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A Feasibility Study of the Safety and Efficacy of a Combined Clopidogrel and Aspirin Regimen following Off-Pump Coronary Artery Bypass Grafting

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ABSTRACT

Objective: Effective antiplatelet therapy may decrease the risk of complications following off-pump coronary artery bypass surgery (CABG). We prospectively evaluated the safety and early efficacy of a combined regimen of clopidogrel and aspirin starting immediately after off-pump CABG.

Methods: One hundred thirty-five consecutive off-pump CABG patients received clopidogrel (75 mg/day) and aspirin (325 mg/day) orally or initially through a nasogastric tube for 3 months, commencing within 6 hours of surgery. Additionally, heparin (10,000 IU/day) was given subcutaneously during the first 4 postoperative days. Clinical events, including death, myocardial infarction (MI), reintervention, angiographically documented graft occlusion, stroke, pulmonary embolism (PE), deep vein thrombosis (DVT), and hemorrhagic events, were recorded. All patients were followed up for 3 months.

Results: Thirteen of 135 off-pump CABG patients had treatment discontinued before discharge because of refractory atrial fibrillation requiring warfarin sodium (Coumadin) (6 patients), gastrointestinal bleeding (1 patient), DVT (1 patient), PE (1 patient), and death (4 patients). The remaining patients were followed up for 3 months. At 1 month, the incidences of the following events were: 3.0% cerebrovascular accidents (3 strokes and 1 transient ischemic attack), 3.0% MI, 0.7% DVT, and 0.7% hemothorax. At 3 months, no additional events had occurred except for 1 patient developing DVT and 2 additional patients developing MI. Coronary angiography was indicated in these last 2 patients. All grafts were found to be patent. However, a native vessel required percutaneous intervention (stenting) in one of these patients.

Conclusions: Early administration of a combined regimen of clopidogrel and aspirin following off-pump CABG is safe and is associated with a relatively low incidence of major adverse cardiac events, bleeding, PE, and DVT. Consequently, its routine administration after off-pump CABG is recommended.

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INTRODUCTION

Recent refinements in surgical techniques and technology have resulted in a greater acceptance of off-pump coronary artery bypass grafting (CABG) procedures among cardiovascular surgeons. However, avoiding the use of cardiopulmonary bypass may lead to certain negative consequences such as postoperative hypercoagulability, which may lead to thrombotic events and compromise graft patency [Cartier 2001, D'Ancona 2001]. Although the incidence of postoperative thromboembolic complications in off-pump CABG studies has been found to be low, the associated morbidity has been pointed out to be worthy of consideration, and postoperative prophylactic therapy in off-pump CABG has been suggested [Cartier 2001, D'Ancona 2001].

As a result of the use of antiplatelet therapy following intracoronary stenting, a decrease in the incidence of subacute stent thrombosis has been noted. Randomized trials have shown that stent implantation combined with the administration of aspirin and ticlopidine or clopidogrel without oral anticoagulation therapy is associated with a low incidence of both subacute stent thrombosis and bleeding complications [CAPRIE Steering Committee 1996, Bertrand 1998, Muller 2000]. Yet ticlopidine has the potentially serious adverse hematologic and gastrointestinal effects of bone-marrow depression, rash, and diarrhea. Clopidogrel, which chemically resembles ticlopidine, was shown in the CAPRIE study to be a safe and efficacious medication for the secondary prevention of vascular events and to result in fewer bleeding complications [CAPRIE Steering Committee 1996]. Clopidogrel with or without aspirin has been suggested to be superior to aspirin alone for the post-CABG prevention of ischemic events [Bhatt 2001]. Currently, however, there are no reports evaluating the safety and efficacy of combined clopidogrel and aspirin therapy following off-pump CABG.

We hypothesized that effective antiplatelet therapy with clopidogrel and aspirin might decrease the risk of events following off-pump CABG without increasing the risk of hematologic complications. As an initial step toward testing this hypothesis, we designed a prospective feasibility study to evaluate the safety and early efficacy of a combined clopidogrel and aspirin regimen starting immediately after off-pump CABG.

Table 1. Patient Preoperative Status*

Patients (M/F), n	135 (103/32)
Age, y	63.6 ± 9.2 (64.0)
Acute MI within 30 d, n	13 (9.6%)
Old MI, n	69 (51.1%)
Redo case, n	7 (5.2%)
Unstable angina, n	107 (79.3%)
Elective surgery, n	103 (76.3%)
Diabetes mellitus, n	50 (37.0%)
Chronic renal failure, n	7 (5.2%)
Hypertension, n	73 (54.1%)
COPD, n	7 (5.2%)
Hyperlipidemia, n	71 (52.6%)
Cerebrovascular disease, n	7 (5.2%)
Peripheral vascular disease, n	16 (11.9%)
Ejection fraction, %	48.5 ± 12.5 (50.0)
Parsonnet score	7.8 ± 7.9 (6.0)

*Values are shown as the mean ± standard deviation (median) where applicable. MI indicates myocardial infarction; COPD, chronic obstructive pulmonary disease.

PATIENTS AND METHODS

Patient Eligibility and Antiplatelet Regimen

All patients undergoing isolated off-pump CABG were considered eligible for inclusion if they did not have chronic atrial fibrillation, were not on warfarin sodium (Coumadin) prior to surgery, did not have any allergy to aspirin or clopidogrel, and had no past medical history of severe gastrointestinal bleeding. A protocol consisting of the following regimen was submitted to and approved by the McGill University Health Center Pharmacy and Therapeutics Committee. Commencing 6 hours after operation, patients simultaneously received clopidogrel (75 mg daily) and aspirin (325 mg daily) orally or initially through a nasogastric tube for 3 months. Additionally, heparin (10,000 IU daily) was given subcutaneously twice a day for 4 days, and omeprazole (20 mg daily) was given orally for gastric protection. After discharge, the patients were followed up at 1 and 3 months after surgery. Any occurrence of the following events led to discontinuation of therapy: death (fatal myocardial infarction [MI], fatal cerebrovascular accidents), gastrointestinal bleeding, atrial fibrillation without rhythm control, severe hemorrhagic events, peripheral vascular events, and pulmonary embolism (PE).

Table 2. Operative and Postoperative Data*

Surgical time, min	209.2 ± 48.6 (200.0)
Saphenous vein graft, n	123 (91.1%)
Radial artery, n	19 (14.1%)
Gastroepiploic artery, n	2 (1.5%)
Left internal mammary artery, n	125 (92.6%)
Right internal mammary artery, n	8 (5.9%)
Anastomoses/patient, n	3.2 ± 1.0 (3.0)
Arterial graft/anastomosis	36.2%
Blood transfusion, n†	41 (31.3%)
Intubation time, h†	13.1 ± 13.1 (9.0)
ICU length of stay, h†	35.7 ± 34.4 (22.0)
Postoperative LOS, d†	7.0 ± 5.8 (6.0)
Inotropic support, h†	5.9 ± 13.8 (0.0)
Mortality, n	4 (3.0%)

*Values are shown as the mean ± standard deviation (median) where applicable. ICU indicates intensive care unit; LOS, length of stay.

†These data exclude those of the deceased patients.

Surgical Technique

All patients underwent off-pump CABG in a routine fashion with mechanical stabilizers and the administration of a low intraoperative dose of 10,000 IU of heparin, with additional amounts given to maintain the activated clotting time between 250 seconds and 350 seconds during the procedure. At the completion of all anastomoses, an appropriate dose of protamine sulfate was given to normalize the activated clotting time.

RESULTS

Participants

From January 1, 2001, to June 30, 2002, 136 consecutive patients underwent isolated off-pump CABG by the principal investigator and were eligible for the study. One of these patients did not receive antiplatelet therapy because of hemodynamic instability (cardiogenic shock) followed by death before therapy could commence. Therefore, 135 patients who received off-pump CABG were included. Patient characteristics are summarized in Table 1. The mean age of the patients was 63.6 (9.2 years (median, 64.0 years). The sample consisted of 103 men (76.3%) and 32 women (23.7%). The mean left ventricular ejection fraction and the mean Parsonnet score were 48.5% (12.5% and 7.8 (7.9, respectively. Table 2 summarizes the operative and postoperative data.

Major Adverse Cardiac Events and Related Events with Clopidogrel and Aspirin

The events are summarized in Table 3. Thirteen patients discontinued the medication before their departure from the hospital. In 4 of the cases, discontinuation was due to death (2 by MI and 2 by stroke). Major bleeding complications requiring blood transfusion occurred in 1 patient (0.7%), and deep vein thrombosis (DVT) occurred in 1 patient. One patient had PE (0.7%), and 6 patients (4.4%) experienced refractory atrial fibrillation and required Coumadin. The remaining 122 patients had complete follow-ups at 1 and 3 months following surgery. Of these 122 patients, 2 patients who had patent grafts according to coronary angiography developed nonfatal MI before hospital discharge. One patient developed a cerebrovascular accident, and another patient developed poplitial artery thrombosis. At 1 month, the following additional events were noted: 1 cerebrovascular accident (0.7%, transient ischemic attack) and 1 hemothorax (0.7%). At 3 months, no additional events had occurred except for the development of MI in 2 additional patients

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Table 3. Cardiac and Noncardiac Events within a 3-Month Period*

	Follow-ups			
	In-Hospital (n = 135/135; 100%); Continued Clopidogrel (n = 122/135; 90.4%); Discontinued Clopidogrel (n = 13/135; 9.6%)	1-Month (n = 122/122; 100%); Continued Clopidogrel (n = 122/135; 90.4%); Discontinued Clopidogrel (n = 0/122; 0%)	3-Month (n = 122/122; 100%); Continued Clopidogrel (n = 121/135; 89.6%); Discontinued Clopidogrel (n = 1/122; 0.8%)	Total (n = 135/135; 100%); Continued Clopidogrel (n = 121/135; 89.6%); Discontinued Clopidogrel (n = 14/135; 10.4%)
Cardiac events, n				
Death	2 (1.5%)	—	—	2 (1.5%)
Myocardial infarction	2	—	—	2
Nonfatal myocardial infarction	2 (1.5%)	0	2 (1.5%)	4 (3.0%)
Delayed tamponade	0	0	0	0
Reintervention	0	0	1 (0.7%)	1 (0.7%)
CABG	0	0	0	0
PTCA	0	0	1	1
Refractory atrial fibrillation	6 (4.4%)	—	—	6 (4.4%)
Noncardiac events, n				
Death	2 (1.5%)	—	—	2 (1.5%)
Stroke	2	—	—	2
Nonfatal cerebrovascular accidents	1 (0.7%)	1 (0.7%)	0	2 (1.5%)
Stroke	1	0	0	1
TIA	0	1	0	1
Hemorrhagic events	1 (0.7%)	1 (0.7%)	0	2 (1.5%)
Hemothorax	0	1	0	1
Upper or lower GI bleeding	1	0	0	1
Peripheral vascular events	2 (1.5%)	0	1 (0.7%)	3 (2.2%)
Arterial disease	1	0	0	1
Deep vein thrombosis	1	0	1	2
Pulmonary embolism	1 (0.7%)	0	0	1 (0.7%)

*CABG indicates coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack; GI, gastrointestinal.

(1.5%) with angiographically patent grafts and DVT in another patient. One of these patients underwent percutaneous intervention on the native vessel (0.7% reintervention rate).

DISCUSSION

Postoperative hypercoagulability is a recognized phenomenon that occurs following most surgeries. It is considered an important contributor to the development of thromboembolic complications such as MI, graft thrombosis, and PE. Asymptomatic DVT has been documented in approximately 46% of patients following conventional CABG, which uses a high dose of intraoperative heparin and heparin reversal with protamine [Reis 1991]. Despite the use of mechanical leg counterpulsation devices for the prevention of DVT in CABG patients, the results of leg ultrasonography prior to discharge have confirmed the presence of DVT in 20% of patients [Goldhaber 1995]. Pulmonary embolism occurs in 0.4% to 3.2% of CABG patients but leads to a high mortality rate [DeLaria 1991, Josa 1993].

Several drug protocols have been advocated for the prevention of thromboembolic complications, and others have been extended in an effort to decrease the risk of graft failure following CABG [Cartier 2001]. Naturally, some of the strategies have been extended to the prevention of coronary stent thrombosis but use more modern antiplatelet therapy. A recent report in the *New England Journal of Medicine* advocated the routine use of aspirin for the reduction of major adverse cardiac events and ischemic complications following conventional CABG [Mangano 2002].

Off-pump CABG is a technique that permits the performance of coronary artery bypass without the use of a heart-lung machine. A recent clinical study suggested that thromboembolic complications appear more frequently following off-pump CABG than with conventional CABG using routine cardiopulmonary bypass [Cartier 2001]. A survey was also conducted recently to identify the use of postoperative antiplatelet medication in off-pump CABG patients by cardiac surgeons [D'Ancona 2001]. Eighty-eight percent of the respondents in the study routinely administered antiplatelet therapy after off-pump CABG. Most of the respondents used aspirin, and only 24% of those respondents used clopidogrel. In our study using a combined regimen of clopidogrel and aspirin, we noted an in-hospital incidence of thromboembolic events, including DVT and PE, of 1.4% following off-pump CABG.

Our study, conducted on a cohort of patients who underwent off-pump CABG, indicates that administering a combined antiplatelet therapy of clopidogrel and aspirin is associated with

a low incidence of thromboembolic events and bleeding. The in-hospital incidence of MI was 3.0%, and at 3 months we noted a 4.5% total incidence of MI. The incidence of reintervention was also low, with only 1 patient requiring stenting to the native coronary artery.

Of interest was the low incidence of postoperative stroke in this review. Only 3 patients developed postoperative stroke (2.2%), an incidence lower than that (3%-4%) reported by Newman et al in a large multicenter study that used neither off-pump techniques nor prophylactic drug therapy [Newman 1996]. In another study, aspirin therapy alone was associated with a 50% reduction in the incidence of stroke (to 1.3%) following CABG [Mangano 2002].

Although one patient who had arteriosclerosis obliterans developed poplitial artery occlusion on the fifth postoperative day, the symptoms diminished on the following day, and a delayed elective angioplasty and stenting of the femoral artery was performed. One hemodynamically stable patient developed a hemothorax and required thoracotomy and drainage on the eighth postoperative day. The combined aspirin-clopidogrel regimen was stopped prior to thoracotomy and was resumed 3 days after surgery.

Clopidogrel in combination with aspirin before CABG has been associated with higher incidences of reexploration (6.8%-9.8%) and other postoperative complications [Yende 2001, Hongo 2002]. However, aspirin therapy during the first 48 hours following CABG has been found to be safe and associated with a decline in the risk of bleeding and reexploration [Mangano 2002]. In our study, there was only 1 case (0.7%) of reexploration for bleeding noted after the start of the regimen. The deferral of the administration of antiplatelet drugs to 6 hours after surgery allowed surgeons to assess any possible surgical bleeding before committing to antiplatelet therapy. A loading dose of clopidogrel was not administered, because one of the concerns was the difficulty in reversing platelet dysfunction when bleeding is noted soon after surgery. This delay, however, does not seem to have affected the effectiveness of this prophylaxis protocol.

Another important consideration is the risk of gastrointestinal bleeding when anticoagulant or antiplatelet drugs are administered following surgery. The baseline incidence of gastrointestinal bleeding after cardiac surgery is generally low (0.3%) [Simic 1999]. In our series, gastrointestinal bleeding occurred in only 1 patient (0.7%) within 1 week after the operation. This finding suggests that the administration of gastric cytoprotective drugs can be effective in reducing the risk of gastrointestinal bleeding when our antiplatelet protocol is administered following open heart surgery.

We noted no specific gastrointestinal symptoms, such as diarrhea, nausea, or allergic exanthema, related to administering this protocol.

Although there is no standard for the administration of antiplatelet therapy following off-pump CABG and there is no consensus on the proper timing or dosage [Topol 2002], our combined regimen of clopidogrel and aspirin following off-pump CABG appears to be effective and is associated with a low incidence of major adverse cardiac events and other undesirable effects. We conclude that early administration of a combined regimen of clopidogrel and aspirin following off-pump CABG can be recommended. A prospective trial comparing this combined regimen with the standard regimen of aspirin alone is warranted.

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