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Effect of Clopidogrel on Midterm Graft Patency following Off-Pump Coronary Revascularization Surgery

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ABSTRACT

Objective. The aim of the study was to evaluate the effect of clopidogrel on midterm graft patency following off-pump coronary revascularization surgery.

Design. Ninety-four consecutive patients who underwent off-pump coronary artery bypass grafting between 1997 and 2002 were studied (58 men, 36 women; 61.7 ± 9.8 years). The initial 36 patients (control group) received 75 to 160 mg acetyl salicylic acid (ASA) as an antiplatelet agent, whereas the consecutive 58 patients (clopidogrel group) received 75 mg clopidogrel postoperatively in addition to ASA. Intraoperatively, graft flow was assessed with transit-time flowmetry in all patients and the peripheral anastomoses were assessed with epicardial ultrasound in 28 patients. Sixty-two patients underwent angiography after a mean of 185 ± 92 days. A total of 82 grafts were evaluated angiographically. Grafts with TIMI flow 2 and 3 were assessed as patent.

Results. At angiographic follow-up, the overall graft patency rate was 84% (31/37) in the control group and 93% (42/45) in the clopidogrel group (*P* value was not significant [ns]). Graft patency rates for left internal mammary artery (LIMA) grafts were 92% (23/25) versus 96% (28/29) (ns), and for saphenous vein grafts were 66% (7/11) versus 87% (14/16) (ns), respectively.

Conclusion. The observed trend toward higher patency rates in patients treated with clopidogrel did not reach statistical significance. Further larger studies are necessary to confirm these preliminary results.

INTRODUCTION

Patency of the left internal mammary (LIMA) graft to the left anterior descending artery (LAD) is the strongest predictor of long-time survival after coronary artery bypass grafting (CABG) [Grover 1994]. One of the major complications after CABG is graft closure. Early closure is often related to technical failure; late closure is largely related to the atherosclerotic process that triggers platelet aggregation. Harvesting the long saphenous vein has a damaging effect on its endothelium to the extent that it becomes a raw surface, favoring platelet aggregation [Unn 1974]. Although off-pump myocardial revascularization may reduce some of the risks and complications observed after on-pump coronary surgery, it is technically more demanding and has a higher incidence of technical failure of the anastomoses [D'Ancona 1997]. Moreover, because most patients undergoing off-pump CABG are not fully heparinized, a hypercoagulable status is observed postoperatively in contrast to patients operated on with the use of a heart-lung machine [Kim 2001]. Accordingly, it has been suggested that this may reduce the patency of the anastomoses, and that patients undergoing off-pump CABG should receive additional anti-thrombotic treatment in the early postoperative phase to improve graft patency.

Clopidogrel, a thienopyridine derivative, is an antiplatelet agent that selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and blocks the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation [Arsan 2004]. The clinical benefits of clopidogrel on patients with acute coronary syndrome, myocardial infarction, and stroke have been demonstrated in many studies [Mishkel 1999; Yusuf 2001; Chu 2004], and clopidogrel is accordingly used worldwide for the long-term prevention of thrombotic cardiovascular events. Whether clopidogrel has any impact on the patency of coronary grafts and anastomoses is not yet fully established.

The present study is a retrospective evaluation of the effect of postoperative clopidogrel on the midterm patency of grafts and anastomoses in a consecutive cohort of patients operated on with off-pump CABG.

MATERIAL AND METHODS

Patient Selection

In this retrospective cohort study, a total of 94 consecutive patients (58 men, 36 women; age 61.7 ± 9.8 years) who underwent isolated off-pump CABG between 1997 and 2002

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Table 1. Demographic and Clinical Data Comparing 2 Groups of Patients Who Underwent Off-Pump Coronary Artery Bypass Grafting*

	Control Group (1997-1999), n = 37	Clopidogrel Group (2000-2002), n = 58	*P*
Age, y	61 ± 9.0	62 ± 10	ns
Female, n	11 (30%)	16 (27.5%)	ns
Male, n	26 (70%)	42 (72.5%)	ns
BMI	26 ± 4	26 ± 4	ns
LVEF, %	67 ± 16	69 ± 12	ns
Hypertension, n	16 (43%)	12 (21%)	ns
Hypercholesterolemia, n	28 (76%)	42 (72%)	ns
Diabetes mellitus, n	3 (8%)	2 (3%)	ns
Previous MI, n	18 (49%)	30 (52%)	ns
Previous PTCA, n	9 (24%)	9 (16%)	ns
Previous CABG, n	1 (3%)	3 (5%)	ns
Medication			
Beta blockers	33 (89%)	49 (84%)	ns
Calcium antagonists	6 (16%)	16 (28%)	ns
ACE inhibitors	7 (19%)	9 (16%)	ns
Nitrates	32 (86%)	39 (67%)	ns
Diuretics	5 (14%)	4 (7%)	ns

*ns indicates not significant; BMI, body mass index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

at Trondheim University Hospital were included. The patients were selected for off-pump surgery after individual preoperative assessment. Initially, preference was given to patients with 1 to 2 vessel-disease, good left ventricular function, and low risk comorbidities. Soon after the procedure was considered to be reproducible in our institution, high-risk patients with 1 to 2 coronary vessel disease were scheduled for beating-heart surgery. The patients were categorized in 2 groups according to the postoperative antiplatelet treatment. A control group (n = 36), which included patients operated on in the period 1997 to 1999, was treated postoperatively with acetyl salicylic acid (ASA) only, whereas patients in the clopidogrel group (n = 58), which included patients who were operated on in the period 2000 to 2002, received clopidogrel postoperatively in addition to ASA. Demographic data, data of diseased coronary arteries, and intraoperative and postoperative data are shown in Tables 1, 2, and 3, respectively.

Surgical Technique

All patients were operated on under general anesthesia. The first 7 patients (7%) were operated on with a small left-sided antero-lateral thoracotomy in the fourth or fifth intercostal space. Since 1998 median sternotomy was used in all cases.

LIMA was used in 80 patients (84%). The LAD was identified and snared with 4-0 pledgeted polypropylene suture (Prolene; Ethicon, Somerville, NJ, USA) about 1 cm proximal to the coronary arteriotomy. After 3 to 5 minutes of ischemic preconditioning, the snare was released. Mechanical stabilizers were used to facilitate suturing of all distal graft anastomoses, except for anastomoses to the main stem of the right coronary artery (RCA). After arteriotomy of the LAD, an intracoronary shunt (Axius coronary shunt; Guidant, Santa Clara, CA, USA) was positioned into the vessel lumen in most of the cases. All coronary anastomoses were performed with a continuous 7-0 or 8-0 polypropylene suture (Prolene).

Table 2. Diseased Coronary Arteries as Assessed by Preoperative Angiography*

Coronary Vessel	Control Group (1997-1999), n = 37, n (%)	Clopidogrel Group (2000-2002), n = 58, n (%)	*P*
Left main stenosis	2 (4)	3 (3)	ns
Left anterior descending artery	29 (56)	53 (56)	ns
Diagonal	2 (4)	14 (15)	ns
Circumflex	4 (8)	6 (6)	ns
Right coronary artery	13 (25)	19 (20)	ns

*ns indicates not significant.

Table 3. Intraoperative and Postoperative Data Comparing 2 Groups of Patients Who Underwent Off-Pump Coronary Artery Bypass Grafting *

	Control Group (1997-1999), n = 37	Clopidogrel Group (2000-2002), n = 58	*P*
Intraoperative			
Operating time, min	131 ± 46	146 ± 38	ns
Number of grafts, n	1.38 ± 0.7	1.6 ± 1.0	ns
Flow rate, mL/min			
LIMA	29 ± 17	26 ± 14	ns
Circumflex	67 ± 13	22	ns
Right	69 ± 31.4	43 ± 20	ns
Postoperative			
Bleeding, mL†	650 ± 406	681 ± 251	ns
Ventilation time, min	379 ± 87	391 ± 108	ns
Inotropic support‡	18 (49%)	36 (62%)	ns
Atrial fibrillation	9 (24%)	19 (33%)	ns

*ns indicates not significant; LIMA, left internal mammary artery.

†Amount of bleeding from chest closure to removal of chest drains the morning after operation.

‡Number of patients requiring inotropes.

A saphenous vein graft was used in 46 patients (48%), and was the predominant choice to the RCA (n = 27, 28%), diagonals (n = 11, 11.6%) and circumflex marginals (n = 8, 8%). A right internal mammary artery graft was used in 3 patients to the right posterior descending artery (PDA), and the radial artery to the PDA was used in 1 patient also.

Antithrombotic Regimens

In 1997 and 1998, all patients received 100 U/kg unfractionated intravenous heparin intraoperatively to reach an activated clotting time (ACT) above 270 seconds without reversal with protamine sulphate at the end of the operation. Since 1999, the patients were fully heparinized with 300 U/kg intravenously, which was reversed to two thirds of its activity with protamine sulphate. The antithrombotic regimen before 2000 was as follows: preoperatively, ASA 75 to 160 mg was prescribed up to the day of the surgery, postoperatively 500 mL of dextran were infused within 8 hours from operation, ASA was continued at the preoperative dose and in addition low molecular weight heparin (LMWH) (enoksaparin 40 mg once daily) was administered. Since 2000, a daily dose of clopidogrel 75 mg from postoperative day 1 for 4 weeks was added to the ASA, dextran, and LMWH regimen. No loading dose of clopidogrel was administered.

Transit-Time Flowmetry

Intraoperatively and prior to epicardial ultrasound, graft flow was controlled with transit-time flowmetry (MediStim Flowmeter; MediStim AS, Oslo, Norway).

Epicardial Ultrasound

After completion of the LIMA-LAD anastomoses and with the stabilizer still in place, epicardial ultrasound imaging of the anastomoses was done in 28 patients (29%) by means of a GE Vingmed system FiVe ultrasound scanner and a GE i13L probe (General Electric, Horten, Norway) as previously reported [Haaverstad 2002]. The complete anastomoses as well as the distal run-off were visualized, and all anastomoses were found to be patent by means of real-time B-mode ultrasound and color Doppler flow.

Postoperative Coronary Angiography

All patients who underwent off-pump CABG in the period from 1997 to 2002 were considered for control coronary angiography. Follow-up coronary angiography was done after 185 ± 92 days in 62 patients (64%): 29 (78%) patients from the control group and 33 (57%) from the clopidogrel group. The catheterization was done through the femoral or radial routes according to the standard technique and analyzed semiquantitatively with assessment of TIMI flow grade [The TIMI Study Group 1984]. The cardiologist who assessed the angiography was blinded for clopidogrel therapy. Thirty-three patients (35%) did not undergo control angiography for the following reasons: calcified aorta, old age, impaired left ventricular function, renal dysfunction, long travel distance, or refusal of angiographic follow-up.

Statistical Analysis

Skewness test was used to assess the distribution of data. The Fisher exact test, Mann-Whitney *U*, and Student *t* test were used to evaluate the differences in demographic data and patency rates between the 2 groups. A P value $<.05$ was considered statistically significant. All results were presented as mean ± standard deviation.

RESULTS

Two patients (2.1%) died within 30 days after surgery. One patient in the control group had a myocardial infarction; she was originally planned for conventional surgery, but was

Table 4. Angiographic Results Comparing the Control Group and the Clopidogrel Group According to the TIMI Classification*

Grafted Vessels, n	TIMI 3 (Open)	TIMI 2 (Stenosis)	TIMI 1 (Partially Occluded)	TIMI 0 (Totally Occluded)
Control group (1997-1999), 29 patients†				
LAD, 25	23	—	2	—
Diagonal, 1	1	—	—	—
Circumflex, 4	2	—	—	2
RCA, 7	5	—	—	2
Total N = 37	n = 31 (84%)	n = 0	n = 2 (5%)	n = 4 (11%)
Clopidogrel group (2000-2002), 33 patients‡				
LAD, 29	28	—	—	1
Diagonal, 8	7	—	—	1
Cicumflex, 2	2	—	—	—
RCA, 6	5	—	—	1
Total N = 45	n = 42 (93%)	n = 0	n = 0	n = 3 (7%)

*LAD indicates left anterior descending artery; RCA, right coronary artery.

†Twenty-nine (81%) of 36 patients, with a total of 37/52 (71%) grafts, underwent angiography.

‡Thirty-three (57%) of 58 patients, with a total of 45/95 (47%) grafts, underwent angiography.

operated on off-pump because of a heavily calcified aorta. The other patient, in the clopidogrel group, died as consequence of a stroke. All the remaining patients were discharged home on the mean eighth postoperative day.

Postoperative Complications

One patient in the control group was reopened for bleeding and 1 patient in the clopidogrel group was reoperated on for mediastinal dehiscence. Five patients (6%) developed perioperative myocardial infarction according to the WHO criteria for postprocedural myocardial infarction [Wong 2005], but there was no difference between the 2 groups (*P* value was not significant [ns]). The number of patients receiving blood transfusion was 4 (11%) in the control group and 9 (16%) in the clopidogrel group (ns). No patients required platelet transfusion.

Angiographic Follow-up

A total of 62 patients (64%) underwent angiography after a mean of 185 ± 92 days. At angiographic follow-up, overall patency rate was 84% (31/37) in the control group versus 93% (42/45) in the clopidogrel group (ns). For LIMA grafts, the patency rates were 92% (23/25) versus 96% (28/29) (ns) and for saphenous vein grafts were 66% (8/12) versus 87% (14/16) (ns). The angiographic results of the 2 groups are presented in Table 4.

DISCUSSION

In this retrospective cohort study, we evaluated the clinical and angiographic outcome of off-pump coronary artery bypass surgery in 2 groups of patients treated with different antiplatetelet regimens. One group was treated with ASA as the single antiplatelet agent, the other group with a combination therapy of ASA and clopidogrel. Although our results showed a trend toward higher graft patency rates in patients treated with ASA and clopidogrel, the difference did not reach statistical significance (*P* = .32). This could indicate that the addition of clopidogrel as an adjuvant antiplatelet agent to ASA postoperatively with the dose and duration used in this study has limited effect on the midterm patency, although clopidogrel acts through a different mechanism and is thus supposed to increase the antiplatelet action.

The results did not show any significant differences in the complication rate postoperatively. In particular, the 2 groups did not differ in terms of postoperative bleeding, the need for blood or platelet transfusion, or reoperation for bleeding, despite the general assumption and a study showing that the use of clopidogrel increases the postoperative bleeding [Kapetanakis 2005]. To the best of our knowledge, there are no published results comparing clopidogrel with other antiplatelet drugs as used postoperatively in terms of postoperative bleeding or patency rate of grafts and anastomoses in off-pump CABG. However, postoperative administration of clopidogrel was reported to be independently associated with decreased symptom recurrence and adverse cardiac events following off-pump CABG [Gurbuz 2006].

Clopidogrel is a pro-drug, which is converted to an active, unstable drug by cytochrome P450 (CYP). The active drug irreversibly blocks one specific platelet adenosine 5'-diphosphate receptor (P2Y12). It was recently suggested that the most abundant human CYP isoform, 3A4, activates clopidogrel [Clarke 2003]. Certain lipophilic statins (ie, simvastatin, atorvastatin, and lovastatin), substrates of the CYP3A4 isoform, competitively inhibit the metabolic activation of clopidogrel. As a result of the interaction with statins, a type of drug that is often administered to patients with ischemic heart disease, the relative clopidogrel-induced platelet inhibition is diminished, especially if administered at a low dose [Neubauer 2003]. Furthermore, clopidogrel administration results in interindividual variability in platelet inhibition. This variable platelet inhibition response to clopidogrel has previously been recognized when clopidogrel efficacy was tested by platelet aggregometry and correlated with CYP3A4 metabolic activity [Lau 2004]. In addition, a recent study by Lev et al [2006] showed that about half of the patients who were resistant to ASA in a group of 110

PCI patients were also resistant to clopidogrel. These findings might be of clinical relevance because clopidogrel has been suggested as alternative therapy for aspirin-resistant patients. Based on these results, it could be anticipated that several of the patients included in our study could be resistant to aspirin, clopidogrel, or both. This might explain the lack of difference in patency rate between the 2 groups as well as the lack of difference in the postoperative bleeding rates. However, in our study, data on drug resistance in the included patients were not registered. In addition, it should be noted that platelet inhibition by clopidogrel is dose related up to a daily dose of 400 mg and that inhibition at higher doses remains stable from 2 to 72 hours [Thebault 1999].

Muller et al recently proposed the administration of a loading dose of clopidogrel (300-600 mg) with the aim of shortening the time of onset of its antiplatelet effect [Muller 2001]. Furthermore, a clopidogrel effect is noticed after 3 to 7 days in healthy subjects [Savcic 1999] and within 9 to 29 days after CABG [David 1999]. Further studies are needed to evaluate the values and hazards of loading doses of clopidogrel after CABG in light of the reduction of onset and resistance to clopidogrel on one hand, and its possible bleeding complication on the other. Future studies on long-term clopidogrel medication would also be of interest to see whether this could improve on graft patency.

Despite the claimed possible advantages of off-pump CABG versus on-pump surgery in terms of reducing postoperative complications, conflicting results are available on grafts patency rates. Some prospective studies showed high patency rates on postoperative angiographic follow-up [Onorati 2005; Kazaz 2006], and these findings have been confirmed by a prospective randomized trial that showed comparable results of patency rates with on- and off-pump CABG as assessed by angiography 1 month postoperatively [Puskas 2004]. However, Kim et al [2001] demonstrated a reduced 1-year patency in venous grafts in patients undergoing off-pump surgery versus on-pump CABG. Furthermore, a recent meta-analysis of prospective randomized trials found a reduced postoperative patency in coronary artery bypass grafts performed during off-pump CABG procedure [Parolari 2005], indicating that the overall patency rate is reduced after off-pump surgery. The patency rates found in the present study were somehow lower (mean, 89%) than those found in some comparable studies. This might be partly caused by the relatively low number of patients and the inclusion of patients who were part of our early experience with off-pump surgery.

Our study has several limitations. The data were derived from a nonrandomized retrospective study, and the number of patients enrolled was low. Furthermore, no loading doses of clopidogrel were administered; the duration was limited to 1 month only in addition to minor variations in the use of other antithrombotic drugs between the 2 groups. It could also be argued that the first group of patients who did not receive clopidogrel includes our initial experience of off-pump revascularization and one might expect a lower graft patency rate. However, the first patients of this series were operated on by surgeons with significant off-pump surgery experience from other centers. Moreover, the adequate flow rates and pulsatile index registered intraoperatively indicate that most graft closures observed in the present study presumably represent later closures caused by platelet aggregation.

Interindividual variability in the response to clopidogrel as well as interindividual differences in the adjunctive intraoperative and immediate postoperative anticoagulation and antithrombotic regimens should also be taken into account. Our data, however, should be used for planning clinical studies with adequate statistical power.

In conclusion, no significant effect of a 75-mg regimen of clopidogrel on coronary graft patency was found by midterm follow-up coronary angiography. However, larger prospective randomized studies are necessary to ascertain the effect of clopidogrel, as well as resistance and interindividual response on grafts patency after off-pump CABG.

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