). The difference between groups was not significant beyond 1 hour after dosing. The mean percent inhibition was significantly higher in Chinese subjects after a single dose of prasugrel 30 mg compared with a single dose of clopidogrel 300 mg at all time points ( $P < 0.001$ ).

#### VASP Phosphorylation Assay

On the VASP phosphorylation assay, the mean baseline (predose) PRI was comparable in Chinese and white subjects (84% and 85%, respectively). After a 30-mg dose of prasugrel, the mean PRI was significantly lower in Chinese than in white subjects at 0.5 and 1 hour after dosing (0.5 hour: 41% vs 63%; 1 hour: 12% vs 39%; both,  $P < 0.01$ ), but did not differ significantly between groups after 1 hour. The mean PRI was significantly lower at all time points in Chinese subjects after a single 30-mg dose of prasugrel compared with a single 300-mg dose of clopidogrel ( $P < 0.001$ ) (Figure 4).

#### Comparison of Analytic Methods

In general, the results for platelet aggregation obtained using the VN-P2Y12 and VASP phosphorylation assays were comparable to those obtained by LTA (Figure 5). The dynamic range appeared to be lower for the VN-P2Y12 assay than for LTA, in that IPA levels >70%, as measured by LTA, were generally at or very close to the maximum limit of the VN-P2Y12 assay.

#### Ex Vivo Addition of Pras-AM

In the experiment involving ex vivo addition of Pras-AM to plasma from Chinese and white subjects, a relationship was observed between the MPA in re-

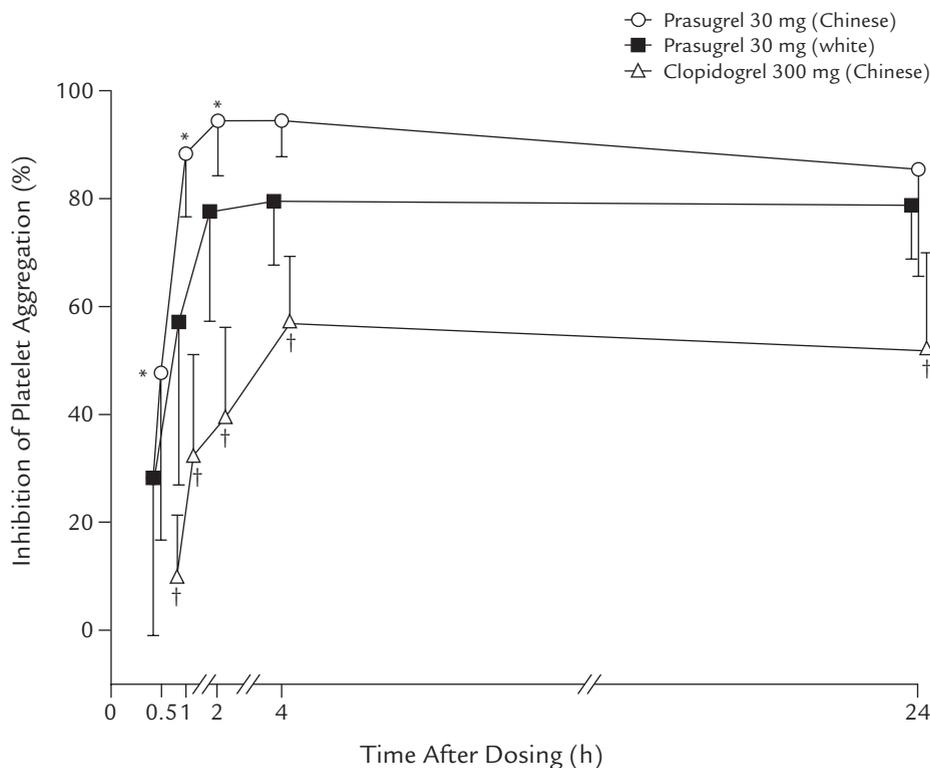


Figure 2. Mean (SD) inhibition of platelet aggregation after a single dose of prasugrel 30 mg in Chinese and white subjects and after a single dose of clopidogrel 300 mg in Chinese subjects, as measured by light transmission aggregometry. Data have been staggered around the time points to improve legibility. \* $P < 0.05$ , Chinese prasugrel subjects versus white prasugrel subjects; † $P < 0.001$ , Chinese prasugrel subjects versus Chinese clopidogrel subjects.

response to 20  $\mu\text{M}$  ADP and the Pras-AM concentration (Figure 6). The largest MPA responses in Chinese and white subjects (6% and 11%, respectively) were measured with 10  $\mu\text{M}$  of Pras-AM, the highest concentration studied. This corresponds to a concentration of 3500 ng/mL, far higher than the peripheral plasma  $C_{\text{max}}$  of the active metabolite (400–500 ng/mL) typically reported after a single 60-mg dose of prasugrel.<sup>9,13–17</sup>

### Pharmacokinetics

The  $C_{\text{max}}$  of Pras-AM occurred at a median time of 30 minutes after dosing in both ethnic groups (Figure 7A), after which concentrations declined biphasically. Plasma concentrations of Clop-AM in Chinese subjects were substantially lower than those of Pras-AM in Chinese and white subjects, and were unmeasurable in most subjects by 4 hours after dosing

(Figure 7B). Because the molecular weights of Pras-AM and Clop-AM differ by <2%, it was deemed appropriate to compare exposures to these 2 moieties without molar conversion.

Pharmacokinetic parameter estimates and weight-normalized estimates for Pras-AM and Clop-AM are summarized in Table I. The geometric mean estimated  $C_{\text{max}}$  for Pras-AM was 67% higher in Chinese than in white subjects (geometric LSM ratio = 1.67; 90% CI, 1.32–2.11); after adjustment for differences in body weight, the estimated  $C_{\text{max}}$  was 39% higher in Chinese than in white subjects (geometric LSM ratio = 1.39; 90% CI, 1.08–1.80). The geometric mean estimated  $\text{AUC}_{0-t}$  for Pras-AM was 47% higher in Chinese than in white subjects (geometric LSM ratio = 1.47; 90% CI, 1.24–1.73); after adjustment for body weight, the estimated  $\text{AUC}_{0-t}$  was 16% higher in Chinese than in white subjects (geometric LSM ratio =

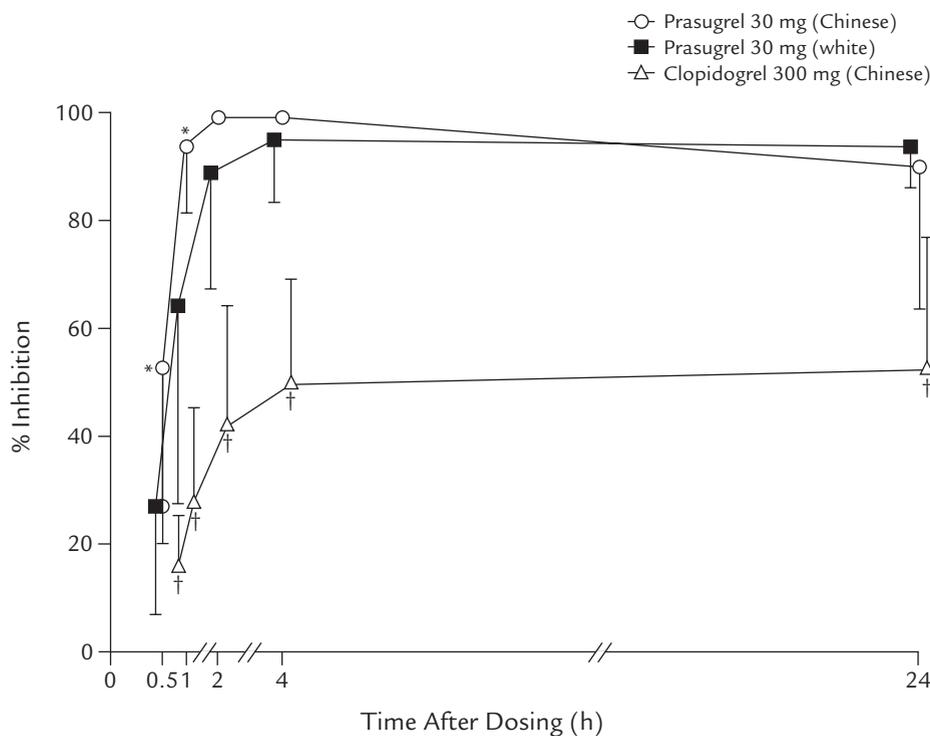


Figure 3. Mean (SD) percent platelet inhibition after a single dose of prasugrel 30 mg in Chinese and white subjects and after a single dose of clopidogrel 300 mg in Chinese subjects, as measured using the VerifyNow P2Y12 assay (Accumetrics, San Diego, California). Data have been staggered around the time points to improve legibility. \* $P < 0.01$ , Chinese prasugrel subjects versus white prasugrel subjects; † $P < 0.001$ , Chinese prasugrel subjects versus Chinese clopidogrel subjects.

1.16; 90% CI, 1.02–1.33). No difference in median  $T_{max}$  was noted. Individual  $C_{max}$  and  $AUC_{0-t}$  estimates overlapped between Chinese and white subjects (Figures 8 and 9); however, 63% and 50% of the respective individual estimates in Chinese subjects were higher than the maximum values in white subjects.

In Chinese subjects who received both prasugrel and clopidogrel, the  $C_{max}$  and  $AUC_{0-t}$  estimates for Clop-AM were approximately one tenth those for Pras-AM ( $C_{max}$ : 30.7 vs 320 ng/mL, respectively;  $AUC_{0-t}$ : 33.6 vs 361 ng · h/mL) (Table I). The  $C_{max}$  of Clop-AM was reached ~1 hour after dosing.

### Tolerability

Apart from events related to venipuncture, prasugrel was well tolerated in both ethnic groups. Most adverse events were mild in severity, and no serious or

severe adverse events were reported during the study. Postprocedural bleeding, specifically bruising at the site of venipuncture, was the most commonly reported adverse event. A higher frequency of bleeding-related adverse events was reported by Chinese subjects after administration of prasugrel (12 of 17) than after administration of clopidogrel (6 of 17), and the incidence of bleeding events was higher in Chinese than in white subjects (5 of 14) after a loading dose of prasugrel 30 mg. The frequencies of bleeding-related adverse events are summarized in Table II.

### DISCUSSION

The relationship between IPA and exposure to the active metabolites of prasugrel and clopidogrel observed in the present study is consistent with that reported in previous studies.<sup>4,13,14</sup> Actual and weight-normalized estimates of Pras-AM exposure were higher in Chi-

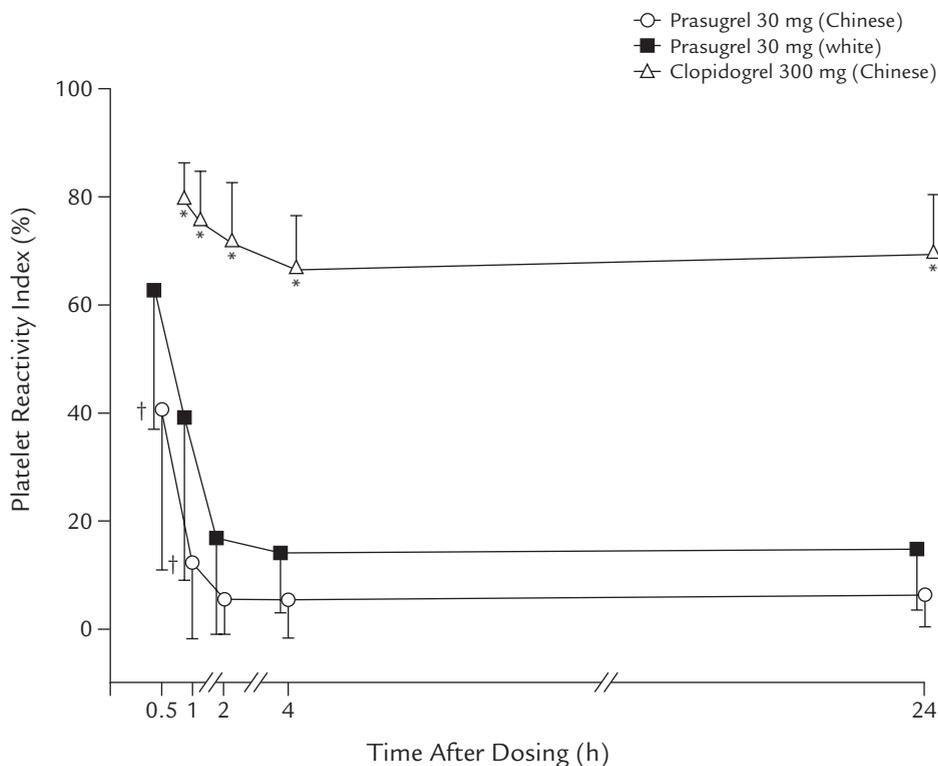


Figure 4. Mean (SD) platelet reactivity index after a single dose of prasugrel 30 mg in Chinese and white subjects and after a single dose of clopidogrel 300 mg in Chinese subjects, as measured using vasodilator-stimulated phosphoprotein phosphorylation flow cytometry. Data have been staggered around the time points to improve legibility. \* $P < 0.001$ , Chinese prasugrel subjects versus Chinese clopidogrel subjects; † $P < 0.01$ , Chinese prasugrel subjects versus white prasugrel subjects.

nese subjects than in white subjects after a 30-mg dose of prasugrel, resulting in greater platelet inhibition in Chinese subjects. The ex vivo assessment of the platelet response to Pras-AM found no meaningful difference in platelet reactivity to ADP between ethnic groups or to the range of Pras-AM concentrations studied.

Prasugrel's greater efficacy compared with clopidogrel in the TRITON-TIMI 38 trial has been attributed to more rapid, higher, and more consistent platelet inhibition.<sup>8</sup> However, greater platelet inhibition was also associated with an increased bleeding risk. The ideal dosing regimen would employ loading and maintenance doses high enough to produce the clinical benefits of increased platelet inhibition without producing an unacceptable bleeding risk.

The 60-mg loading dose was selected during the development of prasugrel to meet a prospectively de-

finied goal of achieving maximal IPA as rapidly as possible without subjecting patients to an excessive bleeding risk. Clinical studies in a predominantly white population found that a single 60-mg loading dose of prasugrel met this objective, whereas lower loading doses did not. Specifically, the maximal IPA after a 60-mg dose of prasugrel in a predominantly white population (healthy subjects and patients with stable atherosclerosis) was 83% with 5  $\mu\text{M}$  ADP and 79% with 20  $\mu\text{M}$  ADP; in both cases, 89% of all subjects attained  $\geq 50\%$  IPA by 1 hour after dosing.<sup>2</sup> In the Phase III TRITON-TIMI 38 trial, bleeding risk within 3 days after the loading dose did not differ significantly between quartiles of active metabolite exposure, suggesting that higher exposures did not discernibly increase the risk of bleeding compared with lower exposures (data not reported).<sup>20</sup> In an earlier dose-ranging study of prasugrel in a population

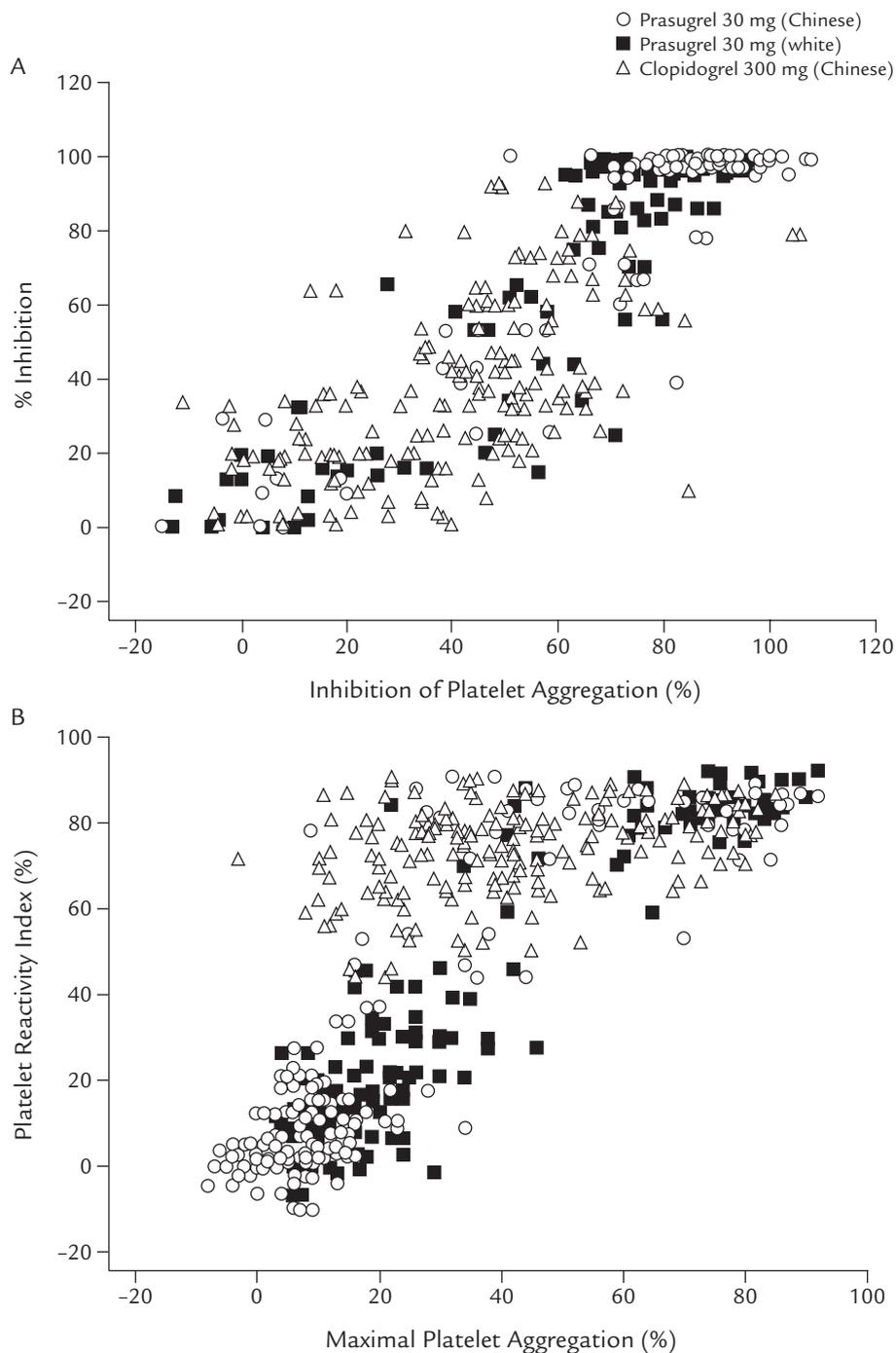


Figure 5. (A) Scatter plot of individual inhibition of platelet aggregation in response to 20  $\mu$ M adenosine diphosphate (ADP) as measured by light transmission aggregometry (LTA) compared with individual percent platelet inhibition as measured using the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) after single loading doses of prasugrel 30 mg and clopidogrel 300 mg; (B) scatter plot of the maximal platelet aggregation in response to 20  $\mu$ M ADP as measured by LTA compared with the platelet reactivity index as measured using vasodilator-stimulated phosphoprotein phosphorylation flow cytometry under the same conditions as in part A.

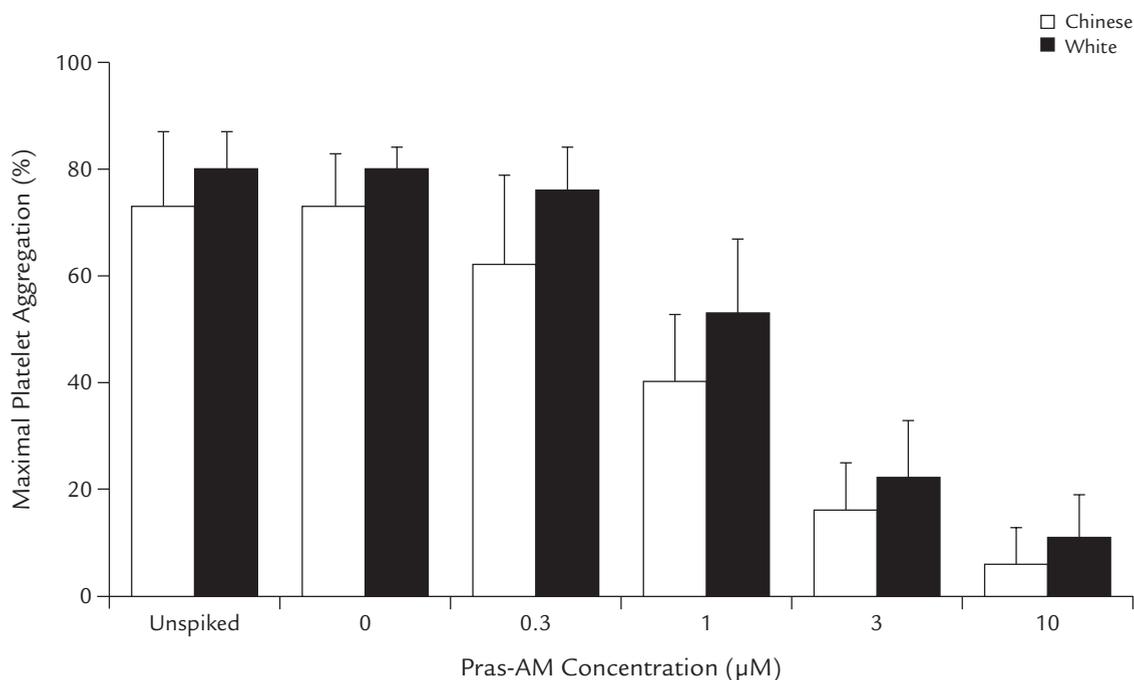


Figure 6. Mean (SD) maximal platelet aggregation in response to 20  $\mu\text{M}$  adenosine diphosphate, as measured by light transmission aggregometry, in Chinese and white subjects after ex vivo addition of increasing concentrations of the active metabolite of prasugrel (Pras-AM).

with stable atherosclerosis, a prasugrel 40-mg loading dose produced IPA that was  $\sim 10$  percentage points lower than that produced by a prasugrel 60-mg loading dose, accompanied by less-rapid platelet inhibition ( $P$  not reported).<sup>6</sup> Considered together, these tolerability, pharmacokinetic, and pharmacodynamic data suggest that 60 mg is an appropriate loading dose for a predominantly white population.

Given the findings of higher overall exposure to Pras-AM and greater platelet inhibition relative to white subjects among Chinese subjects in the present study and Asian subjects in another study,<sup>9</sup> the question arises whether Asian subjects might receive the same benefits from a lower loading dose as are seen in white subjects with a 60-mg loading dose. The data from this study are suggestive, although they cannot provide a definitive answer. The 30-mg loading dose rapidly produced high IPA in Chinese subjects; however, without evaluation of a 60-mg loading dose, it is not possible to know whether the higher loading dose would have produced more extensive or more rapid IPA. As doses increase, IPA eventually reaches a maxi-

mal effect; in the present study, the mean IPA after a 30-mg loading dose in Chinese subjects appeared to be at or near that effect by 1 hour. Nonetheless, it is possible that the rate and extent of response in some individuals may lag behind those in other patients, and a 60-mg loading dose might benefit these slower responders by producing higher IPA more quickly than a 30-mg loading dose. Given the lack of a discernible relationship between active-metabolite exposure and bleeding risk within 3 days after a loading dose in TRITON-TIMI 38,<sup>8</sup> the risk associated with the 60-mg loading dose in Chinese subjects would appear to be negligible, particularly as the loading dose is given in an inpatient setting where patients are closely monitored.

The efficacy of a 30-mg loading dose has not been tested in a predominantly East Asian population. However, a study is planned to assess prasugrel loading doses of 30 and 60 mg in East Asian subjects.<sup>21</sup>

The present study had some limitations. Other possible doses of prasugrel were not studied, including

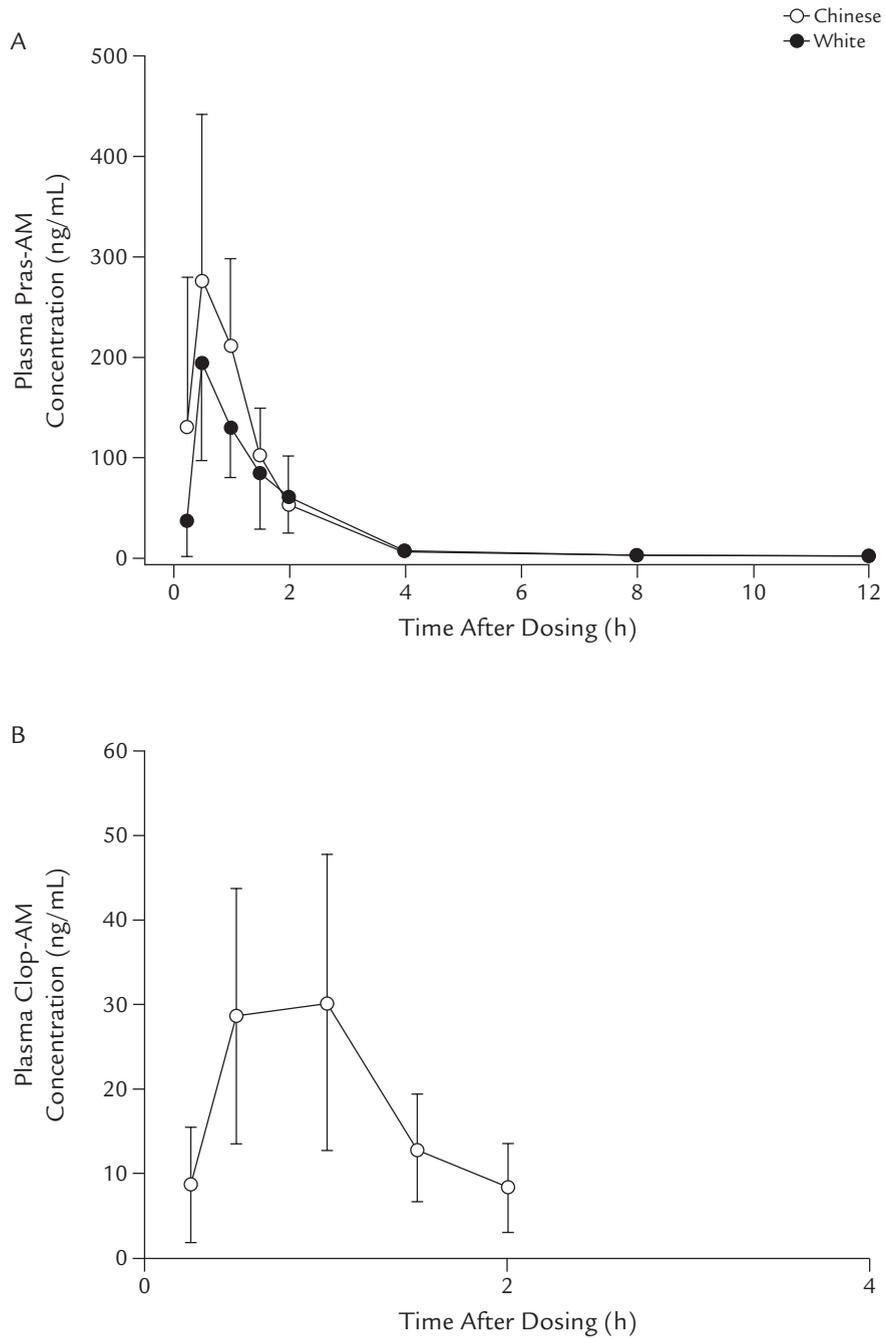


Figure 7. Mean (SD) plasma concentrations of (A) the active metabolite of prasugrel (Pras-AM) after single doses of prasugrel 30 mg and (B) the active metabolite of clopidogrel (Clop-AM) after single doses of clopidogrel 300 mg in Chinese subjects. (Concentrations of Clop-AM were immeasurable in most subjects by 4 hours after dosing.)

Table I. Estimated pharmacokinetic parameters for the active metabolites of prasugrel (Pras-AM) and clopidogrel (Clop-AM) after single doses of 30 and 300 mg, respectively, in Chinese and white subjects. Values are geometric mean (%CV), unless otherwise specified.

Parameter Estimate	Pras-AM			Clop-AM, Chinese Subjects (n = 17)
	Chinese Subjects (n = 16)	White Subjects (n = 14)	Geometric Least Squares Mean Ratio, Chinese/White (90% CI)	
<b>Actual</b>				
AUC <sub>0-t</sub> , ng · h/mL	361 (26)	246 (29)	1.47 (1.24-1.73)	33.6 (61)
C <sub>max</sub> , ng/mL	320 (39)	192 (40)	1.67 (1.32-2.11)	30.7 (56)
T <sub>max</sub> , median (range), h	0.50 (0.25-1.10)	0.50 (0.50-2.00)	-	1.00 (0.50-2.00)
<b>Weight normalized*</b>				
AUC <sub>0-t</sub> , ng · h/mL	324 (19)	279 (19)	1.16 (1.02-1.33)	NA
C <sub>max</sub> , ng/mL	294 (39)	211 (35)	1.39 (1.08-1.80)	NA

NA = not applicable.

\*Weight-normalized estimates were calculated using a linear mixed-effect model with weight as a covariate.

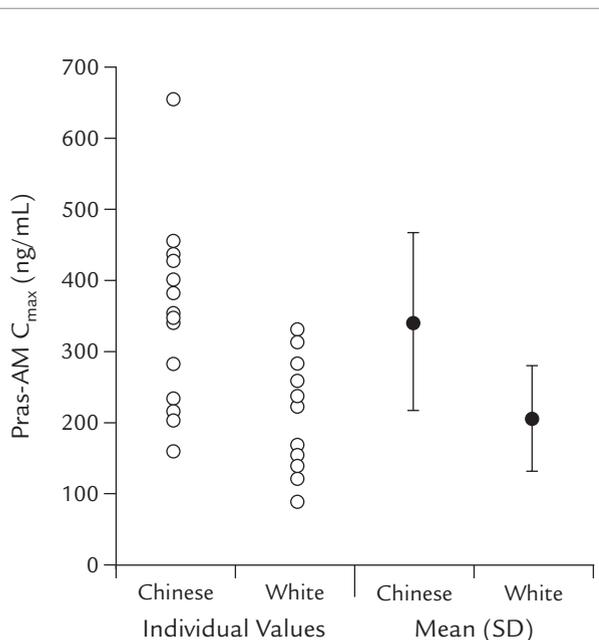


Figure 8. Individual and mean (SD) estimated C<sub>max</sub> for the active metabolite of prasugrel (Pras-AM), by ethnic group.

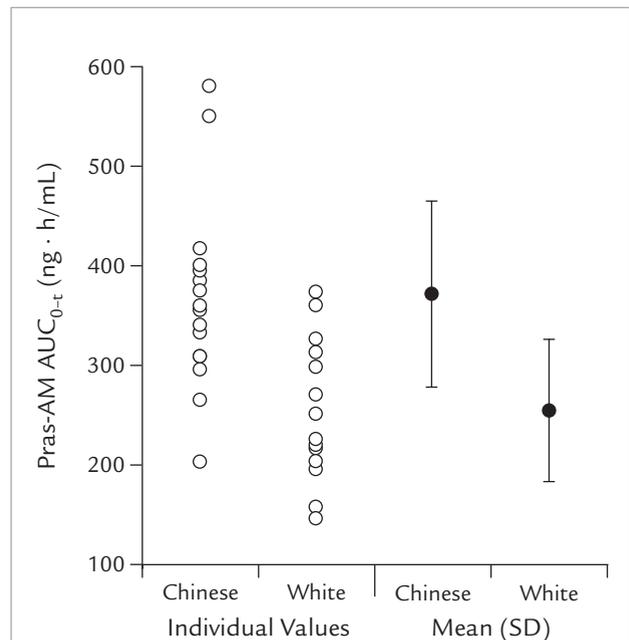


Figure 9. Individual and mean (SD) estimated AUC<sub>0-t</sub> for the active metabolite of prasugrel (Pras-AM), by ethnic group.

Table II. Frequency of bleeding-related adverse events. The first value in each group is the number of subjects with the adverse event; the second value is the number of adverse events.

MedDRA Preferred Term	Prasugrel 30 mg		Clopidogrel 300 mg, Chinese Subjects (n = 17)
	Chinese Subjects (n = 17)	White Subjects (n = 14)	
Total adverse events	12 (19)	5 (6)	6 (8)
Specific adverse events			
Postprocedural bleeding (bruising at venipuncture site)	11 (17)	4 (5)	4 (5)
Contusion	1 (1)	1 (1)	0
Epistaxis	1 (1)	0	1 (1)
Hemoptysis	0	0	1 (1)
Rectal bleeding	0	0	1 (1)

MedDRA = Medical Dictionary for Regulatory Activities.

the approved 60-mg loading dose. The 60-mg dose was assessed in healthy Asian subjects in an earlier study.<sup>9</sup> White subjects in this study did not receive a 300-mg dose of clopidogrel, preventing direct assessment of what their response to clopidogrel would have been. The 300-mg dose of clopidogrel has been extensively studied in previous trials.<sup>3,4,13,14</sup>

## CONCLUSIONS

In this open-label study, the prasugrel 30-mg dose produced greater platelet inhibition and higher concentrations of Pras-AM in Chinese subjects than in white subjects. In Chinese subjects, prasugrel 30 mg produced greater platelet inhibition and higher Pras-AM concentrations than did clopidogrel 300 mg. The pharmacodynamic results were consistent across LTA, the VN-P2Y12 assay, and the VASP phosphorylation assay. Both prasugrel and clopidogrel were generally well tolerated in both ethnic groups.

## ACKNOWLEDGMENTS

Dr. Small, Mr. Payne, Dr. Kothare, Ms. Yuen, Dr. Natanegara, Dr. Loh, Dr. Jakubowski, Dr. Lachno, Ms. Li, Dr. Winters, Dr. Ni, Ms. Tomlin, and Dr. Kelly are employees of and stockholders in Eli Lilly and Company. Dr. Farid was an employee of Eli Lilly at the time of the study and is a stockholder in the company. Dr. Salazar is an employee of Daiichi Sankyo, Inc. The authors have indicated that they have no

other conflicts of interest with regard to the content of this article.

The authors thank Julie Sherman, AAS, and Vivian Thieu, PhD, of Eli Lilly for assistance with the figures.

## REFERENCES

- Gachet C. Regulation of platelet functions by P2 receptors. *Annu Rev Pharmacol Toxicol.* 2006;46:277-300.
- electronic Medicines Compendium. Summary of product characteristics. Efient 5mg & 10mg film-coated tablets (Eli Lilly and Company Limited/Daiichi Sankyo UK Limited). [http://emc.medicines.org.uk/medicine/21504/SPC/Efient+5mg+%26+10mg+film-coated+tablets+\(Eli+Lilly+and+Company+Ltd+Daiichi+Sankyo+UK+Limited\)/#ixzz0MZgmdJ5u](http://emc.medicines.org.uk/medicine/21504/SPC/Efient+5mg+%26+10mg+film-coated+tablets+(Eli+Lilly+and+Company+Ltd+Daiichi+Sankyo+UK+Limited)/#ixzz0MZgmdJ5u). Accessed July 28, 2009.
- Ernest CS II, Small DS, Rohatagi S, et al. Population pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel in aspirin-treated patients with stable coronary artery disease. *J Pharmacokinet Pharmacodyn.* 2008;35:593-618.
- 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;25:357-374.
- Brandt JT, Payne CD, Wiviott SD, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: Magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J.* 2007;153:66.e9-e16.

6. Jernberg T, Payne CD, Winters KJ, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. *Eur Heart J*. 2006;27:1166–1173.
7. Wiviott SD, Trenk D, Frelinger AL, et al, for the PRINCIPLE-TIMI 44 Investigators. 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;116:2923–2932.
8. Wiviott SD, Braunwald E, McCabe CH, et al, for the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
9. Small DS, Kothare P, Yuen E, et al. The pharmacokinetics and pharmacodynamics of prasugrel in healthy Chinese, Japanese, and Korean subjects compared with healthy Caucasian subjects. *Eur J Clin Pharmacol*. 2010;66:127–135.
10. Jakubowski JA, Payne CD, Li YG, et al. A comparison of the antiplatelet effects of prasugrel and high-dose clopidogrel as assessed by VASP-phosphorylation and light transmission aggregometry. *Thromb Haemost*. 2008;99:215–222.
11. Jakubowski JA, Payne CD, Li YG, et al. The use of the VerifyNow P2Y12 point-of-care device to monitor platelet function across a range of P2Y12 inhibition levels following prasugrel and clopidogrel administration. *Thromb Haemost*. 2008;99:409–415.
12. Jakubowski JA, Payne CD, Weerakody GJ, et al. Dose-dependent inhibition of human platelet aggregation by prasugrel and its interaction with aspirin in healthy subjects. *J Cardiovasc Pharmacol*. 2007;49:167–173.
13. Farid NA, Small DS, Payne CD, et al. Effect of atorvastatin on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel in healthy subjects. *Pharmacotherapy*. 2008;28:1483–1494.
14. Small DS, Farid NA, Payne CD, et al. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. *J Clin Pharmacol*. 2008;48:475–484.
15. Small DS, Wrishko RE, Ernest CS II, et al. Effect of age on the pharmacokinetics and pharmacodynamics of prasugrel during multiple dosing: An open-label, single-sequence, clinical trial. *Drugs Aging*. 2009;26:781–790.
16. Small D, Wrishko R, Ernest CS II, et al. Comparison of the pharmacokinetics and pharmacodynamics of prasugrel in subjects with end-stage renal disease and healthy subjects. Presented at: Ninth World Conference on Clinical Pharmacology and Therapeutics; July 27–August 1, 2008; Quebec, Canada.
17. Wallentin L, Varenhorst C, James S, et al. Prasugrel achieves greater and faster P2Y12 receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. *Eur Heart J*. 2008;29:21–30.
18. Farid NA, McIntosh M, Garofolo F, et al. Determination of the active and inactive metabolites of prasugrel in human plasma by liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom*. 2007;21:169–179.
19. Takahashi M, Pang H, Kawabata K, et al. Quantitative determination of clopidogrel active metabolite in human plasma by LC-MS/MS. *J Pharm Biomed Anal*. 2008;48:1219–1224.
20. Salazar DE, Ernest CS II, Wrishko RE, et al. Relationship between exposure to the prasugrel active metabolite with TIMI major/minor bleeding in TRITON-TIMI 38. *Circulation*. 2008;118(Suppl 2):S815. Abstract 4001.
21. ClinicalTrials.gov. A comparison of antiplatelet therapies in Asian subjects with acute coronary syndrome. <http://www.clinicaltrials.gov/ct2/show/NCT00830960?term=A+Comparison+of+Antiplatelet+Therapies+in+Asian+Subjects+With+Acute+Coronary+Syndrome&rank=1>. Accessed April 17, 2009.

---

**Address correspondence to:** David S. Small, PhD, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285. E-mail: dsmall@lilly.com