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

Stephen D. Wiviott, MD; Dietmar Trenk, PhD; Andrew L. Frelinger, PhD; Michelle O’Donoghue, MD; Franz-Josef Neumann, MD; Alan D. Michelson, MD; Dominick J. Angiolillo, MD, PhD; Hanoch Hod, MD; Gilles Montalescot, MD, PhD; Debra L. Miller, RN, RCIS; Joseph A. Jakubowski, PhD; Richard Cairns, MSc; Sabina A. Murphy, MPH; Carolyn H. McCabe, BS; Elliott M. Antman, MD; Eugene Braunwald, MD; for the PRINCIPLE-TIMI 44 Investigators

Background—The increasing use of higher-than-approved doses of clopidogrel in clinical practice is based in part on the desire for greater levels of inhibition of platelet aggregation (IPA). Prasugrel is a new thienopyridine that is more potent than standard-dose clopidogrel in healthy subjects and patients with stable coronary artery disease. The relative antiplatelet effects of prasugrel versus high-dose clopidogrel in percutaneous coronary intervention patients are unknown.

Methods and Results—Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) was a randomized, double-blind, 2-phase crossover study of prasugrel compared with high-dose clopidogrel in patients undergoing cardiac catheterization for planned percutaneous coronary intervention. The primary end point of the loading-dose phase (prasugrel 60 mg versus clopidogrel 600 mg) was IPA with 20 μmol/L ADP at 6 hours. Patients with percutaneous coronary intervention entered the maintenance-dose phase, a 28-day crossover comparison of prasugrel 10 mg/d versus clopidogrel 150 mg/d with a primary end point of IPA after 14 days of either drug. In this study, 201 subjects were randomized. IPA at 6 hours was significantly higher in subjects receiving prasugrel (mean±SD, 74.8±13.0%) compared with clopidogrel (31.8±21.1%; P<0.0001). During the maintenance-dose phase, IPA with 20 μmol/L ADP was higher in subjects receiving prasugrel (61.3±17.8%) compared with clopidogrel (46.1±21.3%; P<0.0001). Results were consistent across all key secondary end points; significant differences emerged by 30 minutes and persisted across all time points.

Conclusions—Among patients undergoing cardiac catheterization with planned percutaneous coronary intervention, loading with 60 mg prasugrel resulted in greater platelet inhibition than a 600-mg clopidogrel loading dose. Maintenance therapy with prasugrel 10 mg/d resulted in a greater antiplatelet effect than 150 mg/d clopidogrel. (Circulation. 2007;116:2923-2932.)

Key Words: anticoagulants • antiplatelet agents • coronary disease • platelets • thrombosis

Pharmacological inhibition of platelets with a combination of aspirin and a thienopyridine is a key strategy for the prevention of recurrent ischemic events in patients with acute coronary syndromes and those undergoing percutaneous coronary intervention (PCI).1–4 Despite important clinical benefits of clopidogrel, significant limitations exist.5 Clopidogrel at approved doses has a delayed antiplatelet effect, requiring a substantial period of pretreatment to achieve the desired antiplatelet effect.6

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From the TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital, Boston, Mass (S.D.W., S.A.M., C.H.M., E.M.A., E.B.); Cardiovascular Division, Massachusetts General Hospital, Boston (M.O.); Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany (D.T., F.-J.N.); Center for Platelet Function Studies, Departments of Pediatrics, Medicine and Pathology, University of Massachusetts Medical School, Worcester (A.L.F., A.D.M.); University of Florida, College of Medicine, Jacksonville (D.J.A.); The Heart Institute, Sheba Medical Center, Tel Hashomer, Sackler Faculty of Medicine, Tel Aviv, Israel (H.H.); Institut de Cardiologie and INSERM Unit 856, Petie-Salpetriere University Hospital, Paris, France (G.M.); Lilly Research Laboratories, Eli Lilly and Co, Indianapolis, Ind (D.L.M., J.A.J.); and Nottingham Clinical Research Ltd, Nottingham, UK (R.C.).

The online Data Supplement, which contains an Appendix listing the participants in Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) can be found with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.740324/DC1.

Guest Editor for this article was James E. Udelson, MD.
Correspondence to Stephen D. Wiviott, MD, Brigham and Women’s Hospital, Cardiovascular Division, 75 Francis St, Boston, MA 02115. E-mail swiviott@partners.org
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clinical effect. In addition, clopidogrel at approved doses achieves a modest antiplatelet effect by laboratory testing, and although no standard definition exists, studies estimate that up to one third of patients have poor antiplatelet responses (or “resistance”) to clopidogrel.

Prasugrel is a third-generation thienopyridine. Both prasugrel and clopidogrel require cytochrome-dependent metabolism for activity; however, prasugrel is more efficient with a single-step rather than a multiple-step process for activation. Studies in healthy volunteers and patients with chronic coronary artery disease have shown that prasugrel is more potent, more rapid in onset, and more consistent in inhibiting platelet aggregation than standard doses of clopidogrel. Because of the frequent use of higher-than-approved LD clopidogrel in clinical practice and the potential future use of higher-MD clopidogrel, we designed the present study to compare prasugrel with higher than the currently approved 300-mg LD and 75-mg/d MD of clopidogrel.

Methods

Patient Population

Subjects were eligible for enrollment if they were at least 18 years of age and were scheduled to undergo cardiac catheterization with planned PCI for angina and at least one of the following: coronary angiography within 14 days with at least 1 lesion amenable to PCI, a functional study within 8 weeks with objective findings of ischemia, or prior PCI or coronary artery bypass graft surgery. Key exclusions included planned PCI for immediate treatment of myocardial infarction, any thienopyridine within 5 days, glycoprotein (GP) IIb/IIIa inhibitor within 7 days or planned use (balloon was permitted), high risk of bleeding, thrombocytopenia, or anemia. All subjects provided written informed consent before participation. A sample size of 96 evaluable subjects with PCI was expected to yield 90% power to demonstrate a 15% absolute difference in inhibition of platelet aggregation (IPA) with 20 µM ADP at 6 hours, assuming α=0.05 and intersubject variability of 25% for clopidogrel and 15% for prasugrel. We estimated that it would be necessary to enroll 180 subjects to obtain 110 subjects with PCI, a telephone call at day 15 was performed to assess clinical events.

Platelet measures included LTA and the VerifyNow P2Y12 assay (Accumetrics, San Diego, Calif) and VASP. For all subjects, measures were performed at 30–5 minutes (except VASP), at 2 hours (±10 minutes), or after completion of the diagnostic angiogram, whichever occurred sooner (except VerifyNow), and 6 hours (±30 minutes) after the LD. For PCI subjects only, platelet measures were performed at 18 to 24 hours, the 15-day visit, and the 29-day visit (except VerifyNow). An independent physician monitored bleeding and adverse event data.

Laboratory Procedures

Before study participation, study participants were trained by core laboratory personnel to ensure consistent LTA protocols among sites, and local tracings were reviewed for quality before the first subject was randomized at each site. Blood was drawn from venipuncture or indwelling catheters. The first 5 mL was to be discarded. For LTA, blood was drawn into a 4.5-mL, 3.2% citrate Vacutainer tube and centrifuged to prepare platelet-rich plasma and platelet-poor plasma. ADP aliquots were prepared centrally and shipped to investigative sites. LTA was determined with 20 µM ADP at 6 hours after sampling. Percent inhibition was reported and corrected for baseline aggregation (IPA at time t after LD)/(IPA at baseline) × 100. Evidence of hemolysis, platelet count of the 100, IPA (final)/thrombin receptor activation peptide–stimulated aggregation (base)]. For VASP assays, sam-

Clinical Perspective

Studies of higher loading doses (LDs) and maintenance doses (MDs) of clopidogrel have reported small but statistically significant improvements in the speed of onset, intensity, and consistency of inhibition. Although there are limited prospective data to support clinical superiority,17,18 many clinicians use higher doses of clopidogrel in clinical practice, and recent guidelines support this practice in selected patients.4,19

Figure 1. Schematic of trial design of PRINCIPLE-TIMI 44.
plewere drawn into a citrated tube, capped, stored, and shipped at ambient temperature to 1 of 2 core labs (University of Massachusetts, Worcester, for US sites and Herz-Zentrum, Bad Krozingen, Germany, for European and Israeli sites). VASP phosphorylation in response to prostaglandin E1, with and without ADP was determined by whole-blood flow cytometry as described in the manufacturer’s brochure (BioCyte, Marseilles, France) using a single lot of fluorescently labeled monoclonal antibody. Flow cytometers were calibrated daily with a single standardization protocol (and a single lot of calibration particles) at both core laboratories. VASP phosphorylation data were displayed as platelet reactivity index (in percent) defined as \[ \frac{\text{MFI(PGE1)} - \text{MFI(PGE1 + ADP)}}{\text{MFI(PGE1)}} \times 100 \], where MFI is mean fluorescence index and PGE1 is prostaglandin E1. A lower platelet reactivity index indicates greater antplatelet effect.

Each determination was assessed for validity by the blinded core laboratory personnel using standardized criteria for each assay type. Conditions that invalidated LTA samples included but were not limited to hemolysis, very low platelet-rich plasma platelet counts (<150 000/µL), and instability of baseline in LTA tracings indicating instability of sample temperature or preagonist sample activation. Samples considered to be invalid were not included in the analyses, and subjects were considered to be nonevaluable for the given measure and time point. For IPA analyses, for a subject to be evaluable at time t, both a valid baseline measurement and time t MPA measurement were required. For MPA, VerifyNow, and VASP samples considered to be invalid were not included in the analyses, an LD and did not receive a GP IIb/IIIa inhibitor, regardless of PCI status. The primary efficacy measure of the MD phase was IPA with 20 μmol/L ADP determined after 14±2 days of prasugrel compared with 14±2 days of high-dose clopidogrel, including both precrossover and postcrossover periods during the MD phase. Thienopyridine hyperresponsiveness was defined as IPA with 20 μmol/L ADP <20% based on previous work.25 Key secondary end points for the LD and MD phases were mean MPA with 20 μmol/L ADP and mean VerifyNow percent inhibition. An MPA >50% on therapy was considered another key prespecified measure of poor response to antiplatelet therapy.15 Additional efficacy measures include primary and key secondary measures at 30 minutes, 2 hours, and 18 to 24 hours; IPA with 5 μmol/L ADP; and IPA (final).

Clinical
The primary safety measure was non–coronary artery bypass graft surgery–related TIMI major or minor bleeding in the treated subjects through the 15-day visit. Bleeding events were adjudicated by an independent clinical events committee if there was a hemoglobin decrease of ≥3 g/dL or if bleeding required medical or surgical therapy or specific laboratory evaluation according to previously published definitions.26 Bleeding events reported by investigators regardless of clinical events committee adjudication were considered adverse hemorrhagic events. The key clinical efficacy end point was clinical events committee–adjudicated major adverse cardiac events, including cardiovascular death, myocardial infarction, and stroke occurring during the combined LD and precrossover MD phase.

Statistical Analysis
Treatment Populations
The LD-phase analysis population consisted of subjects who received the LD of the study drug and did not receive a GP IIb/IIIa inhibitor. This population was used for all analyses of platelet function measures within 24 hours after the LD, although only subjects with PCI had 18- to 24-hour measures. The MD-phase analysis population consisted of subjects who received a PCI regardless of whether they received a GP IIb/IIIa inhibitor. This population was used for all analyses of platelet function measures >24 hours after the LD. In every instance, the analyses considered only subjects with evaluable measurements available for a given time point.

General Considerations
All tests were 2-sided and conducted at an \( \alpha = 0.05 \) level of significance. All CIs presented were 2-sided 95% CIs. Standard 2-sample comparisons between treatment groups were carried out using the following methods unless otherwise specified. Categorical data were compared by use of Pearson’s \( \chi^2 \) test, except when the absolute number of events in each group was <10, in which case Fisher’s exact test was used. Continuous data were compared with a 2-sample \( t \) test. The analyses were performed by the Department of Statistics at Nottingham Clinical Research Ltd (Nottingham, UK) using SAS version 9.1 or S-PLUS 6.2 (SAS Institute Inc, Cary, NC). The TIMI Study Group had full access to raw trial databases, and all key analyses were independently verified.

Study Measures
Means and SDs are used to describe the platelet function measures (IPA, MPA, VASP, and VerifyNow P2Y12 measurements). The primary analysis for LD-phase platelet function measures was assessed by the difference between the treatment groups and analyzed with an ANCOVA model with factors for treatment and study site, and a single covariate for MPA at baseline. This is expressed as adjusted least square (LS) mean difference between treatment arms with 95% CIs or probability value.

The MD-phase primary efficacy measure was analyzed via a hierarchical ANCOVA (or mixed-effects) model with factors for treatment, study site, study phase, treatment order ("carryover"), and subject within treatment order as a random effect and a covariate for MPA value at baseline. For IPA measures, data were included for subjects with evaluable maximal MPA measurements taken before treatment and after 14±2 days of treatment with either of the study medications (ie, precrossover and/or postcrossover visit measurements). The rates of hyperresponsiveness during the MD phase were analyzed with an exact Prescott test for subjects with both day 15 and 29 data available. Key secondary and additional platelet function analyses were performed in the same manner as the primary analyses.

Clinical Measures
Major adverse cardiac events were evaluated in the on-treatment population during the loading and precrossover maintenance period (from LD to 15-day visit). The frequency of major adverse cardiac events was summarized by treatment group and study period among all subjects who were treated with the study medication and received PCI. The primary safety measure, non–coronary artery bypass graft surgery–related TIMI significant bleeding, was compared in the on-treatment precrossover group (through the 15-day visit) using an exact logistic regression model, and the incidence of all bleeding events (TIMI major or minor bleeds and other hemorrhagic nonserious adverse events) was summarized similarly. Events occurring after crossover are reported in a descriptive manner only.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree with the manuscript as written.

Results
There were 201 subjects randomized at 14 investigative sites in 4 countries (see the Appendix in the Data Supplement). Baseline features of the randomized subjects were well matched (Table 1). Pretreatment platelet aggregation was similar with mean MPA with 20 μmol/L ADP in the prasugrel group (mean±SD, 75.7±11.8%) compared with the clopidogrel group (77.0±9.7%; \( P = 0.43 \)). Four subjects received a GP IIb/IIIa inhibitor at the time of PCI and were
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel (n=102)</th>
<th>Clopidogrel (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>28.4</td>
<td>22.2</td>
</tr>
<tr>
<td>Age, mean (25%–75%), y</td>
<td>64 (56–71)</td>
<td>63.8 (57–70)</td>
</tr>
<tr>
<td>Age &gt;65 y, %</td>
<td>54.9</td>
<td>52.5</td>
</tr>
<tr>
<td>BMI, mean, kg/m²</td>
<td>28.7</td>
<td>29.4</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>30.4</td>
<td>28.3</td>
</tr>
<tr>
<td>HTN, %</td>
<td>85.3</td>
<td>77.8</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>16.7</td>
<td>22.2</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>90.2</td>
<td>86.9</td>
</tr>
<tr>
<td>DM, %</td>
<td>32.4</td>
<td>29.3</td>
</tr>
<tr>
<td>Smoker (current), %</td>
<td>17.6</td>
<td>16.2</td>
</tr>
<tr>
<td>Angina, CCS III or IV,</td>
<td>37.3</td>
<td>38.4</td>
</tr>
<tr>
<td>P for index event, %</td>
<td>53.9</td>
<td>57.6</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; MI, myocardial infarction; HTN, hypertension; CABG, coronary artery bypass grafting surgery; DM, diabetes mellitus; CCS, Canadian Cardiovascular Society; statin, hydroxymethyl glutaryl coenzyme A reductase inhibitor; and PCI, percutaneous coronary intervention. P=NS for all comparisons.

Excluded from LD-phase analyses, which therefore included 197 subjects (99 prasugrel, 98 clopidogrel). Across all timepoints, 149 of 1134 potential samples were considered invalid for MPA with 20 μmol/L ADP measurement (13.1%), with the major reasons being hemolysis (n=74), platelet-rich plasma platelet count <150 000/μL (n=22), insufficent sample (n=12), or unstable baseline (n=12). There were no statistically significant differences in the number of evaluable subjects by treatment or differences in baseline characteristics of evaluable compared with nonevaluable subjects or between nonevaluable subjects compared by treatment group. The flow of subjects through the trial and the number evaluable for the key efficacy measures are summarized in Figure 2.

LD-Phase End Points
The primary efficacy end point of IPA with 20 μmol/L ADP at 6 hours after LD was significantly greater after prasugrel 60 mg (mean, 74.8±13.0%) compared with clopidogrel 600 mg (31.8±21.1%), with an LS mean difference of 43.2% (95% CI, 38.0 to 48.4; P<0.0001). In addition to a greater antiplatelet effect (higher mean IPA), subjects treated with prasugrel had more consistent levels of inhibition, with lower intersubject variability (F-test probability value comparing standard deviations <0.0001). The greater antiplatelet effect of the prasugrel LD measured by IPA with 20 μmol/L ADP was apparent after 30 minutes (30.8±29.0% versus 4.9±13.2%; P<0.0001) and maintained through 18 to 24 hours (Figure 3A). Fewer prasugrel-treated subjects met predefined criteria for hyporesponsiveness (Table 2).

Prasugrel also showed greater antiplatelet effect as assessed by the key secondary end points with lower levels of MPA with 20 μmol/L ADP (18.9±9.5% versus 52.1±16.1%), LS mean difference of 33.1% (95% CI, 29.2 to 37.1; P<0.0001), and greater platelet inhibition with the VerifyNow P2Y12 assay (89.5±10.5% versus 83.4±26.1%), LS mean difference of 51.4% (95% CI 45.5 to 57.4), P<0.0001, at 6 hours. Overall, consistent differences between the treatment groups were seen across multiple platelet inhibition measures and time points, including IPA with 5 or 20 μmol/L ADP, MPA with 5 or 20 μmol/L ADP, and IPA (final) with 5 or 20 μmol/L ADP (Table 3). Greater inhibition of ADP signaling as measured by VASP also was demonstrated at each time point (Figure 3B).

MD-Phase End Points
The primary efficacy end point of IPA with 20 μmol/L ADP after 14±2 days of MD therapy (ie, day 15 and 29 data combined) was significantly greater in subjects receiving prasugrel 10 mg/d (mean 61.3±17.8%) compared with clopidogrel 150 mg/d (46.1±21.3%), with an LS mean difference of 14.9% (95% CI, 10.6 to 19.3; P<0.0001). Similar results with highly significant differences between groups were seen for IPA with 20 μmol/L ADP at day 14 and 29 visits (Figure 4A). Prasugrel demonstrated a greater antiplatelet-

Figure 2. Subject disposition. Listed in each box is the number of subjects evaluable for a given measure at a given time point. W/D indicates withdrawal; D/C, discontinuation.
let effect with lower MPA (29.2±13.2% versus 40.9±15.9%), LS mean difference of 11.3% (95% CI, 8.1 to 14.5; \(P<0.0001\)). Greater platelet inhibition with the VerifyNow P2Y12 assay (83.3±16.0% versus 65.1±23.1%), LS mean difference of 18.9% (95% CI, 11.7 to 26.1; \(P<0.0001\)), also was seen at 15 days. Consistent differences between treatment groups were seen across multiple measures of platelet aggregation and time points, including IPA with 5 or 20 \(\mu\)mol/L ADP, MPA with 5 or 20 \(\mu\)mol/L ADP, and IPA (final) with 20 \(\mu\)mol/L ADP (Table 4). In addition, more inhibition of ADP signaling was demonstrated with a lower VASP platelet reactivity index (Figure 4B). Despite the lack of washout period, no carryover effect was seen.

### Table 2. Prevalence of Thienopyridine Hyporesponsiveness

<table>
<thead>
<tr>
<th>Time Point</th>
<th>(n)</th>
<th>Prasugrel, %</th>
<th>Clopidogrel, %</th>
<th>(P)</th>
<th>(n)</th>
<th>Prasugrel, %</th>
<th>Clopidogrel, %</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 0.5 h</td>
<td>143</td>
<td>42.9</td>
<td>87.7</td>
<td>&lt;0.0001</td>
<td>144</td>
<td>50</td>
<td>98.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>At 2 h or after catheterization</td>
<td>152</td>
<td>2.7</td>
<td>55.1</td>
<td>&lt;0.0001</td>
<td>153</td>
<td>8.1</td>
<td>79.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>At 6 h</td>
<td>149</td>
<td>0</td>
<td>27.3</td>
<td>&lt;0.0001</td>
<td>149</td>
<td>0</td>
<td>49.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>At 18–24 h</td>
<td>85</td>
<td>0</td>
<td>30.4</td>
<td>0.0002</td>
<td>86</td>
<td>0</td>
<td>51.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Precrossover MD</td>
<td>86</td>
<td>2.5</td>
<td>15.2</td>
<td>0.06</td>
<td>87</td>
<td>7.5</td>
<td>21.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Postcrossover MD</td>
<td>85</td>
<td>2.2</td>
<td>10</td>
<td>0.18</td>
<td>86</td>
<td>8.7</td>
<td>25.0</td>
<td>0.04</td>
</tr>
<tr>
<td>MD phase</td>
<td>171</td>
<td>2.4</td>
<td>12.8</td>
<td>0.02</td>
<td>173</td>
<td>8.1</td>
<td>23.0</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Precrossover indicates 15-day visit only; postcrossover, 29-day visit only; and MD phase, measures from 15- or 29-day visits.
Clinical End Points
Both treatments were well tolerated. No TIMI major bleeds were observed in either treatment arm during the study period. No subject discontinued study drug prematurely for bleeding. Two subjects (2.0%) in the prasugrel group and no clopidogrel-treated subject experienced a TIMI minor bleeding episode before the crossover. There were no TIMI major or minor bleeding events reported after the LD phase (day 2 to 29) in either treatment group. When all investigator-reported hemorrhagic adverse events (regardless of whether events met TIMI major or minor hemorrhage criteria) were included, a total of 19 subjects (18.6%) in the prasugrel group experienced a bleeding event compared with 14 subjects (14.1%) in the clopidogrel group during the LD and precrossover MD period ($P=NS$). After crossover, 4 subjects in the clopidogrel followed by prasugrel group and no subject in the prasugrel followed by clopidogrel group experienced a hemorrhagic adverse event.

Major adverse cardiac events end points also were infrequent. One subject in the clopidogrel group had acute stent thrombosis resulting in a myocardial infarction and required urgent target vessel revascularization, and 2 subjects in the prasugrel group had periprocedural myocardial infarctions. One subject in the prasugrel followed by clopidogrel group experienced a myocardial infarction after the crossover. No deaths or strokes occurred in either treatment group.

Discussion
In this trial, we compared the effects of a prasugrel 60-mg LD and 10-mg/d MD with high-dose clopidogrel (600-mg LD and 150-mg/d MD) on laboratory measures of platelet function. We observed substantially and statistically significantly greater platelet inhibition with prasugrel at all time points studied during the LD and MD phases. In the LD phase, pretreatment with prasugrel 60 mg before cardiac catheterization in subjects with presumed coronary artery disease showed substantially greater levels of IPA than 600 mg of clopidogrel when measured by LTA (using 2 agonist concentrations and multiple metrics: IPA, IPA [final], and MPA), VerifyNow P2Y12, and VASP platelet reactivity index. Highly significant differences emerged at 30 minutes, the time of the first assessment, and were present at every time point measured throughout the LD phase. Prasugrel also exhibited more rapid onset of antiplatelet effects, and fewer subjects treated with prasugrel had poor response measured with IPA and MPA at each time point.

Published data comparing prasugrel with the standard approved LD of clopidogrel (300 mg) in healthy subjects and patients with chronic coronary artery disease not undergoing cardiac catheterization or PCI showed higher levels of IPA and less variability. The data from PRINCIPLE-TIMI 44 extend the results of preliminary reports of the comparison of 60 mg prasugrel with 600 mg clopidogrel observed in healthy subjects and patients with chronic coronary artery disease. Our findings indicate that prasugrel is more potent and consistent in the setting of procedures such as vascular access and PCI and that prasugrel can be expected to achieve rapid, high, and consistent levels of inhibition of ADP-induced platelet aggregation in this clinical setting.

Several studies have shown increased inhibition, faster onset, and fewer poor responders with 600-mg clopidogrel compared with 300-mg LDs. As a result, testing of even higher LDs of clopidogrel has been undertaken to try to improve further on these parameters. In both the Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis (ALBION)
Table 4. MD-Phase Platelet Function Measures

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>P</th>
<th>LS Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA with 20 μmol/L ADP, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precrossover MD</td>
<td>87</td>
<td>28.5 ± 12.9</td>
<td>41.5 ± 14.1</td>
<td>0.0004</td>
<td>12.1 (7.4–16.8)</td>
</tr>
<tr>
<td>Postcrossover MD</td>
<td>86</td>
<td>29.7 ± 13.6</td>
<td>40.2 ± 17.9</td>
<td>&lt;0.0001</td>
<td>11.0 (6.1–16.9)</td>
</tr>
<tr>
<td>MD Phase</td>
<td>173</td>
<td>29.2 ± 13.2</td>
<td>40.9 ± 15.9</td>
<td>&lt;0.0001</td>
<td>11.3 (8.1–14.5)</td>
</tr>
<tr>
<td>VerifyNow P2Y12, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precrossover MD</td>
<td>103</td>
<td>83.3 ± 16.0</td>
<td>65.1 ± 23.1</td>
<td>&lt;0.0001</td>
<td>18.9 (11.7–26.1)</td>
</tr>
<tr>
<td>IPA to 5 μmol/L ADP, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precrossover MD</td>
<td>87</td>
<td>63.3 ± 17.6</td>
<td>48.5 ± 19.1</td>
<td>0.0006</td>
<td>12.9 (5.7–20.0)</td>
</tr>
<tr>
<td>Postcrossover MD</td>
<td>86</td>
<td>62.9 ± 16.4</td>
<td>52.2 ± 20.3</td>
<td>0.002</td>
<td>12.1 (4.6–19.6)</td>
</tr>
<tr>
<td>MD phase</td>
<td>173</td>
<td>63.1 ± 16.9</td>
<td>50.2 ± 19.6</td>
<td>&lt;0.0001</td>
<td>12.8 (8.9–16.7)</td>
</tr>
<tr>
<td>IPA (final) with 20 μmol/L ADP, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precrossover MD</td>
<td>86</td>
<td>88.3 ± 16.3</td>
<td>73.1 ± 26.4</td>
<td>0.001</td>
<td>14.0 (5.9–22.1)</td>
</tr>
<tr>
<td>Postcrossover MD</td>
<td>85</td>
<td>88.2 ± 20.7</td>
<td>72.6 ± 26.7</td>
<td>0.0008</td>
<td>16.8 (7.2–26.4)</td>
</tr>
<tr>
<td>MD phase</td>
<td>171</td>
<td>88.2 ± 18.6</td>
<td>72.9 ± 26.3</td>
<td>&lt;0.0001</td>
<td>14.5 (8.1–20.0)</td>
</tr>
</tbody>
</table>

n indicates number of subjects with evaluable measure; precrossover MD, 15-day visit only; postcrossover MD, 29-day visit; and MD phase, all measures from 15- or 29-day visits. Values for prasugrel and clopidogrel are mean ± SD. The prespecified primary point of IPA with 20 μmol/L ADP is shown in Figure 4.

The ISAR-CHOICE 2 study randomized 60 patients after successful PCI to 150 or 75 mg/d clopidogrel. Both showed greater platelet inhibition with 150 compared with 75 mg/d but also the persistence of variability of response and the presence of poor responders. No clinical outcomes data with high- compared with standard-MD clopidogrel are available. Findings of an improved pharmacological profile have led some to speculate that higher-MD clopidogrel may result in improved clinical outcomes, although few have adopted this into clinical practice at this time.

PRINCIPLE-TIMI 44 is the first study to compare prasugrel with high-MD clopidogrel in any patient population. The results of our study extend the observation regarding the pharmacological superiority of a MD of prasugrel 10 mg/d to a higher-than-standard dose of clopidogrel (150 mg/d) with greater levels of inhibition and fewer patients with poor response. Furthermore, this study suggests that even if a 150-mg/d MD of clopidogrel is adopted in the future, greater inhibition of platelet function would be achieved with prasugrel 10 mg/d.

As would be expected from greater platelet inhibition data, rates of hemorrhagic events tended to be higher, although not statistically different, in the prasugrel-treated subjects. If these trends toward more bleeding events are confirmed in larger trials, it will be important to assess the balance among efficacy, safety, and tolerability with prasugrel. The present study was not powered to detect clinical efficacy differences between the 2 treatment groups, and there were too few major adverse cardiovascular events in the present study to draw any meaningful conclusions in this regard.

A growing body of literature links poor antiplatelet response to clopidogrel to adverse clinical outcomes, including recurrent ischemic events, periprocedural myocardial infarction, and stent thrombosis. Although these data establish an association between aggregation and ischemic events, it remains uncertain whether this is merely a marker of risk or a modifiable risk factor. The Antithiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARTMYDA)-2 study comparing 600 versus 300 mg clopidogrel before PCI showed lower rates of periprocedural MI with the higher dose. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction 38...
Study Limitations

LTA requires very precise sample conditions and processing. Even among expert sites with experience in platelet function testing, a significant proportion of samples did not meet prespecified conditions and were excluded from analyses. This had the potential to reduce the power of the study to detect a difference between treatments, although highly significant differences were still seen. There were no significant differences in baseline characteristics among subjects who were evaluable or not evaluable for the primary end point or among nonevaluable subjects between therapies, making any influence on the study outcomes unlikely. The number of nonevaluable subjects in a controlled study with experienced sites raises concern about the utility of LTA for routine clinical monitoring. The absence of a washout period between MD treatments also could be considered limiting; however, this could not be performed acutely because of the use of coronary stents in PCI subjects. The duration of treatment should have been adequate to remove any influence of the prior therapy, and no carryover effect was observed.

Conclusions

Among subjects undergoing cardiac catheterization and planned PCI, a 60-mg prasugrel LD resulted in more rapid
onset and higher and more consistent levels of antiplatelet effect than a 600-mg clopidogrel LD given at least 30 minutes before catheterization. Similarly, prasugrel 10 mg/d resulted in higher and more consistent levels of antiplatelet effect than 150 mg/d clopidogrel. If a clinical goal is to achieve higher levels of IPA, this can be done more effectively with prasugrel than high-dose clopidogrel.

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Disclosures

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18. Wolfram RM, Torguson RL, Hassani SE, Xue Z, Gevikorn N, Pichard AD, Satler LF, Kent KM, Waksman R. Clopidogrel loading dose (300 versus 600 mg) strategies for patients with stable angina pectoris sub-
A growing literature relates the extent and variability of antiplatelet response to clopidogrel to clinical ischemic events. In part, the increasing use of higher-than-approved doses of clopidogrel in clinical practice is based on the desire for greater levels of inhibition of platelet aggregation and more rapid onset of antiplatelet effect. Prasugrel is a new thienopyridine that is more potent than standard-dose clopidogrel in healthy subjects and patients with stable coronary artery disease. The relative antiplatelet effects of prasugrel versus high-dose clopidogrel in percutaneous coronary intervention patients are unknown. Therefore, we addressed this question in the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial, comparing prasugrel 60-mg loading dose followed by 10 mg/d versus clopidogrel 600-mg loading dose followed by 150 mg/d in 201 patients undergoing cardiac catheterization for planned percutaneous coronary intervention. Greater inhibition of platelet aggregation at all time points measured from 30 minutes to 24 hours was observed with patients receiving prasugrel compared with high-loading-dose clopidogrel. During the maintenance-dose phase, greater inhibition of platelet aggregation also was seen in subjects receiving prasugrel compared with high-maintenance-dose clopidogrel. The trial was not powered for clinical end points. Bleeding tended to be more frequent with prasugrel, although no significant differences were observed. Prasugrel has been compared with standard-dose clopidogrel in a large-scale clinical events trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction 38 [TRITON-TIMI 38]), and the data from the present study demonstrate that greater inhibition of platelet aggregation is seen with prasugrel compared with high-loading-dose and high-maintenance-dose clopidogrel.
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


for the PRINCIPLE-TIMI 44 Investigators

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