# Platelet Response to Clopidogrel Is Attenuated in Diabetic Patients Undergoing Coronary Stent Implantation

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Type 2 diabetes is accompanied by platelet function disorders leading to an accelerated process of atherosclerosis and increased risk for atherothrombotic complications (1–4). Previous data (5,6) suggest a worse outcome for diabetic patients after acute coronary events. Recently, a high variability of response to clopidogrel measured by platelet function tests has been reported (7) among patients with percutaneous coronary intervention (PCI), and hyporesponsiveness to clopidogrel has been considered to influence cardiac outcome in these patients (8–10). Impaired response to antiplatelet therapy in diabetic patients has been reported (11,12) in small patient collectives. However, little is known about the effects of type 2 diabetes on response after a 600-mg clopidogrel loading dose in large unselected cohorts of patients with symptomatic coronary artery disease (CAD).

## RESEARCH DESIGN AND METHODS

— Type 2 diabetic and nondiabetic patients treated by coronary stenting for symptomatic CAD were consecutively enrolled in this study. The protocol was approved by the local ethics committee, and signed informed consent was obtained from all patients. Patients with known platelet function disorders, thrombocytopenia ($<10^5$ cells/mm$^3$), or any contraindications against clopidogrel were excluded. A loading dose of 600 mg clopidogrel was given to all patients before PCI, followed by 75 mg every day. All patients received a daily dose of 100 mg aspirin before PCI. A standard dose of heparin was given to all patients immediately before PCI unless there were no contraindications. Type 2 diabetes was defined according to the recommendations of the American Diabetes Association (13).

Patient blood was collected ≥6 h (46.6 ± 99.3 h) after administration of 600 mg clopidogrel, when maximum platelet inhibition was expected (14). Among the subgroups of diabetic and nondiabetic patients, there was no significant time difference between PCI and light transmittance aggregometry (LTA). Blood samples were collected in 3.8% citrate plasma, as described. Percentage of platelet aggregation was assessed with the turbodimetric method using a Chronolog-Lumi aggregometer (Chronolog, Havertown, PA) with Aggro-Link software 5 min after addition of 20 μmol/l ADP or 5 μg/ml collagen.

We performed a $\chi^2$ test for analysis of dichotomous variables. Differences between means of continuous variables with a normal distribution were evaluated with Student's *t* test. *U* test (Mann-Whitney) was applied to compare platelet aggregation between two subgroups, and a Kruskal-Wallis test was used for comparison of multiple groups. We considered $P < 0.05$ as statistically significant. Analyses were performed with SPSS (Version 13.0; SPSS, Chicago, IL).

## RESULTS

— In this study, 485 patients were consecutively enrolled. Of these, 161 (33.2%) had diabetes, 264 (54%) underwent elective procedure for stable angina, and 221 (46.0%) were treated by PCI for acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, ST elevation myocardial infarction). For diabetic patients, mean A1C was 7.7 ± 1.6% and mean blood glucose levels 172 ± 63 mg/dl.

Posttreatment platelet reactivity to clopidogrel, measured by ADP-induced LTA, was lower in diabetic patients (40.0 vs. 31.8%, $P = 0.01$). There was no significant impact of diabetes on collagen-induced aggregation (42.5 vs. 36.7%, $P = 0.1$).

In a subgroup analysis of patients with coronary stenting for stable angina and patients with ACS, diabetic patients with ACS showed significantly higher posttreatment aggregation (ADP 46.3%, $P = 0.002$ and collagen 45.7%, $P = 0.005$) compared with nondiabetic patients with ACS (Fig. 1). A1C levels did not significantly influence platelet activity in this cohort (44.1 vs. 38.8%, $P = 0.18$).

ADP-induced aggregation was highest in diabetic patients with acute coronary events 6–12 h after first administration of clopidogrel. Thereafter, platelet inhibition was similar in diabetic and nondiabetic patients (Fig. 1). Diabetic patients were slightly older than nondiabetic patients, more frequently suffered from severe left ventricular dysfunction, and received less β-blockers and statins, whereas diuretics were given more frequently. In univariate analysis, there was no significantly different distribution of age, sex, comedication, or cardiovascular risk factors between time groups except for a slightly higher ratio of smokers, mea-

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**Abbreviations:** ACS, acute coronary syndrome; ARMYDA, Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty; CAD, coronary artery disease; EPISTENT, Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial; LTA, light transmittance aggregometry; PCI, percutaneous coronary intervention; RPA, residual platelet activity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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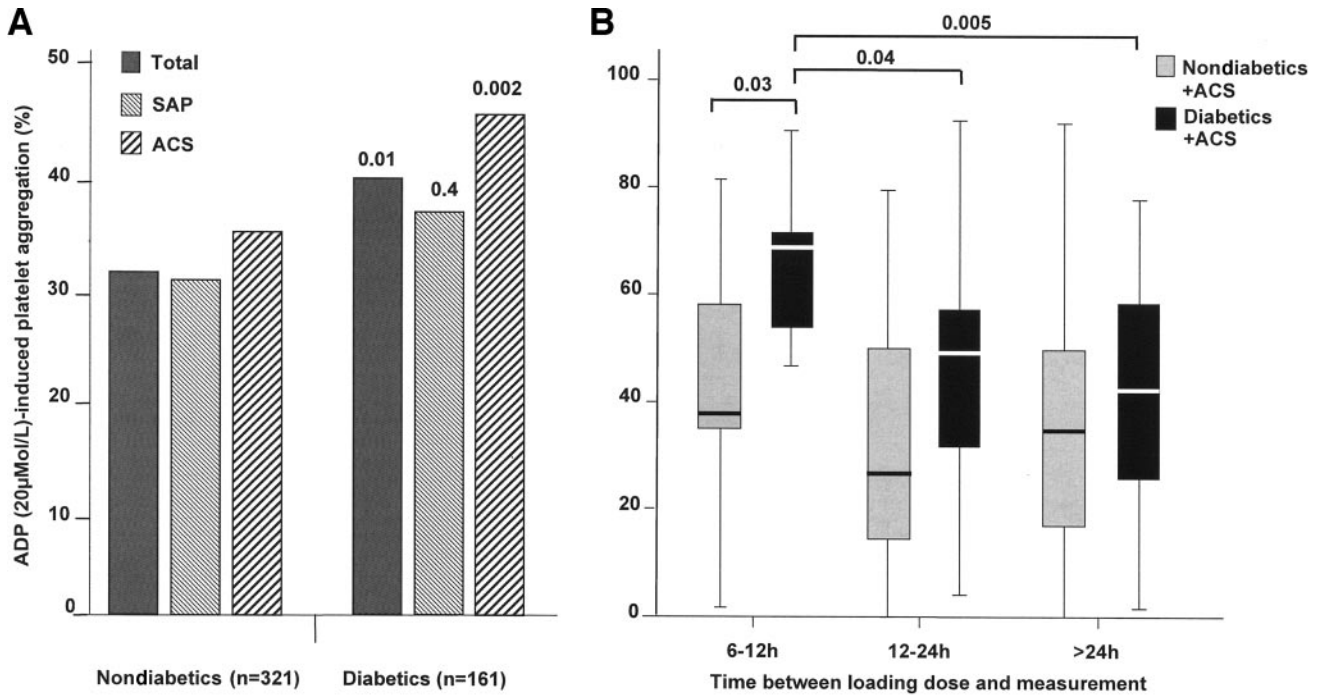


**Figure 1**—A: *Residual ADP (20 μmol/l)-induced platelet aggregation after a 600-mg clopidogrel loading dose in nondiabetic and diabetic patients with subgroups of patients with stable angina and ACS.* P *values describe differences between nondiabetic and diabetic subgroups.* B: *Box plot representing interindividual time dependency of response to clopidogrel measured by ADP (20 μmol/l)-induced platelet aggregation in nondiabetic and diabetic patients with ACS. Each box shows the median, quartiles, and extreme values within a time category.*

sured 6–12 h after a clopidogrel loading dose.

**CONCLUSIONS** — The principal finding of this consecutive study is that diabetic individuals with ACS show a lower response to a 600-mg clopidogrel loading dose. We measured platelet activity by LTA (with ADP), which has been established (7,14) as a reliable method for monitoring clopidogrel effects. As an additional marker of platelet reactivity, we assessed collagen-induced aggregation. Thus, we found type 2 diabetes to be associated with a decreased platelet response in a heterogenous patient cohort with symptomatic CAD. Although diabetic individuals frequently present with other cardiovascular risk factors (such as hypertonus and dyslipidemia) that contribute to chronic platelet activation, we could not observe a significant difference of these factors between diabetic and nondiabetic patients.

The present data suggest that diabetes has a substantial influence on residual platelet activity (RPA) observed in patients with acute coronary events. Thus, diabetic patients presenting with ACS might be at increased risk for recurrent atherothrombotic events partly due to suboptimal platelet inhibition. We did not evaluate relative inhibition by measuring pretreatment reactivity. However, at a time point of >6 h after a 600-mg clopidogrel loading dose, when maximum platelet inhibition is expected (14), RPA was enhanced in diabetic patients. Also, we did not evaluate the influence of insulin therapy on RPA. There are reports (15,16) in the literature that insulin therapy is associated with increased platelet activity in diabetic cardiovascular patients.

Although not intraindividually measured, we observed a time-dependent effect of platelet response ≤24 h. This effect was most distinctive in patients with ACS and mostly independent of other factors in univariate analysis.

In a study of 16 diabetic and 36 nondiabetic patients, Angiolillo et al. (12) found that platelet response was attenuated after a 300-mg clopidogrel loading dose. This difference was still detectable ≤24 h later. The present study suggests that a 600-mg clopidogrel loading dose is not sufficient to overcome this effect, especially in diabetic patients with ACS.

Previous data (17) indicate that platelet hyperactivity plays a major role in the development of thrombotic complications in diabetes. There are data suggesting that diabetic patients gain a higher benefit from an intensified antiplatelet regimen after PCI. In the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)-2 trial (18), 255 patients, including 31% diabetic patients, were randomized to receive either a 300- or 600-mg clopidogrel loading dose 4–8 h before procedure. At 30-day follow-up, the primary end point of death, myocardial infarction, or target vessel revascularization occurred in 4% of patients in the high–loading dose group versus 12% of those in the conventional–loading dose group ($P = 0.041$). In the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT) (19,20), additional treatment of diabetic patients with the platelet glycoprotein IIb-IIIa blockade for coronary stenting resulted in a reduction of 6-month death and myocardial infarction rate from 12.7 to 6.2% compared with stent placebo.

It is well recognized that platelet function in diabetic patients is different from that in nondiabetic patients. Moreover, diabetic patients show a reduced response to aspirin, which is probably related to an altered megakaryopoiesis (21–23). Here, we demonstrate that platelets from diabetic individuals with ACS do not adequately respond to clopidogrel therapy in a time-dependent man-

ner. This can be explained by altered resorption, altered liver metabolism, or altered platelet response. Although diabetic patients benefit from the antithrombotic effects of clopidogrel (24), both previous and present data suggest that an intensified antiplatelet therapy in type 2 diabetic patients with acute coronary events might improve cardiovascular outcome. Further randomized trials are needed to demonstrate the clinical benefit of an intensified or alternative antiplatelet regimen (e.g., novel antiplatelet substances such as prasugrel) in diabetic patients.

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