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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

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Trials

Aims This study was designed to compare the degree of inhibition of platelet aggregation (IPA) of prasugrel with that of clopidogrel in stable aspirin-treated patients with coronary artery disease (CAD).
Methods and results Subjects ($n = 101$) were randomly assigned to the following loading dose (LD) (day 1)/maintenance dose (MD) (days 2–28) combinations: prasugrel, 40 mg/5 mg; 40 mg/7.5 mg; 60 mg/10 mg; 60 mg/15 mg; or clopidogrel, 300 mg/75 mg. Turbidometric platelet aggregation was measured at multiple timepoints during the study. At 4 h after dosing, with 20 μM ADP, both prasugrel LDs achieved significantly higher mean IPA levels (60.6% and 68.4 vs. 30.0%, respectively; all $P < 0.0001$) and lower percentage (3 vs. 52%, $P < 0.0001$) of pharmacodynamic non-responders (defined as IPA <20%) than clopidogrel. Prasugrel 10 and 15 mg MDs achieved consistently higher mean IPA than clopidogrel 75 mg at day 28 (all $P < 0.0001$). At pre-MD on day 28, there were no non-responders in the 10 and 15 mg prasugrel group, compared with 45% in the clopidogrel group ($P = 0.0007$).
Conclusion In this population, 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.

Introduction

Thienopyridine derivatives inhibit platelet aggregation by blocking adenosine diphosphate (ADP)-dependent activation of platelets via the platelet $P2Y_{12}$ receptor.[1] Several studies have documented that a combination of aspirin and clopidogrel reduces both percutaneous coronary intervention related and spontaneous ischaemic events in patients with non-ST-elevation acute coronary syndrome (ACS) and patients undergoing PCI for stable coronary artery disease (CAD).[2,3] Therefore, the addition of clopidogrel has been recommended as standard care in these patients.[4]

However, subacute stent thrombosis still occurs in 1–3% of the patients receiving dual antiplatelet therapy.[5] Recent studies have demonstrated a marked interindividual variability of clopidogrel's capacity to inhibit platelet aggregation with a substantial proportion (11–34%) of the patients considered non-responders to clopidogrel treatment.[6–9] Thus, a more potent and consistent inhibitor of ADP-dependent platelet activation may offer the potential for improved clinical outcomes in ACS and PCI.

Prasugrel (CS-747) is a new thienopyridine derivative that is ~10 times more potent than clopidogrel in preclinical studies.[10] Prasugrel has been evaluated both in healthy individuals and in a recently reported study in patients undergoing elective or urgent PCI in which it was shown to result in low and similar rates of bleeding when compared with clopidogrel.[11]

The primary objective of the current 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) and maintenance dose (MD) regimen.

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Methods

Patients

Two centres in two countries (Sweden and USA) enrolled patients between November 2002 and October 2003. This randomized (with stratification by centre), partially blind, parallel-group study was conducted in adult male and female patients with CAD, aged 40–75 years. Ethical review board approval was obtained for the study and written informed consent was obtained from each subject. Subjects were eligible for enrolment in the study if they had CAD, defined as subjects diagnosed with chronic stable angina, prior history of unstable angina or acute myocardial infarction, previous coronary revascularization or CAD in at least one coronary vessel at angiography; peripheral artery occlusive disease (intermittent claudication, ankle-brachial index <0.9, or previous peripheral vascular intervention); or a documented previous history of cerebrovascular disease, including ischaemic stroke or history of a previous transient ischaemic attack.

Subjects were excluded from the study if they met any of the following criteria: ACS or PCI within 30 days, peripheral artery occlusive disease within 30 days of hospitalization or requiring previous amputation, history or presence of bleeding disorder, and history of recent surgery or severe trauma. Subjects were also excluded if there was evidence of active hepatic disease, uncontrolled hypertension, arrhythmia, or severe congestive heart failure.

Subjects were also excluded if they had taken thienopyridines, antiplatelet agents (other than aspirin), inhibitors (ciprofloxacin, clarithromycin, erythromycin, fluconazole, fluvoxamine, itraconazole, ketoconazole), or inducers (barbiturates, carbamazepine, phenytoin, rifampicin) of cytochrome P4503A4. In addition, proton pump inhibitors and H_2 receptor antagonists were discontinued prior to the run-in period.

Study design

All subjects received enteric-coated aspirin (325 mg/day, Ecotrin®, GlaxoSmithKline) during a 7-day, open-label, run-in period and throughout the treatment period. After the run-in period, subjects were randomized to LD of study drug on day 1 and MD for 27 days. For logistical reasons, the patients were followed during dosing for a range of 26–32 days. A final study visit was scheduled between 7 and 14 days after the last MD. Prasugrel, supplied as the 2.5, 5, and 10 mg tablets of the base formulation, was manufactured by Sankyo Product Development Laboratories, Shinagawa-ku, Tokyo, Japan. Clopidogrel (Plavix®, Sanofi-Synthelabo) was supplied as 75 mg tablets available commercially. Subjects were randomly assigned to one of five dosing regimens for the treatment period: (i) prasugrel 40 mg LD/5 mg MD; (ii) prasugrel 40 mg LD/7.5 mg MD; (iii) prasugrel 60 mg LD/10 mg MD; (iv) prasugrel 60 mg LD/15 mg MD); or (v) clopidogrel 300 mg LD/75 mg MD. The present study was double blind with respect to the prasugrel dose administered, while both aspirin and clopidogrel were dosed in an open-label manner.

Pharmacodynamic measurements

Venous blood samples of $\sim$15 mL were collected in one-tenth volume of 3.8% sodium citrate at the following timepoints: (i) visit 1 (day 1)—pre-dose (duplicate samples), 2, 4, and 6 h post-dose; (ii) visit 2 (day 7–14)—two post-dose samples collected on the same day at least 1 h apart; (iii) visit 3 (day 26–32)—samples collected pre-dose, 2, 4, and 6 h post-dose.

All laboratory personnel conducting the platelet aggregation studies were blinded as to patient treatment. Platelet-rich and platelet-poor plasma were prepared by differential centrifugation at room temperature. There was no adjustment of platelet count performed. Platelet aggregation studies were completed within 3 h of sample collection. Turbidometric platelet aggregation was performed using platelet-rich plasma, with 0% light transmittance set with subject platelet-rich plasma and 100% transmittance set with subject platelet-poor plasma. The aggregometers used were as follows: in the US, a Bio-Data Model PAP-4; in Sweden a Chronolog 490. Agonists used at each site were from the same source and prepared identically. Platelet aggregation was allowed to proceed for 8 min following addition of the agonist (5 or 20 μM ADP). The maximal platelet aggregation (MPA_t) response during that time was recorded and used for data analysis. IPA was calculated using the following formula: $\%IPA = [(MPA_0 - MPA_t)/MPA_0] \times 100$, where MPA_0 is the MPA at baseline on aspirin alone and MPA_t = MPA at time t on study drug plus aspirin.

Adverse events

Laboratory tests were performed at screening, prior to the first dose of study drug (day -1, day 1, or the run-in visit) and on visits 2 and 3. All unexpected signs and symptoms were recorded throughout the treatment period. Physical examinations were performed at screening and at the post-study visit.

Statistical analysis of platelet aggregation data

IPA data were analysed using a linear mixed-effect model with baseline MPA as a covariate, with fixed effects for dosing regimen, time since first dosing, study site, and for the interactions between dosing regimen and time since first dosing and respectively, between dosing regimen and site as fixed effects, and finally with subject as a random effect. The model allowed intersubject and intrasubject variabilities to be different across the treatment groups and time since first dosing. This analysis was implemented using the SAS MIXED procedure (SAS Institute Inc., Cary, NC, USA, version 8.2).

The primary comparison of interest was between the four prasugrel MD groups and the clopidogrel MD group on day 28 at pre-dose. A second comparison of interest was between the two prasugrel LD groups and the clopidogrel LD group on day 1 at 4 h post-dose. Dunnett's adjustment for multiple comparisons to one control (clopidogrel) was used in both cases. For other comparisons, an overall test was run first, and this test being significant, individual tests were then run between each pair of treatments. All statistical tests performed were two-sided and carried out at the 0.05 significance level.

Statistical analysis of pharmacodynamic non-responders

In order to further characterize the effect of prasugrel and clopidogrel on IPA, the percentage of pharmacodynamic non-responders in each treatment group was analysed. For this analysis, a thienopyridine non-responder on aspirin was defined by IPA criteria as an individual not achieving $\geq$20% IPA to 20 μM ADP by 4 h after an LD or not maintaining $\geq$20% IPA at subsequent pre-dose timepoints during MD administration. With 5 μM ADP as the agonist, the criterion defining a non-responder was not maintaining $\geq$25% IPA. This definition was derived from a model based on data acquired from previous investigations of clopidogrel in healthy human subjects, including intrasubject and intersubject variability, coefficient of variation of the method to determine IPA, and an assumed incidence of 20–30% non-responders in the population (data on file, Eli Lilly and Company). Non-responders were also characterized using the definition derived by Gurbel *et al.*[6,12] This approach defines non-responders as those having an absolute difference between baseline MPA and post-treatment MPA (ΔMPA) of $<$10% with either 5 or 20 μM ADP as the agonist. Non-responder rates among treatment groups were compared using Fisher's exact test.

Results

Patients

A total of 101 subjects were enrolled in the study (Sweden, $n = 83$; USA, $n = 18$). *Figure 1* illustrates the disposition of patients in the study. There were two discontinuations, one due to administration of an incorrect LD (50 mg prasugrel instead of 60 mg) and one at the request of the investigator because of inadequate venous access. Thus, a total of 99 subjects completed the study. All subjects were Caucasian and had CAD. Baseline characteristics and mean baseline MPA responses were consistent across treatment groups (*Table 1*).

Inhibition of platelet aggregation

Figure 2A and *B* illustrates the mean IPA for the LDs and MDs of prasugrel or clopidogrel at all study timepoints by treatment group. At 4 h after the LD on day 1, both the 40 and 60 mg LDs of prasugrel demonstrated at least a doubling of mean

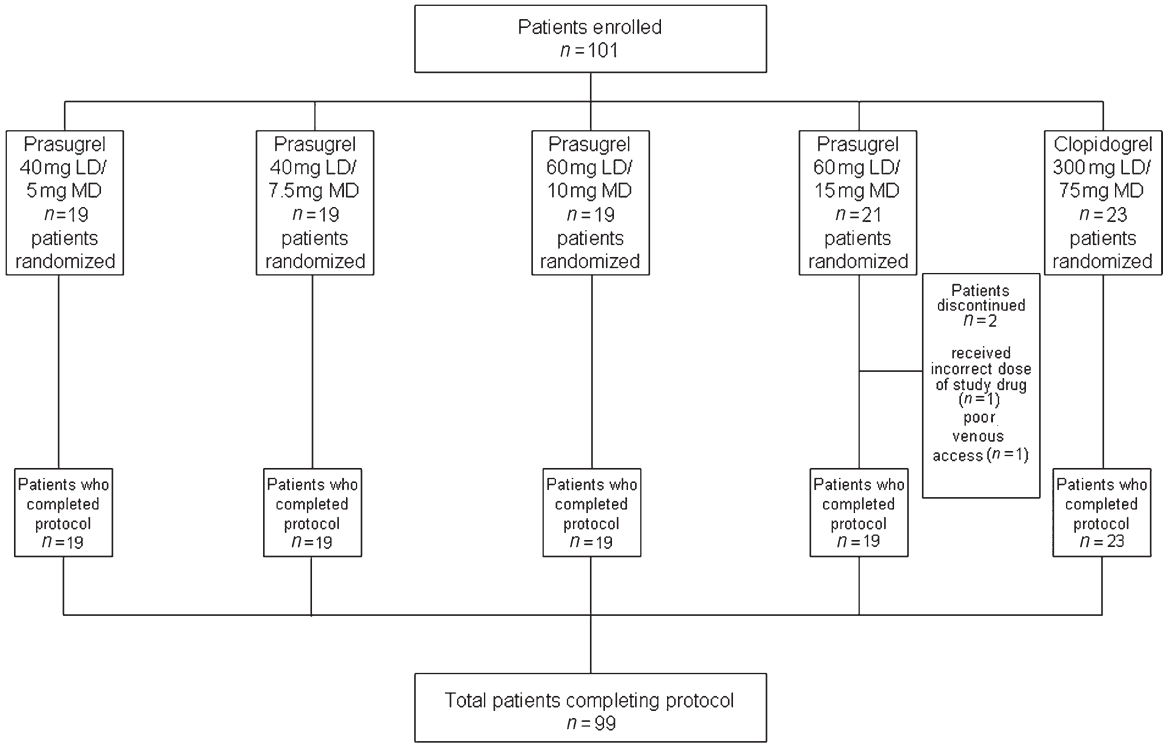

Figure 1 Patient flow through the study.

Table 1 Baseline characteristics of all enrolled subjects

	Prasugrel				Clopidogrel	All subjects ($n = 101$)
LD/MD	40 mg/5 mg ($n = 19$)	40 mg/7.5 mg ($n = 19$)	60 mg/10 mg ($n = 19$)	60 mg/15 mg ($n = 21$)	300 mg/75 mg ($n = 23$)	
Gender						
Male	16	11	18	14	21	80
Female	3	8	1	7	2	21
Age (years, mean ± SD)	65 ± 8.7	65 ± 7.9	65 ± 6.4	63 ± 7.5	61 ± 8.0	64 ± 7.7
Body weight (kg, mean ± SD)	84.7 ± 13.6	84.2 ± 10.0	86.6 ± 14.0	84.7 ± 16.7	86.1 ± 13.1	85.3 ± 13.4
Baseline MPA response with 5 μM ADP (%, mean ± SD)	60.6 ± 16.6	64.3 ± 9.7	65.6 ± 8.7	63.3 ± 10.1	61.4 ± 13.5	63.0 ± 12.0
Baseline MPA response with 20 μM ADP (%, mean ± SD)	72.5 ± 14.1	78.5 ± 9.3	78.2 ± 8.8	74.5 ± 7.5	75.2 ± 7.3	75.7 ± 9.6
Hypertension	10	9	11	10	8	48
Diabetes	2	0	2	4	2	10
Statin	12	12	13	16	16	69
Previous MI	9	10	14	11	12	56
Smokers	3	4	2	3	5	17

LD, loading dose; MD maintenance dose; MPA, maximum platelet aggregation; ACE, angiotensin-converting enzyme; MI, myocardial infarction.

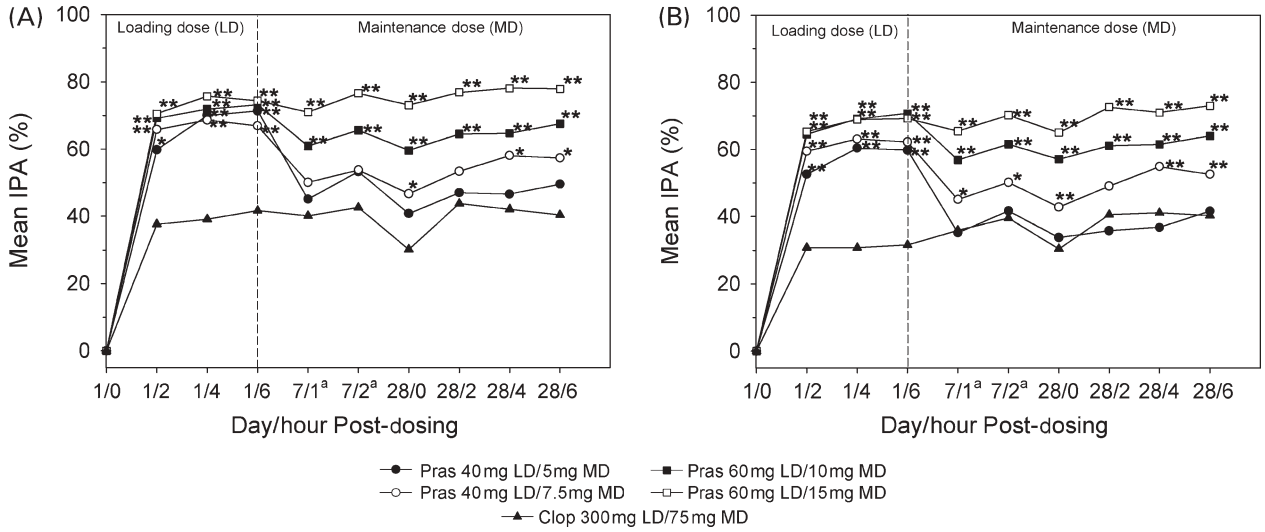

Figure 2 Mean inhibition of aggregation (IPA) induced by ADP over time in each dosing group. Panel A, the agonist is 5 μM ADP. Panel B, the agonist is 20 μM ADP. Values on the left side of the dashed line represent samples obtained pre-loading dose up to 6 h post-LD. Values on the right side of the dashed line represent samples obtained during the MD period. IPA values are adjusted for intersite variability. Statistically significant IPA of prasugrel dose vs. clopidogrel dose at each timepoint is indicated, *$P < 0.05$, **$P < 0.01$. [a]Samples designated as #1 and #2 (see Methods) at the 7 day timepoint. Pras, prasugrel; Clop, clopidogrel.

Table 2 Summary of the inhibition of aggregation (5 and 20 μM ADP agonist) after prasugrel or clopidogrel LD and MD

Hours post-dose	Dose (mg)	ADP 5 μM Mean % IPA (95% CI)	ADP 20 μM Mean % IPA (95% CI)
	LD		
2 h*	Prasugrel/40, $n = 36$	61.7 (55.1, 68.3)**	55.1 (49.1, 61.1)**
	Prasugrel/60, $n = 39$	70.0 (63.7, 76.3)**	64.4 (58.0, 70.8)**
	Clopidogrel/300, $n = 23$	35.9 (28.8, 42.9)	30.2 (22.9, 37.5)
4 h*	Prasugrel/40, $n = 37$	67.8 (62.0, 73.6)**	60.6 (55.1, 66.0)**
	Prasugrel/60, $n = 38$	73.8 (68.3, 79.2)**	68.4 (62.8, 73.9)**
	Clopidogrel/300, $n = 23$	37.0 (24.7, 49.4)	30.0 (22.7, 37.4)
6 h*	Prasugrel/40, $n = 37$	68.6 (63.0, 74.2)**	60.0 (54.4, 65.7)**
	Prasugrel/60, $n = 38$	74.8 (69.3, 80.3)**	69.6 (64.2, 75.0)**
	Clopidogrel/300, $n = 23$	40.7 (30.7, 50.7)	31.1 (23.5, 38.7)
	MD		
Day 7 (sample 2)	Prasugrel/5, $n = 18$	55.9 (42.8, 69.1)	42.9 (33.6, 52.3)
	Prasugrel/7.5, $n = 19$	56.0 (44.6, 67.4)	50.8 (43.5, 58.1)
	Prasugrel/10, $n = 19$	67.5 (57.4, 77.6)††	62.2 (55.6, 68.7)††
	Prasugrel/15, $n = 19$	78.9 (68.3, 89.6)††	71.0 (63.8, 78.2)††
	Clopidogrel/75, $n = 23$	45.0 (32.8, 57.2)	40.4 (33.7, 47.1)
Day 28 (0 h)	Prasugrel/5, $n = 19$	41.2 (30.1, 52.2)	34.5 (27.1, 41.9)
	Prasugrel/7.5, $n = 19$	46.6 (36.0, 57.1)†	43.4 (36.1, 50.7)†
	Prasugrel/10, $n = 19$	59.3 (49.1, 69.5)††	57.5 (50.2, 64.8)††
	Prasugrel/15, $n = 19$	73.1 (62.8, 83.4)††	65.8 (58.7, 72.8)††
	Clopidogrel/75, $n = 22$	30.5 (20.4, 40.6)	31.2 (23.9, 38.4)

LD, loading dose; MD, maintenance dose; IPA, inhibition of platelet aggregation.
*$P < 0.01$ for overall test, for both ADP 5 and 20 μM.
**$P < 0.01$ vs. clopidogrel 300 mg LD.
†$P < 0.05$.
††$P < 0.01$ vs. clopidogrel 75 mg MD.

IPA compared with the 300 mg LD of clopidogrel (60.6% and 68.4 vs. 30.0%, respectively; 20 μM ADP, all $P < 0.0001$, *Figure 2B* and *Table 2*). With either 5 or 20 μM ADP, the mean IPA levels for both LDs of prasugrel at 2, 4, and 6 h post-LD were statistically greater than that achieved with the 300 mg LD of clopidogrel (*Table 2*). Although the overall levels of IPA were higher at one site, the relative treatment effects observed were the same at each site (*Figure 3A* and *B*).

During the MD phase, the level of platelet inhibition maintained was dose-related for the four prasugrel doses (*Figures 2A*, *B*, and *3B*). The prasugrel 10 and 15 mg daily MDs resulted in significantly higher mean levels of IPA than the

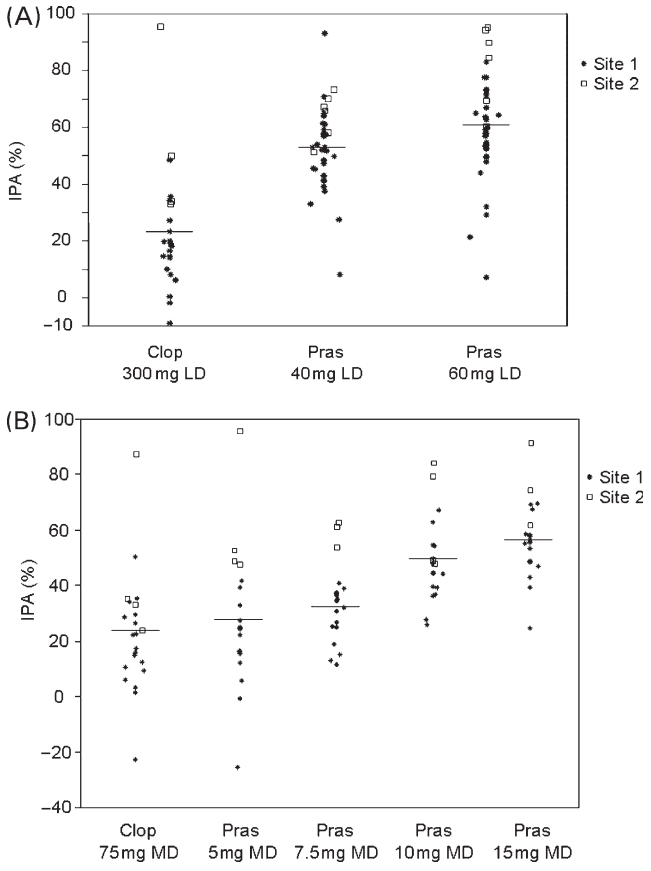

Figure 3 Distribution of IPA with 20 μM ADP as agonist. Panel A illustrates IPA values on day 1 at 4 h post-LD. Panel B illustrates IPA values on day 28 at pre-MD. Stars represent IPA values obtained at site 1 and the open squares represent IPA values obtained at site 2. The horizontal line represents the mean of the entire treatment group. Pras, prasugrel; Clop, clopidogrel.

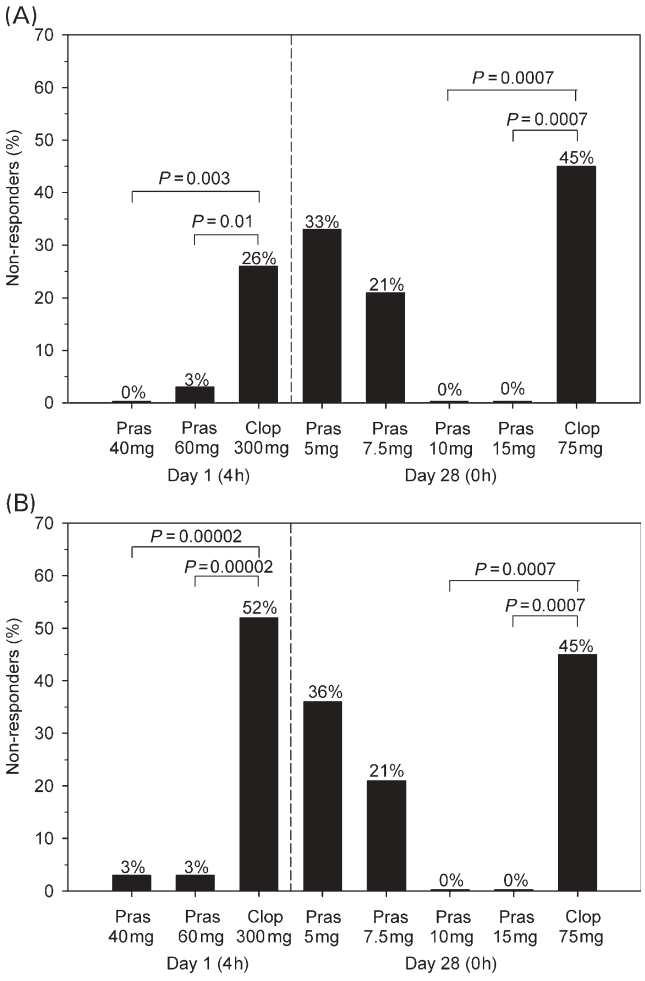

Figure 4 Percentage of non-responders on day 1 at 4 h post-LD, and on day 28 at pre-MD. For this study, a non-responder was defined as a subject with IPA <25% in response to 5 μM ADP (panel A) or <20% in response to 20 μM ADP (panel B). Bars to the left of the dashed line represent the percentage of non-responders 4 h post-LD. Bars to the right of the dashed line represent the percentage of non-responders on day 28 at pre-maintenance dose. Only statistically significant differences (*P*-value < 0.05) between groups are indicated. Pras, prasugrel; Clop, clopidogrel.

clopidogrel 75 mg MD on both day 7–14 and on day 28 using either 5 or 20 μM ADP ($P \leq 0.01$ at all timepoints, *Table 2*). At pre-dose on day 28, the primary MD timepoint of interest, both the 10 and 15 mg MDs of prasugrel maintained greater mean IPA compared with the 75 mg MD of clopidogrel (57.5% and 65.8 vs. 31.2%, respectively; 20 μM ADP, $P \leq 0.01$, *Figure 2B* and *Table 2*).

Pharmacodynamic non-responders

The percentage of non-responders at 4 h post-LD on day 1 and pre-MD on day 28, as defined by the model-based criteria of IPA <25% in response to 5 μM ADP or IPA <20% in response to 20 μM ADP is illustrated in *Figure 4*.

Adverse events

The majority of adverse events were rated as mild in severity and no subject discontinued study drug dosing due to an adverse event. Only one patient (receiving prasugrel 5 mg MD + aspirin) was classified as having a serious adverse event after being hospitalized on day 29 because of unstable angina.

The number of bruising and minor bleeding events were similar in the three lower prasugrel dose groups and the clopidogrel group (*Table 3*). In the highest prasugrel MD group (15 mg), the increase in minor bruising (mainly bruises on the extremities at sites of venipuncture or bleeding times) and minor bleeding events (predominantly self-limiting episodes of epistaxis) observed was not statistically significant. No bleeding events required medical intervention or were associated with a decrease in haematocrit. In an exploratory analysis, there was no apparent correlation between the level of IPA achieved and the occurrence of these minor bleeding events.

Discussion

The present trial is the first to examine the dose-dependent pharmacodynamic effects of prasugrel, a new $P2Y_{12}$ ADP receptor antagonist, in an aspirin-treated population with stable atherosclerotic disease. Both prasugrel LDs (40 and 60 mg) achieved significantly higher IPA compared with clopidogrel 300 mg LD. During daily dosing, prasugrel demonstrated dose-dependent IPA, with prasugrel 10 and 15 mg MDs maintaining significantly higher IPA compared with clopidogrel 75 mg MD. In addition, the percentage of

Table 3 Adverse events in all enrolled subjects

	Number of adverse events (number of subjects) [percent of subjects]				
	Prasugrel				Clopidogrel
LD/MD	(40/5 mg) ($n = 19$)	(40/7.5 mg) ($n = 19$)	(60/10 mg) ($n = 19$)	(60/15 mg) ($n = 21$)	(300/75 mg) ($n = 23$)
Bruising [%]	35 (12) [63]	49 (13) [68][a]	34 (12) [63]	47 (15) [71]	25 (11) [48]
Bleeding [%]	2 (2) [11]	5 (4) [21]	3 (2) [11]	12 (6) [29]	7 (5) [22]
Bruising and bleeding [%]	37 (13) [68]	54 (15) [79][a]	37 (13) [68]	59 (17) [81]	31 (15) [65]
Epistaxis [%]	1 (1) [5]	2 (1) [5]	2 (1) [5]	8 (5) [24]	4 (2) [9]

Values in parentheses are the number of patients with the specified adverse event. Values in brackets are the percentage of patients within a treatment group with the specified adverse event. The following events are incorporated under the description of bleeding events: epistaxis, gingival bleeding, haemoptysis, tongue haemorrhage, blister, wound, conjunctival haemorrhage, blood in stool, and haematuria (microscopic). No bleeding events were associated with a decrease in haematocrit. Bruising was most often associated with the study procedures (venipucture, bleeding times). LD, loading dose; MD, maintenance dose.

[a] The number of events in this treatment group was skewed because of a disproportionately high number of bruises reported by one subject (19 separate adverse events of contusion).

non-responders was significantly lower in patients treated with a prasugrel 40 or 60 mg LD compared with clopidogrel 300 mg (3 vs. 52%, respectively) and a prasugrel 10 or 15 mg MD compared with clopidogrel 75 mg (0 vs. 45%, respectively).

Both drugs were well tolerated with a similar incidence of bruising and bleeding events in the three lower dose prasugrel groups and the clopidogrel group. Minor bruising episodes were common and were frequently associated with the study procedures such as venipuncture. There was a modest increase in the incidence of minor bleeding events in the highest dose prasugrel group. The majority of the bleeding events were considered mild to moderate in severity and did not result in discontinuation of study drug. In this study, there was no observed association between the level of IPA on study drug and incidence of bleeding.

In previously published studies, with 20 μM ADP as the agonist, mean IPA observed with clopidogrel 300 mg LD ranges from ∼20 to 40%.[13,14] In this study, with either 5 or 20 μM ADP as the agonist, prasugrel 40 and 60 mg LD achieved at least a doubling of mean IPA compared with a mean IPA of about 30% observed with clopidogrel 300 mg LD.

In recent studies of 600 mg clopidogrel, utilizing 20 μM ADP as the agonist, as we employed in the current study, IPA levels of ∼31–32% were reported.[15,16] These IPA values are all substantially lower than the 64% IPA that we report here with the prasugrel 60 mg LD. However, given the lack of standardization in the measurement of IPA, determination of the relative levels of IPA achieved by the 60 mg prasugrel LD and the higher 600 mg clopidogrel LD requires a randomized comparison in a clinical trial (such studies are currently ongoing).

A potentially important observation made in the current study is the apparent lower non-responder rate associated with prasugrel. Although previous studies have used empiric definitions of non-responders,[6,7,9,17] there is to date no consensus on how to define pharmacodynamic non-responders to thienopyridine treatment. In the present study, a non-responder was defined, using a model-based approach, as an individual not achieving ≥20% IPA to 20 μM ADP by 4 h after an LD or at pre-dose timepoints under MD administration. The difference in non-responder definition used in this study is a major reason for the higher percentage of non-responders with clopidogrel 300 mg LD (52%) seen in this study compared with previous studies (25–30%).[6,7]

Using the ΔMPA criteria for non-responders reported by Gurbel *et al.*[6,12] the percentage of clopidogrel non-responders in this study is lower and comparable to the literature (∼20% non-responders with the clopidogrel 300 mg LD and 30% with the clopidogrel 75 mg MD), reflecting the lower threshold of platelet inhibition required to be considered a pharmacodynamic responder to clopidogrel with this criteria. Similar to the results obtained using the model-based approach in the current study, the percentage of non-responders for prasugrel using Gurbel's definition was still only 3% in the prasugrel 40 and 60 mg LD groups (and 0, 0, 10, and 20% at the prasugrel MDs of 15, 10, 7.5, and 5.0 mg, respectively).

In addition, in contrast to the results reported by Gurbel *et al.*[6] suggesting a decrease in clopidogrel non-responders over time (from 31% at 5 days to 15% at 30 days), in the present study, there was a persistent high level of non-responders (45%, *Figure 3*) to clopidogrel MD even after 28 days of daily treatment. Although assays for the active metabolites of prasugrel and clopidogrel were not available at the time of the current study, subsequent studies indicate differences in the pharmacokinetic profile of prasugrel are consistent with its greater and more consistent pharmacodynamic response.[18,19]

Some studies have suggested that patients with clopidogrel resistance have an increased risk of subsequent stent thrombosis or other cardiovascular events.[7,9,20] There are several potential mechanisms behind the high percentage of clopidogrel non-responders including variations in the absorption of the prodrug and generation and clearance of the active metabolite.[21] Additional mechanisms for thienopyridine resistance may include differences in receptor expression, differences in post-receptor signalling pathways, and $P2Y_{12}$ receptor polymorphisms that have been demonstrated to contribute to varying degrees of platelet aggregation to ADP.[22]

Study limitations

There were several limitations to this study. At present, there is no agreed upon standard for defining non-responders to platelet inhibition with thienopyridines, thus our model-based methodology must be taken in context with varying approaches to defining non-responders in the literature. In addition, in this short-term study of a small population of stable CAD patients, there was only one clinical endpoint of note (serious adverse event of hospitalization for unstable angina), which makes it difficult to gauge the clinical significance of findings regarding higher levels of IPA and lower non-responder rates with prasugrel.

There was variation in the aggregation responses between the two sites that participated in the study, possibly due to methodological differences or differences in ethnic origins of the patient population leading to potential CYP polymorphisms. However, separate analyses of data from each site still support the higher levels of IPA observed with prasugrel 60 mg LD and 10 mg MD over the clopidogrel 300 mg LD and 75 mg MD, results consistent with subsequent studies and with those reported by other investigators.[6,7,12]

Furthermore, clopidogrel was dosed in an open-label manner; this approach should not have altered IPA responses to clopidogrel, but potentially could have impacted the reporting of adverse events. Finally, we cannot rule out the possibility of different IPA response or non-responder rates with either prasugrel or clopidogrel in an acute treatment situation in contrast to the elective setting in this study.

Conclusion

In conclusion, when added to aspirin in patients with stable atherosclerotic disease, prasugrel achieves significantly greater IPA with a significantly lower percentage of pharmacodynamic non-responders compared with clopidogrel. Prasugrel and clopidogrel were well-tolerated and the adverse event profiles were comparable. This study also helped to characterize the IPA associated with LDs and MDs of prasugrel evaluated in the recently completed JUMBO TIMI-26 phase 2 trial performed in the setting of urgent and elective PCI.[11] These combined findings support the selection of the prasugrel 60 mg LD with a 10 mg MD, currently being evaluated against clopidogrel in the TRial to Assess Improvement in Therapeutic Outcome by Optimizing Platelet InhibitioN with Prasugrel (TRITON) TIMI-38 phase 3 clinical trial in ACS patients undergoing PCI.

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