

Cardiovascular Biology and Cell Signalling

Functional impact of high clopidogrel maintenance dosing in patients undergoing elective percutaneous coronary interventions

Results of a randomized study

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Summary

The currently recommended maintenance dose of clopidogrel is often associated with inadequate platelet inhibition, suggesting the need for a higher dose. The aim of this pilot study was to assess the functional impact of a high (150 mg/day) maintenance dose of clopidogrel in patients undergoing elective percutaneous coronary intervention (PCI). This is a prospective, randomized, platelet function study which was performed in elective PCI patients assigned to treatment with either a 75 mg (n=20) or 150 mg (n=20) daily maintenance dose of clopidogrel for 30 days; afterwards, all patients resumed standard dosing. Platelet aggregation was performed using light transmittance aggregometry following 20 μ M and 5 μ M adenosine diphosphate (ADP) stimuli 30 days after randomization and 30 days after resuming standard dosing. Patients treated with 150 mg/day clopi-

dogrel had lower 20 μ M ADP-induced platelet aggregation compared to patients on 75 mg/day (52.1 \pm 9% vs. 64.0 \pm 8%; $p < 0.001$; primary endpoint). The dose-dependent effect was confirmed by the absolute and relative increase in platelet aggregation after resuming standard dosing ($p < 0.001$). No changes were observed in patients randomized to standard dosing. Parallel findings were observed following 5 μ M ADP stimuli for all assessments. A broad variability in clopidogrel-induced antiplatelet effects was observed irrespective of dosing. In conclusion, a 150 mg/day maintenance dose regimen of clopidogrel is associated with reduced platelet reactivity and enhanced platelet inhibition compared to that achieved with the currently recommended 75 mg/day in patients undergoing elective PCI.

Keywords

Clopidogrel, platelet, coronary stenting

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Introduction

Variability in individual responsiveness to clopidogrel is an emerging clinical problem (1). Numerous factors account for inadequate clopidogrel-induced antiplatelet effects, among which inadequate dosing plays a pivotal role (1–4). Dose finding studies supporting currently recommended dosages of clopidogrel were designed to achieve a degree of platelet inhibition similar to 250 mg/bid of ticlopidine (1,5). Importantly, these studies did not take into consideration the prothrombotic milieu of high risk subjects, such as those with acute coronary syndromes or

undergoing percutaneous coronary interventions (PCI). These factors have represented the basis for the continuous debate over the optimal dosing of clopidogrel which has emerged in recent years.

Numerous investigations have shown that using a higher (\geq 600 mg) than normal (300 mg) clopidogrel loading dose regimen enhances platelet inhibition and improves response profiles (3, 4, 6, 7). Of note, preliminary findings have found that a 600 mg loading dose of clopidogrel is associated with improved clinical outcomes in patients undergoing PCI (8–10). However, the effects of a high loading dose of clopidogrel are limited to the early

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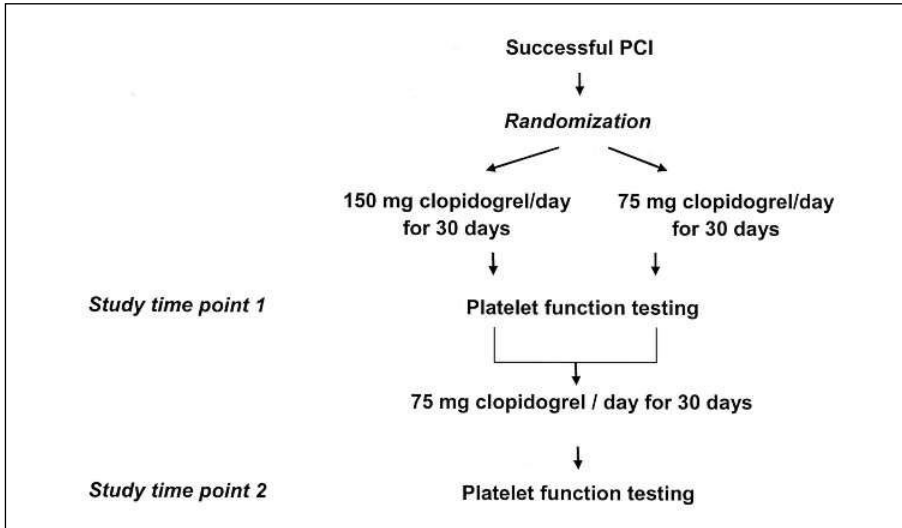


Figure 1: Flow-diagram of the study.

phase of treatment and patients may have inadequate clopidogrel-induced antiplatelet effects when in the maintenance phase of standard treatment (75 mg/daily) (11–18), suggesting the need for a higher maintenance dose regimen. This is also supported by the observation that re-administration of a 600 mg loading dose of clopidogrel in patients already on maintenance treatment leads to further platelet inhibition (19). However, to date, limited data have been available on clopidogrel-induced antiplatelet effects when a high maintenance dose is used (16, 20, 21). The aim of this study was to assess the degrees of post-treatment platelet reactivity and platelet inhibition achieved with 150 mg/day of clopidogrel compared with 75 mg/day. We hypothesized that a 150 mg/day maintenance dosing of clopidogrel exerts enhanced antiplatelet effects.

Materials and methods

Patient population

Patients undergoing elective PCI with coronary stent implantation were eligible for this study. All patients were on chronic treatment with aspirin and were administered a 600 mg loading dose of clopidogrel immediately after the interventional procedure. All patients were treated with low-dose aspirin (≤ 100 mg/daily). This dose of aspirin was chosen in order to reduce the risk of bleeding in patients on dual antiplatelet therapy (22). Major exclusion criteria included: acute and recent (< 3 months) myocardial infarction; blood dyscrasia; serum creatinine level > 2 mg/dL; active bleeding or bleeding diathesis; gastrointestinal bleed within six months; hemodynamic instability; cerebrovascular accident within three months; any malignancy; concomitant use of other antithrombotic drugs (oral anticoagulants, dipyridamole, ticlopidine, cilostazol) or non-steroid anti-inflammatory drugs; platelet count $< 100 \times 10^6/\mu\text{L}$; hematocrit $< 25\%$; liver disease (bilirubin level > 2 mg/dL).

Study design

This was a platelet function study with a randomized and prospective design. Patients who had undergone successful PCI were eligible for randomization. Patients were screened at the post-in-

terventional care units of the two participating institutions. Using a computer-based randomization system, patients were randomized to receive a daily clopidogrel maintenance dose with either 150 mg (two 75 mg tablets) or 75 mg (one 75 mg tablets). The assigned clopidogrel maintenance dose regimen initiated the morning following the interventional procedure and was maintained for 30 days, after which time platelet function was assessed (study time point 1). Thereafter, all patients resumed the standard 75 mg/daily dose and platelet function was assessed once again after 30 days (study time point 2). The latter analysis was performed in order to have a platelet function value while all patients were in the steady state phase of standard dose treatment. It was performed at this time point rather than earlier after PCI (e.g. at hospital discharge) because pharmacokinetic and pharmacodynamic profiles vary in the early phase of treatment (1–3, 6); therefore platelet function values obtained may not reflect the steady state phase. In addition, an assessment at a later time point rather than shortly after PCI would ensure the absence of interventional procedure related factors on platelet reactivity. Blood samples were drawn by operators blinded to the patient's treatment assignment. Laboratory personnel were also blinded to treatment assignments. Patient compliance to antiplatelet treatment was assessed by interview and pill counting. A flow diagram of the study is illustrated in Fig. 1.

The study complied with the Declaration of Helsinki and was approved by the locally appointed ethics committee. All of the patients gave their informed written consent. The present study met all requirements for exemption from the Investigational New Drug (IND) regulations [21 CFR 312.2 (b)] established by the Food and Drug Administration. An independent data safety monitoring committee was instituted for adjudication of adverse clinical events.

Platelet aggregation

Blood samples for platelet aggregation were collected from an antecubital vein. Samples were collected in tubes containing 3.8% trisodium citrate two to four hours after antiplatelet therapy intake and processed within one hour after blood drawing. The first 2–4 ml of blood were discarded to avoid spontaneous pla-

telet activation. Platelet aggregation was performed using light transmittance aggregometry (LTA) according to standard protocols (11–17). In brief, platelet aggregation was assessed using platelet rich plasma (PRP) by the turbidimetric method in a 2-channel aggregometer (Chrono-Log 490 Model, Chrono-Log Corp., Havertown, PA, USA) with the Aggrolink software package (Chrono-Log Corp., Havertown, PA, USA) following 5 and 20 μM adenosine diphosphate (ADP) stimuli. Samples were centrifuged at 120 g for 10 min to recover platelet rich plasma (PRP) and further centrifuged at 850 g for 10 min to recover platelet poor plasma (PPP). Platelet concentration of PRP was adjusted to 2x10⁵/μl by adding homologous PPP. Light transmission was adjusted to 0% with PRP and to 100% for PPP for each measurement. Aggregation was measured at peak. Inhibition of platelet aggregation (IPA) was defined as the percent decrease in aggregation obtained after randomization (study time point 1) compared with that achieved once standard dosing was resumed (study time point 2): IPA (%) = [(intensity of aggregation at study time point 2) – (intensity of aggregation at study time point 1)] / (intensity of aggregation at study time point 2). The absolute change in platelet aggregation was defined as: (intensity of aggregation at study time point 2) – (intensity of aggregation at study time point 1). Arachidonic acid-induced platelet aggregation was also performed in order to assess responsiveness to aspirin, defined as < 20% platelet aggregation following 0.5 mg/ml arachidonic acid stimuli (16).

Endpoints and sample size calculation

The primary endpoint of the study was 20 μM ADP-induced platelet aggregation 30 days after PCI (study time point 1). We hypothesized that a 150 mg maintenance dose of clopidogrel would lead to a 20% absolute reduction of platelet aggregation compared to 75 mg (40±18% in patients randomized to 150 mg maintenance dose versus 60±18% in patients maintained on 75 mg of clopidogrel). Thus, 19 patients per group would be required to provide a 90% power to detect a statistical difference between groups with a two-sided α-level of 0.05.

Statistical analysis

Continuous variables are presented as mean ± SD. Categorical variables are expressed as frequencies and percentages. Paired and unpaired *t*-tests were used for intra-group and inter-group comparisons of continuous variables, respectively. Differences between categorical variables were assessed by means of the Fisher’s exact test. Cumulative distribution curves were generated using absolute changes in platelet aggregation between the 2 study time points as variables to qualitatively describe individual variations in clopidogrel-induced antiplatelet effects. To assess how the degree of platelet reactivity affects drug response achieved with a 150mg/day of clopidogrel, patients were divided into 3 groups according to tertiles of ADP-induced platelet aggregation while on standard dosing. Patients were defined as having high, moderate, and low platelet reactivity from the highest to lowest tertile, respectively (3). Comparisons between groups were made by one-way analysis of variance (ANOVA). Only patients who successfully completed both visits and were compliant to therapy were considered for the analysis. A p-value <0.05 was considered statistically significant. Statistical analy-

Table 1: Baseline characteristics and medical treatment of the study population.

	75 mg (n=20)	150 mg (n=20)	P-value
Age (years)	67 ± 12	59 ± 12	0.036
Gender (male), n (%)	13 (65)	14 (70)	1.00
Risk factors/past medical history, n (%)			
Diabetes mellitus	7 (35)	6 (30)	1.00
Smoking	4 (20)	8 (40)	0.30
Dyslipidemia	12 (60)	12 (60)	1.00
Hypertension	14 (70)	14 (70)	1.00
Obesity (BMI>30 Kg/m2)	7 (35)	11 (55)	0.34
Prior myocardial infarction	3 (15)	6 (30)	0.45
Prior CABG	1 (5)	2 (10)	0.55
Multivessel CAD	14 (70)	11 (55)	0.51
Platelet count (x 1000/mm ³)	254.4 ± 55.5	225.4 ± 58.5	0.10
Haematocrit (%)	39.8 ± 4.3	40.1 ± 4.3	0.40
Creatinine (g/dL)	1.19 ± 0.45	1.03 ± 0.25	0.30
Treatment, n (%)			
Beta-blockers	13 (65)	15 (75)	0.73
Nitrates	5 (25)	2 (10)	0.41
ACE-Inhibitors/ARB	14 (70)	10 (50)	0.33
Lipid-lowering agents			
CYP3A4 metabolizing statin	15 (75)	16 (80)	0.71
Non-CYP3A4 metabolizing statin	5 (25)	4 (20)	1.00

BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass grafting; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; CYP3A4, cytochrome P450 3A4 isoenzyme.

sis was performed using a SPSSv13.0 software (SPSS Inc. Chicago, IL).

Results

A total of 62 patients were eligible for the study. Of these, 16 refused to participate, withdrew consent or did not complete the two study visits; six patients were excluded due to non compliance to antiplatelet therapy. Hence, a total of 40 patients were available for analysis who were randomized to a 150 mg (n=20) or 75 mg (n=20) daily maintenance dose of clopidogrel. Baseline demographics and medical treatment of the study population are summarized in Table 1. There were no differences between the study groups except for age, which was higher in patients randomized to standard dosing. There was a similar use of CYP3A4 and non-CYP3A4 metabolizing statins between the two groups. CYP3A4 metabolizing statins were not associated with clopidogrel-in-

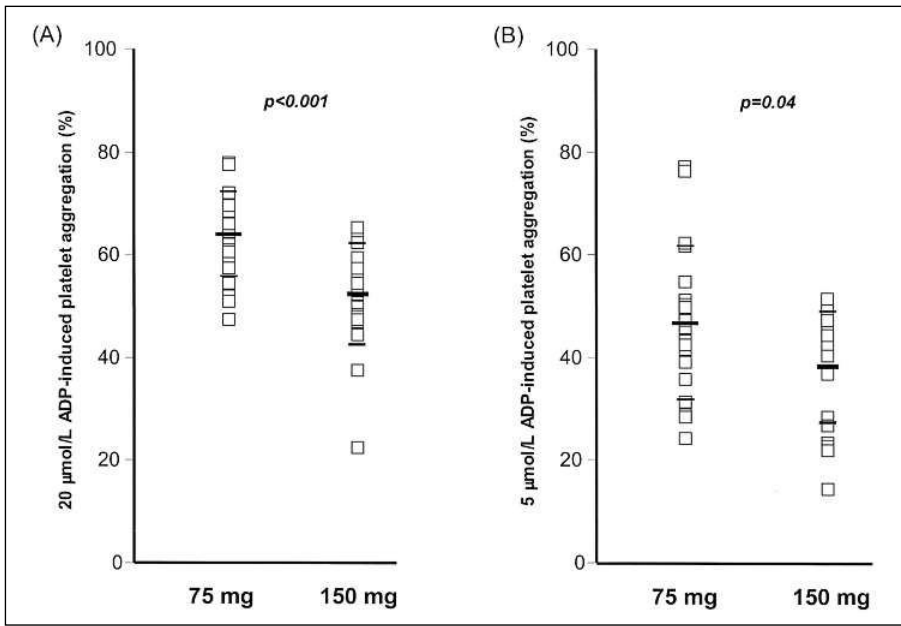


Figure 2: Platelet aggregation following: A) 20 μM and B) 5 μM adenosine diphosphate (ADP) stimuli 30 days after randomization to either 75 mg (n=20) or 150 mg (n=20) daily maintenance dose of clopidogrel. Values are expressed as percentage (%) of maximum platelet aggregation. Boxes represent individual measurements; bars denote mean ± SD.

duced antiplatelet effects (data not shown). There were no bleeding complications or other clinical events during the study period. The 150 mg/day maintenance dose of clopidogrel was not associated with any side effect.

One month following randomization (study time point 1), patients assigned to a 150 mg clopidogrel maintenance dose had significantly lower platelet aggregation values following stimuli with both 20 μM (52.1±9% vs 64.0±8%; $p<0.001$; primary endpoint) and 5 μM (38.0±10% vs 46.9±15%; $p=0.04$) ADP stimuli compared to patients randomized to a 75 mg dose (Fig. 2). One month after resuming standard treatment (study time point 2), patients assigned to the 150 mg dose experienced a significant increase in platelet aggregation ($p<0.001$; Table 2). There were no changes in platelet aggregation between the two study time points in patients randomized to standard dosing (Table 2). A 150 mg maintenance dose of clopidogrel was associated with

enhanced IPA following 20 μM ($p<0.001$) and 5 μM ($p=0.05$) ADP stimuli, while no changes were observed in patients on standard dosing (Fig. 3). All patients were responsive to aspirin (arachidonic acid induced platelet aggregation < 20% in all patients).

A 150 mg/day maintenance dose of clopidogrel was associated with enhanced antiplatelet effects, although a broad individual variation in the degree of antiplatelet effects achieved, as shown by the cumulative distribution curves of absolute changes in 20 and 5 μM ADP-induced platelet aggregation (Fig. 4), was observed. In patients treated with a high maintenance dose, 50% (n=10) and 60% (n=12) had > 10% absolute change in 20 and 5 μM ADP-induced platelet aggregation, respectively. Patients with high platelet reactivity while on a standard 75 mg/day dose, defined as the upper tertile of ADP-induced platelet aggregation in the steady state phase of treatment, had greater responsiveness to 150 mg/day compared to patients with moderate and low platelet reactivity (Fig. 5).

Table 2: Platelet aggregation data.

	T1	T2	p-value *
20 μM ADP			
75 mg	64.0±8	63.4±10	0.71
150 mg	52.1±9	61.7±10	<0.001
p-value **	<0.001	0.58	
5 μM ADP			
75 mg	46.9±15	48.2±13	0.63
150 mg	38.0±10	47.5±11	<0.001
p-value **	0.04	0.78	

Data are expressed as mean ± SD values of percentage of platelet aggregation. ADP, adenosine diphosphate; T1, 30 days after randomization; T2, 30 days after resuming standard dosing; * indicates intra-group comparisons between the two study time points; ** indicates inter-group comparisons between the two study time points.

Discussion

In this randomized prospective study we confirmed the hypothesis that a high maintenance dose (150 mg/daily) of clopidogrel in patients undergoing PCI with stent implantation is associated with a significantly lower post-treatment platelet reactivity compared to a standard dosage (75 mg/daily). The dose-dependent effect of clopidogrel was also supported by the increase in platelet aggregation when standard dosing was resumed. However, despite an overall improvement in post-treatment platelet reactivity and platelet inhibition among patients randomized to a high maintenance dose of clopidogrel, these effects were not homogeneous and antiplatelet effects remained broadly variable irrespective of the dosage used.

Variability in individual responsiveness to clopidogrel is an emerging clinical problem (1). Inadequate clopidogrel-induced antiplatelet effects have been associated with a recurrence of

Figure 3: Inhibition of: A) 20 mM and B) 5 mM adenosine diphosphate (ADP) induced platelet aggregation in patients randomized to 75 mg and 150 mg daily maintenance doses of clopidogrel. Values are expressed as a percentage (%) of platelet aggregation. Error bars indicate standard deviations of the mean.

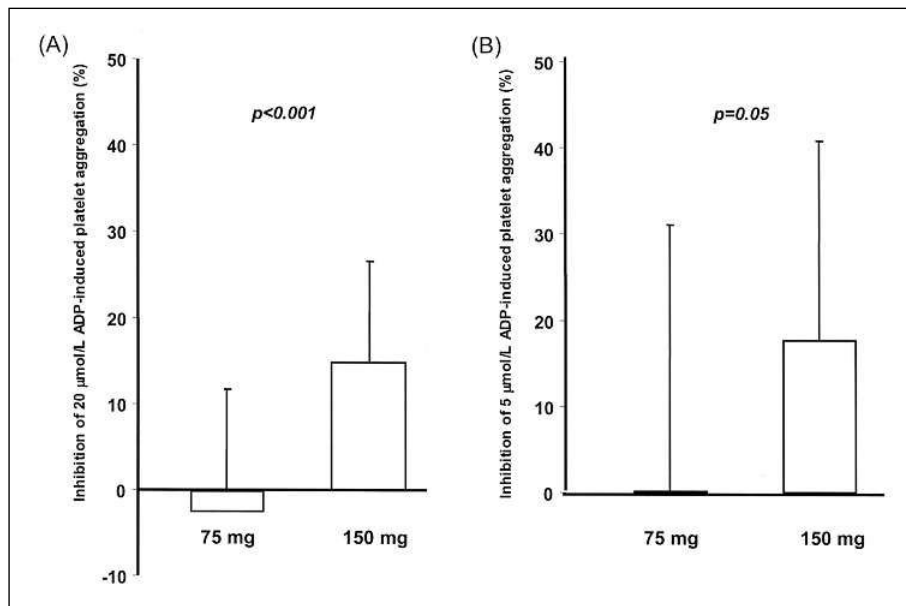
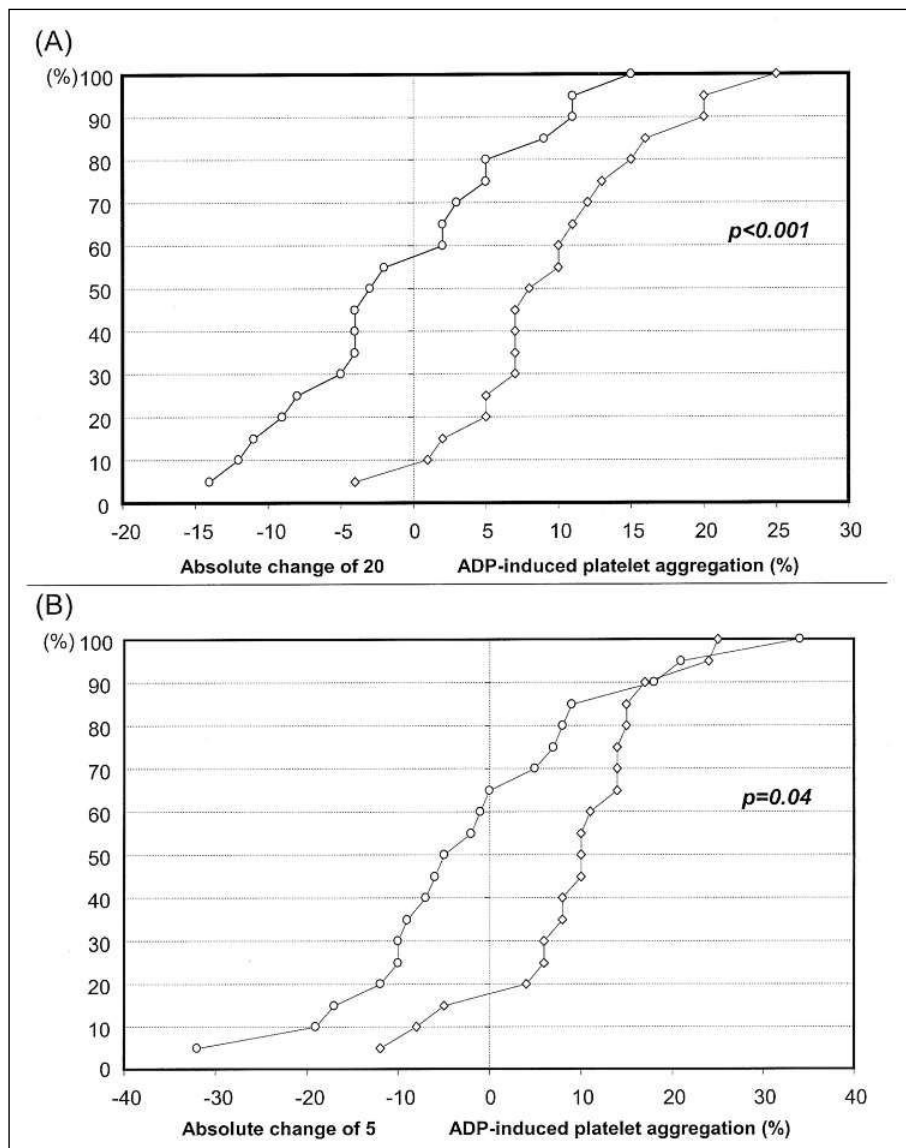


Figure 4: Cumulative distribution curves of absolute changes of: A) 20 mM and B) 5 mM adenosine diphosphate (ADP) induced platelet aggregation in patients randomized to 75 mg (circles) and 150 mg (boxes) daily maintenance doses of clopidogrel. Values are expressed as percentage (%) platelet aggregation. Circles and boxes represent individual changes.



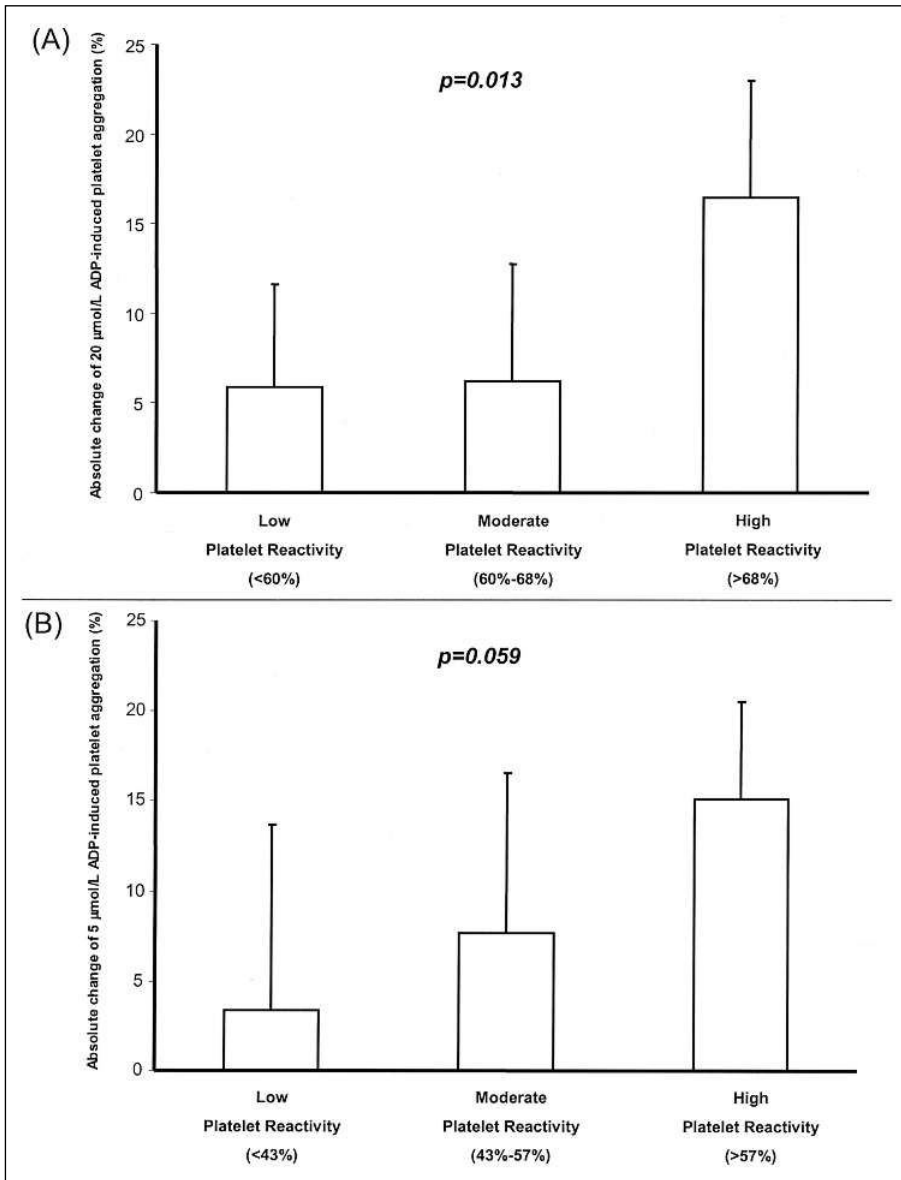


Figure 5: Absolute changes of: A) 20 μmol/L and B) 5 μmol/L adenosine diphosphate (ADP) induced platelet aggregation in patients treated with 150 mg/day of clopidogrel according to the degree of platelet reactivity (high, moderate, or low) while on standard 75 mg/day dosing. Values are expressed as percentage (%) of platelet aggregation. Error bars indicate standard deviations of the mean.

ischemic events, including stent thrombosis (1, 17, 23–34). The majority of these studies have mostly been performed following administration of a loading dose in patients undergoing PCI, in whom insufficient dosing has been demonstrated to be a key determinant of inadequate clopidogrel-induced antiplatelet effects. In fact, high loading doses (≥ 600 mg) accelerate and enhance platelet inhibition compared to a standard 300 mg loading dose (3, 4, 6, 7). Of note, a 600 mg loading dose has shown to improve short-term clinical outcomes (8–10). These clinical benefits are primarily driven by a reduction in peri-procedural myocardial infarction rates. These findings are in line with the biological effects of high clopidogrel dosing, which prevail during the first 24–48 hours after its administration (1, 3). However, inadequate clopidogrel-induced antiplatelet effects may be present in the maintenance phase of therapy (11–18). This is of concern since patients rely on their daily maintenance dose for long-term prevention of ischemic events. Most recently, inadequate platelet inhibition determined in patients while in their maintenance phase

of clopidogrel treatment has been associated with poor long-term clinical outcomes (17–18). Since age is a variable that may contribute to differences in drug metabolism, it may be argued that this may have influenced clopidogrel-induced antiplatelet effects in the present study since patients randomized to 75 mg dosing were slightly older than those assigned to 150 mg. Nevertheless, we did not find any differences in platelet aggregation between the two groups once they had both resumed standard dose treatment.

The potential for using a 150 mg/day maintenance dose of clopidogrel has recently been raised in the updated 2005 ACC/AHA/SCAI guidelines on PCI (35). In fact, a new class IIb indication with a level of evidence C states 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 less than 50% inhibition of platelet aggregation is demonstrated (35). Although this approach is currently used in clinical practice, there is limited data to support it.

To date, only one study has evaluated the impact of a 150 mg maintenance dose of clopidogrel in patients undergoing PCI (20). In this study, a 150 mg daily maintenance dose of clopidogrel was associated with a significant reduction in post-treatment platelet reactivity 30 days following PCI compared to 75 mg. However, in contrast to our investigation, in this report platelet function was only assessed at a single time point, thus impeding to assess changes in platelet aggregation compared to standard dose treatment and to identify patients in whom high dosing is most biologically effective. In our current study, we confirm the impact on post-treatment platelet reactivity of 150mg/day of clopidogrel post-PCI. In addition, we demonstrate the dose-dependent effect of clopidogrel by showing enhanced changes in platelet aggregation over time once patients resumed standard dosing. Similar findings were observed in the OPTIMUS (Optimizing anti-Platelet Therapy In diabetes MellitUS) study (16). However, this study was not performed in patients undergoing PCI and in which a 150 mg maintenance dose was utilized selectively in diabetic patients presenting with suboptimal clopidogrel-induced antiplatelet effects while on chronic treatment (16). Enhanced platelet inhibition using clopidogrel 150 mg was also shown in a non-selective cohort of patients with low-responsiveness to standard dosing while in the maintenance phase of treatment (21). Indeed, none of the studies available testing a 150 mg maintenance dose of clopidogrel, including the present, were designed to evaluate the safety and efficacy of this dose regimen. The safety and efficacy of high clopidogrel dosing, which includes a 150 mg/day maintenance dose, is currently being evaluated in the CURRENT/OASIS-7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for InterventionS) trial (1).

Numerous studies have demonstrated that there is great inter-individual variability in clopidogrel-induced antiplatelet effects achieved when using standard treatment regimens (1–3), suggesting that this phenomenon could be overcome by increasing the dose (3, 4, 6, 7). Although high loading dose regimens reduce the levels of platelet reactivity, this does not narrow the range of antiplatelet effects achieved, which persist highly variable (3, 4, 6, 7, 36). Pharmacokinetic profiles of clopidogrel, and not the potency of its active metabolite per se, account for the broad range of variation in clopidogrel-induced antiplatelet effects (37). New P2Y₁₂ receptor antagonists (prasugrel, AZD6140, cangrelor) characterized by more favorable pharmacokinetic profiles have been associated with more homogenous pharmacodynamic effects (1, 38). It is currently being investigated whether the more potent platelet inhibition and lower variation in antiplatelet effects achieved with these novel agents also translate into better clinical outcomes (1, 38).

A broad range of inter- and intra-individual variability in antiplatelet effects were observed in the present study when using a higher than standard maintenance dose of clopidogrel. However, we did show that the antiplatelet effects achieved with a 150 mg/day maintenance dose regimen were more pronounced in patients with high platelet reactivity while on 75 mg/day, while these were less marked in patients with lower degrees of platelet reactivity. Although the cut-off value of post-treatment platelet reactivity to define when standard dose clopidogrel is less effective is not established, maximal platelet aggregation following

20 μ M ADP stimuli greater than 50% identified the majority (~90%) of patients developing adverse ischemic events post-PCI (26). Accordingly, in the OPTIMUS study this cut-off value was used as a criterion for randomization with 150 mg clopidogrel (16). In the current study a cut-off value was not used as a criterion for randomization and in which, similar to ISAR-CHOICE 2, all patients were randomized irrespective of their platelet function value (20). In particular, we observed that patients with maximal platelet aggregation following 20 μ M ADP stimuli greater than 68% benefitted the most from high maintenance dose treatment. However, in patients with platelet function below this value, the magnitude of the changes were less notable, suggesting this as a cut-off value to be considered for 150 mg clopidogrel maintenance dosing. It is important to note that although patients with lower responsiveness to standard dose clopidogrel benefit most from a higher dosage, the degree of platelet inhibition achieved in these patients using 150 mg still does not yield that of patients with adequate response to standard dosing (21, 39). This suggests that there is a need for alternative and more potent antiplatelet agents in these patients (1, 38). Indeed, it may be argued that in the present study effectiveness to standard clopidogrel dosing was assessed 30 days after the randomization phase was completed, questioning the ideal and practical time point to perform this assessment. Although the assessment of platelet function following PCI, before hospital discharge, has been shown to be associated with adverse outcomes (26), further studies are warranted to find out if this represents an ideal time point to establish whether or not to use more aggressive antiplatelet drug regimens (40–41).

In conclusion, a 150 mg/day maintenance dose regimen of clopidogrel is associated with reduced platelet reactivity and enhanced platelet inhibition compared to that achieved with the currently recommended 75 mg/day in patients undergoing elective PCI. Despite the enhanced clopidogrel-induced antiplatelet effects achieved with a high maintenance dose of clopidogrel, these were not homogeneous and were more pronounced in patients with high platelet reactivity while on standard dosing. Ongoing studies are evaluating the safety and efficacy of high dose regimens of clopidogrel and of newer generation P2Y₁₂ receptor antagonists with more potent antiplatelet effects.

Study limitations

Platelet function before clopidogrel treatment was not assessed. Therefore, our study cannot determine the degree of responsiveness achieved with regard to its pre-thienopyridine treatment status. However, the objectives of this study were to assess how platelet function profiles using a high maintenance dose of clopidogrel compare with those achieved when using a standard dose. The degree of posttreatment platelet reactivity was chosen as the primary endpoint as this has been shown to be a better determinant of ischemic risk than responsiveness (1, 40–41).

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