Randomized Comparison of a High Clopidogrel Maintenance Dose in Patients With Diabetes Mellitus and Coronary Artery Disease

Results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) Study

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Background—After treatment with clopidogrel, patients with type 2 diabetes mellitus (T2DM) have reduced platelet inhibition compared with patients who are not diabetic. Whether platelet inhibition can be enhanced by increasing clopidogrel maintenance dosage in T2DM patients is unknown. The aim of this pilot study was to assess the functional impact of a high maintenance dose in T2DM patients with suboptimal clopidogrel-induced antiplatelet effects.

Methods and Results—T2DM patients on chronic dual antiplatelet therapy were screened to identify suboptimal clopidogrel responders. The latter were randomized to 30-day treatment with a standard (75 mg; n=20) or high (150 mg; n=20) daily maintenance dose. Platelet function was assessed at 3 time points: baseline, 30 days after randomization, and 30 days after resuming standard dosing. Platelet function parameters included adenosine diphosphate–induced (20 and 5 μmol/L) maximal and late platelet aggregation, inhibition of platelet aggregation, platelet disaggregation, and P2Y12 reactivity index. A total of 64 T2DM patients were screened to identify 40 suboptimal responders. After randomization, maximal adenosine diphosphate–induced (20 μmol/L) platelet aggregation was significantly reduced in the 150-mg group compared with the 75-mg group (P=0.002; primary end point). However, suboptimal clopidogrel response was still present in 60% of patients on the 150-mg regimen. All other platelet function parameters showed enhanced clopidogrel-induced antiplatelet effects with 150 mg, which returned to baseline values after resumption of standard dosing.

Conclusions—A 150-mg maintenance dose of clopidogrel is associated with enhanced antiplatelet effects compared with 75 mg in high-risk T2DM patients. However, enhanced ex vivo platelet reactivity continues to persist, the clinical implications of which are unknown and need to be evaluated in large-scale clinical trials. (Circulation. 2007;115:708-716.)

Key Words: clopidogrel ■ diabetes mellitus ■ platelets ■ thrombosis

The P2Y12 receptor plays a pivotal role in platelet aggregation.1 This role is emphasized by the results of clinical trials that demonstrate improvement of long-term clinical outcomes in patients treated with the P2Y12 receptor antagonist clopidogrel.2-4 However, a high interindividual variability in platelet response to clopidogrel has been described.5,6 The fact that subjects with suboptimal platelet inhibition by clopidogrel are at increased risk of cardiovascular ischemic events7-10 represents an alarming clinical problem.

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Inadequate dosing has been postulated as one of the mechanisms for suboptimal clopidogrel-induced antiplatelet effects.11,12 Previous investigations have shown that administration of a higher clopidogrel loading dose enhances platelet inhibition and leads to better response profiles than standard dosing.11,12 In addition, results from small studies suggest that, in patients undergoing percutaneous coronary interventions, the use of a high loading dose of clopidogrel may improve clinical outcomes.13,14 Despite the short-term improvement in platelet response with high loading dosage regimens of clopidogrel, patients may continue to have elevated platelet reactivity in the maintenance phase of antiplatelet therapy.15-19 Of note, readministration of a loading dose of clopidogrel in patients already on maintenance
treatment evokes further platelet inhibition. This observation has raised the hypothesis that an increase of the maintenance dose of clopidogrel may further enhance platelet inhibition, particularly in high-risk patients. However, platelet function assessments with a high clopidogrel maintenance dose regimen in high-risk patients are still lacking. Patients with type 2 diabetes mellitus (T2DM) are characterized by enhanced platelet reactivity and reduced in vitro inhibition, particularly in high-risk patients. However, platelet function assessments with a high clopidogrel maintenance dose regimen in high-risk patients are still lacking.

Patients with type 2 diabetes mellitus (T2DM) are characterized by enhanced platelet reactivity and reduced in vitro inhibition, particularly in high-risk patients. Recent studies have shown that T2DM patients have reduced response to P2Y12 receptor antagonists, including clopidogrel, compared with nondiabetic subjects. T2DM patients are characterized by an upregulated status of the P2Y12 pathway, which in theory may be overcome by the use of more potent P2Y12 antagonists or higher doses of clopidogrel.

The aim of the this pilot study was to assess the impact of a high maintenance dose of the P2Y12 receptor antagonist clopidogrel on platelet function profiles in T2DM patients with coronary artery disease (CAD) on long-term dual antiplatelet therapy who demonstrate suboptimal platelet inhibition. Our hypothesis was that a daily maintenance dose of 150 mg clopidogrel will lead to enhanced platelet inhibition compared with conventional dosage (75 mg) in these high-risk patients.

Methods

Patient Population and Study Design

Patients were eligible for the study if they had T2DM according to criteria from the World Health Organization Report, were on insulin or oral hypoglycemic medication, and were between the ages of 25 and 80 years. All patients included had documented CAD, as all patients had previously undergone percutaneous coronary interventions, and were in a steady state phase of clopidogrel treatment (75 mg daily). Pharmacokinetic and pharmacodynamic profiles may vary profoundly in the initial days or weeks after initiation of dual antiplatelet therapy. Thus, only patients in the maintenance phase of treatment (>30 days from initiation) were included. All patients were also treated with low-dose aspirin (81 mg daily). This dose of aspirin was chosen to reduce bleeding risk in patients on dual antiplatelet therapy. Major exclusion criteria included known allergies to aspirin or clopidogrel; impaired glucose tolerance or T2DM without pharmacological treatment; gestational diabetes, or transient hyperglycemia; blood dyscrasia; serum creatinine level >2 mg/dL; active bleeding or bleeding diathesis; gastrointestinal bleeding within prior 6 months; hemodynamic instability; cerebrovascular accident within 3 months; any malignancy; concomitant use of other antiplatelet therapy. The Optimizing anti-Platelet Therapy In diabetes Mellitus (OPTIMUS) study was a randomized, single-center, prospective, parallel-group platelet function study of patients with T2DM and CAD. Patients were recruited from the outpatient cardiology clinic of our hospital. All patients who met inclusion criteria underwent screening to define their degree of posttreatment platelet reactivity and identify patients with suboptimal clopidogrel-induced antplatelet effects (study time point 1). Only patients with suboptimal clopidogrel responses were eligible for randomization. With the use of a computer-based randomization system, suboptimal clopidogrel responders were assigned to receive a daily clopidogrel maintenance dose with either 150 mg (two 75-mg tablets) or 75 mg (one 75-mg tablets). After randomization, the assigned clopidogrel maintenance dose regimen was maintained for 30 days, at which time platelet function was reassessed (study time point 2). Thereafter, all patients resumed the standard 75-mg daily dose and platelet function was assessed once again after 30 days (study time point 3).

Platelet Function Analysis

Blood samples for platelet function assays were collected from an antecubital vein using a 21-gauge needle 2 to 4 hours after antiplatelet therapy intake. The first 2 to 4 mL of blood were discarded to avoid spontaneous platelet activation. Platelet function measures

Figure 1. Flow diagram of the study.
included assessments of platelet aggregation and the P2Y12 reactivity ratio. Platelet aggregation was performed with light transmittance aggregometry in all patients according to standard protocols. In brief, blood was collected in sodium-citrate tubes. Platelet aggregation was assessed with platelet-rich plasma (PRP) by the turbidimetric method in a 2-channel aggregometer (Chrono-Log Corp., Havertown, Pa) after stimulation with 5 or 20 μmol/L adenosine diphosphate (ADP). PRP obtained as a supernatant after centrifugation of citrated blood at 800 rpm for 10 minutes. The isolated PRP was kept at 37°C before use. Platelet-poor plasma was obtained by a second centrifugation of the blood fraction at 2500 rpm for 10 minutes. The platelet count in PRP was adjusted to the range of 250,000/μL by dilution with autologous plasma when platelet count was out of range. Light transmission was adjusted to 0% with PRP and to 100% platelet-poor plasma for each measurement. Curves were recorded for 6 minutes. Aggregation was measured at maximal aggregation (Aggmax) and at 5 minutes (Agg50). Aggmax is reflective of the activity of both the P2Y12 (involved in initiation of changes in platelet shape and platelet aggregation) and P2Y12 (involved in stabilization of the platelet aggregates) purinergic receptors. However, clopidogrel only blocks the P2Y12 receptor. Therefore, Aggmax is more reflective of the activity of the P2Y12 receptor and stabilization of aggregation. Inhibition of platelet aggregation (IPA) was defined as the percent decrease in aggregation values (Aggmax and Agg50) obtained at baseline and after treatment: IPA (%) = (intensity of aggregation at baseline) − (intensity of aggregation at 30 days) ÷ (intensity of aggregation at baseline). Percentage of platelet disaggregation between Aggmax and Agg50 values was defined as: disaggregation (%) = 100 × (1 − Aggmax ÷ Agg50). Arachidonic acid-induced platelet aggregation was also performed in order to assess compliance and responsiveness to aspirin, defined as Aggmax <20% after stimulus with 0.5 mg/mL arachidonic acid.

The P2Y12 reactivity ratio was determined through measurement of the phosphorylation status of the vasodilator-stimulated phosphoprotein (VASP) by flow cytometry according to standard protocols. The phosphorylation status of VASP (VASP-P) was measured by quantitative flow cytometry (Beckman Coulter FC500, Miami, Fla). In brief, VASP-P levels were quantified with labeled monoclonal antibodies with a commercially available kit (Biocytex Inc., Marseille, France). The P2Y12 reactivity ratio was calculated after measurement of VASP-P levels after stimulation with PGE1 by mean fluorescence intensity (MFI PGE1) and also PGE1 + ADP (MFI PGE1 + ADP). The P2Y12 reactivity ratio is [MFI PGE1 − MFI PGE1 + ADP] × [MFI PGE1] × 100%. A reduced P2Y12 reactivity ratio is indicative of more enhanced clopidogrel-induced inhibition.

**Definition of Suboptimal Clopidogrel Responders**

Clopidogrel responsiveness was defined according to the percentage of Aggmax with light transmittance aggregometry. Patients with a 20 μmol/L ADP-induced Aggmax >50% were considered as suboptimal responders. This Aggmax threshold value was selected on the basis of previous findings demonstrating that patients with such degrees of posttreatment platelet reactivity are at higher risk of ischemic events.

**End Points and Sample Size Calculation**

The primary end point of the study was Aggmax after stimulus with 20 μmol/L ADP 30 days after randomization (at study time point 2). We hypothesized that Aggmax at this time point would be 45±15% in patients randomized to a maintenance dose of 150 mg versus 65±15% in patients maintained on a clopidogrel dose of 75 mg. Estimation of platelet function values were based on our previous reports in patients with T2DM. Thus, 17 patients per group would be required to provide a power of 80% to detect statistical difference between groups with a 2-sided α-level of 0.05.

Other platelet function measures included Aggmax after stimulus with 5 μmol/L ADP; Aggmax after stimulus with 5 and 20 μmol/L ADP; IPA of Aggmax and Agg50 after stimulus with 5 and 20 μmol/L ADP; disaggregation after stimulus of 5 and 20 μmol/L ADP; and P2Y12 reactivity ratio. Inter- and intragroup group comparisons of these platelet function measures were performed at various time points.

**Statistical Analysis**

Normally distributed continuous variables are presented as means±SD. Variables were analyzed for a normal distribution with the Kolmogorov-Smirnov test. Categorical variables are expressed as frequencies and percentages. Differences between groups were assessed with the Fisher exact test for categorical variables. Paired t tests were used for comparison of normally distributed continuous variables in the same group. Unpaired t tests were used for comparison of normally distributed continuous variables between the 2 groups. P<0.05 was considered statistically significant. Statistical analysis was performed with SPSSv14.0 software (SPSS Inc. Chicago, Ill.).

**Results**

Platelet function screening was performed in a total of 64 patients with an Aggmax of 58.05±14.5% induced by 20 μmol/L ADP. Of these, 40 patients (62.5%) showed suboptimal clopidogrel response and were randomized. At study time point 1, Aggmax induced by 20 μmol/L ADP was 66±2% in the 40 patients with suboptimal clopidogrel response, versus 39.9±8% in the remaining 24 patients not eligible for randomization. No differences in baseline demographics existed between patients eligible and ineligible for randomization (data not shown). Baseline demographics of patients randomized to daily clopidogrel maintenance doses of 75 mg (n=20) versus 150 mg (n=20) are shown in Table I. No differences in baseline characteristics existed except for a slightly higher age in patients randomized to the maintenance dose of 150 mg clopidogrel. Use of CYP3A4- and non-CYP3A4-metabolizing statins was similar between the 2 groups. CYP3A4-metabolizing statins were not associated with clopidogrel-induced antiplatelet effects in the present study. Platelet counts (107/μL) were similar between the 2 groups: 307±86 (75-mg group) versus 279±54 (150-mg group) (P=0.21). All patients were compliant and responsive to aspirin. No bleeding complications occurred during the study. No changes in medical therapy, which included T2DM medications or antianginal therapy, occurred during the study. Finally, no patients interrupted clopidogrel or aspirin therapy as a result of side effects.

**Maximal ADP-Induced Platelet Aggregation Profiles**

No differences existed in baseline (study time point 1) Aggmax after stimulus with 20 μmol/L ADP between the 2 groups (Table 2). One month after randomization (study time point 2), patients assigned to a clopidogrel maintenance dose of 150 mg experienced a significant reduction in Aggmax compared with their baseline values and compared with patients randomized to a dose of 75 mg (P=0.002; Figure 2). No changes in Aggmax were observed among patients randomized to standard dosing. Eight patients in the 150-mg maintenance dose group (40%) had an Aggmax after stimulus with 20 μmol/L ADP <50% at study time point 2 versus none in the 75-mg dose group. Intergroup comparisons also showed higher IPA in the 150-mg maintenance dose group (Figure 3A). Cumulative distribution curves of changes in Aggmax and IPA after stimulus with 20 μmol/L ADP illustrate the
Agglate were observed in the 75-mg group at all study time points. ACE inhibitors/ARB; and CYP3A4, cytochrome P450 3A4 isoenzyme.

TABLE 2. Agg max and Agglate Values After Stimulus With 20 μmol/L ADP

<table>
<thead>
<tr>
<th>Study Time Point</th>
<th>75 mg</th>
<th>150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=20)</td>
<td>(n=20)</td>
</tr>
<tr>
<td>Aggmax (μmol/L ADP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 μmol/L ADP</td>
<td>64.9±9</td>
<td>59.7±12</td>
</tr>
<tr>
<td>5 μmol/L ADP</td>
<td>50.7±11</td>
<td>41.3±15</td>
</tr>
<tr>
<td>P</td>
<td>0.32</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD of percentage (%) platelet aggregation. P values reported in the table refer to intergroup comparisons. At study time point 2, patients in the 150-mg dose group had Aggmax and Agglate significantly lower versus study time points 1 and 3 (P<0.001 for intra- and intergroup comparisons). Intergroup comparison also showed lower platelet reactivity (Table 2) and higher IPA (Figure 3A) in the high maintenance group.

At study time point 3, patients assigned to 150-mg dose experienced a return to Aggmax values comparable to those observed at baseline after a switch back to standard dosing (Table 2). In patients assigned to standard dosing, no significant differences in platelet aggregation existed at all 3 study time points (Table 2), a finding that demonstrated a persistent suboptimal response to standard clopidogrel maintenance dose.

**Late ADP-Induced Platelet Aggregation Profiles**

No differences existed in baseline (study time point 1) Aggmax parameters between the 2 groups (Table 2). One month after randomization (study time point 2), patients assigned to a 150-mg clopidogrel maintenance dose experienced a 20% and 15% reduction in Aggmax after stimulus with 20 and 5 μmol/L ADP, respectively (Table 2). No significant changes were observed in patients on the 75-mg dose (Table 2). Intergroup comparison also showed lower platelet reactivity (Table 2) and higher IPA (Figure 3B) in patients assigned to a 150-mg dose at study time point 2. At study time point 3, results paralleled those of Aggmax (Table 2).

**Platelet Disaggregation**

Disaggregation of ADP-aggregated platelets by clopidogrel was similar in both groups at baseline after stimulus with 20 and 5 μmol/L (Figure 5). One month after randomization, patients assigned to a high clopidogrel maintenance dose experienced an increase in platelet disaggregation, whereas no significant changes were observed in patients kept on standard dosing (Figure 5). Enhanced platelet disaggregation...
was observed in patients assigned to a 150-mg versus those receiving a 75-mg maintenance dose. Thirty days after discontinuation of high clopidogrel dose, disaggregation values returned to values comparable with baseline (Figure 5).

**P2Y12 Reactivity Ratio**

At baseline (study time point 1), the P2Y12 reactivity ratio was similar in patients randomized to standard and high clopidogrel maintenance dosing (Figure 6). One month after randomization (study time point 2), the P2Y12 reactivity ratio significantly reduced in patients assigned to the high clopidogrel maintenance dose regimen; the P2Y12 reactivity ratio was also lower compared with patients kept on standard dosing. The P2Y12 reactivity ratio returned to values comparable with baseline in patients randomized to a high clopidogrel maintenance dose regimen after resumption of a standard clopidogrel maintenance dose, whereas no significant changes were observed in patients on standard dosing (Figure 6).

**Discussion**

This randomized prospective study is the first to confirm the hypothesis that a high maintenance dose (150 mg daily) of clopidogrel in a high-risk group of patients with T2DM and CAD enhances platelet inhibition, as assessed by multiple biological determinants of platelet function, compared with a standard dose (75 mg daily). The dose-dependent effect of clopidogrel was confirmed by the return to baseline values of all platelet function measures after discontinuation of the high-dose regimen and recommencement of standard dosing. However, despite an overall improvement in platelet function profiles among patients randomized to a high maintenance dose of clopidogrel, response to antiplatelet therapy remained variable and a considerable proportion of patients persisted with enhanced platelet reactivity. In addition, our study provides further evidence that most patients with T2DM continue to exhibit increased platelet reactivity despite dual antiplatelet therapy, which makes this high-risk group a target population for evaluation of more aggressive antiplatelet treatment regimens.

In patients diagnosed with acute coronary syndromes and/or treated with percutaneous coronary interventions, adjunctive treatment with clopidogrel in combination with aspirin has been shown to be superior to aspirin alone for secondary prevention of ischemic events, including in patients with diabetes mellitus. In addition, clopidogrel has been shown to be superior to aspirin, especially in patients with diabetes mellitus. However, despite the clinical benefit associated with clopidogrel treatment, diabetic patients continue to have a higher risk of ischemic events compared with nondiabetic patients, a difference that may be attributed, at least in part, to suboptimal responsiveness to antiplatelet therapy.

Suboptimal clopidogrel-induced antiplatelet effects observed with currently recommended dosing regimens have been reported by various investigators with the suggestion that they contribute to poor clinical outcomes. Dose-finding studies that support the currently recommended doses of clopidogrel were designed to achieve a level of platelet inhibition similar to 500 mg of ticlopidine per day. These dose-finding studies did not take into consideration the prothrombotic milieu of high-risk subjects, such as T2DM. Previous reports have shown that suboptimal clopidogrel responsiveness poses considerable risk of ischemic events. High loading doses (≥600 mg) have been proposed as a strategy to accelerate and enhance platelet inhibition compared with a standard loading dose of 300 mg and to improve short-term clinical outcomes compared with standard clopidogrel therapy. However, the antiplatelet effects of clopidogrel front-loading are confined to the initial phase of therapy, and patients rely on their daily maintenance dose for long-term prevention of ischemic events. Our study confirms that a long-term maintenance strategy with standard recommended doses is suboptimal in most patients with T2DM and CAD. Furthermore, our study shows that improvements in...
platelet inhibition are transient and confined to the period of high
doses of clopidogrel therapy, and that high platelet reactivity
is a persistent state in these patients.

Patients with T2DM have increased platelet reactivity and
reduced in vitro responsiveness to antiplatelet agents, which
include P2Y12 receptor antagonists, compared with nondia-
betic subjects.18,19,21 Numerous mechanisms can account for
platelet dysfunction in T2DM.31 In vitro studies have shown
that insulin reduces platelet aggregation by inhibition of the
P2Y12 pathway.21,22,32 In fact, human platelets are targets of
the effects of insulin, which interacts with its own receptor on
the platelet surface and leads to loss of Gi activity. This loss
reduces suppression of cyclic adenosine monophosphate,
which thus inhibits P2Y12 signaling and reduces platelet
reactivity.21,22 However, platelets of T2DM patients are also
targets of the insulin resistance phenomenon that typically
affects T2DM patients and results in decreased sensitivity to
insulin.32 This decreased sensitivity leads in turn to upregu-
lation of the P2Y12 pathway and increased platelet reactivity
in diabetic platelets. Other mechanisms responsible for sub-
optimal clopidogrel-induced antiplatelet effects in T2DM
include increased exposure to ADP, increased cytosolic levels
of calcium, and increased platelet turnover.32

Suboptimal responsiveness to clopidogrel represents an
emerging clinical entity. This phenomenon has been associ-
ated with recurrence of ischemic events, which include stent
thrombosis.7–10,28,31 Stent thrombosis may lead to severe
consequences and has become a major concern in the era of
drug-eluting stents. Importantly, diabetes mellitus has been
identified as an independent predictor of stent thrombosis.33
Current guidelines (class IIb indication, level of evidence C)
state that in patients in whom stent thrombosis may be
catastrophic or lethal, platelet aggregation studies may be
considered and the dose of clopidogrel increased to 150 mg
per day if <50% inhibition of platelet aggregation is demon-
strated.34 A similar approach may be utilized in clinical
practice, but essentially no data exist on the efficacy, either
biological or clinical, of this treatment regimen.

The present study provides the first biological evidence
that 150 mg of clopidogrel may indeed improve platelet
inhibition in high-risk patients who are suboptimal respond-
ers under current standard antiplatelet therapy. Nevertheless,
our study also shown that more than half of the patients
continued to exhibit platelet aggregation <50%, which has
been considered a therapeutic threshold for P2Y12 inhibi-
tion.10 These findings highlight the potential need for more
effective antithrombotic strategies to tackle the diabetic
platelet and that individualized therapy may be required.35
However, individualized therapy with higher maintenance
doses of current medications or with additional or more
potent antiplatelet agents is not yet supported by clinical
studies. Furthermore, large-scale clinical studies have clearly
shown the benefit of standard antiplatelet treatment regimens
in diabetic patients, as recommended in current guidelines, and the results of this pilot ex vivo platelet function analysis should not lead physicians to change their medical practice, as they have not been shown to have clinical implications. Novel and more potent oral P2Y12 receptor antagonists and drugs that inhibit platelet thrombin receptors are currently under clinical investigation and have been shown to have less response variability. These agents may represent potential future alternatives for treating these high-risk patients.

**Conclusion**

In conclusion, this study demonstrates that the currently recommended maintenance dose of clopidogrel is associated with a high incidence of suboptimal response among patients with T2DM and CAD. Based on the results of various platelet function assessments, our study demonstrates the overall biological effectiveness of a 150-mg maintenance dose regimen compared with standard doses of 75 mg in high-risk patients. At the same time, our study found that some patients continue to show high platelet aggregation levels despite increased doses of clopidogrel, a finding that suggests the need for further improvement in our antiplatelet strategies, the clinical implications of which need to be evaluated in large-scale clinical trials.

**Study Limitations**

The present study did not account for performance of multiple significance tests or for potential correlation among various measures of platelet function. Also, our study was not powered to evaluate the risk of bleeding with the use of high-dose clopidogrel in association with aspirin. Thus, the lack of adverse effects in the present study should be interpreted with caution. In addition, the study was not designed to measure clinical outcomes. Therefore, the results of this pilot study need to be considered as exploratory and our laboratory findings should not be applied to clinical practice. Before development of large randomized clinical effectiveness trials that test aggressive antiplatelet therapy, the safety and biological effectiveness, as comprehensively investigated in the present study, of such strategies must be determined. Ultimately, numerous definitions have been reported to describe clopidogrel-induced antiplatelet effects. However, recent studies suggest that posttreatment platelet reactivity rather than responsiveness is a better determinant of ischemic risk. Given that our patient population was composed of patients already treated with clopidogrel, post-treatment platelet reactivity was the most applicable definition of poor response to clopidogrel-induced antiplatelet effects.
effects in our study. In addition, the methods and cut-off values used in our study have been shown to identify patients at highest risk of development of future ischemic events, and this work has been suggested as a therapeutic guide in clopidogrel-treated patients.10

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Disclosures
Dr Angiolillo and Dr Zenni are on the speakers’ bureau and the consultant/advisory board for Bristol Myers Squibb and Sanofi-Aventis. The other authors report no conflicts.

References
Suboptimal response to antiplatelet agents is an emerging clinical entity. Recent investigations have focused on identification of patients with suboptimal antiplatelet drug response. In particular, numerous investigations have identified patients with diabetes mellitus (DM) to exhibit reduced platelet inhibition compared with non-DM patients treated with recommended doses of antiplatelet agents. These findings may explain why DM patients continue to have an increased atherothrombotic risk even with the use of antiplatelet agents. Results from recent investigations demonstrate that selective use of specific antiplatelet agents or modification of their dosage may improve functional response profiles in DM patients. In particular, the Optimizing anti-Platelet Therapy In diabetes Mellitus (OPTIMUS) study demonstrates that specific targeting of the upregulated P2Y12 pathway of platelets from high-risk DM patients, with a higher clopidogrel maintenance dosage, significantly increases platelet inhibition. However, a considerable number of patients continue to exhibit enhanced platelet reactivity. Whether the laboratory findings from this study translate into better clinical outcomes without an increase in bleeding hazards warrants further investigation. Future investigations will need to evaluate how specific blockade of dysfunctional targets of the diabetic platelet as well as tackling plasmatic components extrinsic to the platelet (ie, thrombin), but which contribute to platelet activation and thrombosis, will hamper the prothrombotic status of these high-risk patients. Hopefully, this will lead to an era of individualized antithrombotic treatment regimens to overcome the “one size fits all” concept, performed through routine measurements of platelet activity in the same way that blood sugar, blood pressure, and cholesterol are followed to help guide therapy.
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