

# Effect of clopidogrel on bleeding and transfusions after off-pump coronary artery bypass graft surgery: impact of discontinuation prior to surgery

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## Abstract

**Objective:** The use of antiplatelet drugs to treat acute myocardial infarction, unstable angina, acute coronary syndrome and secondary prevention following percutaneous coronary interventions is well accepted. However, it constitutes a serious risk of bleeding for patients undergoing coronary artery bypass grafting surgery (CABG). We evaluated the effect of aspirin and clopidogrel (CPDG), both irreversible platelet aggregation inhibitors, on operative bleeding and determined the optimal timing for their discontinuation before surgery. **Method:** Between July 2001 and December 2004, we reviewed our experience with 453 patients undergoing off-pump CABG surgery (OPCAB) who received CPDG ( $n = 101$ ) or not ( $n = 352$ ) preoperatively, and compared the intraoperative and postoperative bleeding to determine risks factors associated with blood or platelet transfusions. **Results:** Clopidogrel in OPCAB surgery is associated with higher intraoperative (702.24 ml vs 554.13 ml,  $p = 0.03$ ) and postoperative bleeding (864.93 ml vs 603.75 ml,  $p = 0.03$ ). The mean operative blood loss is higher in patients still on CPDG at the time of surgery compared to patients off CPDG at least 72 h before surgery (802 ml vs 554.13 ml,  $p < 0.0001$ ). Blood loss in the later subgroup of patients is comparable to the control group without CPDG ( $p = \text{NS}$ ). Clopidogrel is associated with more platelet transfusions (OR = 11.79, [1.48; 93.86]). **Conclusion:** Blood loss is higher in OPCAB patients receiving clopidogrel before surgery. However, discontinuation of clopidogrel three days (72 h) prior to the operation demonstrated a similar blood loss pattern compared to a control group. Clopidogrel is associated with more platelets, but not red blood cell transfusions following OPCAB surgery.

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## 1. Introduction

Platelet-rich intracoronary thrombi are central to the pathogenesis of acute coronary syndromes. The use of antiplatelet drugs to treat acute myocardial infarction (AMI), unstable angina, acute coronary syndrome (ACS) and secondary prevention following percutaneous intervention (PCI) is more and more frequent since clinical trials have established the efficacy of glycoprotein (GP) IIb/IIIa inhibitors and of platelet adenosine diphosphate (ADP) receptor blockers in decreasing mortality, recurrent myocardial infarction in ACS, and reducing the incidence of urgent CABG surgery after unsuccessful PCI [1,2]. Clopidogrel (CPDG), by blocking the platelet ADP receptor, prevents

fibrinogen binding and inhibits platelet adhesion and aggregation [3].

However, one of the main concerns with CPDG pretreatment is a possible increase in major bleeding and reoperation for bleeding in patients who need to undergo CABG surgery [4]. Postoperative mediastinal blood loss following on-pump CABG surgery is increased with the use of CPDG [5]. However, the etiology of mediastinal blood loss is multifactorial [5,6]. Re-exploration for bleeding is required in 2–3% of patients following CABG surgery and postoperative bleeding is associated with significant increase in length of intensive care unit (ICU) stay, number of transfusions and respiratory complications [7,8,11].

When clinical circumstances permit, the American Heart Association (AHA) recommends discontinuation of CPDG five days before CABG surgery [9,10]. However, this class I recommendation is based on a weak level of evidence and did not address bleeding due to off-pump CABG surgery (OPCAB). The risk of increased blood loss following CPDG use in OPCAB surgery has not yet been extensively studied. Bleeding could

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be less significant than on-pump CABG surgery since cardiopulmonary bypass has a deleterious effect on the inflammation and coagulation cascade.

## 2. Patients and methods

Between July 2001 and December 2004, data were prospectively collected on 453 consecutive patients undergoing OPCAB surgery at the CHUM-Notre-Dame Hospital in Montreal. Baseline demographics, standard comorbidity factors and preoperative medications were collected for all patients in the study. Patients were divided in two groups: OPCAB surgery with prior CPDG use ( $n = 101$ ) or not (control group,  $n = 352$ ). Exclusion criteria were cardiopulmonary bypass procedures or conversions to on-pump surgery, and patients having discontinued CPDG use more than 1 week prior to the operation. Urgent and emergent surgeries were included. All patients were kept on aspirin (ASA) prior to surgery and no antifibrinolytic drugs were used. Patients admitted for elective surgery were advised to stop clopidogrel according to standard recommendations 5–7 days prior to their operation. Intravenous heparin was given 1 mg/kg of weight after the mammary artery takedown. Anticoagulation was maintained with the activated clotting time (ACT) twice the normal value or above 250 s for all patients during the OPCAB surgery. The heparin was then completely reversed at the end of surgery to obtain an ACT less than 125 s.

Intraoperative bleeding data was recorded from anesthesiology charts and surgeon operative reports. The initial 24 h postoperative bleeding was measured directly from mediastinal and pleural drainage system in the ICU. Blood product transfusion was documented after surgery for all patients. Groups were compared for blood loss and blood product transfusion requirements following OPCAB surgery. The primary objective was to assess the risk associated with the use of CPDG prior to OPCAB surgery. The secondary objective was to determine a minimal safe period to discontinue CPDG before OPCAB surgery.

Preliminary analysis was done comparing patients discontinuing CPDG 24, 48, 72, 96 and 120 h prior to OPCAB surgery. With significant differences in blood loss and blood transfusion products found at 72 h instead of the 120 h (5 days) cut-off, we decided to divide the CPDG patients into two subgroups: those on CPDG up to 72 h ( $n = 63$ ) and those who had discontinued CPDG more than 72 h ( $n = 37$ ) prior to surgery. All patients received a loading dose of 300 mg of CPDG, followed by the standard maintenance dosage of 75 mg daily. Transfusion protocols were used in all patients in the ICU. Red blood cells (RBC) were transfused when the hemoglobin count was lower than 75 mg/dl and platelet transfusions were prescribed when chest tube drainage was significant (more than 200 cc/h for the first 3 h and more than 100 cc/h for 6 h).

## 3. Statistical analysis

Patient characteristic parameters were expressed as mean  $\pm$  SED or simple frequencies and percentages. For continuous variables, the comparison of groups was

performed using the parametric (*t*-test) or nonparametric (Wilcoxon) test depending on the distribution. For categorical variables, the comparison of groups was performed using the Pearson chi-square test. To detect any differences in perioperative and postoperative bleeding loss between the groups, independent sample *t*-tests were performed. Paired sample *t*-tests were used to compare bleeding loss data for the two CPDG subgroups and the control group. Univariate and multivariate logistic regression were used to identify predictors of RBC and platelet transfusions. Statistical analysis was performed with the computer software SAS (SAS Institute Inc., Cary, NC, USA). A *p*-value less than 0.05 was considered statistically significant.

## 4. Results

Of the 453 patients, 101 were on CPDG prior to the surgery compared to 352 not taking CPDG (control group). Table 1 outlines patient demographics. There was no major difference between groups in respect to age, sex distribution, left ventricular ejection fraction, left main disease, preoperative GPIIb/IIIa use, intra-aortic balloon pump or incidence of percutaneous intervention. Also the emergency status, defined as an emergent or salvage surgery done within 12 h of catheterization lab, and the number of bypasses were equivalent between CPDG and control group. Right internal mammary artery use was higher in the CPDG group (10.9% vs 4.6%;  $p = 0.02$ ).

Blood loss data after OPCAB surgeries are presented in Fig. 1. Intraoperative and postoperative bleeding was significantly higher in the CPDG group compared to control ( $702 \pm 22$  ml vs  $554 \pm 20$  ml,  $p = 0.03$  and  $865 \pm 31$  ml vs  $604 \pm 23$  ml,  $p = 0.03$ , respectively). Red blood cell and platelet transfusions were more prevalent in the CPDG group compared with control (65% and 46% vs 18% and 4%,  $p = 0.0011$  and  $p < 0.0001$ , respectively) (Fig. 2). There were no statistical differences in reoperation for bleeding, postoperative myocardial infarction rate, renal failure requiring mechanical support or strokes between groups. The hospital length of stay or mortality was not significantly

Table 1  
Baseline demographic characteristics, intervention and medical therapy prior to surgery

	Control group	Clopidogrel group	<i>p</i> -Value
Mean age	64 $\pm$ 10	64 $\pm$ 11	0.88
LVEF (%)	53 $\pm$ 15	54 $\pm$ 14	0.86
Left main disease (%)	113 (32.1)	38 (37.6)	0.30
Preoperative GP IIb/IIIa (%)	32 (9.1)	13 (12.9)	0.26
Preoperative IABP (%)	35 (9.9)	15 (14.9)	0.17
Preoperative PCI (%)	38 (10.8)	7 (6.9)	0.25
Emergency surgery <sup>a</sup> (%)	32 (9.1)	12 (11.9)	0.40
LIMA (%)	352 (100)	101 (100)	N/A
RIMA (%)	16 (4.6)	11 (10.9)	0.02
Number of bypass	3.19 $\pm$ 0.88	3.18 $\pm$ 0.88	0.92

LVEF: left ventricular ejection fraction; IABP: intra-aortic balloon pump; PCI: percutaneous intervention; LIMA: left internal mammary artery; RIMA: right internal mammary artery.

<sup>a</sup> Emergency surgery: emergent or salvage surgery done within 12 h of catheterization lab.

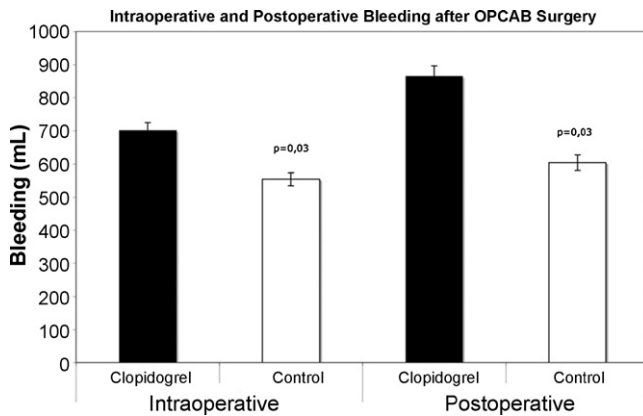


Fig. 1. Intraoperative and postoperative bleeding after off-pump coronary artery bypass surgery. The use of clopidogrel prior to surgery enhances blood loss after off-pump coronary artery bypass graft surgery ( $p < 0.05$  vs control).

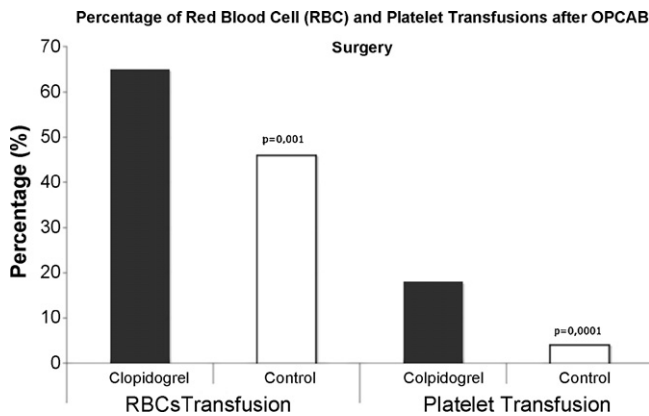


Fig. 2. Percentage of red blood cell and platelet transfusions for control and clopidogrel groups. (RBCs = red blood cells). Clopidogrel prior to off-pump coronary artery bypass graft surgery is associated more red blood cell and platelet transfusions ( $p < 0.05$  vs control).

different ( $8.18 \pm 5.95$  days vs  $7.61 \pm 9.05$  days,  $p = 0.10$  and  $6.9\%$  vs  $4.8\%$ ,  $p = 0.21$ ) (Table 2).

Subgroup analysis of CPDG patients who discontinued CPDG at least 72 h before going to surgery ( $n = 37$ ) differed from those still on CPDG within 72 h of surgery ( $n = 63$ ). The

Table 2  
Postoperative results

	CPDG ( $n = 101$ )	No CPDG ( $n = 352$ )	$p$ -Value
Reoperation for bleeding	7 (6.9%)	14 (4.0%)	0.20
Postoperative MI	2 (2.0%)	13 (3.7%)	0.24
Postoperative renal failure (requiring renal support)	4 (4.0%)	4 (1.1%)	0.25
Strokes	0	6 (1.7%)	0.21
Preoperative Hb	$128 \pm 19$	$131 \pm 18$	0.25
Hb at discharge	$94 \pm 13$	$98 \pm 13$	0.25
Mortality	7 (6.9%)	17 <sup>a</sup> (4.8%)	0.21
Hospital LOS	$8.18 \pm 5.95$	$7.61 \pm 9.05$	0.10

CPDG: clopidogrel, MI: myocardial infarction, Hb: hemoglobin, LOS: length of stay.

<sup>a</sup> Six deaths were not cardiac or postoperative related complications (two metastatic cancers, one traumatic hip fracture, and three patients with loss of interest in life, loss of autonomy and severe denutrition unable to go on rehabilitation).

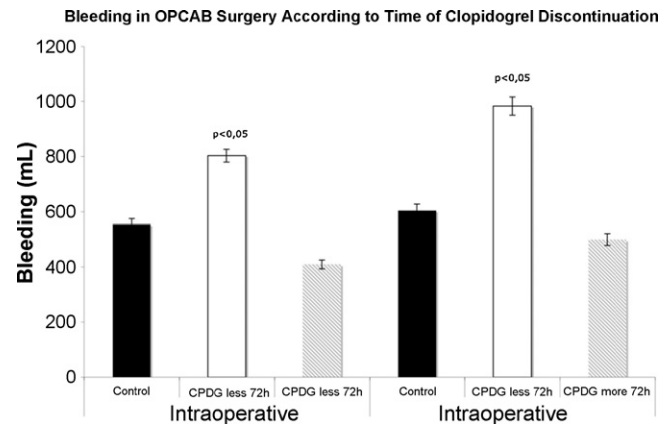


Fig. 3. Bleeding in OPCAB surgery according to time of clopidogrel discontinuation. Dark: control; white: clopidogrel less 72 h; striped: clopidogrel more 72 h. Patients on clopidogrel 72 h prior to OPCAB surgery have more postoperative bleeding compared to the control group or patients with discontinuation of the medication more than 3 days before surgery ( $p < 0.05$  vs control).

Table 3  
Univariate analyses for predictive factors of red blood cell transfusions

	Odds ratio	95% CI	$p$ -Value
Age	1.094	1.043–1.147	0.0002
Number of bypass	0.833	0.485–1.432	0.51
Preoperative GPIIb/IIIa	1.516	0.373–6.167	0.56
Left main disease	2.814	1.053–7.521	0.04
RIMA	1.301	0.312–5.420	0.72
LVEF	0.979	0.945–1.013	0.22
LVEF <35%	4.664	0.988–22.012	0.05
Emergency	6.326	0.771–51.884	0.09
Clopidogrel	1.152	0.628–3.665	0.35

RIMA: right internal mammary artery; LVEF: left ventricular ejection fraction; CI: confidence interval.

Age (OR: 1.09, 95% CI: 1.04–1.15,  $p = 0.0002$ ) and left main disease (OR: 2.81, 95% CI: 1.05–7.52,  $p = 0.04$ ), were identified as significant risk factors for increased RBC transfusions.

results are shown in Fig. 3. Patients on CPDG within 72 h of surgery experienced more intra-perioperative and postoperative blood loss compared to controls ( $802 \pm 22$  ml vs  $554 \pm 20$  ml and  $983 \pm 33$  ml vs  $604 \pm 23$  ml,  $p < 0.05$ ). Patients off CPDG for more than 72 h had intraoperative and postoperative blood loss comparable to the control group ( $409 \pm 16$  ml vs  $554 \pm 20$  ml and  $499 \pm 21$  ml vs  $604 \pm 23$  ml,  $p = \text{NS}$ ).

Univariate and multivariate analyses were then performed to predict blood product transfusions, using logistic and linear regression techniques with eight independent variables (age, number of bypass, preoperative GPIIb/IIIa use, left main disease, right internal mammary artery use, LVEF, low under 35% LVEF, emergency surgery and clopidogrel use). As displayed in Tables 3–5, only the patient's age at the time of surgery (OR: 1.09, 95% CI: 1.04–1.15,  $p = 0.0002$ ) and the presence of left main disease (OR: 2.81, 95% CI: 1.05–7.52,  $p = 0.04$ ), were identified as significant risk factors for increased RBC transfusions. Clopidogrel was not a predictor of RBC transfusions in this OPCAB population (OR: 1.51, 95% CI: 0.63–3.67,  $p = 0.35$ ). Clopidogrel and left main disease were independent risk factors for increased platelet

Table 4  
Univariate analyses for predictive factors of platelet transfusions

	Odds ratio	95% CI	p-Value
Age	1.016	0.967–1.067	0.54
Number of bypass	0.967	0.496–1.885	0.92
Preoperative GPIIb/IIIa	1.048	0.204–5.385	0.96
Left main disease	3.768	1.224–11.605	0.02
RIMA	1.196	0.229–6.249	0.83
LVEF	0.991	0.951–1.032	0.65
LVEF < 35%	1.101	0.274–4.421	0.89
Emergency	3.238	0.820–12.784	0.09
Clopidogrel	11.786	1.480–93.863	0.02

RIMA: right internal mammary artery; LVEF: left ventricular ejection fraction; CI: confidence interval.

Clopidogrel, left main disease and emergency surgery were identified as predictors of platelet transfusions.

Table 5  
Multivariate analyses for predictive factors of platelet transfusions

	Odds ratio	95% CI	p-Value
Left main disease	3.24	1.03–10.47	0.0495
Clopidogrel	10.46	1.29–84.69	0.03

CI: confidence interval.

Clopidogrel is an independent risk factor for increased platelet transfusions (OR: 10.46, 95% CI: 1.29–84.69,  $p = 0.03$ ) as well as a left main disease (OR: 3.24, 95% CI: 1.03–10.47,  $p = 0.0495$ ).

transfusions (OR: 10.46, 95% CI: 1.29–84.69,  $p = 0.03$ ; and OR: 3.24, 95% CI: 1.03–10.47,  $p = 0.0495$ ).

## 5. Comment

This study was undertaken to assess the effect of clopidogrel in OPCAB surgery. OPCAB surgery differs from standard on-pump CABG since patients receive less heparin and are less exposed to cardiopulmonary bypass complications with known documented deleterious effects on platelet activation and coagulation system regulation. The association of ASA, CPDG and at times GPIIb/IIIa in the preoperative setting is a cause for concern, because complete inhibition of platelet function causes serious bleeding. Chu et al. have shown that CPDG taken 4 days prior to surgery was associated with increase bleeding and reoperation for bleeding [5]. Hongo et al. [12] also reported increased postoperative bleeding, RBC transfusions and reoperation for bleeding in patients on CPDG within 7 days of their operation. The American Heart Association guidelines recommend discontinuation of CPDG five days prior to CABG surgery. This level of evidence C recommendation is based on an *ad hoc* analysis of a subgroup of patients from the CURE bleeding complications after coronary artery bypass surgery using cardiopulmonary bypass [6].

In this study, bleeding was increased in patients on CPDG prior to OPCAB surgery when compared to a cohort not taking this antiplatelet medication. Patients on CPDG received more RBC and platelet transfusions as well, but the reoperation rate was similar. A subgroup analysis of patients without CPDG for at least 72 h before surgery had comparable intraoperative and postoperative blood losses when compared to the control group. Their transfusion needs were not different from control. This observation suggests that

stopping CPDG intake 3 days prior to OPCAB surgery would lessen the risk of bleeding to the level of the control group. This differs from previously mentioned studies because OPCAB surgery is performed without the cardiopulmonary induced coagulopathy.

Using standard ICU transfusion protocols in which platelet products were given more liberally to correct the CPDG mediated coagulation defect, CPDG was not an independent risk factor for RBC transfusions. On the other hand, CPDG was a significant independent predictor of platelet transfusions in a multivariate logistic regression model. Although CPDG patients are more prone to receive platelet transfusions, the risks of reoperations and life threatening hemorrhages in this study was not increased.

A strong independent predictor of RBC and platelet transfusions was the presence of left main disease. Since these patients may be considered by the referring cardiologist to be at higher risk, they frequently receive additional anticoagulation or adjunctive treatment such as intravenous heparin, low molecular weight heparin, GPIIb/IIIa inhibitors or a more aggressive approach with antiplatelet therapy. Although heparin and GPIIb/IIIa inhibitors have a short half-life and are stopped in a timely manner (more than 6 h prior to surgery), their combined effects with CPDG and ASA might last longer.

This study was undertaken to assess the risks of bleeding associated with the use of clopidogrel in OPCAB surgery especially since the optimal timing of its discontinuation before CABG surgery is controversial. CPDG use prior to OPCAB surgery is associated with increased blood loss and platelet transfusions, but it did not increase the reoperation rate, the length of stay or the mortality in this study. When CPDG cannot be stopped before surgery, platelet transfusion can safely be given postoperatively to correct the coagulopathy. Aprotinin and other anti-fibrinolytics can also be given at the time of surgery for better hemostasis, although little documented evidence has been reported [13]. Blood conservation strategies, such as the cell-saver device, could be useful in these patients to minimize blood transfusions, but it remains to be studied in rigorous trials.

Discontinuation of CPDG three days prior to OPCAB surgery may shift the risk of bleeding towards the control level. However, clopidogrel use within 72 h of OPCAB surgery is associated with more blood losses and blood product transfusions. Patients with left main disease may represent a specific subset where routine administration of clopidogrel would have more adverse effects. This study brings forward again a word of caution for routine administration of clopidogrel even for OPCAB surgeries and urges surgeons to implement additional strategies for blood hemostasis and conservation.

## 6. Limitations

This study is a retrospective non-matched cohort analysis. Although techniques of multivariate analysis may adequately control for measurable biases, unmeasured bias may still exist and influence the presented results. Also, the non-blinded nature of the study may influence the threshold in the intensive care unit for blood product transfusions, which

might impact the transfusion rate between the two groups of patients.

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