Antiplatelet Therapy

Patients With Poor Responsiveness to Thienopyridine Treatment or With Diabetes Have Lower Levels of Circulating Active Metabolite, but Their Platelets Respond Normally to Active Metabolite Added Ex Vivo

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Objectives
We evaluated the prevalence and mechanism of poor responsiveness to clopidogrel and prasugrel in coronary artery disease patients with and without diabetes.

Background
Low platelet inhibition by clopidogrel is associated with ischemic clinical events. A higher 600-mg loading dose (LD) has been advocated to increase responsiveness to clopidogrel.

Methods
In this study, 110 aspirin-treated patients were randomized to double-blind treatment with clopidogrel 600 mg LD/75 mg maintenance dose (MD) for 28 days or prasugrel 60 mg LD/10 mg MD for 28 days. Pharmacodynamic (PD) response was evaluated by light transmission aggregometry and vasodilator-stimulated phosphorylation. The PD poor responsiveness was defined with 4 definitions previously associated with worse clinical outcomes. Active metabolites (AM) of clopidogrel and prasugrel were measured. Clopidogrel AM was added ex vivo.

Results
The proportion of patients with poor responsiveness was greater in the clopidogrel group for all definitions at all time points from 1 h to 29 days. Poor responders had significantly lower plasma AM levels compared with responders. Patients with diabetes were over-represented in the poor-responder groups and had significantly lower levels of AM. Platelets of both poor responders and diabetic patients responded fully to AM added ex vivo.

Conclusions
Prasugrel treatment results in significantly fewer PD poor responders compared with clopidogrel after a 600-mg clopidogrel LD and during MD. The mechanism of incomplete platelet inhibition in clopidogrel poor-responder groups and in diabetic patients is lower plasma levels of its AM and not differences in platelet P2Y12 receptor function. (J Am Coll Cardiol 2008;52:1968–77) © 2008 by the American College of Cardiology Foundation

Thienopyridines, including clopidogrel and prasugrel, act via antagonism of the P2Y12 receptor and have been used successfully to prevent thrombotic events in patients with acute coronary syndromes and in patients undergoing stent implantation (1,2). Since the first report of a variable response to clopidogrel (3), many studies have shown a high prevalence of patients with pharmacodynamic (PD) poor responsiveness to clopidogrel using a large number of definitions (4–13). The most relevant definitions of PD poor responders are those that have been associated with worse clinical outcomes. In the literature at least 4 definitions of insufficient platelet inhibition (poor responders) by clopidogrel have been linked to clinical end points: 1) change in maximal platelet aggregation (ΔMPA) <10% associated with post-percutaneous coronary intervention (PCI) myonecrosis (5–7); 2) MPA >50% associated with...
post-procedural ischemic events 1 year after PCI (8–10); 3) residual platelet aggregation (RPA) at 6 min >14% linked to 30-day major adverse cardiac events post-PCI (14); and 4) platelet reactivity index (PRI) with vasodilator-stimulated phosphoprotein (VASP) >50% linked to subacute stent thrombosis (13,15,16). Furthermore, diabetic patients have consistently been shown to be poor responders to clopidogrel, with worse clinical outcomes (1,2,17–19). The mechanisms for the poor response to clopidogrel in some patients are unclear, although genetic, metabolic, cellular, and clinical factors have been proposed (20). More recent work suggests that reduced generation of active metabolite (AM) may contribute to clopidogrel poor responsiveness (21).

We recently examined the effect of 60-mg prasugrel compared with a 600-mg clopidogrel loading dose (LD) and found a faster onset and greater platelet inhibition with prasugrel treatment because of more efficient generation of its AM (22). Prasugrel 60 mg, compared with 300-mg clopidogrel, reduces the number of poor responders according to a Bayesian definition of poor responders (23). A 600-mg clopidogrel LD has been advocated to decrease clopidogrel response variability.

The aims of the present study were to use previously published clinically relevant definitions of low PD platelet inhibition to: 1) determine the number of PD poor responders to a clopidogrel 600-mg LD and 75-mg maintenance dose (MD) compared with a prasugrel 60-mg LD followed by 10-mg MD; 2) evaluate the PD poor-responder groups by characterization of the pharmacokinetics of clopidogrel and prasugrel AMs; and 3) examine P2Y12 receptor function in PD poor responders by the addition of the clopidogrel AM ex vivo.

**Methods**

**Patients and study design.** This randomized, double-blind, double-dummy, 2-arm, parallel-group study was conducted in adult male and female patients with stable coronary artery disease, ages 40 to 75 years (Fig. 1). The detailed protocol and main results have been published elsewhere (22). All patients were administered an LD of either prasugrel 60 mg or clopidogrel 600 mg on Day 1 followed by either prasugrel 10 mg or clopidogrel 75 mg as a once-daily MD for a total of 28 ± 3 days. On Days 1 and 2, 14 ± 3, and 29 ± 3, study medications were administered at the study site after an overnight fast.

**PD analyses.** Light transmission aggregometry (LTA). The adenosine 5’-diphosphate (ADP)-induced platelet aggregation was measured in platelet-rich plasma by LTA on Day 1 at baseline (pre-dose); 30 min, 60 min, 2 h, 4 h, and 24 ± 4 h post-LD; Day 14 ± 3; and Day 29 ± 3. The LTA was performed within 180 min from venipuncture on a BioData PAP-4 optical aggregometer (Alpha Laboratories, Eastleigh, United Kingdom), with temperature maintained at 37°C and using each subject’s platelet-poor plasma to set 100% light transmission. Platelet aggregation was allowed to proceed for approximately 7 min after addition of 5-μM ADP. The MPA was the highest value achieved during this observation period. In addition, the mean change from baseline (pre-LD) in MPA (ΔMPA) was calculated for each time point and used for statistical analyses. The RPA was the level of platelet aggregation present at 6 min after addition of the ADP agonist. The ADP concentration used was 5 μM for ΔMPA <10%, MPA >50% and RPA >14%.

**VASP PHOSPHORYLATION.** The VASP phosphorylation assay was performed using a commercially available method according to the manufacturer’s specifications (Biocytex Platelet VASP kit, Marseille, France). The VASP assay is a commercial kit in which the concentration of ADP is not disclosed.

**Pharmacokinetic analyses.** Concentration of AM. Plasma concentrations of prasugrel AM (R-138727) and clopidogrel AM (R-130964) were analyzed in samples obtained at 30 min and 1, 2, 4, and 6 h post-LD, during the MD period on Day 2 pre-MD, and on Days 14 and 29 at 30 min and 1, 2, and 4 h post-MD as previously described (22).

**ADDITION OF CLOPIDOGREL AM EX VIVO.** The AM of clopidogrel (10-μM final concentration; provided by Daiichi Sankyo Co., Ltd., Tokyo, Japan) was added ex vivo to samples collected at baseline (pre-LD) and pre-dosed on Day 29 as previously described (22,24).

**Statistical analyses.** The geometric mean area under the curve (AUC) for the AM, with the corresponding 95% confidence limits, was calculated for the PD poor and good responder groups, respectively, after LD and during MD. Differences between groups were evaluated using the Student t test. The values of the AUC were transformed to natural logarithms before analyses. Similar analyses were performed for diabetic compared with nondiabetic patients after LD and during MD. Differences between groups were evaluated with analysis of variance adjusted for treatment. Ex vivo LTA and VASP data from the ex vivo addition of clopidogrel AM experiment were analyzed to compare the platelet response in treated and untreated samples from the same individual. Differences between groups were evaluated with an analysis of variance model compensating for treatment. Differences in
the relative number of diabetic patients in the poor-responder compared with good-responder groups were evaluated with Cochran-Mantel-Haenszel statistics compensating for treatment. The software used for statistical analyses was SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

**Results**

**Patients.** A total of 110 subjects (55 in each arm) were enrolled in the study (101 men and 9 women), and 106 subjects completed the study: 54 on prasugrel and 52 on clopidogrel (Fig. 1).

**Proportion of poor responders according to 4 clinically relevant definitions of poor responders.** The proportion of patients with PD poor responsiveness varied between 9.6% and 92.5% in the clopidogrel-treated patients, depending on definitions and time after thienopyridine LD, despite the high 600-mg clopidogrel LD (Fig. 2A, Table 1). In contrast, the proportion of patients with poor responsiveness varied between 0% and 16.4% in the prasugrel-treated patients, depending on definitions and time after thienopyridine LD (Fig. 2A, Table 1). Similar results were found during the MD phase at pre-dose on Day 29 thienopyridine MD (Fig. 2B, Table 1). During MD the number of clopidogrel poor responders varied between 15% and 53% using the ΔMPA <10%, MPA >50%, or VASP PRI >50% definitions, whereas the prasugrel poor responders varied between 2% and 4%. The RPA >14% definition resulted in the highest number of PD poor responders, up 63% to 72% for clopidogrel and 22% to 28% for prasugrel. The proportion of patients with PD poor responsiveness was greater in the clopidogrel group compared with prasugrel-treated patients for all tested definitions both following LD and during MD.

**Pharmacokinetics of AM after oral administration of study drug.** For all 4 definitions of poor response, patients defined as PD poor responders at 2 h after the clopidogrel LD had a significantly lower AM AUC than did patients who were PD responders: ΔMPA <10% 0.160 ± 0.057 μM·h versus 0.263 ± 0.028 μM·h, p < 0.01; MPA >50% 0.186 ± 0.041 μM·h versus 0.264 ± 0.035 μM·h.
that the groups did not differ in baseline P2Y12 receptor function. There was no difference in PRI (%) at baseline, indicating a baseline and after ex vivo addition of the clopidogrel AM.

The number of poor responders was higher in the clopidogrel-treated group at all time points regardless of definition of poor responsiveness. Likewise, patients defined as PD poor responders to clopidogrel, based on the Day 29 MD PD response, had significantly lower clopidogrel AM AUC after MD than did PD responders: ∆MPA <10% 0.045 ± 0.013 μM·h versus 0.067 ± 0.018 μM·h, p < 0.01; MPA >50% 0.049 ± 0.011 μM·h versus 0.068 ± 0.009 μM·h, p < 0.01; RPA >14% 0.057 ± 0.007 μM·h versus 0.072 ± 0.0017 μM·h, p = 0.05; VASP (PRI) >50% 0.049 ± 0.0008 μM·h versus 0.074 ± 0.01 μM·h, p < 0.01 (poor responders vs. good responders respectively) (Fig. 3A).

The number of PD poor responders in the prasugrel-treated patients was small in most groups, and a statistical comparison of AM levels therefore was not possible.

Inhibition of P2Y12 receptors evaluated by the VASP assay at baseline and after addition of AM ex vivo in poor responders compared with responders. Inhibition of P2Y12 receptors is more specifically assessed with the VASP phosphorylation assay because, in contrast to LTA, effects on the P2Y1,ADP receptor are not detected. We therefore compared the PD poor-responder group (defined as VASP PRI >50%) to the responder group at baseline and after ex vivo addition of the clopidogrel AM. There was no difference in PRI (%) at baseline, indicating that the groups did not differ in baseline P2Y12 receptor function. There also was no difference in the reduction of PRI (%) after addition of AM either before LD or during MD, indicating that the P2Y12 receptor function and affinity for the AM is similar for poor responders and good responders (Fig. 4).

The numbers of diabetic patients in 4 clinically relevant definitions of poor responders. Ten patients in the prasugrel-treated group and 9 in the clopidogrel-treated group were previously diagnosed as having diabetes. The fraction of patients with diabetes was consistently higher among PD poor-responder patients at most of the treatment time points (evaluated with Cochrane-Mantel-Haenszels test, diabetes mellitus vs. nondiabetes mellitus, adjusted for treatment number of patients in subgroups).

Pharmacokinetics of AM after oral administration of study drugs in diabetic patients. Compared with patients without diabetes, there was a trend toward a lower AM AUC in diabetic patients taking clopidogrel or prasugrel (Fig. 5). Statistical evaluation of all clopidogrel- and prasugrel-treated patients, with compensation for treatment, yielded significantly lower levels of AM in patients with diabetes at post-LD 2 h (p = 0.0064) and at MD Day 29 (p = 0.0047) compared with those without diabetes.

Inhibition of P2Y12 receptors evaluated by the VASP assay in diabetic compared with nondiabetic patients. We examined PRI (%) in the diabetic patients compared with nondiabetic patients. There was a trend toward higher PRI (%) in both clopidogrel- and prasugrel-treated diabetic patients, both after LD and during MD (Fig. 6). Statistical evaluation of all clopidogrel- and prasugrel-treated patients, using an analysis of variance model compensating for treatment, showed a significantly higher PRI (%) for the thienopyridine treatment in patients with diabetes compared with nondiabetic patients both at 2 h post-LD (p = 0.01) and MD Day 29 (p = 0.02). However, no statistical difference or trend was seen at baseline or at the 2 time points at which AM was added (Fig. 6).

Regression analysis for AM (AUC) versus VASP reactivity index (PRI) in poor-responder subjects defined as RPA >14%. Regression analysis for AM (AUC) versus VASP reactivity index (PRI) in poor-responder subjects defined as RPA >14% at MD Day 29 showed a linear and significant correlation (p < 0.001) (Fig. 7).

Discussion

This study shows that, compared with clopidogrel, prasugrel treatment results in a lower proportion of patients with a poor response using 2 distinct PD assays and several different definitions of PD poor responder previously linked to worse clinical outcomes. The PD poor responders were consistently fewer in the prasugrel-treated patient group...
after LD and during MD despite comparison with the higher 600-mg clopidogrel LD. We found that both PD poor responders and diabetic patients had relatively lower levels of circulating AM. However, the platelets from both poor responders and diabetic patients responded fully to the clopidogrel AM added ex vivo.
A poor response to thienopyridines has been shown to be clinically important, associated with coronary ischemic events and stent thrombosis, which in turn are associated with long-term mortality (4–13,25). We therefore examined the prevalence of PD poor responders to thienopyridines in aspirin-treated patients with stable coronary artery disease. We used 2 different assays and 4 different PD definitions of poor responders that all have previously been shown to be associated with an increase in ischemic coronary events. Prasugrel treatment consistently resulted in few PD poor responders according to any of the 4 definitions during the whole 1-month treatment period (Fig. 2, Table 1). During maintenance dosing the number of clopidogrel poor responders varied between 15% and 53% using the ΔMPA <10%, MPA >50%, or VASP PRI >50% definitions, whereas the prasugrel poor responders varied between 2% and 4%. The RPA >14% definition resulted in the highest number of PD poor responders, from 63% to 72% for clopidogrel and 22% to 28% for prasugrel.

In the clinical situation, it is important to rapidly achieve platelet inhibition when a patient with an acute coronary syndrome is to be treated in the PCI laboratory. A 600-mg clopidogrel dose has been shown to achieve a more rapid platelet inhibition compared with 300 mg (26). In the present study, despite the use of the higher 600-mg LD, clopidogrel resulted in PD poor-responder rates between 19% and 92% during the first 2 h after the LD. In contrast, a 60-mg prasugrel LD resulted in poor-responder rates between 0% and 16%. The reduced number of PD poor responders on prasugrel is likely an

**Table 2** Relative (%) and Absolute Numbers (n) of Diabetic Patients Among Poor Responders

<table>
<thead>
<tr>
<th>Definition of Poor Responder</th>
<th>Time</th>
<th>Clopidogrel No DM (%) (n)</th>
<th>Clopidogrel DM (%) (n)</th>
<th>Prasugrel No DM (%) (n)</th>
<th>Prasugrel DM (%) (n)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔMPA &lt;10% to 5 μM ADP</td>
<td>LD, 1 h</td>
<td>37.8 (17)</td>
<td>75.0 (6)</td>
<td>0.0 (0)</td>
<td>18.2 (2)</td>
<td>0.004</td>
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<tr>
<td></td>
<td>LD, 2 h</td>
<td>18.2 (8)</td>
<td>25.0 (2)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.656</td>
</tr>
<tr>
<td></td>
<td>LD, 4 h</td>
<td>6.8 (3)</td>
<td>25.0 (2)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.112</td>
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<tr>
<td></td>
<td>LD, 24 h</td>
<td>11.1 (5)</td>
<td>37.5 (3)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.057</td>
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<tr>
<td></td>
<td>MD, Day 14</td>
<td>11.1 (5)</td>
<td>37.5 (3)</td>
<td>0.0 (0)</td>
<td>9.1 (1)</td>
<td>0.012</td>
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<tr>
<td></td>
<td>MD, Day 29</td>
<td>15.9 (7)</td>
<td>50.0 (4)</td>
<td>0.0 (0)</td>
<td>9.1 (1)</td>
<td>0.007</td>
</tr>
<tr>
<td>MPA &gt;50% to 5 μM ADP</td>
<td>LD, 1 h</td>
<td>62.2 (28)</td>
<td>87.5 (7)</td>
<td>6.8 (3)</td>
<td>18.2 (2)</td>
<td>0.073</td>
</tr>
<tr>
<td></td>
<td>LD, 2 h</td>
<td>22.7 (10)</td>
<td>62.5 (5)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.024</td>
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<td></td>
<td>LD, 4 h</td>
<td>20.5 (9)</td>
<td>50.0 (4)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.079</td>
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<tr>
<td></td>
<td>LD, 24 h</td>
<td>20.0 (9)</td>
<td>62.5 (5)</td>
<td>0.0 (0)</td>
<td>9.1 (1)</td>
<td>0.003</td>
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<td>MD, Day 14</td>
<td>22.2 (10)</td>
<td>50.0 (4)</td>
<td>0.0 (0)</td>
<td>9.1 (1)</td>
<td>0.029</td>
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<td></td>
<td>MD, Day 29</td>
<td>25.0 (11)</td>
<td>50.0 (4)</td>
<td>0.0 (0)</td>
<td>9.1 (1)</td>
<td>0.048</td>
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<tr>
<td>RPA &gt;14% to 5 μM ADP</td>
<td>LD, 1 h</td>
<td>91.1 (41)</td>
<td>100.0 (8)</td>
<td>13.6 (6)</td>
<td>27.3 (3)</td>
<td>0.168</td>
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<td>LD, 2 h</td>
<td>56.8 (25)</td>
<td>100.0 (8)</td>
<td>0.0 (0)</td>
<td>9.1 (1)</td>
<td>0.005</td>
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<td>45.5 (20)</td>
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<td>0.0 (0)</td>
<td>10.0 (1)</td>
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<td>LD, 24 h</td>
<td>55.6 (25)</td>
<td>87.5 (7)</td>
<td>2.3 (1)</td>
<td>9.1 (1)</td>
<td>0.048</td>
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<td></td>
<td>MD, Day 14</td>
<td>68.9 (31)</td>
<td>87.5 (7)</td>
<td>20.9 (9)</td>
<td>27.3 (3)</td>
<td>0.289</td>
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<td></td>
<td>MD, Day 29</td>
<td>59.1 (26)</td>
<td>87.5 (7)</td>
<td>25.6 (11)</td>
<td>36.4 (4)</td>
<td>0.119</td>
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<td>PRI &gt;50% VASP</td>
<td>LD, 1 h</td>
<td>80.0 (36)</td>
<td>100.0 (8)</td>
<td>9.1 (4)</td>
<td>9.1 (1)</td>
<td>0.300</td>
</tr>
<tr>
<td></td>
<td>LD, 2 h</td>
<td>51.1 (23)</td>
<td>87.5 (7)</td>
<td>2.3 (1)</td>
<td>9.1 (1)</td>
<td>0.096</td>
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<tr>
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<td>LD, 24 h</td>
<td>53.3 (24)</td>
<td>87.5 (7)</td>
<td>0.0 (0)</td>
<td>9.1 (1)</td>
<td>0.073</td>
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<tr>
<td></td>
<td>MD, Day 14</td>
<td>46.7 (21)</td>
<td>87.5 (7)</td>
<td>0.0 (0)</td>
<td>9.1 (1)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>MD, Day 29</td>
<td>40.0 (18)</td>
<td>75.0 (6)</td>
<td>2.3 (1)</td>
<td>9.1 (1)</td>
<td>0.037</td>
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</table>

Poor responders were defined according to 4 definitions previously associated with clinical outcome. Diabetic patients were over-represented among poor responsive patients at most of the treatment time points. The p value was analyzed in the whole population regardless of treatment.

ADP = adenosine 5'-diphosphate; DM = diabetes mellitus; other abbreviations as in Table 1.
important factor for the reduced rates of ischemic events, including significant reductions in stent thrombosis, shown for prasugrel during both the acute and the MD phases of the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction) study (2).

Although several studies have shown that definitions of PD poor responders to clopidogrel are associated with worse clinical outcomes, the physiological differences resulting in the poor response in patients has not been fully elucidated. Genetic alterations in the P2Y12 gene resulting in functional differences have been found (27), but they have not been confirmed by others (28,29), and when we recently examined the incidence of myocardial infarction and risk factors in over 10,000 patients, we did not find any genetic association with the P2Y12 receptor (30). Statin coadministration has not been confirmed as a factor in clopidogrel resistance (31). Instead, a correlation between plasma concentrations of AM and the level of ADP inhibition has been shown (21,22).

Regardless of the definition used, all PD poor-responder groups in our study had lower levels of circulating AM. This was true not only in the mixed group of clopidogrel- and prasugrel-treated patients but also in the patients treated only with clopidogrel (Fig. 3). Thus, PD poor responders are defined by reduced generation of AM. This strongly suggests that the clinically at-risk poor-responder patients most likely differ in their absorption of pro-drug or their
metabolic profile regarding conversion of the pro-drug to the AM. In this regard, there is evidence that variation in the gene encoding cytochrome P450 2C19 that results in decreased 2C19 function is associated with decreased formation of the AM of clopidogrel and a corresponding decrease in the PD response to clopidogrel (32).

There was a clear linear correlation between circulating AM (AUC) versus the VASP reactivity index (PRI%) in poor-responder subjects defined as RPA >14% (Fig. 7). This indicates that the level of AM is crucial for platelet inhibition even within the group of poor responders.

However, a difference in platelet function or receptor affinity for the antagonist could also explain the poor responders. To examine the P2Y$_{12}$ receptor function without confounding effects of the P2Y$_1$ receptor, we used the VASP assay (33). Baseline responsiveness to ADP did not differ between PD poor responders and responders, excluding a generally higher level of platelet reactivity as an explanation for poor response to thienopyridine treatment. Furthermore, addition of AM ex vivo gave a similar near maximal inhibition in both groups, suggesting that the P2Y$_{12}$ receptor-antagonist interactions are unaffected in poor responders.

Angiolillo et al. (17,18) have shown that patients with diabetes mellitus have a higher number of clopidogrel nonresponders and a reduced sensitivity to clopidogrel, and that high platelet reactivity in diabetic patients (MPA >50%) on dual antiplatelet therapy is associated with a higher risk of long-term adverse cardiovascular events. In agreement with their findings, we found a consistently high fraction of diabetic patients in the PD poor-responder groups (Table 2). Despite a similar number of diabetic patients in the treatment groups, there were very few poor-responder diabetic patients in the prasugrel group. The problem of diabetic poor responders seems to be largely confined to the clopidogrel-treated patients. This observation is consistent with the effect on clinical outcomes in diabetic patients in the TRITON study, in whom prasugrel reduced the cardiovascular risk by 30% (2).

Similar to the overall PD poor-responder group, the diabetic patient subpopulation had significantly lower levels of circulating active thienopyridine metabolite (Fig. 5). The diabetic patients did not differ in baseline ADP-stimulated aggregation in the current study, but had an attenuated thienopyridine effect after both LD and MD. However, the responsiveness to added AM was unaffected by the presence of diabetes. Together these results indicate that PD poor responsiveness to clopidogrel in diabetic patients is attributable to insufficient generation of AM, not to alterations in platelet P2Y$_{12}$ receptor function.

The reason that diabetic patients have lower levels of AM is unclear. We are not aware of any effect of diabetes on cytochrome P-450 activity reported in the literature. We could speculate an increased activity of esterases in diabetic patients, which would convert more of the clopidogrel pro-drug into inactive metabolite. This has been seen for aspirin resistance, in which increased activity of plasma esterases hydrolyzed acetylsalicylic acid to a higher extent in
patients with type 2 diabetes (34). Another possibility is that reduced gastric motility in diabetic patients could lead to slower absorption of the pro-drugs or that alterations at the megakaryocyte level changes platelet turnover and receptor expression.

**Conclusions**

Prasugrel treatment results in significantly fewer PD poor responders compared with clopidogrel after LD and during MD, even after the higher 600–mg clopidogrel LD. The impaired platelet inhibition in the clopidogrel poor-responder groups and in diabetic patients reflects lower plasma levels of AM and not differences in platelet P2Y$_{12}$ receptor function.

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**REFERENCES**


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