European Heart Journal (2005) **26**, 576–583
doi:10.1093/eurheartj/ehi074

Clinical research

Clopidogrel administration prior to coronary artery bypass grafting surgery: the cardiologist's panacea or the surgeon's headache?

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Received 3 May 2004; revised 28 September 2004; accepted 16 November 2004; online publish-ahead-of-print 21 February 2005

KEYWORDS
Clopidogrel;
Coronary artery bypass graft surgery;
Re-operation due to bleeding;
Transfusion rates;
Haemostasis

Aims Thrombotic complications after percutaneous coronary intervention procedures have decreased in past years mainly due to the use of clopidogrel antiplatelet therapy. However, the risk of bleeding due to enhanced and irreversible platelet inhibition in patients who will require surgical coronary revascularization instead has not been adequately addressed in the literature. The purpose of this study was to evaluate the effect of pre-operative clopidrogel exposure in haemorrhage-related re-exploration rates, peri-operative transfusion requirements, morbidity, and mortality in patients undergoing coronary artery bypass grafting (CABG) surgery.

Methods and results A study population of 2359 patients undergoing isolated CABG between January 2000 and June 2002 was reviewed. Of these, 415 (17.6%) received clopidogrel prior to CABG surgery, and 1944 (82.4%) did not. A risk-adjusted logistic regression analysis was used to assess the association between clopidogrel pre-medication (vs. no) and haemostatic re-operation, intraoperative and post-operative blood transfusion rates, and multiple transfusions received. Haemorrhage-related pre-operative risk factors identified from the literature and those found significant in a univariate model were used. Furthermore, a sub-cohort, matched-pair by propensity scores analysis, was also conducted. The clopidogrel group had a higher likelihood of haemostatic re-operation [OR = 4.9, (95% CI, 2.63–8.97), $P < 0.01$], an increase in total packed red blood cell transfusions [OR = 2.2, (95% CI, 1.70–2.84), $P < 0.01$], multiple unit blood transfusions [OR = 1.9, (95% CI, 1.33–2.75), $P < 0.01$] and platelet transfusions [OR = 2.6, (95% CI, 1.95–3.56), $P < 0.01$]. Surgical outcomes and operative mortality [OR = 1.5, (95% CI, 0.36–6.51), $P = 0.56$] were not significantly different.

Conclusion Pre-operative clopidogrel exposure increases the risk of haemostatic re-operation and the requirements for blood and blood product transfusion during, and after, CABG surgery.

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Introduction

Research is expanding the clinical applicability of clopidogrel, a potent, irreversible adenosine 5′ diphosphate (ADP) receptor antagonist, which acts synergistically with aspirin to block fibrinogen binding, thus preventing platelet aggregation and clot stabilization.[1]

Following the encouraging results of the Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE)[2] and Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE)[3] trials, which demonstrated a 10–20% risk reduction for cardiovascular death, myocardial infarction (MI), and cerebrovascular accident (CVA) in patients with acute coronary syndrome,[4] many emergency room physicians, internists, and cardiologists have been aggressively prescribing prophylactic antiplatelet therapy with clopidogrel.[5] Although there is no doubt that this proves beneficial to the majority of patients, a proportion of them will subsequently have to undergo surgical coronary revascularization with repressed platelet function.

Furthermore, clopidogrel administration has reduced the substantially high (18–24%) rate of occlusive stent thrombosis seen initially after percutaneous coronary intervention (PCI), to a more acceptable ($\leq$2%) level.[6–11] Clopidogrel's potent anti-aggregating effect,[12] rapid onset of action,[13] low incidence of serious side-effects,[2,14] and better tolerability[2,15,16] have established it, in combination with aspirin, as the standard of care for stent thrombosis prevention.[17] In many catheterization suites across the country, clopidogrel and aspirin are given to patients prior to angiography and PCI to ensure adequate prophylactic platelet inhibition during coronary stent implantation.[18] However, a number of patients pre-medicated with this combination are then found to have a coronary anatomy more amenable to surgical revascularization.

Cardiac surgeons, anaesthesiologists, and intensivists have become concerned about the prevalence of enhanced and irreversible platelet inhibition when these patients present for coronary artery bypass grafting (CABG) surgery.[19] Consequently, we evaluated the effect of pre-operative clopidrogel in haemorrhage-related re-exploration rates, peri-operative transfusion requirements, morbidity, and mortality in a large cohort of patients undergoing CABG surgery utilizing a risk-adjusted statistical methodology.

Methods

Patient population and data

After receiving approval from our institution's investigational review board (IRB) we identified all patients undergoing isolated, primary CABG surgery between January 2000 and June 2002 using our cardiac surgery research database. Patients who underwent emergent or salvage operations, who had a mini-lateral thoracotomy or a mini-sternotomy (MIDCAB), or had other cardiac or vascular surgical procedures were excluded from the study. Patients with recent pre-operative exposure to coumadin, platelet glycoprotein (GP) IIb/IIIa inhibitors, or to thrombolytics were also excluded from the analysis. A total of 2359 patients was identified and analysed. These patients represented the coronary revascularization practice of five different surgeons (PJC, SWB, MKCD, ASB, KRP) for the study period.

Pre-operative patient characteristics, intraoperative variables, and post-operative outcomes were collected prospectively during the patients' hospitalization and entered into a research database as part of routine clinical practice. Patients were contacted via telephone 30 days post-hospital discharge as part of routine follow-up.

Study group creation and anticoagulation

All patients who, within 7 days of surgery, were either on a daily oral regimen of 75 mg of clopidogrel or received a 300-mg oral loading dose prior to PCI, made up the clopidogrel study group. They were compared with a control of those patients who had no exposure or whose surgery was postponed for at least 7 days after discontinuing clopidogrel. Both patient groups received aspirin prior to surgery. A comparable intraoperative heparin anticoagulation regimen was utilized in all patients whether cardiopulmonary bypass (CPB) was used or not. Initial heparin dose was calculated using a minimum standard of 400 units/kg with additional dosing administered during the procedure, in order to maintain a target activated clotting time (ACT) value greater than 480 s.

Haemorrhagic outcomes evaluated

The study's primary endpoint was the incidence of re-exploration due to bleeding, exclusive of any other cardiac or non-cardiac cause. Re-exploration due to haemorrhage was indicated when chest tube drainage exceeded 500 mL/h in the first hour, 400 mL/h in the first 2 h, 300 mL/h in the first 3 h, 200 mL/h in the first 4 h, or in the case of cardiac tamponade. Ultimately, the decision for haemorrhagic re-exploration rested with the surgeons, who share uniformity in clinical practice.

Persistent intraoperative bleeding was controlled by first examining all surgical causes, reversing heparin with protamine in an attempt to normalize the ACT, and then initiating packed red blood cell (PRBC) transfusion as required. Aminocaproic acid was administered in all patients undergoing CPB, but aprotinin, factor VII, or other agents were not routinely used.

Operative blood loss plus intra- and post-operative transfusion rates and amounts were recorded for the principal blood product types, including PRBC, platelets, and fresh frozen plasma (FFP). Clinical practice guidelines recommended PRBC transfusion at a haematocrit of $<$22 for patients younger than 65 years or $<$24 for patients of 65 years or older. The need for additional blood product transfusions remained at the discretion of the individual surgeon, anaesthesiologist, or intensivist.

Definitions

Diabetes was defined as a history of diabetes mellitus, regardless of disease duration and oral agent or insulin medication. Renal failure was defined as a serum creatinine value of $\geq$2.0 mg/dL. History of CVA was defined as a history of a central neurological deficit persisting for more than 72 h. Chronic obstructive pulmonary disease (COPD) was defined as chronic lung disease (emphysema, chronic bronchitis, or not otherwise specified) of a severity of an FEV_1 50–75% of predicted, and/or on chronic steroid or bronchodilator therapy. Left ventricular ejection fraction (LVEF) was categorized as normal ($\geq$45%), mildly (35–44%), moderately (25–34%), or severely ($\leq$24%) decreased. Post-operative CVA was defined as a post-operatively occurring

new focal neurological deficit diagnosed by clinical findings and confirmed by a neurologist or by brain imaging [head computed tomography (CT), or magnetic resonance imaging (MRI)], persisting for more than 72 h after onset, and having been noted before discharge or death. Post-operative MI was diagnosed by the presence of two of the following: prolonged (>20 min) chest pain not relieved by rest and/or nitrates, serial ECG showing new ischaemic changes, an enzyme level elevation (CK-MB >5% of total creatinine phosphokinase, CK > 2 × normal, lactate dehydrogenase (LDH) subtyp. 1 > LDH subtype 2 or troponin I > 0.8 μg/mL) or new wall motion abnormalities as documented by post-operative echocardiogram. Operative mortality was defined as any death occurring within 30 days of surgery unless the cause of death was clearly unrelated to the procedure.

Statistical analysis

Data are expressed as percentages, mean value ± standard deviation, or as median (minimum, maximum). Continuous variables were compared using Student's *t*-test assuming normal distributions or the Wilcoxon rank sum test for variables with non-normal distributions. Dichotomous variables were compared via the χ^2 test or Fisher's exact test when cell counts were less than five. Ordinal categorical data were compared using the Cochran–Armitage test for trends. In all tests *P*-values of 0.05 or less were considered significant. Mortality risk scores using Parsonnet's mortality prediction model were calculated to assess differences in pre-operative risk and as indicators of study group variability.[20,21]

Multivariable logistic regression models were used to investigate the association of clopidogrel with the need for re-operation due to bleeding, the PRBC and platelet transfusion rates, the transfusion of multiple PRBC units, and the operative mortality. Forward stepwise selection was used to identify significant confounding variables. Potential pre-operative confounding factors offered to the logistic regression models included: age, female gender, diabetes, hypertension, renal failure and haemodialysis, decreased LVEF, pre-operative haematocrit values, African ancestry, weight, urgent case priority, repeat CABG, use of CPB, and number of grafted vessels. These factors have been reported in the literature as important determinants of peri-operative haemorrhage.[22–24] Also offered to the logistic models were any significant or closely associated ($P \leq 0.15$) risk factors from the univariate analysis (history of MI). Model fit analysis was evaluated using the Hosmer and Lemeshow goodness-of-fit statistic, as well as residual diagnostics (deviance and dfBetas). The c-statistic was reported as a measure of predictive power. The presence of multi-colinearity among the independent variables was checked using diagnostics such as the variation inflation factor and tolerance. The linearity assumption for continuous variables included in the models was tested by determining whether the interactions between the predictors and their natural logs significantly affected the logit dependent variable by including the interaction terms in the analysis for each outcome of interest.

Furthermore, to reduce the effect of pre-operative variability between the groups, a propensity score matched-pair analysis was performed. Propensity scores or the probability of being selected to receive clopidogrel were computed for each patient using a logistic regression model which included, and so controlled for, the haemorrhage-associated variables of age, gender, diabetes, hypertension, African ancestry, weight, nature of case, repeat CABG surgery, beating heart vs. conventional CABG surgery, and number of grafts performed. Patients who received no clopidogrel were randomly matched to patients with an equal score that did. Previous studies have shown that matching on predicted probabilities (propensity scores) can control for selection bias.[25,26] Based on the propensity score, the method used for matching was the greedy algorithm, which initially matches to 5 followed by 4, 3, 2, and 1 decimal points. A comparison of the distribution of baseline characteristics in the propensity-matched population was performed to determine how well it reflected the original sample group. The general estimating method in a logistic regression model, which adjusted for correlations between matched sets, was used to evaluate the effect of clopidogrel on mortality and the post-operative haemorrhagic outcomes of interest.[27] Multiple outcomes were tested without controlling for the type I error rate. All statistical analyses were performed with SAS for Windows Version 8.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and pre-operative risk

The clopidogrel study group comprised of 415 (17.6%) patients while 1944 (82.4%) patients acted as surgical controls. Patient demographic and pre-operative characteristics are presented in *Table 1*. As expected, a higher proportion of clopidogrel-receiving patients had a history of MI (44.8 vs. 35.0%, $P < 0.01$) and required urgent revascularization (29.2 vs. 17.3%, $P < 0.01$). However, overall the study groups appeared comparable in pre-operative characteristics as the average risk scores calculated using Parsonnet's model were not statistically significant [12.0 (0–44) (Clopidogrel) vs. 12.0 (0–59), $P = 0.74$].

Peri-operative outcomes

Table 2 displays peri-operative characteristics and outcomes. There were no significant differences between the groups in the distribution of patients operated on a beating heart vs. the conventional approach, the number of grafts performed, or the length of CPB (for those patients who were placed on CPB). The distributions of aprotinin administration, peri-operative intra-aortic balloon pump (IABP) use, the need for prolonged mechanical ventilation, the length of stay in the intensive care unit (ICU), the post-operative stroke rate, the incidence of post-operative renal failure, and the need for haemodialysis were also not statistically significant.

Haemorrhage-related re-exploration

The unadjusted incidence of re-exploration due to bleeding in the group that received clopidogrel was 5.8 vs. 1.3% for the control group ($P < 0.01$) (*Table 2*). A separate breakdown analysis by individual surgeon did not reveal significant variations between them. Subsequently the risk-adjusted logistic regression analysis confirmed a 4.9-fold (95% CI = 2.63–8.97, $P < 0.01$) increased likelihood of haemorrhage-induced re-exploration in the patients who received clopidogrel (*Table 3*).

After propensity score matching of all the clopidogrel-receiving patients to a comparable set of

Table 1 Patient demographic and pre-operative characteristics (univariable analysis)

	Control group ($n = 1944$)	Clopidogrel group ($n = 415$)	P
Age	65.0 ± 10.6	63.9 ± 11.1	0.07[a]
Female gender	512 (26.3)	128 (30.8)	0.06
Diabetes	670 (34.5)	140 (33.7)	0.78
Hypertension	1324 (68.1)	272 (65.5)	0.31
Congestive heart failure	148 (7.6)	34 (8.2)	0.69
History of MI	680 (35.0)	186 (44.8)	< 0.01
History of CVA	7 (0.4)	0 (0.0)	0.59[b]
Renal failure	59 (3.0)	18 (4.3)	0.18
Haemodialysis	29 (1.5)	5 (1.2)	0.82
COPD	5 (0.3)	0 (0.0)	0.59[b]
Peripheral vascular disease	264 (13.6)	52 (1.2)	0.63
LVEF			0.97[c]
>45%	990 (50.9)	212 (51.1)	
35–45%	559 (28.8)	114 (27.5)	
25–35%	321 (16.5)	78 (18.8)	
<25%	74 (3.8)	11 (2.7)	
Haematocrit	40.3 (22.4−43.5)	39.9 (25.1−56.0)	0.10[d]
African ancestry	390 (20.1)	72 (17.4)	0.21
Weight, lbs	182 (71−394)	180 (87–332)	0.04[d]
Urgent case	337 (17.3)	121 (29.2)	<0.01
Repeat CABG surgery	109 (5.6)	25 (6.0)	0.74
Parsonnet's score	12.0 (0–59)	12.0 (0–44)	0.74[d]

Values are expressed as n (%), as mean ± SD, or as median (minimum–maximum).
χ^2 tests are used for all comparisons unless noted otherwise. No adjustments were made for multiple testing.
[a]Student's t-test.
[b]Fisher's exact test.
[c]Cochran–Armitage trend test.
[d]Wilcoxon rank sum test.

controls ($n = 415$), a 5.7-fold (95% CI = 1.81–18.15, $P < 0.01$) increased probability for haemorrhage-related re-exploration was demonstrated by the general estimating model analysis (*Table 4*).

Allogeneic-blood transfusion requirements

The unadjusted univariable analysis demonstrated that the group that received clopidogrel had a higher rate of intraoperative PRBC (30.4% vs. 22.1%, $P < 0.01$), platelet (5.1 vs. 1.8%, $P < 0.01$) and FFP (3.9 vs. 1.6%, $P < 0.01$) transfusions plus a higher rate of intraoperative blood loss (*Table 2*). Post-operative transfusion rates were also increased in the group which was administered clopidogrel with 54.5 vs. 37.7%, ($P < 0.01$), of patients receiving PRBC transfusions, 19.0 vs. 8.7% receiving platelets ($P < 0.01$), and 13.0 vs. 7.7% ($P < 0.01$) receiving FFP transfusions (*Table 2*). The clopidogrel-receiving patients also required higher amounts of intra- and post-operative PRBC transfusion (*Table 2*). When clinical practice by individual surgeon was examined, no significant disparities were found between them with regard to blood product selection or intra- and post-operative transfusion rates.

In the risk-adjusted multivariable logistic regression analysis model, the predicted odds of receiving a peri-operative blood transfusion were increased 2.2-fold (95% CI = 1.70–2.84, $P < 0.01$) after clopidogrel administration (*Table 3*). Age, female gender, history of MI, renal failure and haemodialysis, pre-operative haematocrit, African ancestry, weight, urgent and repeat CABG surgery, and more than four vessels grafted emerged as independent predictors for increased blood transfusion (*Table 3*). In contrast, being operated on a beating heart was associated with decreased transfusion requirements (OR = 0.4%, 95% CI = 0.32–0.48, $P < 0.01$). Clopidogrel administration was also associated with a 90% increase in the odds of receiving multiple units of peri-operative blood transfusion ($P < 0.01$) (*Table 3*).

Similarly, patients that received clopidogrel had a 2.6-fold (95% CI = 1.95–3.56, $P < 0.01$) increased likelihood for peri-operative platelet transfusion with age, female gender, pre-operative haemodialysis, and weight being associated risk factors (*Table 3*).

In the matched-pair (matched patients $n = 830$) analysis, clopidogrel administration was associated with an increased need for PRBC (OR = 1.9, 95% CI = 1.38–2.52, $P < 0.01$), multiple unit (OR = 2.3, 95% CI = 1.52–3.52, $P < 0.01$), and platelet (OR = 2.3, 95% CI = 1.52–3.57, $P < 0.01$) transfusion (*Table 4*).

Operative mortality

The unadjusted operative mortality rate was not statistically different between the two groups (1.7 vs. 1.4%,

Table 2 Patient peri-operative characteristics and outcomes (univariable analysis)

	Control group ($n = 1944$)	Clopidogrel group ($n = 415$)	P
Beating heart vs. conventional CABG	1291 (66.4)	281 (67.7)	0.61
Number of new grafts			0.35[a]
1	92 (4.7)	26 (6.3)	
2	335 (17.2)	70 (16.9)	
3	671 (34.5)	138 (33.3)	
4	569 (29.3)	128 (30.8)	
5	234 (12.0)	50 (12.1)	
6	43 (2.2)	3 (0.7)	
Cardiopulmonary bypass time, min	68.0 (15.0−190.0)	66.5 (30.0–188.0)	0.47[b]
Intraoperative PRBC	429 (22.1)	126 (30.4)	<0.01
Intraoperative PRBC amount, mL	500 (250–1750)	500 (250–2 000)	<0.01[b]
Intraoperative platelet rate	35 (1.8)	21 (5.1)	<0.01
Intraoperative platelet amount, mL	300 (100−600)	300 (250−550)	0.25[b]
Intraoperative FFP rate	31 (1.6)	16 (3.9)	<0.01
Intraoperative FFP amount, mL	833 (50–1700)	687 (350–1400)	0.79[b]
Intraoperative blood loss, mL	400 (100–2000)	400 (100–6000)	<0.01[b]
IABP	13 (0.7)	1 (0.2)	0.49[a]
Aprotinin use	24 (1.2)	7 (1.7)	0.46
Need for prolonged mechanical ventilation	70 (3.6)	16 (3.9)	0.80
ICU length of stay, days	1 (0−50)	1 (1−28)	0.08[b]
Post-operative stroke rate	32 (1.7)	12 (2.9)	0.09
Post-operative MI rate	14 (0.7)	9 (2.2)	<0.01
Post-operative PRBC rate	732 (37.7)	226 (54.5)	<0.01
Post-operative PRBC amount, mL	500 (250–4250)	500 (250–6250)	<0.01[b]
Post-operative platelet rate	170 (8.7)	79 (19.0)	<0.01
Post-operative FFP rate	150 (7.7)	54 (13.0)	<0.01
Re-operation due to haemorrhage	25 (1.3)	24 (5.8)	<0.01
Post-operative renal failure	27 (1.4)	7 (1.7)	0.64
Post-operative need for haemodialysis	10 (0.5)	1 (0.2)	0.70[c]
Length of stay, days	5 (1−128)	5 (1−84)	0.02[b]
Operative mortality	28 (1.4)	7 (1.7)	0.71

Values are expressed as n (%) or as median (minimum–maximum).
χ^2 tests are used for all comparisons unless noted otherwise. No adjustments were made for multiple testing or confounding risk factors.
[a]Cochran–Armitage trend test.
[b]Wilcoxon rank sum test.
[c]Fisher's exact test.

$P = 0.71$). Advanced age, renal failure, and haemodialysis were identified in the multivariable logistic regression model as predictors of mortality, while pre-operative clopidogrel administration was not (*Table 3*). Similarly, in the matched-pair analysis, clopidogrel administration did not emerge as a significant predictor of operative mortality (*Table 4*).

Discussion

Intuitive logic dictates that patients exposed to clopidogrel prior to undergoing surgical coronary revascularization will experience noticeable increases in post-operative bleeding, transfusion requirements, and subsequent need for haemostatic re-exploration. Maybe that is why, excluding a number of small, empirical reports in various cardiac surgery forums, the literature lacks large sample studies unequivocally demonstrating increased haemorrhagic complications in patients operated on after clopidogrel administration. Yende and Wunderinkl[19] were among the first to report that patients receiving combined clopidogrel and aspirin prior to CABG were almost six times more likely to require re-operation to control haemorrhage and had a 20% increase in PRBC transfusion requirements.[20] Likewise, in a more recently published study evaluating 59 patients who received clopidogrel within 7 days of CABG, an increase in re-operation due to haemorrhage, chest tube drainage, and average PRBC, platelet, and FFP amounts transfused was reported.[5] However, these studies contained small cohorts of exposed patients and did not adjust their outcomes for pre-operative haemorrhage-related risk co-factors. Therefore awareness about clopidogrel-associated haemorrhagic complications is still limited outside the cardiac surgery scientific community.

In contrast, well-publicized, large, randomized, double-blind, multi-centre studies such as the CAPRIE trial, which reported a significant decrease in the relative risk of MI, ischaemic stroke, and vascular death with prophylactic clopidogrel therapy, or the CURE

Table 3 Haemorrhagic outcomes of interest and significant predictors (multivariable analysis)

Outcome	Predictors	OR	95% CI	*P*
Re-operation due to bleeding[a] ($n = 2359$)	Clopidogrel	4.9	(2.63, 8.97)	<0.01
	Weight	1.0	(0.98, 1.00)	0.05
Received blood transfusion[b] ($n = 2359$)	Clopidogrel	2.2	(1.70, 2.84)	<0.01
	Age	1.0	(1.02, 1.04)	<0.01
	Female gender	2.1	(1.69, 2.73)	<0.01
	History of MI	1.2	(1.00, 1.49)	0.05
	Renal failure	2.9	(1.50, 5.45)	<0.01
	Haemodialysis	2.4	(0.99, 6.12)	0.05
	Pre-operative haematocrit	0.9	(0.93, 0.97)	<0.01
	African ancestry	1.5	(1.15, 1.91)	<0.01
	Weight	1.0	(0.98, 0.99)	<0.01
	Urgent CABG	1.4	(1.07, 1.73)	<0.01
	Repeat CABG	1.6	(1.03, 2.38)	0.03
	Beating heart CABG	0.4	(0.32, 0.48)	<0.01
	4 to 6 vessels grafted	1.3	(1.07, 1.58)	<0.01
Received platelets[c] ($n = 2359$)	Clopidogrel	2.6	(1.95, 3.56)	<0.01
	Age	1.02	(1.00, 1.04)	<0.01
	Female gender	0.6	(0.41, 0.83)	<0.01
	Haemodialysis	3.7	(1.64, 8.37)	<0.01
	Weight	0.99	(0.99, 1.00)	<0.01
Received multiple units of blood[d] ($n = 1191$)	Clopidogrel	1.9	(1.33, 2.75)	<0.01
	Age	1.0	(1.00, 1.03)	0.03
	Pre-operative haematocrit	0.9	(0.90, 0.96)	<0.01
	Repeat CABG	2.4	(1.19, 4.66)	<0.01
	Beating heart CABG	0.5	(0.38, 0.69)	<0.01
Operative mortality[e] ($n = 2359$)	Clopidogrel	1.2	(0.49, 2.91)	0.70
	Age	1.1	(1.05, 1.15)	<0.01
	Renal failure	5.2	(1.98, 13.85)	<0.01
	Haemodialysis	8.4	(2.08, 33.97)	<0.01

[a]Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 4.58$, df = 8, $P = 0.80$, C-statistic = 0.74.
[b]Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 10.10$, df = 8, $P = 0.26$, C-statistic = 0.80.
[c]Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 7.89$, df = 8, $P = 0.44$, C-statistic = 0.68.
[d]Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 11.85$, df = 8, $P = 0.16$, C-statistic = 0.67.
[e]Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 3.62$, df = 8, $P = 0.89$, C-statistic = 0.83.

Table 4 Haemorrhagic outcomes of interest and significant predictors (propensity score matched analysis)

Outcomes (matched pairs = 415, $n = 830$)	Predictors	OR	95% CI	*P*
Re-operation due to bleeding	Clopidogrel	5.7	(1.81, 18.15)	<0.01
Received blood transfusion	Clopidogrel	1.9	(1.38, 2.52)	<0.01
	Pre-operative haematocrit	0.8	(0.80, 0.87)	<0.01
	Renal failure	3.4	(0.99, 11.89)	0.05
Received platelets	Clopidogrel	2.3	(1.52, 3.57)	<0.01
	LVEF (<35%)	1.7	(1.12, 2.70)	<0.01
	Renal failure	2.2	(1.00, 4.71)	0.05
Received multiple units of blood	Clopidogrel	2.3	(1.52, 3.52)	<0.01
	Pre-operative haematocrit	0.9	(0.90, 0.98)	<0.01
Operative mortality	Clopidogrel	1.5	(0.36, 6.51)	0.56
	Renal failure	11.7	(1.99, 68.42)	<0.01

trial, a placebo-controlled study of patients presenting within 24 h of the onset of acute coronary symptoms, which demonstrated a 20% reduction in cardiovascular mortality, MI, and CVA after aspirin and clopidogrel administration, continue to expand the drug's clinical applicability and usage.[1–4,17–19]

Similarly the Clopidogrel for the Reduction of Events During Observation (CREDO) study, which demonstrated

a 35% reduction in mortality, MI, and need for urgent target vessel revascularization with clopidogrel administration prior to PCI,[28] confirmed the earlier reports demonstrating the drug's efficacy in preventing post-intervention stent occlusion.[6–11]

Therefore, clopidogrel has become engrained in cardiovascular practice as the standard of care for the management of acute coronary syndrome and as prophylaxis for coronary stent thorombosis in interventional cardiology. It is of great concern that, as the indications for clopidogrel use expand, an increasing percentage of patients presenting for surgical coronary revascularization do so subject to irreversible platelet inhibition. Consequently, the intrinsic advantages in clinical outcome conferred by clopidogrel's anti-aggregant properties, especially in unstable patients, need to be balanced against the possible bleeding complications.

In this study we were able to demonstrate that patients who were exposed to clopidogrel and subsequently had to undergo CABG surgery had a higher incidence of hard-to-manage intraoperative bleeding and associated blood transfusion requirements. Subsequent post-operative demands for PRBC, platelets, and FFP transfusion, and ensuing need for haemostatic re-operation were also higher in the clopidogrel group.

After adjusting for pre-operative risk factors, the clopidogrel-receiving group had a two-fold increase both in overall blood transfusions received and in the quantity administered. Other independent predictors for blood transfusion such as age, female gender, history of MI, renal failure and haemodialysis, pre-operative haematocrit, African ancestry, weight, urgent and repeat CABG surgery, and more than four grafted vessels were not unexpected, since all have been previously identified in the literature.[22–24] Platelet transfusion was almost three times more likely in the clopidogrel-exposed group, while the odds of requiring surgical re-operation to control post-operative haemorrhage were five times higher in that group.

To reduce the effect of pre-operative variability between the groups we matched all the clopidogrel-receiving patients with an equal set of controls through propensity scoring analysis. The matched-pair analysis confirmed that the clopidogrel group patients were two times more likely to receive blood transfusion and similarly were more likely to receive multiple units of blood, or platelets, or require subsequent haemostatic re-operation.

These findings have considerable clinical implications since they clearly and unequivocally demonstrate that pre-operative clopidogrel administration prior to CABG surgery significantly increases the haemorrhagic sequelae that patients experience. Blood product transfusion exposes patients to infectious complications and immunological reactions, while surgical re-exploration due to bleeding has been shown to increase the need for mechanical ventilation, the total length of the hospital stay, and operative mortality.[17,29,30] Furthermore, a recent study has demonstrated that post-operative blood transfusion is an independent predictor of increased long-term mortality after cardiac surgery and thus has a direct impact on patient prognosis.[31]

A significant number of patients are exposed to clopidogrel during diagnostic coronary angiography and concurrent PCI, by receiving a prophylactic loading dose prior to the procedure. Conversely a number of these patients are found to have coronary anatomy more amenable to surgical revascularization. The current strategy of delaying surgery until platelet function has adequately recovered not only increases the patient's risk of complications and associated hospitalization costs but also is not applicable in patients who require urgent or emergent surgical revascularization. In those patients, platelet transfusion has been utilized to control persistent haemorrhage post-operatively. However, new research has suggested that considerable heterogeneity of clopidogrel-induced platelet inhibition exists among patients receiving a loading dose preceding PCI.[32–35] Muller and colleagues proposed that patients undergoing elective PCI do not attain the expected inhibitory effect following a short-term 300-mg clopidogrel loading dose.[35] More significantly, a recent study demonstrated that pre-treatment with a 300-mg loading dose of clopidogrel either 24 h before, or immediately after, stent implantation did not result in a pronounced inhibition of the platelet and coagulation system in patients undergoing elective coronary stent implantation.[36] Furthermore, Gurbel *et al.* recently proposed that ~30 and 15% of patients exhibit clopidogrel resistance at 5 and 30 days, respectively.[34] Therefore, given this recent evidence what may be optimal is a modification of the current practice of clopidogrel administration until after appropriate coronary anatomy for PCI has been identified. Since, for many patients, its onset of action will not take effect until many hours after the catheterization, regardless of the timing of administration, this policy should not incur any significant risks.

Study limitations

Limitations of this study include all those inherent to any retrospective single-institution analysis. All data elements, however, were prospectively entered in a cardiac surgery research database according to pre-specified definitions and the data analysis was performed using appropriately risk-adjusted statistical models in order to adjust for differences in pre-operative risks factors. One might suggest that surgeons and anaesthetists could be aware of patients who received antiplatelet agents pre-operatively, possibly lowering their threshold for administering blood products to them. Although such a bias might have occurred with certain secondary endpoints, it is unlikely to have affected the primary endpoint (need for re-exploration due to haemorrhage). Furthermore, a breakdown analysis by individual surgeons revealed uniformity in blood product utilization, which refutes any bias assertions.

Conclusion

This study unequivocally demonstrated, through the use of a large sample size and risk-adjusted methodology, that clopidogrel administration prior to CABG increases peri-operative bleeding risk, transfusion demands, and the need for surgical re-exploration to control the haemorrhage.

Acknowledgements

We would like to acknowledge the contribution of the late Dr Albert J. Pfister in the conception and design of this study.

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