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Relationship between postoperative clopidogrel use and subsequent angiographic and clinical outcomes following coronary artery bypass grafting

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Abstract

Dual antiplatelet therapy with both aspirin and clopidogrel is increasingly used after coronary artery bypass grafting (CABG); however, little is known about the safety or efficacy. We sought to determine the relationship between postoperative clopidogrel and clinical and angiographic outcomes following CABG. We evaluated 3,014 patients from PREVENT IV who underwent CABG at 107 US sites. Postoperative antiplatelet therapy was left to physician discretion. Risk-adjusted angiographic and clinical outcomes were compared in patients taking and not taking clopidogrel 30 days post-CABG. At 30 days, 633 (21 %) patients were taking clopidogrel. Clopidogrel users were more likely to have peripheral vascular (15 vs. 11 %) and cerebrovascular disease (17 vs. 11 %), prior myocardial infarction (MI) (46 vs. 41 %), and off-pump surgery (33 vs. 18 %). Clopidogrel use was associated with statistically insignificant higher graft failure (adjusted odds ratio 1.3; 95 % confidence interval [CI] [1.0, 1.7]; $P = 0.05$). At 5-year follow-up, clopidogrel use was associated with similar composite rates of death, MI, or revascularization (27 vs. 24 %; adjusted hazard ratio 1.1; 95 % CI [0.9, 1.4]; $P = 0.38$) compared with those not using clopidogrel. There was an interaction between use of cardiopulmonary bypass and clopidogrel with a trend toward lower 5-year clinical events with clopidogrel in patients undergoing off-pump CABG. In this observational analysis, clopidogrel use was not associated with better 5-year outcomes following CABG. There may be better outcomes with clopidogrel among patients having off-pump surgery. Adequately powered randomized clinical trials are needed to determine the role of dual antiplatelet therapy after CABG.

Keywords

Clopidogrel; CABG; Dual antiplatelet therapy; Coronary artery bypass surgery; Outcomes

Introduction

The effectiveness of aspirin to prevent graft occlusion and improve clinical outcomes after coronary artery bypass grafting (CABG) has been established and is endorsed by the American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines [1–3]. Despite aspirin therapy, however, graft occlusion and recurrent ischemic events continue to recur in many patients following CABG [4–6].

The addition of dipyridamole or anticoagulation with warfarin has not been shown to be associated with beneficial effects on either graft patency or clinical events [7, 8]. Evidence for the use of adenosine diphosphate (ADP) receptor antagonists, including ticlopidine or clopidogrel, is limited [9, 10]. Based on studies involving small numbers of patients, clopidogrel or alternative ADP receptor antagonist has been recommended following CABG

for aspirin-allergic patients [8]. Current guidelines also recommend postoperative clopidogrel in addition to aspirin for patients who undergo CABG following non-ST-segment elevation acute coronary syndromes [11–13].

Despite the absence of data from a large randomized clinical trial, dual antiplatelet therapy with aspirin and clopidogrel is increasingly used early following non-urgent CABG in contemporary clinical practice, particularly in patients not supported with cardiopulmonary bypass [14, 15]. The objective of this observational analysis was to assess the clinical characteristics and the angiographic and clinical outcomes of patients receiving clopidogrel plus aspirin compared with aspirin alone following CABG using data from the completed large multicenter PREVENT IV (Project of Ex-vivo Vein graft Engineering via Transfection IV) trial.

Methods

Patient population

The design of the PREVENT IV trial has been previously published [16]. In brief, this was a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial assessing the efficacy of edifoligide, an oligonucleotide E2F transcription factor decoy, designed to prevent neo-intimal hyperplasia and vein graft failure. PREVENT IV enrolled 3,014 patients at 107 sites in the United States in 2002 and 2003. Institutional review board approval was obtained at all sites and all patients gave written informed consent prior to participation.

Patients were eligible for inclusion if they were 18–80 years of age and undergoing a first isolated CABG with at least 2 planned vein-graft implantations. Major exclusion criteria included prior cardiac surgery and planned concomitant valve surgery. The first 2,400 patients enrolled were assigned to an angiographic cohort and scheduled to return for angiography 12–18 months after surgery. Postoperative medications, including clopidogrel, were left to the discretion of the treating physicians; however, they were encouraged to follow ACC/AHA practice guidelines [13].

For the purpose of this analysis, we included all patients enrolled in the PREVENT IV study with the exception of those who died prior to 30 days postoperatively ($n = 41$) and those with unknown clopidogrel use ($n = 16$).

Outcome measures

In PREVENT IV, follow-up angiography was conducted at the enrolling site using standardized angiographic techniques. All angiograms were sent to the PERFUSE angiographic core laboratory (Boston, MA) for analysis using quantitative coronary angiography. Internal mammary, vein, and other arterial grafts were assessed for both graft failure (75% stenosis) and occlusion. Patients who died prior to scheduled angiography were not included in this angiographic analysis. Patients who underwent angiography for clinical reasons and were found to have graft failure or occlusion before 12 months were not required to undergo additional protocol angiography.

Clinical endpoints were assessed by follow-up visit and mail or telephone survey at 6 and 9 months and at 1, 2, 3, 4, and 5 years following CABG. Endpoints included the following major adverse cardiac events: death, myocardial infarction (MI), or repeat revascularization. All suspected MIs and revascularization procedures were adjudicated by a blinded, independent clinical events committee using prespecified criteria.

Postoperative MI was defined as either spontaneous (creatinine kinase [CK]-MB $>2 \times$ the upper limit of normal [ULN] or new Q waves >30 ms in 2 contiguous leads), after percutaneous coronary intervention (CK-MB $>3 \times$ ULN or new Q waves >30 ms in 2 contiguous leads), or after CABG (CK-MB $>10 \times$ ULN or $>5 \times$ ULN with new Q waves >30 ms in 2 contiguous leads). For patients with no available electrocardiograms and CK-MB samples, MI could be defined by the presence of “myocardial infarction,” “heart attack,” or similar term documented in the medical record indicating that an MI had occurred after the initial CABG procedure.

Statistical analysis

Patients were categorized into 2 groups based on whether or not they were taking clopidogrel at discharge and continuing on clopidogrel at 30 days postoperatively. Baseline patient and operative characteristics were summarized in terms of frequencies and percentages for categorical variables and by the median (25th, 75th percentiles) for continuous variables. Differences in characteristics between patients with and without clopidogrel were assessed using the Wilcoxon rank-sum test for continuous variables and the Chi square or Fisher’s exact test for categorical variables. All tests of significance were 2-tailed.

Angiographic outcomes, including both graft failure (75% stenosis) and graft occlusion, were compared at the individual graft level before and after risk adjustment using a multivariable model. Adjustments were made for patient-level clustering, weight, creatinine clearance, prior MI, history of peripheral vascular disease, history of cerebrovascular disease, length of procedure, on-bypass procedure, worst graft quality, worst target artery quality, endoscopic vein harvesting, use of composite grafts, and the propensity to be on clopidogrel at 30 days.

Risk-adjusted analyses of clinical outcomes (death, MI, or revascularization) were assessed using the Cox proportional hazards model. Covariates adjusted for included age, history of congestive heart failure, prior MI, body mass index, creatinine clearance, left ventricular ejection fraction, lung disease, diabetes, history of peripheral vascular disease, history of cerebrovascular disease, hypercholesterolemia, hypertension, liver disease, left main coronary artery disease, on-pump surgery, use of internal mammary artery, endoscopic vein harvesting, worst target artery quality, other concomitant procedures, and the propensity to be on clopidogrel at 30 days. Cumulative event rates for the composite clinical outcome were calculated by the Kaplan–Meier method after excluding events occurring in the first 30 days. The statistical significance of differences in outcomes between the 2 groups was assessed with the log-rank test. Hazard ratios [HR] and 95 % confidence intervals [CI] were calculated with the Cox model. Finally, we tested for interactions between clopidogrel use and both on- versus off-pump CABG and endoscopic versus open vein graft harvesting on

both adjusted angiographic and clinical outcomes. Statistical significance was defined by a *P* value of <0.05. All analyses were performed with SAS software (SAS Institute, Inc., Cary, NC).

Results

Study population

Rates of medication use were documented in 99.5 % of PREVENT IV patients after hospital discharge. Aspirin was used in 91 % of patients. Of the 3,014 patients in the PREVENT IV trial, 633 (21 %) were taking clopidogrel at 30 days postoperatively and 2,324 (77 %) were not. Among the patients taking clopidogrel postoperatively, a minority (43 %) remained on clopidogrel at 1 year. Substantial between-site variation existed in the use of clopidogrel (Fig. 1). Among the 2,400 patients enrolled in the angiographic cohort, angiographic follow-up was completed in 1819 patients (76 %). The median (25th, 75th percentile) time to angiographic follow-up was 12.6 (12.2, 13.4) months. Five-year follow-up was completed in 2,865 (95 %) patients.

Baseline characteristics

Patient baseline characteristics are shown in Table 1. Patients receiving clopidogrel were more likely to have a history of hyperlipidemia (80.4 vs. 75.5 %), prior MI (46.3 vs. 40.8 %), prior stroke (8.4 vs. 4.5 %), cerebrovascular disease (16.9 vs. 11.3 %), and peripheral vascular disease (14.7 vs. 11.4 %), but were less likely to have preoperative atrial fibrillation (3.8 vs. 7.6 %). Patients taking clopidogrel postoperatively were also more likely to have been on clopidogrel preoperatively (10.7 vs. 6.8 %).

Surgical characteristics are shown in Table 2. Patients taking clopidogrel were less likely to have used cardiopulmonary bypass (66.5 vs. 82.0 %) and had longer procedure duration (median 240 vs. 229 min). The duration of postoperative mechanical ventilation, intensive care unit stay, and total hospital stay did not differ between patients using and not using clopidogrel. At 30 days, use of the secondary prevention therapies aspirin, angiotensin-converting enzyme inhibitors, and beta-blockers were similar between the groups; however, use of HMG-CoA reductase inhibitors tended to be higher among clopidogrel users (77.9 vs. 72.4 %).

Table 3 displays the independent clinical correlates with clopidogrel use in descending order of their model Chi square values. The c-statistic of the model was 0.76.

Clinical and angiographic outcomes

Clopidogrel users had higher unadjusted rates of both graft failure (odds ratio [OR] 1.6; 95 % CI [1.3, 2.0]; *P* < 0.001) and graft occlusion (OR 1.5; 95 % CI [1.2, 1.9]; *P* < 0.001) (Table 4). After adjustment, although no longer statistically significant, trends towards worse angiographic outcomes remained in patients using clopidogrel for graft failure (OR 1.3; 95 % CI [1.0, 1.7]; *P* = 0.05) and for graft occlusion (OR 1.3; 95 % CI [0.97, 1.6]; *P* = 0.08). Results were similar when considering only vein grafts (data not shown).

Clinical outcomes are shown in Table 5. Unadjusted event rates were non-significantly higher in patients on clopidogrel. An adjusted Cox proportional hazards model revealed similar risks of death (HR 1.0; 95 % CI [0.72, 1.4]; $P = 0.99$), death or MI (HR 1.1; 95 % CI [0.8, 1.5]; $P = 0.47$), and death, MI, or revascularization (HR 1.1; 95 % CI [0.9, 1.4]; $P = 0.38$) among clopidogrel users and non-users (Fig. 2).

A statistically significant interaction was found between the use of cardiopulmonary bypass and clopidogrel (Table 6, Fig. 3). A trend toward lower 5-year clinical event rates was observed with clopidogrel among patients undergoing off-pump CABG, but not in those in whom surgery was performed with cardiopulmonary bypass (P for interaction <0.05 for all clinical events) (Table 6). No interaction was seen between use of endoscopic vein harvesting and clopidogrel for clinical outcomes ($P = 0.98$). No interaction was found between the investigational agent edifoligide and clopidogrel.

Discussion

Our study suggests that clopidogrel use following CABG is common, with 1 of every 5 CABG patients receiving clopidogrel postoperatively. However, clopidogrel use varied widely among sites, with some prescribing it to almost all their patients while others to hardly any (Fig. 1). Patients with previously documented atherosclerosis in any cardiovascular bed (prior MI or cerebrovascular disease), on preoperative clopidogrel, those undergoing off-pump surgery, or receiving endoscopic vein graft harvesting were more likely to be taking clopidogrel following CABG. Clopidogrel use was associated with a trend toward higher rates of vein graft failure 12–18 months following surgery. Although clopidogrel use was not associated with a lower rate of clinical events in the overall population, a significant interaction was found between clopidogrel and the use of cardiopulmonary bypass with a trend toward lower event rates with clopidogrel among patients having off-pump surgery, but not among those having surgery with cardiopulmonary bypass.

Our findings of wide variation in the use of clopidogrel are consistent with those observed by others who demonstrated that cardiac surgeons and cardiologists widely and inconsistently prescribe clopidogrel to patients following CABG [14]. This heterogeneity stems from the lack of definitive evidence regarding the efficacy and safety of clopidogrel in this population. Proponents of post-CABG clopidogrel use justify this primarily based on subgroup post hoc analyses of randomized trials and observational data.

The effects of clopidogrel plus aspirin were examined in a post hoc analysis in patients with recent acute coronary syndromes using data from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial [17]. Among the subgroup of patients treated with CABG during the initial hospitalization, the frequency of cardiovascular death, MI, or stroke before CABG was 4.7 % for placebo versus 2.9 % for clopidogrel (relative risk [RR] 0.56; 95 % CI [0.29, 1.08]); however, this effect was primarily driven by a reduction in the number of events prior to surgery, with no evident benefit among the patients receiving clopidogrel postoperatively (3 % RR reduction; 95 % CI [0.74, 1.26]) [18]. Moreover, postoperative clopidogrel was associated with an excess of life-threatening bleeding (30 %

increased risk; 95 % CI [0.90, 1.83]) despite study medication being restarted in only 75 % (1,451/1,928) of patients and stopped for a median of 10 days after CABG [18].

The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial showed no difference in the primary composite endpoint of cardiovascular death, MI, or stroke between groups treated with clopidogrel plus aspirin versus placebo plus aspirin. A trend toward more frequent severe bleeding, the trial's primary safety endpoint, was observed in the clopidogrel plus aspirin arm (clopidogrel 1.7 % vs. placebo 1.3 %; $P = 0.09$). Subgroup analysis of patients with a history of CABG ($n = 3,079$) revealed event rates consistent with our findings of 9.9 % in the clopidogrel plus aspirin group and 8.5 % in the placebo plus aspirin group (HR 1.05; $P = 0.70$) [19].

CASCADE (Clopidogrel After Surgery for Coronary Artery Disease), a small randomized placebo-controlled trial, evaluated the impact of clopidogrel and aspirin versus aspirin alone on graft patency and clinical outcomes after CABG. This trial compared clopidogrel plus aspirin with aspirin alone in 113 CABG patients, including evaluation of saphenous vein graft intimal hyperplasia using intra-vascular ultrasound through 1 year postoperatively in 90 patients. Patients first received study drug, without bolus, when postoperative chest tube drainage had decreased to <50 mL/h for 2 consecutive hours. Investigators found a non-significant 14.8 % reduction in the primary outcome of intravascular ultrasound-measured vein graft intimal hyperplasia in the clopidogrel group [20]. Additionally, in this small trial that was underpowered for clinical events, there were no differences in secondary endpoints of vein graft patency, postoperative cardiovascular events, or major bleeding.

In another small randomized comparison, Gao and colleagues compared aspirin plus clopidogrel to aspirin alone in 249 patients undergoing elective CABG at Fuwai Hospital [21]. Antiplatelet therapies were initiated postoperatively when chest tube drainage had decreased to <30 mL/h for 2 consecutive hours. Three-month follow-up computed tomography angiography (CTA) was performed in 90 % of patients with no difference in vein graft patency (92 vs. 86 %). However, multivariate analysis for predictors of graft patency found dual anti-platelet therapy to be associated with increased vein graft patency [21]. In the off-pump setting, Mannacio and colleagues randomized 300 off-pump CABG patients to aspirin plus clopidogrel versus aspirin alone with 12-month CTA and clinical follow-up. Dual antiplatelet therapy was found to be associated with reduced vein occlusion rate (7.4 vs. 13.1 %; $P = 0.04$) among off-pump patients [22].

Data specific to the efficacy/effectiveness of clopidogrel in patients undergoing off-pump CABG are sparse despite clinical interest in use of dual antiplatelet therapy for these patients. In a single-surgeon observational study, Gurbuz and colleagues found postoperative clopidogrel to be associated with fewer adverse cardiac events among off-pump CABG patients [23]. In a larger observational study, Kim and colleagues examined 15,067 CABG patients between 2003 and 2006 from 52 academic medical centers and affiliate hospitals in the United States and found clopidogrel plus aspirin to be associated with lower in-hospital mortality (0.95 vs. 1.78 %, $P = 0.048$) [24]. Although only short-term clinical outcomes were assessed, the relative effect of aspirin and clopidogrel use versus aspirin alone did not appear to differ significantly between on-pump and off-pump CABG

groups and study results were similar when the analyses were restricted to patients without acute coronary syndrome [24].

Early graft occlusion after CABG is known to result from platelet thrombus due to endothelial damage and altered blood flow in the graft. Clopidogrel is thought to potentially act in a synergistic fashion with aspirin in preventing the early platelet thrombus in bypass grafts. While some clinicians discontinue clopidogrel 1 month after off-pump surgery, the present data suggest a longer treatment beyond 30 days may be beneficial, and duration of therapy remains to be investigated. Several groups have endorsed that hemostatic mechanisms are altered to a much lesser extent in patients undergoing off-pump as opposed to on-pump CABG surgery [25, 26]. It is possible that the lack of associated benefit with clopidogrel in on-pump (versus off-pump) patients was due to a greater baseline postoperative hemostatic derangement in these patients due to the use of cardiopulmonary bypass.

It remains to be evaluated whether newer, more potent antiplatelet agents, including the thienopyridine prasugrel [27] and reversible ADP antagonist ticagrelor [28], as well as novel anticoagulants, including factor X [29] and II inhibitors [30], might improve post-CABG angiographic and clinical outcomes, particularly among patients undergoing on-pump surgery. Observational analysis using data from the PLATO (Platelet inhibition and patient Outcomes) trial showed promising results for the use of ticagrelor in the post-CABG setting. The PLATO trial subgroup undergoing CABG, with study drug stopped within 7 days of surgery ($n = 1,260$), revealed a reduction in all-cause mortality for patients receiving ticagrelor (4.6 vs. 9.2 %; HR 0.49; $P = 0.002$) compared with those receiving clopidogrel [31]; however, with no difference in ischemic events or bleeding.

Limitations

As the present study is observational, measured or unmeasured confounders could have influenced our findings. Bleeding complications were not captured as part of the PREVENT IV trial protocol and these data were therefore not available for the present study. The PREVENT IV trial found that edifoligide does not affect outcomes following CABG surgery, however, failure to use evidence-based medications was associated with long-term outcomes following CABG surgery [32]. Overall, only 90 % of CABG patients received aspirin and 70 % a lipid-lowering agent, and these results likely influenced the high event rates observed in the PREVENT IV trial [33]. Although no interaction with edifoligide was observed, it is possible that this agent and/or other factors unique to the PREVENT IV population limit the generalizability of these findings [16, 34].

Conclusion

In this observational analysis, clopidogrel use was not associated with better 5-year outcomes following CABG. There may, however, be better outcomes with clopidogrel among patients having off-pump CABG. Adequately powered randomized clinical trials are needed to determine the role of dual antiplatelet therapy after CABG.

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Fig. 1.
Distribution of clopidogrel use across the 107 study sites that participated in PREVENT IV

Fig. 2. Risk-adjusted Kaplan–Meier curves for **a** death; **b** the composite of death and MI; and **c** the composite of death, MI, or revascularization in patients using and not using clopidogrel at 30 days

Fig. 3. Forest plot of risk-adjusted 5-year clinical outcomes for postoperative clopidogrel use according to on- or off-pump CABG (point estimates shown with 95 % CI)

Table 1

Baseline characteristics according to clopidogrel use

Characteristics	30-Day postoperative clopidogrel		P Value
	Yes (n = 633)	No (n = 2,324)	
Age, median (25th, 75th), yrs	64 (55, 70)	63 (56, 71)	0.83
Female	22.9	20.0	0.11
Non-white race	8.4	9.3	0.48
Weight, median (25th, 75th), kg	88 (75, 100)	88 (77, 100)	0.37
Medical history			
Hypertension	75.7	74.8	0.66
Diabetes mellitus	38.7	37.5	0.59
Current smoking	23.1	22.9	0.98
Hyperlipidemia	80.4	75.5	0.01
Chronic lung disease	15.3	15.6	0.88
Preoperative AF/flutter	3.8	7.6	0.001
Prior MI (any)	46.3	40.8	0.01
Prior MI within 1 month	20.1	20.0	0.96
Prior PCI	28.8	25.3	0.08
Congestive HF	9.3	9.4	0.96
Prior stroke	8.4	4.5	< 0.001
Cerebrovascular disease	16.9	11.3	< 0.001
Peripheral vascular disease	14.7	11.4	0.03
History of liver disease	1.4	1.9	0.43
Renal failure	2.4	2.0	0.59
Cardiogenic shock	0.8	0.8	0.94
Presenting features			
Preoperative NYHA class			0.33
I	42.0	39.9	
II	34.2	33.2	
III	15.4	18.6	
IV	8.4	8.3	
LVEF, median (25th, 75th), %	50 (40, 60)	50 (40, 60)	0.48
2 diseased vessels or left main (> 75 % stenosis)	79.8	78.9	0.94
Preoperative antiplatelet agents			
Aspirin	50.2	51.7	0.51
Clopidogrel	10.7	6.8	0.001

Values are presented as percentages, unless otherwise indicated

AF atrial fibrillation, *HF* heart failure, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *NYHA* New York Heart Association, *PCI* percutaneous coronary intervention

Table 2

Operative and postoperative characteristics according to clopidogrel use

Characteristics	30-Day postoperative clopidogrel		P Value
	Yes (n = 633)	No (n = 2,324)	
Urgent/emergent/emergent salvage procedure	51.5	51.4	0.68
Internal mammary artery graft	94.0	91.8	0.07
Endoscopic vein graft harvesting	67.2	55.9	< 0.001
Surgery duration, median (25th, 75th), min	240 (198, 281)	229 (191, 268)	0.001
Cardiopulmonary bypass	66.5	82.0	< 0.001
Duration of CPB, median (25th, 75th), min	105 (84, 128)	99 (79, 122)	0.003
Number of treatment-eligible vein grafts			0.281
1	2.1	2.8	
2	60.2	59.8	
3	31.1	32.2	
4	5.8	4.9	
Worst target artery quality			0.10
Good	41.9	43.4	
Fair	33.9	36.3	
Poor	24.2	20.3	
Postoperative duration, median (25th, 75th)			
Mechanical ventilation, hours	7.0 (5.0, 13.0)	8.0 (4.3, 15.0)	0.68
Intensive care unit stay, hours	26.0 (22.0, 48.0)	25.5 (22.0, 46.0)	0.06
Hospital stay, days	6.0 (5.0, 8.0)	6.0 (5.0, 8.0)	0.85
Edifoligide (vs. placebo) treatment	46.6	50.9	0.06
Other medications at 30 days			
30-day aspirin	90.4	91.7	0.31
ACE inhibitor	34.9	36.4	0.49
ARBs	7.7	6.5	0.27
Beta-blockers	81.2	79.0	0.23
HMG-CoA reductase inhibitor	77.9	72.4	0.006

Values are presented as percentages, unless otherwise indicated

ACE angiotensin-converting enzyme, ARB angiotensin receptor blockers, CPB cardiopulmonary bypass, HMG-CoA = 3-hydroxy-3-methyl glutaryl coenzyme A

Table 3

Multivariable predictors of clopidogrel use 30 days post-CABG

	<i>P</i> Value	Odds Ratio (95 % CI)
Absence of postoperative warfarin use	< 0.001	4.69 (2.95, 7.46)
Off-pump surgery	< 0.001	1.93 (1.54, 2.41)
Cerebrovascular disease	< 0.001	1.98 (1.50, 2.62)
Use of endoscopic vein graft harvesting	< 0.001	1.45 (1.18, 1.79)
Clopidogrel use prior to surgery	0.001	1.75 (1.25, 2.43)
Prior MI	0.002	1.38 (1.13, 1.68)
Absence of postoperative stroke	0.020	5.00 (1.29, 19.20)

CI confidence interval, *MI* myocardial infarction

Table 4

Angiographic per patient rates of graft failure and occlusion*

	30-Day postoperative clopidogrel		Unadjusted		Adjusted	
	Yes (n = 391) (%)	No (n = 1,428) (%)	OR (95 % CI)	P Value	OR (95 % CI)	P Value
Graft failure (75 % stenosis)	57.0	45.3	1.60 (1.28, 2.01)	< 0.001	1.29 (1.00, 1.68)	0.052
Graft occlusion	49.1	38.7	1.53 (1.22, 1.91)	< 0.001	1.26 (0.97, 1.64)	0.080

CI confidence interval, *OR* odds ratio

* Includes any graft (vein, internal mammary or other arterial)

Table 5

Clinical events at 5 years

	30-Day postoperative clopidogrel		Unadjusted		Adjusted	
	Yes	No	HR (95 % CI)	P Value	HR (95 % CI)	P Value
Death, MI, or revascularization			1.19 (1.00, 1.41)	0.054	1.10 (0.89, 1.35)	0.379
No.	629	2318				
No. of events	167	537				
5-year event rate	27.0 %	23.7 %				
Death or MI			1.21 (0.95, 1.53)	0.128	1.11 (0.83, 1.49)	0.466
No.	633	2321				
No. of events	88	273				
5-year event rate	14.3 %	12.1 %				
Death			1.09 (0.83, 1.43)	0.557	1.00 (0.72, 1.39)	0.991
No.	633	2324				
No. of events	66	224				
5-year event rate	10.8 %	9.9 %				

CI confidence interval, *HR* hazard ratio, *MI* myocardial infarction

Table 6

Interaction between clopidogrel use and on- versus off-pump surgery on clinical outcome

	On Clopidogrel	Not on Clopidogrel	Adjusted HR (95 % CI) With Interaction	Interaction <i>P</i> Value
Death, MI, or revascularization			On-pump: 1.24 (0.99, 1.56)	0.0226
No.	629	2,318	Off-pump: 0.75 (0.51, 1.11)	
No. of events	167	537		
5-year event rate	27.0 %	23.7 %		
Death or MI			On-pump: 1.43 (1.05, 1.96)	0.0018
No.	633	2,321	Off-pump: 0.53 (0.30, 0.94)	
No. of events	88	273		
5-year event rate	14.3 %	12.1 %		
Death			On-pump: 1.35 (0.94, 1.92)	0.0014
No.	633	2,324	Off-pump: 0.40 (0.20, 0.80)	
No. of events	66	224		
5-year event rate	10.8 %	9.9 %		

CI confidence interval, *HR* hazard ratio, *MI* myocardial infarction