Prasugrel compared with high-dose clopidogrel in acute coronary syndrome

The randomised, double-blind ACAPULCO* study

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Summary

Compared with the approved dose regimen of clopidogrel (300-mg loading dose [LD], 75-mg maintenance dose [MD]), prasugrel has been demonstrated to reduce ischaemic events in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). In ACS, antiplatelet effects of a prasugrel MD regimen have not been previously compared with either a higher clopidogrel MD or after switching from a higher clopidogrel LD. The objective of this study was to evaluate the antiplatelet effect of a prasugrel 10-mg MD versus a clopidogrel 150-mg MD in patients with ACS who had received a clopidogrel 900-mg LD. Patients with non-ST elevation ACS, treated with aspirin and a clopidogrel 900-mg LD, were randomised within 24 hours post-LD to receive a prasugrel 10-mg or clopidogrel 150-mg MD. After 14 days of the initial MD, subjects switched to the alternative treatment for 14 days. The primary endpoint compared maximum platelet aggregation (MPA, 20 μM adenosine diphosphate [ADP]) between prasugrel and clopidogrel MDs for both periods. Responder analyses between treatments were performed using several platelet-function methods. Of 56 randomised subjects, 37 underwent PCI. MPA was 26.2% for prasugrel 10 mg and 39.1% for clopidogrel 150 mg (p<0.001). The prasugrel MD regimen reduced MPA from the post-900-mg LD level (41.2% to 29.1%, p=0.003). Poor response ranged from 0% to 6% for prasugrel 10 mg and 4% to 34% for clopidogrel 150 mg. Thus, in ACS patients a prasugrel 10-mg MD regimen resulted in significantly greater platelet inhibition than clopidogrel at twice its approved MD or a 900-mg LD.

Keywords

Prasugrel, high-dose clopidogrel, thienopyridine switching

Introduction

In patients with non-ST-elevation acute coronary syndromes (ACS), a clopidogrel 300-mg loading dose (LD) followed by a 75-mg daily maintenance dose (MD), with aspirin, resulted in a 20% reduction of ischaemic events at one year compared with aspirin alone (1). Several studies, however, have shown that clopidogrel LDs >300 mg result in higher platelet inhibition, faster onset of action, and fewer poor responders in both clopidogrel-naïve and clopidogrel-treated patients (2–12). Moreover, some of these studies suggest high or very high LDs of clopidogrel afford greater clinical benefit compared with the 300-mg LD (6, 9, 12). Likewise, the approved clopidogrel 75-mg MD achieves a modest antiplatelet effect, and poor response to clopidogrel remains a concern, the prevalence of which has been reported in up to 44% of patients (13, 14). Studies have shown improvement in platelet inhibition with clopidogrel 150 mg compared with 75 mg and a reduction in the variability of response, but still with a significant proportion of poor response (10, 14–16). Though clinical outcome data with high doses of clopidogrel are sparse, many clinicians use, and international societies recommend, clopidogrel LD regimens higher than the dose tested in pivotal trials and officially approved by regulatory authorities (17), and high doses of clopidogrel MD regimens are increasingly used.
Prasugrel, a thienopyridine recently approved as a therapeutic agent for the prevention of thrombotic cardiovascular events in patients presenting with acute coronary syndrome who will be managed with PCI, has demonstrated faster onset of action and higher and more consistent levels of platelet inhibition compared with clopidogrel in healthy subjects and in patients with stable coronary artery disease (18–20). In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, prasugrel was associated with significantly reduced rates of thrombotic events, but with increased risk of major bleeding, compared with the approved standard dose regimen of clopidogrel in patients with ACS undergoing percutaneous coronary intervention (PCI) (21). Thus far, two studies have demonstrated a significantly greater antiplatelet effect with prasugrel compared with high doses of clopidogrel. In the first study, the prasugrel 60-mg LD/10-mg MD treatment regimen was compared with the clopidogrel 600-mg LD and 75-mg once-daily MD, in aspirin-treated patients with coronary artery disease, (22) and in the second, Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction (PRINCIPLE-TIMI) 44, prasugrel 60-mg LD/10-mg MD was compared with a clopidogrel 600-mg LD/150-mg MD regimen in patients with stable coronary disease undergoing planned PCI (23).

The goal of the present study was to evaluate the antiplatelet effect of the prasugrel 10-mg MD versus the clopidogrel 150-mg MD in ACS patients who received a high clopidogrel loading dose of 900 mg.

Methods

Study population

Subjects with unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI) ACS were eligible for the study if they were aged 18 to 84 years, inclusive, and were to receive a clopidogrel 900-mg LD as part of their care. Criteria for UA/NSTEMI ACS included at least one of the following: 1) cardiac ischaemic symptoms suggestive of an ACS (24) with the last episode of ischaemic symptoms ≤48 hours prior to randomisation; symptoms included, but were not limited to, prolonged anginal pain at rest (>10 minutes [min]), severe, new-onset angina (Canadian Cardiovascular Society [CCS] Class III), or destabilisation of previously stable angina; 2) new persistent or transient ST-segment depression ≥1 mm or transient (<20 min) ST-segment elevation, or T-wave inversion in one or more electrocardiogram leads; 3) creatinine kinase MB fraction or troponin T or I greater than the upper limit of normal. Angiography and PCI were not requirements for study entry, and subjects taking chronic clopidogrel were not excluded.

Key exclusion criteria included overt ST-segment elevation myocardial infarction (STEMI), cardiogenic shock, refractory ventricular arrhythmia, New York Heart Association (NYHA) class IV congestive heart failure, uncontrolled hypertension, high risk of bleeding, and the use of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, except as “bail-out” during PCI.

This study was approved by the local ethics committee, CPP – Ile de France VI Groupe Hospitalier Pitie-Salpetriere, and all subjects provided written informed consent before participation. Enrollment began in March 2007 and was suspended at 56 randomised subjects on 22 October 2007 following the results from the TRITON-TIMI 38 trial (21), which suggested excess bleeding risk with prasugrel in subjects not excluded from our study (≥75 years of age, body weight <60 kg, history of stroke or transient ischaemic attack [TIA]), although the study safety monitor had previously recommended continuation of the study. Subsequently, it was determined sufficient data were available for analysis and the study was not resumed (described below). Eleven subjects (seven in the prasugrel-clopidogrel treatment sequence and four in the clopidogrel-prasugrel sequence) were terminated from the study early because of the trial’s suspension.

Study protocol

The ACAPULCO study was conducted at four study sites in Paris, France. In accordance with the local practice at these sites, subjects received an oral LD of commercially available clopidogrel 900 mg (as a single dose or cumulative dose when a dose <900 mg had previously been administered). Aspirin LD (250–500 mg, oral or intravenously) was administered in the open-label phase (Visit 1). This was followed by a double-blind, randomised, daily MD, crossover phase in which subjects were randomly assigned at Visit 2 to receive either prasugrel 10 mg or clopidogrel 150 mg for 14 ± 2 days. Subjects then switched at Visit 3 to the alternative MD treatment for an additional 14 ± 2 days until Visit 4. All subjects received oral daily aspirin (≤100 mg) during the MD phase (Fig. 1).

For the MD phase, study treatments were provided as orally-administered tablets of 10-mg prasugrel (hydrochloride salt) and 75-mg clopidogrel, each with matching placebo. Study treatment was initiated 16–28 hours (h) after the LD and continued daily thereafter without regard to food.

The first blood sample for platelet-function measures was collected irrespective of whether subjects were on chronic clopidogrel treatment or had previously received a clopidogrel LD for the ACS event. However, true pre-LD baseline platelet aggregation is available only in clopidogrel-naive subjects. Additional blood samples were collected 6–18 h after the 900-mg LD and 16–28 h after the last MD at Visit 3 and Visit 4.

Laboratory procedures

All pharmacodynamic evaluations were conducted at a central laboratory by personnel blinded to treatment assignment.
For light transmission aggregometry (LTA), blood was collected into 4.5-ml, 3.8% citrate tubes and then centrifuged to obtain platelet-rich (PRP) and platelet-poor plasma. Platelet aggregation in response to 5 and 20 μM adenosine diphosphate (ADP) was measured in PRP with a model 490-4D aggregometer (Chrono-Log Corporation, Kordia, Netherlands), with temperature maintained at 37°C. Maximum (MPA) and residual platelet aggregation (RPA), measured at 6 min after the addition of ADP, were assessed. For subjects with a clopidogrel-free initial blood sample, inhibition of maximum platelet aggregation (IPA) and inhibition of residual platelet aggregation (IRPA) were calculated only as a percent decrease of the MPA or RPA from baseline by the following formula:

\[ 1 - \frac{(PA_t)}{(PA_0)} \times 100\% \]

in which PA\(_t\) is the platelet aggregation (maximum or residual) at time (t) post-dose and PA\(_0\) is the PA at baseline.

For the VerifyNow™ P2Y12 (VN-P2Y12) assay (Accumetrics Corporation, San Diego, CA, USA), blood was collected into 2-ml Greiner Bio-One 3.8% citrate tubes. Device-reported data were recorded as either P2Y\(_{12}\) platelet reaction units (PRU) or % inhibition. In subjects who were clopidogrel-naïve at baseline, calculated % inhibition was determined from PRU data using the same equation as above for IPA and IRPA. Samples for vasodilator-stimulated phosphoprotein (VASP) assays were collected in 1.8-ml citrated tubes, and VASP phosphorylation was measured using whole blood flow cytometry, as described by the manufacturer’s instructions (Biocytex, Marseilles, France) and reported as the platelet reactivity index (PRI%). The VASP index, in which lower PRI% values indicate greater P2Y\(_{12}\) receptor blockade, was calculated using the median fluorescence intensity (MFI) of samples incubated with prostaglandin E1 (PGE\(_1\)) and ADP, according to the following formula:

\[ \text{VASP index} = \left[ 1 - \frac{(\text{MFI(PGE}_1) - \text{MFI(PGE}_1 + \text{ADP})/\text{MFI(PGE}_1)} \right] \times 100\% \]

**Pharmacodynamic endpoints**

The primary efficacy measure was MPA to 20 μM ADP determined after 14 days of prasugrel 10 mg compared with 14 days of clopidogrel 150 mg that included data from both the pre-crossover (Visit 3) and post-crossover (Visit 4) MD phases.

Secondary endpoints included pre- to post-LD change in MPA, change in MPA from LD to the end of the first MD period for both study treatments, and a comparison between prasugrel and clopidogrel MDs (for both MD periods combined and separately at each visit) for all pharmacodynamic measures. Poor response to treatment was assessed using the following published threshold criteria: MPA to 20 μM ADP >50% (15); RPA to 5 μM ADP >14% (25); PRI% ≥50% (26); and PRU ≥240 (27).
Safety and tolerability

Bleeding and adverse event reports were collected and evaluated with serious adverse events reported within 30 days of study-drug discontinuation. Bleeding was categorised as major, minor, or insignificant (minimal) bleeding according to the TIMI criteria (28) and severe or life-threatening, moderate, or minor bleeding according to Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) definitions (29). Treatment-emergent adverse events were summarised using the Medical Dictionary for Regulatory Activities (MedDRA; Version 9.1) preferred term.

Statistical analyses

The LD-phase analysis population consisted of subjects who received a cumulative clopidogrel 900-mg LD and had an evaluable pharmacodynamic measurement (MPA, RPA, PRU, and PRI%) for at least one of the crossover periods. Using an intent-to-treat analysis, the MD-phase analysis population consisted of subjects with an evaluable pharmacodynamic measurement and who received at least one dose of either the clopidogrel MD or prasugrel MD. Subjects receiving bail-out GP IIb/IIIa inhibitors during PCI were excluded from the LD analysis.

Baseline subject characteristics were compared with t-tests for the means of continuous variables or with Pearson's chi-squared test for categorical data. A p<0.05 (two-sided) was considered significant.

For the primary analysis, an analysis of covariance (ANCOVA) crossover model evaluated MPA to 20 μM ADP at the end of the two 14-day treatment periods, with treatment (prasugrel 10 mg and clopidogrel 150 mg), study site, and period as fixed effects, and subject as a random effect. Least squares (LS) estimates of the difference in means were presented with a 95% CI and a two-sided p-value for the treatment effect. A separate analysis of the ANCOVA models compared MPA with prasugrel and clopidogrel to 20 μM ADP at Visit 3 and at Visit 4. The change in MPA from pre-LD to that following the LD and the change from LD to the first MD were assessed with paired t-tests. The methods used for the primary analyses, including separate analyses at Visit 3 and Visit 4, were conducted on the following additional platelet function measures: IPA with 5 and 20 μM ADP, MPA with 5 μM ADP; RPA and IRPA with 5 and 20 μM ADP; PRI%; and PRU.

The proportion of poor responders was compared between prasugrel 10 mg and clopidogrel 150 mg at the end of the two 14-day treatment periods for all responder thresholds using Prescott's test. A descriptive analysis of the proportion of poor responders with the clopidogrel LD was also conducted.

Bleeding or treatment-emergent adverse events occurring during the LD phase (LD to three days after the LD) were compared between treatment groups with Fisher's exact test. During the MD phase of the study, the incidence of these events was compared using Prescott's test. All statistical analyses were performed with SAS versions 8.2 and 9.1 (SAS Institute Inc., Cary, NC, USA).

Prior to study initiation, a sample size of 70 randomised subjects was planned for 60 subjects to complete the study. The study sample size, however, was recalculated when data from the PRINCIPLE-TIMI 44 trial became available near the time of study suspension (23). The following assumptions were made in the recalculation: MPA to 20 μM ADP of 30% and 40% for prasugrel and clopidogrel, respectively; a common standard deviation (SD) of MPA to 20 μM ADP of 18%; and a correlation between MPA readings within subjects of 0.5. By simulation, an estimated 20 subjects per sequence (40 subjects in total) would provide >90% power to detect a difference of 10% in MPA to 20 μM ADP between prasugrel and clopidogrel. Sample-size calculations were based on an ANCOVA model with treatment as a fixed effect and subject as a random effect.
Results

Study population and baseline characteristics

Sixty subjects (48 men and 12 women) received a cumulative clopidogrel 900-mg LD, four of whom were not randomised to MD treatment because they did not fulfill all inclusion/exclusion criteria. Of the 56 randomised subjects, two who were randomised to clopidogrel 150 mg withdrew after randomisation and prior to receiving an MD. Fifty-four subjects received at least one MD of prasugrel or clopidogrel, and 41 subjects completed the study per protocol (Fig. 2).

Baseline demographics were representative of an ACS population, and no statistically significant differences in medical history were observed between the treatment sequences (data not shown). Baseline characteristics for all randomised subjects are in Table 1. The index ACS event characteristics are shown in Table 2; no significant differences were noted between treatment sequences (data not shown). The majority of subjects underwent PCI for their ACS event, and low-molecular-weight heparin was the most commonly used anticoagulant.

Light transmission aggregometry measures

Initial pre-LD and post-LD MPA levels were similar between the two MD-treatment sequences (prasugrel 10-mg/clopidogrel 150-mg sequence vs. clopidogrel 150-mg/prasugrel 10-mg sequence: 64.5% vs. 65.2% pre-LD [p=0.898] and 37.7% vs. 39.7%, post-LD [p=0.667], respectively).

The primary endpoint analysis demonstrated that the LS mean MPA to 20 μM ADP was statistically significantly lower following the prasugrel 10-mg MD compared with the clopidogrel 150-mg MD (26.2% for prasugrel vs. 39.1% for clopidogrel; p<0.001; data for Visits 3 and 4 combined; Fig. 3). Similar results were observed with other measures of LTA.

Subjects’ use of chronic clopidogrel maintenance treatment at the study entry did not affect the MPA results for the comparison between the two study treatments (p=0.170 for the interaction).

Table 1: Summary of subject baseline characteristics for all randomised subjects.

<table>
<thead>
<tr>
<th>Subject demographics</th>
<th>All randomised subjects (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>Male</td>
<td>47 (84%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>53 (95%)</td>
</tr>
<tr>
<td>Age (years), mean ± SD (range)</td>
<td>61 ± 12 (37–84)</td>
</tr>
<tr>
<td>Body weight (kg), mean ± SD (range)</td>
<td>80 ± 14 (56–123)</td>
</tr>
<tr>
<td>BMI (kg/m2), mean ± SD (range)</td>
<td>27 ± 4 (21–43)</td>
</tr>
</tbody>
</table>

Medical history at baseline

<table>
<thead>
<tr>
<th>Medical history at baseline</th>
<th>All randomised subjects (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI, n (%)</td>
<td>16 (29%)</td>
</tr>
<tr>
<td>CHF, n (%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>37 (66%)</td>
</tr>
<tr>
<td>Hyperlipidaemia, n (%) *</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>PAD, n (%)</td>
<td>15 (27%)</td>
</tr>
<tr>
<td>Peptic ulcer disease, n (%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Prior CVA, n (%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Prior TIA, n (%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>17 (30%)</td>
</tr>
<tr>
<td>Use of beta-blockers, n (%)</td>
<td>44 (79%)</td>
</tr>
<tr>
<td>Use of statins, n (%)</td>
<td>55 (98%)</td>
</tr>
<tr>
<td>Chronic aspirin use, n (%)</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>Chronic clopidogrel 75-mg use, n (%)</td>
<td>19 (34%)</td>
</tr>
</tbody>
</table>

Previous procedures

<table>
<thead>
<tr>
<th>Previous procedures</th>
<th>All randomised subjects (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior PCI, n (%)</td>
<td>24 (43%)</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

* Subjects with a history of both hypercholesterolemia and hypertriglyceridaemia. BMI, body mass index; MI, myocardial infarction; CHF, congestive heart failure; PAD, peripheral artery disease; CVA, cerebrovascular accident; TIA, transient ischaemic attack; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; UA, unstable angina.

Table 2: Characterisation of index ACS event for all randomised subjects.

<table>
<thead>
<tr>
<th>Reason for acute presentation</th>
<th>Overall (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSTEMI, n (%)</td>
<td>23 (41.1%)</td>
</tr>
<tr>
<td>UA, n (%)</td>
<td>33 (58.9%)</td>
</tr>
<tr>
<td>Subjects who underwent PCI, n (%)</td>
<td>37 (66.1%)</td>
</tr>
<tr>
<td>Subjects who received GP IIb/IIIa inhibitors, n (%)</td>
<td>8 (14.3%)</td>
</tr>
<tr>
<td>Subjects who received LMWH, n (%)</td>
<td>51 (91.1%)</td>
</tr>
<tr>
<td>Subjects who received UFH, n (%)</td>
<td>12 (21.4%)</td>
</tr>
<tr>
<td>Mean aspirin LD ± SD (mg)</td>
<td>327.8 ± 138.2</td>
</tr>
</tbody>
</table>

Light transmission aggregometry measures

The mean MPA decreased from 64.8% pre-LD to 38.6% following administration of the clopidogrel 900-mg LD. Prasugrel 10-mg MD also significantly reduced MPA from the post-900-mg LD level (41.2% to 29.1%, p=0.003). Mean MPA to 20 μM ADP was significantly lower with prasugrel 10 mg than with clopidogrel 150 mg in each MD period (28.9% vs. 38.2% at Visit 3 [p=0.008]; 25.0% vs. 42.5% at Visit 4 [p<0.001; Fig. 3]).
Other platelet-function measures

Greater platelet inhibition with the prasugrel MD compared with the clopidogrel MD was also demonstrated with the VN-P2Y12 assay and with the VASP platelet reactivity index (Table 4). Good correlation between device-reported % inhibition and calculated % inhibition (as % decrease PRU from baseline) was observed (r=0.688; data not shown).

Responder analyses

There was a lower rate of poor response with the prasugrel MD compared with the high-dose clopidogrel MD (Table 5). The rate of poor response for the prasugrel MD ranged from 0% to 6% compared with 4% to 34% for the clopidogrel MD. For the clopidogrel LD, the rate of poor response ranged from 12% to 51%.

For subjects who received both MDs, their individual responses to the clopidogrel LD and prasugrel and clopidogrel MDs are depicted with the poor response threshold by the various criteria in Figure 4. Of the subjects who did not respond to the clopidogrel 900-mg LD, 44% (4/9; with MPA to 20 μM ADP >50%), 57% (4/7; with RPA to 5 μM ADP >14%), 45% (9/20; with PRI ≥50%), and 20% (1/5; with PRU ≥240) remained poor responders to the clopi-
dogrel 150-mg MD. Conversely, 89% (8/9; with MPA to 20 μM ADP >50%), 86% (6/7; RPA to 5 μM ADP >14%), 90% (18/20; with PRI ≥50%), and 100% (5/5; with PRU ≥240) of the clopidogrel 900-mg LD poor responders responded to prasugrel 10-mg MD.

Safety and tolerability

There were no discontinuations in the study related to an adverse event, nor were there any non-CABG-related TIMI major or GUSTO severe/life-threatening bleeding events. The majority of the bleeding events were at sites related to cardiac catheterisation procedures or venipuncture, and these were not considered to be sufficiently serious to preclude continued participation in the study. Four subjects (two on each study treatment) experienced bleeding in the first MD-treatment period, including a retro-peritoneal haematoma in one of the prasugrel-treated subjects who re-received a GP IIb/IIIa inhibitor. One subject experienced a single bleeding event (subconjunctival haemorrhage) in the second treatment period during prasugrel treatment.

One death was reported in the study, which occurred during a prasugrel MD period in a patient with known metastatic cancer; the death was not attributed to the study drug by the investigator.

Discussion

The ACAPULCO study demonstrated for the first time in an ACS population that a prasugrel 10-mg MD regimen provided greater antiplatelet effect than a clopidogrel 150-mg MD regimen. Also, observed for the first time with multiple measures in the ACAPULCO study, switching to a prasugrel 10-mg MD regimen from a 900-mg clopidogrel LD significantly achieved further platelet inhibition. The ACAPULCO study complements the TRITON-TIMI 38 trial (21), which demonstrated that prasugrel prevented more ischaemic events than clopidogrel in a similar ACS population. TRITON, however, has been challenged for not reflecting current clinical practice, because the lower, approved clopidogrel-dosing

### Table 4: VASP and VerifyNow™ P2Y12 measures in the maintenance dose phase.

<table>
<thead>
<tr>
<th>Endpoint (VASP (%))</th>
<th>n</th>
<th>Prasugrel 10 mg (mean ± SD)</th>
<th>Clopidogrel 150 mg (mean ± SD)</th>
<th>Difference (prasugrel-clopidogrel) (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mean ± SD) Day 14</td>
<td>27</td>
<td>21.5 ± 13.4</td>
<td>40.6 ± 22.5</td>
<td>−19.1 (−29.4, −8.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(mean ± SD) Day 29</td>
<td>22</td>
<td>22.8 ± 15.7</td>
<td>38.1 ± 19.8</td>
<td>−15.3 (−26.1, −4.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Combined data*</td>
<td>49</td>
<td>23.7</td>
<td>40.5</td>
<td>−16.8 (−23.1, −10.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 5: Prevalence of poor response using a variety of threshold criteria for both maintenance and loading doses.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Criteria</th>
<th>MPA to 20 μM ADP &gt;50%</th>
<th>RPA to 5 μM ADP &gt;14%</th>
<th>PRI ≥50%</th>
<th>PRU ≥240</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maintenance dose periods combined</strong></td>
<td>Prasugrel, n (%)</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel, n (%)</td>
<td>12 (26%)</td>
<td>10 (21%)</td>
<td>16 (34%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td><strong>Loading dose</strong></td>
<td>Prasugrel, n (%)</td>
<td>10 (23%)</td>
<td>7 (16%)</td>
<td>22 (51%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel, n (%)</td>
<td>12 (26%)</td>
<td>10 (21%)</td>
<td>16 (34%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

* For combined data, least squares mean values are presented for prasugrel and clopidogrel. PRI%, platelet reactivity index; PRU, platelet reaction units; VASP, vasodilator-associated stimulated phosphoprotein.
The prasugrel 60 mg loading dose (LD) and 10 mg maintenance dose (MD) regimen has been shown to reduce ischaemic events in patients with acute coronary syndrome (ACS) undergoing PCI compared with the approved dose regimen of clopidogrel (300 mg LD/75 MD).

In a previous study in patients with stable coronary artery disease undergoing elective PCI, the prasugrel 60 mg LD/10 mg MD resulted in greater antiplatelet effect compared to a clopidogrel 600 mg LD/150 mg MD regimen.

What does this paper add?
- The prasugrel 10 mg MD results in significantly greater inhibition of platelet aggregation than the clopidogrel 150 mg MD in patients with ACS.
sitive biological measure of clopidogrel response by LTA (31). Similar results were also observed with other LTA measures IPA and IRPA, and with two different ADP (5 and 20 μM ADP) concentrations. The consistency of results was also noted with the bedside VN-P2Y12 assay and the VASP assay, which is a more specific indicator of ADP-induced platelet P2Y12 receptor antagonism (32) and, consequently, a more accurate marker of thienopyridine effects. The correlation between the LTA, VN-P2Y12, and VASP assays has also been observed in previous studies (33, 34).

Studies have shown higher platelet inhibition with the clopidogrel 150-mg MD than with the standard clopidogrel 75-mg MD (16, 35, 36). In PRINCIPLE-TIMI 44, the prasugrel 10-mg MD resulted in greater antiplatelet effect than the clopidogrel 150-mg MD (23). Similar results were observed in the current ACAPULCO study, which included patients with ACS, in whom intense platelet activation requires high, consistent, and stable IPA. The benefits of prasugrel on platelet inhibition were observed despite the initial high clopidogrel LD, and after crossover to the alternate study drug, demonstrating that switching from one drug to the other has no impact on the platelet inhibitory effect of each drug. Importantly, this study shows that a significant decrease in platelet inhibition results from switching to twice the approved clopidogrel MD from a prasugrel MD. Though a physician might choose to lower the level of platelet inhibition during long-term maintenance therapy in a patient with an increased bleeding risk, the TRITON study clearly demonstrated that patients < 75 years old and ≥60 kg treated with a prasugrel 10 mg MD had a significantly lower rate of atherothrombotic events, including stent thrombosis, without an increase in major bleeding (21).

The impact of a higher clopidogrel-dosing regimen on clinical outcomes in patients with ACS undergoing an early invasive strategy was assessed in the CURRENT-OASIS 7 trial (Clopidogrel optimal dose Usage to Reduce Recurrent EveNTs) (37–39). This study evaluated the effects of a clopidogrel 600-mg LD followed by a daily 150-mg MD for one week then by 75 mg daily, compared with the standard clopidogrel 300-mg/75-mg dose regimen. While CURRENT-OASIS 7 did not meet its primary efficacy endpoint to show a difference between the two clopidogrel regimens tested in the entire population, among the large subgroup of patients who underwent PCI improved outcomes were demonstrated with the higher clopidogrel dose regimen. Thus, the greater level of platelet inhibition with a prasugrel 10-mg MD than a clopidogrel 150-mg MD demonstrated in ACAPULCO may confer even further improvement of clinical outcome in ACS patients.

Although the thresholds for effect remain undefined, several studies suggest greater inhibition of platelet aggregation and activation are associated with higher efficacy in ACS or PCI (21, 27, 40–44). In fact, recent studies have reported that there is a higher risk of atherothrombotic events in patients with CYP 450 2C19 variants that reduce the conversion of clopidogrel to its active metabolite, resulting in less pharmacodynamic effect (45–48). In a recent report of patients experiencing stent thrombosis on clopidogrel, poor antiplatelet response to doses of clopidogrel up to 900 mg was overcome by prasugrel (49). Many different definitions of poor response exist based on different tests and different thresholds for these tests. In the ACAPULCO study, four previously published definitions of poor response, all of which have been linked with clinical outcome, were used (16, 25–27). Using all four definitions, fewer than 6% of patients were considered as poor responders with prasugrel 10 mg, while prevalence of poor response was 2–10 times higher with clopidogrel, both after loading (900 mg) or during the maintenance phase of treatment (150 mg).

Among its limitations, our study was not sized to assess clinical efficacy and safety, and although no serious bleeding was observed with high levels of platelet inhibition, no conclusions regarding these results can be made for either treatment. Additionally, we were unable to collect true baseline data for approximately 30% of the sample, because these subjects had received chronic clopidogrel treatment at study entry. The short duration of treatment is another limitation. Lastly, variability of platelet biology measurements is a concern with the LTA, VN-P2Y12, and VASP assays in a multicenter study. The ACAPULCO study reduced this concern by using an established network of cardiology centers in the same city with a single laboratory, which has been evaluated before in previous randomised studies (4, 50). Additionally, while each of the three platelet function tests employed in the ACAPULCO study has inherent limitations regarding variability and specificity, it is noteworthy that in the current study the relative response to study drugs was consistent irrespective of the test employed.

**Abbreviations**

ACAPULCO, a randomised, double-blind, cross-over study comparing the pharmacodynamic response in subjects with acute coronary syndrome receiving 14 days 10-mg maintenance dose prasugrel versus 14 days of 150-mg maintenance dose clopidogrel after using a 900-mg loading dose of clopidogrel to reduce ongoing platelet activation; ACS, acute coronary syndrome; ADP, adenosine diphosphate; ANCOVA, analysis of covariance; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; CI, confidence interval; CURRENT-OASIS 7, Clopidogrel optimal dose Usage to Reduce Recurrent EveNTs; GP IIb/IIIa, glycoprotein IIb/IIIa; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; IPA, inhibition of maximum platelet aggregation; IRPA, inhibition of residual platelet aggregation; LD, loading dose; LS, least squares; LTA, light transmission aggregometry; MD, maintenance dose; MedDRA, Medical Dictionary for Regulatory Activities; MPA, maximum platelet aggregation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PGE1, prostaglandin E1; PRI, platelet reactivity index; PRINCIPLE-TIMI 44, Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation –Thrombolysis in Myocardial Infarction 44 trial; PPR, platelet-rich plasma; PRU, platelet reaction units; RPA, residual platelet aggregation; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38; UA/NSTEMI, unstable angina/non-ST elevation myocardial infarction; VASP, vasodilator-stimulated phosphoprotein.
In conclusion, in ACS, after a high clopidogrel LD, switching to the prasugrel 10-mg MD may be an option that improves the level of platelet inhibition. Furthermore, the prasugrel 10-mg MD results in significantly greater IPA than the clopidogrel 150-mg MD.

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