Premature preoperative discontinuation of antiplatelet drug therapy in cardiovascular risk patients: a preliminary study on the role of P2Y12 receptor monitoring

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Background and objective **In high-bleeding risk procedures, discontinuation of antiplatelet drug therapy with clopidogrel may be requested by surgeons, usually 7–10 days before the surgical procedure. New platelet function tests, such as the vasodilator-stimulated phosphoprotein phosphorylation assay, may help to assess the perioperative status of the clopidogrel-specific P2Y12 receptor.**

Methods **Using vasodilator-stimulated phosphoprotein phosphorylation assay, the platelet reactivity index (PRI) was measured in 80 individuals, including 20 healthy volunteers, 20 cardiologic patients under full antiplatelet drug therapy with clopidogrel and aspirin, 20 surgical patients without any antiplatelet drugs and 20 patients under clopidogrel, discontinued 7 days before the surgical procedure.**

Results **The mean PRI (95% confidence interval) in healthy volunteers was 86 (82–89%) and that in the surgical control group was 77% (72–81%). In cardiologic patients under full antiplatelet therapy, mean PRI was 51% (42–60%). In the clopidogrel discontinuation group, PRI increased from 51% (40–62%) on day 0 to 65% (57–74%) on day 3 and to 76% (69–84%) on day 5. On the morning of surgery, mean PRI was 85% (80–91%). The PRI values on the 5th day were equivalent to those of the surgical control group (mean difference −0.4%, 95% confidence interval −8.6% to 7.8%, $P = 0.9$). Fifty-five percent of the patients in the discontinuation group had a PRI of more than 50% on day 0.**

Conclusion **The study using vasodilator-stimulated phosphoprotein phosphorylation assay, one of the new platelet function assays for the assessment of inhibition of platelet P2Y12 receptor, demonstrates that the PRI on day 5 after discontinuation of clopidogrel is equivalent to a surgical control group and it questions the rigid practice of delaying surgery for 7–10 days, particularly in patients without a clopidogrel effect.** *Eur J Anaesthesiol* **27:138–145**

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Introduction

Antiplatelet drug therapy with clopidogrel and aspirin has become the standard treatment for patients with acute coronary syndrome treated either medically or with percutaneous coronary intervention (PCI) [1–3]. Recent guidelines from national and international task forces recommend a 12-month dual antiplatelet therapy after placement of a drug-eluting stent (DES) and a minimum of 3–4 weeks after bare metal stent (BMS) implantation [4–6]. Premature discontinuation substantially increases the risk of stent thrombosis, myocardial infarction and cardiac death [7,8]. Further indications for clopidogrel with or without aspirin include stent placement in other vessels, such as carotid stenting, and stroke prevention [9,10].

Since the first retrospective study in 2000 [11] and our first case report in the anaesthesiologic literature [12], numerous retrospective studies, case reports as well as a few prospective studies and reviews have signalled the potentially catastrophic risk of premature preoperative discontinuation in noncardiac surgery and the small edge between stent thrombosis and surgical bleeding [13,14]. In 2007, the new American Heart Association/American College of Cardiology (AHA/ACC) guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery stated that the risk of withdrawing antiplatelet therapy should be weighed against the benefit of reduction in bleeding complications from the planned surgery [15]. If thienopyridines must be discontinued before major surgery, aspirin should be continued and the thienopyridine restarted as soon as possible [15].

In a few surgical procedures including neurosurgery, prostate surgery and some others, the responsible surgical

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team may insist on preoperative discontinuation of clopidogrel and aspirin [16–18].

Clopidogrel is a prodrug, activated in the liver to a metabolite that is a specific and irreversible inhibitor of the platelet P2Y12 receptor. Adequate monitoring of platelet function in cardiovascular disease and particularly in antiplatelet therapy remains a relevant problem for the clinician. Light transmission aggregometry (LTA) is still considered to be the gold standard test but has some limitations. New platelet function tests, such as P2Y12 receptor assays, could help to navigate high-risk patients through the perioperative period. The new vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay is currently the most specific P2Y12 assay available [19]. It is a flow cytometry assay employing monoclonal antibodies specific for vasodilator-stimulated phosphoprotein phosphorylation [19]. A good correlation between VASP phosphorylation assay and LTA has been found [20–23].

The goal of our study was to assess preoperative platelet function with the new VASP phosphorylation assay in those patients for whom surgeons had requested preoperative discontinuation of clopidogrel and aspirin 7 days before surgery because of a high-bleeding complication risk. In addition, we specifically addressed the question of normalization of platelet function on day 5.

Methods

The study was approved by the Ethics Committee of the Medical University of Graz, Graz, Austria, and written informed consent was obtained from all individuals. We prospectively enrolled 80 individuals (20 healthy volunteers and 60 patients). To assess centre-specific reference values for the platelet reactivity index (PRI), we included 20 healthy volunteers and 20 surgical patients scheduled for noncardiac surgery. Healthy volunteers and the surgical control patients confirmed that they had not taken clopidogrel or aspirin within the last month. In addition, we included 20 patients after percutaneous cardiac intervention, who were under full dual antiplatelet therapy with 75 mg clopidogrel and 100 mg aspirin daily.

For the clopidogrel discontinuation group, we prospectively enrolled 20 consecutive patients between 2006 and 2008. Study inclusion required that patients be under either monotherapy with 75 mg clopidogrel or dual antiplatelet drug therapy with 75 mg clopidogrel and 100 mg aspirin for more than 1 month, scheduled for noncardiac surgery, with the surgeon's request for preoperative discontinuation of antiplatelet therapy 7 days before the surgical procedure.

The following parameters were measured in all groups: PRI, platelet count [in whole blood and platelet-rich plasma (PRP)], international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, D-dimer, antithrombin and LTA.

Blood sampling

Venous blood was drawn into 3.8% trisodium-citrated Vacutainer tubes (Greiner Bio-One, Kremsmünster, Austria) for platelet aggregation, platelet flow cytometry, coagulation tests and platelet count. Samples were transported to the laboratory with the pneumatic tube transportation system (Swisslog, Steinhagen, Germany) and were analysed within 3 h. For the clopidogrel discontinuation group, blood samples were drawn on four occasions: on the day of the last dose of clopidogrel and aspirin (D0), 3 days after discontinuing clopidogrel and aspirin (D3), 5 days thereafter (D5) and 7 days thereafter on the morning before noncardiac surgery (D7).

Platelet flow cytometry

To determine the VASP phosphorylation state of whole blood, we used a standardized flow cytometric assay (platelet VASP; Diagnostica Stago [Biocytex], Asnières, France). According to Aleil *et al.* [24], a citrated blood sample was incubated with PGE1 or with PGE1 and ADP for 10 min and fixed with paraformaldehyde, after which the platelets were permeabilized with nonionic detergent. The cells were labelled with a primary monoclonal antibody against serine 239-phosphorylated VASP (16C2), followed by a secondary fluorescein isothiocyanate-conjugated polyclonal goat antimouse antibody. The total duration of the preparation following the procedure specified by the supplier did not exceed 30 min. Analyses were performed on a Becton Dickinson (Plymouth, UK) FACS Calibur flow cytometer at a medium rate, the platelet population was identified from its forward and side scatter distribution and 30 000 platelets were gated. A PRI was calculated from the median fluorescence intensity (MFI) of samples incubated with PGE1 or PGE1 and ADP according to the formula

$$\mathrm{PRI} = \left[\frac{\mathrm{MFI}_{(\mathrm{PGE1})} - \mathrm{MFI}_{(\mathrm{PGE1+ADP})}}{\mathrm{MFI}_{(\mathrm{PGE1})}}\right] \times 100.$$

The intraassay coefficient of variation is reported to be less than 5%, and the interassay coefficient of variation less than 8% [25].

Platelet aggregation

Platelet aggregation analysis (Chronolog 560CA; Chronolog Instruments, Haverton, Pennsylvania, USA) was performed *ex vivo* on citrated PRP and calibrated with autologous platelet-poor plasma (PPP). PRP was obtained after centrifugation of whole blood (110*g*, 10 min). PPP was prepared from the same blood sample after centrifugation (4000*g*, 15 min). Platelet aggregation was induced by adenosine diphosphate 5 μmol l^{-1} (Sigma – Aldrich, St. Louis, Missouri, USA). The

increase in light transmission was recorded for 10 min after the addition of the aggregating agonist. Agonist-induced aggregation was evaluated in PRP by measuring the variation of light transmission, assuming that light transmission was 100% in PPP and 0% in unstimulated PRP.

Coagulation tests

PPP was prepared after centrifugation (4000*g*, 15 min). INR, APTT, fibrinogen, D-dimer and antithrombin tests were performed with a Behring Coagulation System BCS (Siemens, formerly Dade Behring, Wien, Austria). Coagulation tests were determined with Dade Behring reagents (Siemens, formerly Dade Behring).

Clinical management

One day after the last dose of clopidogrel or aspirin, low molecular weight heparin (enoxaparin) was given at a dose of 1 mg kg^{-1} daily. Preoperative, intraoperative and postoperative management was left to the discretion of the attending anaesthesiologist. Postoperative reinstitution of antiplatelet therapy was planned as early as possible, usually on the first or second postoperative day, but was a surgical decision.

Perioperative complications

Bleeding complications were defined as surgical redo due to bleeding associated with the surgical procedure and the need to transfuse one or more units of packed red cells due to blood loss associated with the surgical procedure. The threshold for transfusion was left to the attending physician.

Ischaemic complications were defined as

(1) major adverse cardiac events (nonfatal myocardial infarction or cardiac death);
(2) cerebrovascular complications (stroke);
(3) peripheral ischaemic complications involving the lower extremity.

Statistical analysis

Data are presented as means and 95% confidence intervals (CIs) or as absolute and relative frequencies. The agreement of the platelet recovery index (PRI) and the platelet aggregation analysis (LTA) was analysed by the Bland and Altman method. Comparisons between the study groups (healthy volunteers, cardiologic patients, surgical control patients and the clopidogrel discontinuation group at day 0) were performed using one-way analysis of variance (ANOVA) and posthoc Tukey–Kramer multiple-comparison tests. The time course of the discontinuation group was analysed by repeated measures ANOVA and posthoc Tukey–Kramer comparisons. In addition, two-sample *t*-tests were used to compare the PRI of the surgical control group to that of the discontinuation group at each of the four time points. As these tests are considered to be exploratory, no corrections for multiple testing were made.

The level of significance was set at a P value of less than 0.05. The statistical software package SPSS 15.0 (SPSS, Inc., Chicago, Illinois, USA) was used for analysis.

Results

Complete data were collected from 80 individuals (20 healthy volunteers, 20 cardiologic patients, 20 surgical control patients and the 20 patients in the clopidogrel discontinuation group). Demographic characteristics, indication for antiplatelet therapy, comorbidities, preoperative medications, anaesthesia and postoperative complications are summarized in Table 1.

Platelet reactivity index

Mean values ± SD of PRI are presented in Fig. 1. In the healthy volunteers' group, the mean PRI was 86% (82–89%). No individual had a PRI less than 50%. In the surgical control group, the mean PRI was 77% (72%–81%). In this group as well, no patient had a PRI less than 50%.

In the cardiologic control group, the median PRI was 51% (40–62%), and 55% of the patients had a PRI less than 50%. PRI of the clopidogrel discontinuation group on day 0 was 51% (40–62%), including 55% of the patients with a PRI more than 50%.

PRI increased to 65% (57–74%) on day 3 ($P < 0.05$) and to 76% (69–84%) on day 5 ($P < 0.05$), see also Table 2. On the morning of surgery, mean PRI was 85% (80–91%). Eighty percent of the patients had a PRI of more than 50% on day 3, 90% at day 5 and 100% at day 7.

The exploratory *t*-tests comparing PRI on each day for the discontinuation group with the surgical control group showed significant differences for the data of the days 0, 3 and 7 whereas the difference for that of day 5 was −0.4 with a 95% CI of −8.6 to 7.8. An equivalency test based on two one-sided *t*-tests showed equivalency within bounds of ± 20% ($P < 0.001$) (Table 2).

On day 7, the PRI in the discontinuation group was significantly higher than in the surgical control patients ($P = 0.018$). In two patients, the PRI increased to values that were never seen in healthy volunteers and surgical control patients.

Coagulation tests and light transmission aggregometry

Table 2 shows the data of all coagulation tests and LTA. There were no clinically significant changes. Figure 2 shows the Bland and Altman Plot for PRI and LTA, indicating a fair correlation.

Table 1 Baseline characteristics and clinical data

	Controls			
Group	Healthy ($n = 20$)	Surgical ($n = 20$)	Cardiac ($n = 20$)	Discontinuation ($n = 20$)
Patient's characteristics				
Age (years)	41 (36–45)	67 (62–71)	70 (64–75)	72 (66–78)
Sex M/F	8/12	17/3	15/5	16/4
Type of surgery				
Urologic		16 (80)		11 (55)
Orthopaedics		4 (20)		7 (35)
Major abdominal		0 (0)		1 (5)
Other		0 (0)		1 (5)
Indication for antiplatelet therapy				
Coronary stenting			18 (90)	7 (35)
Type (BMS/DES)			12/6	4/4
Time stenting to surgery (months)				10 (1–20)
Percutaneous valve			2 (10)	0 (0)
Peripheral stenting			0 (0)	2 (10)
Stroke			0 (0)	7 (35)
CAD			0 (0)	4 (20)
Comorbidities				
Previous MI		0 (0)	8 (40)	8 (40)
Coronary artery disease		1 (5)	19 (95)	11 (55)
Hypertension		12 (60)	20 (100)	16 (80)
Diabetes		6 (30)	4 (20)	6 (30)
Stroke		0 (0)	0 (0)	6 (30)
Renal insufficiency[a]		3 (15)	4 (20)	9 (45)
Preoperative medications				
Clopidogrel		0 (0)	20 (100)	20 (100)
Aspirin		0 (0)	20 (100)	11 (55)
Betablockers		0 (0)	20 (100)	11 (55)
ACE inhibitors		3 (15)	19 (95)	8 (40)
Ca-antagonists		2 (10)	2 (10)	4 (20)
Statins		0 (0)	17 (85)	11 (55)
Omeprazol		3 (15)	3 (15)	13 (65)
Anaesthesia				
General		10 (50)		17 (85)
Regional		9 (45)		3 (15)
Combined		1 (5)		0 (0)
Duration (min)		88 (65–111)		74 (54–95)
ICU admission		0 (0)		1 (5)
Hospital stay (days), mean (95% CI)		7 (5–8)		9 (5–13)
Postoperative complications				
MACCE		0 (0)		0 (0)
Redo due to bleeding		0 (0)		0 (0)
Transfusion needs				
PRC		0 (0)		3 (15)
PLT		0 (0)		0 (0)
Intrahospital death		0 (0)		0 (0)

BMS, bare metal stent; CAD, acute coronary syndrome medically treated; DES, drug eluting stent; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PLT, platelets; PRC, packed red cells. [a] Creatinine $> 2\,mg\,dl^{-1}$. Data are mean (95% CI) or numbers of patients.

Clinical outcome

In the 20 patients of the clopidogrel discontinuation group, there were no major adverse cardiac or cerebrovascular events or deaths during hospitalization.

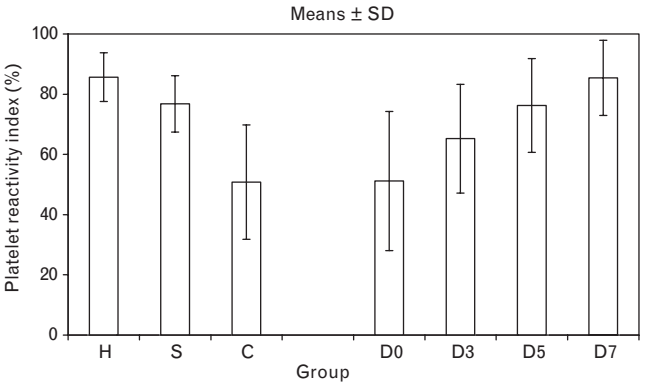
Discussion

Perioperative antiplatelet drug regimes have to balance the risk of life-threatening ischaemic events against severe surgical bleeding complications. If thienopyridines have to be discontinued, aspirin should be given, particularly to patients with previous placement of a DES. Some procedures, however, have been identified in which the surgical concern about major intraoperative and postoperative bleeding results in discontinuation of clopidogrel and aspirin. These procedures may include prostate surgery, intracranial surgery, posterior chamber eye surgery and a few others.

Perioperative caregivers responsible for navigating their high-risk patients through the perioperative scenario have to consider strategies in order to minimize the patient risk. This includes appropriate timing of discontinuation of drugs, monitoring of platelet function and bridging with alternative drugs.

LTA by Born is historically the gold standard test but has major disadvantages as a clinical test. Newer options for platelet function testing have recently been developed, particularly monitoring of P2Y12 receptors. The coupling of P2Y12 to the inhibition of adenylate cyclase by an inhibitory G-protein has been exploited to measure the reactivity of the receptor in the presence of P2Y12 inhibitors [26]. Vasodilator-stimulated phosphoprotein is phosphorylated by protein kinases that are activated

Fig. 1



Mean ± SD of platelet reactivity index (%) of the healthy volunteers and all patients' groups. H, healthy volunteers; S, surgical control group; C, cardiologic group; D0, 3, 5, 7, clopidogrel discontinuation group with the four time points (days 0, 3, 5, 7). For significance levels, see Table 2.

by cyclic adenosine monophosphate. Flow cytometry allows quantification of the amount of phosphorylated VASP by monoclonal antibodies as a measure of unblocked P2Y12 [26]. The advantages of the VASP assay include direct dependence on clopidogrel's target, low sample volume and the use of whole blood [27]. VASP phosphorylation assay is selective for thienopyridine effects and not affected by other commonly used platelet inhibitors such as aspirin. Its disadvantages include its expense and the need for sample preparation, a flow cytometer and an experienced technician; further, VASP phosphorylation assay is not a bedside test [27,28].

In the reference study of Aleil *et al.* [24], the mean values of PRI were similar in the groups of healthy volunteers and patients not receiving clopidogrel ($78.3 \pm 4.6\%$ and $79.0 \pm 4.1\%$). The mean PRI in patients treated with clopidogrel was significantly lower ($61.1 \pm 17\%$). The PRI expressed as mean percentage platelet reactivity is inversely correlated with clopidogrel treatment efficacy. According to the criteria of Barragan *et al.* [29], patients are good responders to clopidogrel if PRI is less than 50% and poor responders if PRI is more than 50%.

In our study, the mean PRI increased from 51% on day 0 to 76% on day 5. On the basis of these data and the data of our control groups, the VASP values in our study already reached normal values on the 5th day. Currently, the clinical impact of absolute VASP values is being discussed in the cardiologic literature. Barragan *et al.* [29] demonstrated that this assay could discriminate patients having a high risk of intracoronary stent thrombosis despite a thienopyridine regime. Blindt *et al.* [23] confirmed these data, demonstrating in a prospective risk stratification study of stent thrombosis that patients with a VASP-PRI more than 48% seem to have a significantly increased risk. A posttreatment ADP-induced platelet aggregation identified low responders to dual antiplatelet therapy with an increased risk of recurrent cardiovascular events [30]. Recently, Bonello *et al.* [25] found in a prospective randomized multicentre study that adjusting the clopidogrel loading dose to the VASP-PRI may significantly improve clinical outcome.

The issue of when to stop clopidogrel preoperatively is controversial and ranges between 5 and 14 days both for noncardiac and cardiac surgery. In healthy volunteers who had received clopidogrel $75\,mg\,day^{-1}$ for 7 days, platelet function recovered to normal 7 days after the last clopidogrel dose [31]. The Task Force of the French Society of Anaesthesiology and Intensive Care recommends stopping aspirin and clopidogrel 5 days before planned surgery without alternative therapies or stopping aspirin and clopidogrel 10 days before with alternative therapies [18]. In addition, the recent guidelines of the European Society of Cardiology recommend that when patients are scheduled for coronary artery bypass grafting, surgery should be postponed for 5 days for clopidogrel withdrawal if clinically feasible [6].

According to the ACC/AHA recommendations of 2004, clopidogrel should be withdrawn for at least 5–7 days before elective coronary artery bypass grafting [32].

The common practice of withdrawing antiplatelet agents 7–10 days before a surgical procedure is based on the assumption that the antiplatelet effects of drugs such as clopidogrel and aspirin are in a 'therapeutic range' and are stopped to 'normalize' them. This ignores our current knowledge from cardiologic trials that low response or no response to clopidogrel may occur in up to 30% of coronary patients and is more likely to be found among those with high-pretreatment platelet reactivity [33]. The cause of clopidogrel resistance, or better nonresponsiveness, is not known. Proposed mechanisms include reduced bioavailability resulting from poor absorption, low cytochrome P450 activity, drug interactions, noncompliance and accelerated platelet turnover [34–36]. In our clopidogrel discontinuation group, 55% of our patients had a PRI value more than 50% on day 0, and on day 5 only two patients (10%) had a PRI less than 50%. In a surgical setting, the findings from cardiologic trials would not favour or justify a rigid preoperative strategy of postponing surgery for 7–10 days for patients who are clopidogrel nonresponders.

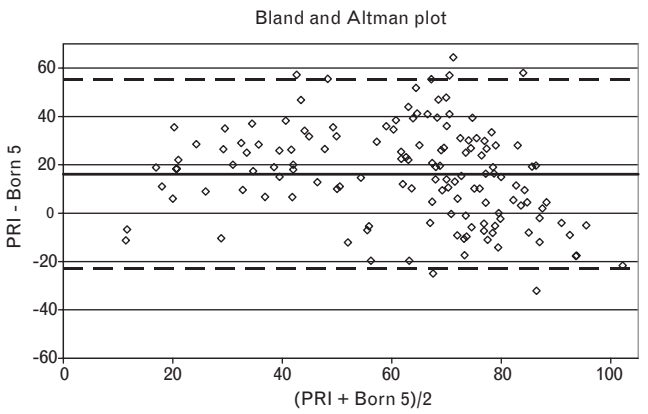
Thirteen patients in the discontinuation group were taking omeprazole. In one recent prospective study, a greater chance of being a clopidogrel 'bad' responder was reported, when patients under clopidogrel were treated with omeprazol [37]. The randomized trial, however, was limited by the fact that the incidence of clopidogrel nonresponders in each group was not known [38].

Table 2 **Coagulation tests and aggrometry data**

Group						Discontinuation		
	Significance	Healthy (H)	Controls surgical (S)	Cardiac (C)	Day 0 (D0)	Day 3 (D3)	Day 5 (D5)	Day 7 (D7)
PRI[a]	*	86 (82–89)	77 (72–81)	51 (42–60)	51 (40–62)	65 (57–74)	76 (69–84)	85 (80–91)
	†	C, D0	C, D0	H, S	H, S		–	–
	‡				D3, D5, D7	D0, D7	D0	D0, D3
LTA 5[b]	*	69 (65–74)	75 (68–83)	26 (19–32)	38 (26–49)	49 (38–60)	57 (48–66)	66 (56–75)
	†	C, D0	C, D0	H, S	H, S		–	–
	‡				D5, D7	D7	D0	D0, D3
Platelets WB[c]	*	205 (180–230)	180 (153–207)	147 (127–168)	171 (158–184)	150 (136–165)	160 (145–175)	157 (141–174)
	†	C		H			–	–
	‡				D0		–	D3
Platelets PRP[d]	*	435 (387–483)	433 (362–503)	349 (299–399)	353 (313–394)	305 (260–351)	323 (276–370)	314 (277–350)
	†						–	–
	‡				D0		–	D3
INR[e]	*	0.92 (0.89–0.95)	0.96 (0.92–0.99)	1.02 (0.93–1.10)	0.94 (0.92–0.96)	0.93 (0.90–0.96)	0.93 (0.90–0.96)	0.95 (0.91–0.99)
	†	C		H			–	–
	‡						–	–
APTT[f]	*	33 (31–34)	33 (32–34)	42 (29–55)	34 (32–35)	34 (31–36)	36 (33–38)	34 (32–36)
	†						–	–
	‡						–	–
Fibrinogen[g]	*	296 (261–331)	427 (351–504)	508 (421–595)	444 (373–515)	481 (397–564)	477 (388–567)	492 (402–583)
	†	S, C, D0	H	H	H		–	–
	‡						–	–
D–Dimer[h]	*	0.3 (0.2–0.5)	110 (52–169)	1.4 (0.8–2.1)	106 (55–158)	98 (57–139)	92 (44–141)	130 (45–215)
	†	S, D0	H, C	S, D0	H, C		–	–
	‡						–	–
AT[i]	*	120 (105–134)	99 (93–105)	94 (89–98)	131 (51–210)	95 (87–102)	90 (86–95)	86 (81–90)
	†						–	–
	‡						–	–

ANOVA, analysis of variance; APTT, activated partial thromboplastin time; AT, antithrombin; CI, confidence interval; LTA, light transmission aggregometry; INR, international normalized ratio; PRI, platelet reactivity index; WB, whole blood. * Mean (95% CI). † Significantly different from group (one-way ANOVA: H, S, C, D0). ‡ Significantly different from group (repeated-measures ANOVA: D0–D7). [a] Platelet reactivity index (%). [b] Born aggregometry (maximum aggregation in %); stimulated with 5 μmol l^{-1} ADP. [c] 10^3 platelets in whole blood (normal range 125–395 μL^{-1}). [d] 10^3 platelets in platelet-rich plasma. [e] International normalized ratio (normal range $<$ 1.30). [f] Activated partial thromboplastin time (normal range 26–36 s). [g] Fibrinogen (normal range 170–400 mg dl^{-1}). [h] D-Dimer (normal range $<$ 200 μg l^{-1}). [i] Antithrombin (normal range $>$ 75%).

Fig. 2



Bland and Altman plot for platelet reactivity index and light transmission aggregometry. Solid line indicates mean deviation (16.0) and dashed lines indicate limits of agreement (−23/+55). PRI, platelet reactivity index.

There are some limitations of the study. First, the group of patients with preoperative discontinuation of clopidogrel or clopidogrel and aspirin in high-bleeding risk procedures was relatively small and will remain so. Moreover, during our study period, primary caregivers sometimes stopped clopidogrel and aspirin 10–14 days before hospitalization, and, in some other cases, surgeons were unwilling to follow a strict protocol. These patients could not be included in the study.

Second, despite technical advances in newer assays, the measurement of receptor-linked platelet reactivity remains a complex field. It is difficult to transfer laboratory results to clinical outcome events and particularly to use such laboratory data to guide therapy [26]. Restrictive interpretation of such data is mandatory. Nevertheless, Kleiman [28] recently wrote in an editorial that there may be potential utility in directing therapy on the basis of a pathway-specific assay of the biological activity of an antiplatelet drug.

Third, theoretically, normalization of platelet function, for example, on the 5th preoperative day after discontinuation could be followed by a hyperreactive period of clopidogrel rebound. Premature discontinuation of thienopyridine therapy was associated with increased morbidity and mortality in a recent large retrospective cohort trial [7]. Elsewhere, proinflammatory and prothrombotic platelet activity was measured in diabetic patients [39]. This would also be of particular interest in a surgical setting. The high PRI values of two patients on day 7 could be interpreted as some degree of hyperreactivity or rebound, but the number of patients was too small and the question not the goal of this study.

Fourth, the discontinuation group was inhomogeneous with respect to the indication of antiplatelet therapy and the risk of premature discontinuation, for example, the perioperative risk differs between a patient with a DES and a patient with a peripheral stent; however, the group was homogeneous with respect to the imperative request of surgeons to stop clopidogrel in a defined type of high bleeding risk procedures, independent of the cardiovascular risk.

In conclusion, the study demonstrates that in cardiovascular risk patients awaiting noncardiac surgery, the preoperative PRI on day 5 after discontinuation of clopidogrel is statistically not different from that of a surgical control group. The study questions the rigid practice of delaying surgery for 7–10 days, particularly in those patients who already present preoperatively without clopidogrel effects. In the near future, new platelet function assays will have to be validated to determine their usefulness, particularly in high-risk patients and procedures, in assessing the appropriate level of antiplatelet drug therapy in a perioperative setting.

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