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Dual Protection Therapy with Staged Coronary Artery Bypass Surgery and Stenting in Patients with Left Main Coronary Artery Stenosis: Long-Term Results from a Single Center

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ABSTRACT

Objective: We evaluated the efficacy and safety of dual protection therapy with staged coronary artery bypass grafting (CABG) and bare-metal stenting (BMS) in patients with left main coronary artery (LMCA) disease.

Background: CABG is currently the preferred therapy for complex LMCA disease; however, the long-term patency rates of these grafts are unsatisfactory, and stenting alone for LMCA may be associated with the potentially fatal consequences of stent thrombosis or restenosis.

Methods: Between January 1997 and October 2005, 42 patients underwent staged bypass surgery and BMS, with the latter procedure performed 2 weeks after the initial CABG. Of these patients, 40 received left internal mammary artery (LIMA) grafts, 34 saphenous vein grafts, 6 radial artery grafts, and 3 right IMA (RIMA) grafts. Minimally invasive bypass surgery was performed in 10 patients.

Results: There were no operative complications. Forty-two stents were implanted in 42 lesions without complications. During the follow-up period of 135 ± 55 months, 1 patient died of cancer, 2 of cardiac causes, and 5 patients (12%) experienced target lesion revascularization. The target vessel failure rate was 24%. Forty patients (95%) underwent a 6-month angiographic follow-up. Restenosis was noted in 7 patients (18%). Reocclusion was also noted in 5 LIMA grafts, 5 saphenous vein grafts, 1 radial artery graft, and 1 RIMA graft. Only 1 patient experienced both restenosis of LM stenting and total occlusion of the 2 bypass grafts.

Conclusions: Dual protection therapy with staged CABG and stenting is not an appropriate therapeutic strategy because of unacceptable graft patency rate. A higher occlusive rate of the bypass grafts may result from decreased blood flow because of competing blood flow between the bypass graft and the native coronary vessel.

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INTRODUCTION

Left main coronary artery (LMCA) disease is found by coronary angiography in 3%–5% of patients with ischemic chest pain, congestive heart failure, or cardiogenic shock [Cohen 1975]. Coronary artery bypass graft (CABG) is the therapy of choice in patients presenting with such conditions. The Veterans Administration (VA) Cooperative Study revealed the superiority of surgical intervention over medical treatment in terms of survival outcomes [Takaro 1976]. However, the long-term patency of the CABG is unsatisfactory, with only 50% patency of the vein graft remaining at 10 years [Bourassa 1994]. In addition, the long-term results of less invasive therapy with balloon angioplasty for unprotected LMCA stenosis have been poor [Ellis 1997]. Advances in the development of devices, drugs, and techniques, such as newly designed stents, debulking devices, effective antiplatelet agents, and intravascular ultrasound (IVUS), have enabled the use of stenting as an alternative option in select patients with LMCA disease [Park 1998; Silvestri 2000; Black 2001; Suarez 2001; Tan 2001; Park 2003; Serruys 2009; Park 2010]. However, stent thrombosis and restenosis pose the potential risks of sudden death or severe left ventricular failure in patients undergoing LM stenting [Ellis 1997; Park 1998; Park 2003]. Currently, hybrid coronary interventions combine surgical and catheter-based procedures for the treatment of coronary artery disease (CAD) [Bonatti 2010]. Over the past decade, we have utilized a strategy of "double protection," which involves staged CABG and bare-metal stenting (BMS), for treating patients with LMCA stenosis. Herein, we report the long-term results of this dual protection therapy.

METHODS

Ethics Statement

The study protocol was reviewed and approved by the ethics committee of our hospital, and written informed consent was obtained from all patients.

Patient Population

The CAPTAIN (Cardiovascular Atherosclerosis and Percutaneous TrAnsluminal INterventions) registry is a

physician-initiated prospective single-center observational study in a tertiary medical center, which enrolls consecutive patients undergoing stent implantation. A total of 42 patients with LMCA stenosis who agreed and underwent sequential CABG and LMCA stenting between January 1997 and October 2005 in the registry were enrolled. We included symptomatic patients with angiographic evidence of ≥50% stenosis of the LMCA diameter. We excluded patients who had LMCA disease associated with a diffuse or long stenotic lesion in the left anterior descending artery (LAD) or left circumflex artery (LCX) considered unsuitable for stenting; patients for whom the use of aspirin, ticlopidine, or clopidogrel was contraindicated; and those who refused to undergo this procedure. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score for each patient was calculated retrospectively by scoring all coronary lesions with a stenosis diameter of ≥50% in vessels with a diameter of ≥1.5 mm by using the SYNTAX score algorithm [Sianos 2005].

Surgical Procedure

Thirty-two patients (76%) underwent a standard operation with a median thoracotomy, and 10 (24%) underwent CABG using a minimally invasive technique with a limited (10–20 cm) left anterior parasternal thoracotomy [Lin 1998]. The left internal mammary artery (LIMA), right IMA (RIMA), saphenous vein, and radial artery were harvested and used as grafts during the operation; 1, 37, and 4 patients received 1, 2, and 3 grafts, respectively. The average number of grafts was 2.1 ± 0.9 per patient. A total of 83 bypass grafts were connected to the LAD (42) or the LCX (41), including 40 LIMA grafts, 34 saphenous vein grafts, 6 radial artery grafts, and 3 RIMA grafts that were bypassed to the LAD or LCX because of LMCA stenosis. The following were considered high surgical risk factors: age >75 years, prior cardiac surgery, LVEF <35%, renal failure, inadequate distal coronary runoff, and severe respiratory failure. Operative mortality was defined as death within 30 days of surgery.

Stenting Procedure

All patients underwent LMCA BMS approximately 2 weeks after bypass surgery. Stent implantation was performed through the right femoral arteries using standard techniques, and a regimen comprising heparin and aspirin/ticlopidine or clopidogrel was administered. In patients with distal bifurcation lesions, a tube stent was deployed from the LMCA to the proximal portion of the LAD or LCX, depending on which vessel was the largest or dominant. If the stent compromised the other side branch, the kissing balloon technique was employed through the previously implanted stent strut. Forty-two stents were deployed, including 2 Palmaz–Schatz stents, 9 Multilink stents, 6 Duet stents, 4 Tristar stents, 6 Penta stents, 10 Bx velocity stents, 3 S7 stents, and 2 Express stents. Oral anticoagulants and heparin were not administered after the procedure. Adjunctive high-pressure balloon inflation (≥16 atm) was applied after stent deployment. IVUS and debulking devices were not used. In-hospital major adverse cardiovascular events (MACE) were defined as cardiac- or procedure-related death, ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation MI (non-STEMI), or a severe peripheral vascular event requiring surgical repair. Patients were followed up at the outpatient clinic. Coronary angiography was repeated 6 months after the procedure, or when recurrent myocardial ischemia was suspected. Repeat balloon angioplasty was performed if the patient had recurrent angina and if the restenotic lesion showed ≥50% stenosis. Quantitative angiographic analysis was performed. Binary restenosis was defined as a stenosis diameter ≥50% during follow-up angiography. Clinical follow-ups were scheduled for 1, 2, 3, and 6 months and once every 3 months after the first year. Medical records related to the clinical status, medical management, and occurrences of any adverse events were obtained.

Study Endpoints

The primary clinical endpoint was the target vessel failure (TVF) rate during long-term follow-up. TVF was defined as the composite of death, MI, emergent CABG, and target vessel revascularization. The primary angiographic endpoint was binary restenosis of both the LMCA stent and the bypass graft at the 6-month follow-up angiographic study.

Statistical Analysis

Categorical data have been presented as absolute numbers and percentages. Continuous data have been presented as the mean ± standard deviation (SD) values. A P value of <.05 was considered statistically significant. Demographic, procedural, and angiographic variables were tested to identify significant univariate correlates of restenosis. Multiple stepwise logistic analysis was performed to identify independent predictors of binary angiographic restenosis.

RESULTS

Patient and Lesion Characteristics

Patient and lesion characteristics are shown in Tables 1 and 2.The mean age of the patients was 61 ± 10 years; among these patients, 31 (74%) were men, 21 (50%) had hypertension, and 6 (14%) had diabetes. Twelve of the 42 patients (29%) had isolated left main trunk disease, 13 (31%) had additional 1-vessel CAD, 8 (19%) had 2-vessel CAD, and 9 (21%) had 3-vessel CAD. Six (14%) of patients had experienced a recent MI, and 27 (64%) had unstable angina. The mean LVEF was 60 ± 15%, and 6 patients (14%) had an LVEF <35%. Eight patients (19%) were in the surgical high-risk group. Of the 42 lesions in the left main trunk, 14 (33%) were ostial lesions, 7 (17%) were shaft lesions, and 21 (50%) were distal lesions. Fourteen of the 21 distal lesions (33%) were found to extend to the proximal LAD, 5 (12%) to the proximal LCX, and 2 (5%) to both the LAD and LCX. A type A lesion was noted in 1 patient (2%), type B1 in 9 patients (22%), type B2 in 27 (64%), and type C lesion in 5 (12%). The average length of the lesion was 12 ± 5 mm; the lesions were segmental in 28 patients (67%), eccentric in 25 (60%), calcified in 10 (24%), and bent (≥45°) in 1 (2%). The mean SYNTAX score was 26.8 ± 11.5.

Table 1. Patient Characteristics

No. of patients	42
Age, years	61 ± 10
Male	31 (74%)
Hypertension	21 (50%)
Diabetes mellitus	6 (14%)
Smoking	15 (36%)
Dyslipidemia	25 (59%)
Family history of CAD	2 (5%)
CAD	
Left main trunk only	12 (29%)
1 Vessel	13 (31%)
2 Vessel	8 (19%)
3 Vessel	9 (21%)
Recent infarction	6 (14%)
Unstable angina	27 (64%)
LVEF, %	60 ± 15
LVEF <35%	6 (14%)

Table 2. Lesion Characteristics

No. of lesions	42
Site	
Ostial	14 (33%)
Shaft	7 (17%)
Distal	21 (50%)
Involving LAD	14 (33%)
Involving LCX	5 (12%)
Involving LAD + LCX	2 (5%)
Type	
A	1 (2%)
B1	9 (22%)
B2	27 (64%)
C	5 (12%)
Lesion length, mm	12 ± 5
SYNTAX score	26.8 ± 11.5
Lesion morphology	
Segmental	28 (67%)
Eccentric	25 (60%)
Calcification	10 (24%)
Bending ≥45°	1 (2%)
Maximal balloon diameter, mm	3.79 ± 0.48
Balloon/vessel diameter, mm	1.08 ± 0.06
Maximal balloon inflation pressure, atm	14.3 ± 2.5

Procedural Results

The procedural success rate was 100% for both CABG and stenting. No operative mortality was noted. The postoperative course was uneventful for all patients. At the time of stenting (approximately 2 weeks after bypass surgery), 8 grafts (10%) were totally occluded, including 1 in the LIMA, 5 in the saphenous vein, 1 in the radial artery, and 1 in the RIMA. One lesion with a 60% stenotic lesion was noted in a saphenous vein the grafts. A total of 42 stents were implanted, of which 21 were implanted within the main trunk, with 16 extending to the LAD and 5 to the LCX. The maximum balloon diameter was 3.79 ± 0.48 mm, and the balloon versus vessel diameter ratio was 1.08 ± 0.06. The maximal balloon inflation pressure was 14.3 ± 2.5 atm. There were no mortalities, MIs (STEMI or non-STEMI), acute or subacute stent thromboses, or vascular complications at the access site.

Angiographic Follow-up

Angiographic follow-up data are shown in Tables 3 and 4. A follow-up coronary angiography was performed in 40 of the 42 patients (95%) at a mean follow-up period of 203 ± 49 days. Of the other 2 patients, 1 died of cancer within 6 months of stenting and the other refused angiographic follow-up. The percentage diameter of stenosis was 71% ± 11% before stenting, 4% ± 8% immediately after stenting, and 32% ± 22% at follow-up. The minimal luminal diameter (MLD) was 1.02 ± 0.42 mm before stenting, 3.36

Table 3. Quantitative Angiographic Measurements at 6-Month Follow-pp

No. of patients	40
No. of lesions	40
Days to follow-up	203 ± 49
Before stenting	
% Diameter stenosis	71 ± 11
MLD, mm	1.02 ± 0.42
RVD,* mm	3.51 ± 0.45
LVEF, %	59 ± 15
After stenting	
% Diameter stenosis	4± 8
MLD, mm	3.36± 0.44
RVD, mm	3.51 ± 0.42
Follow-up	
% Diameter stenosis	32 ± 22
MLD, mm	2.41 ± 0.89
RVD, mm	3.55± 0.46
LVEF, %	62 ± 14
Acute gain, mm	2.34 ± 0.55
Late loss, mm	0.95± 0.72
Net gain, mm	1.39± 0.94
Loss index	0.41± 0.41
Restenosis rate	7 (18%)

*RVD indicates reference vessel diameter.

± 0.44 mm immediately after stenting, and 2.41 ± 0.89 mm at follow-up. The acute gain was 2.34 ± 0.55 mm, the late loss was 0.95 ± 0.72 mm, the net gain was 1.39 ± 0.94 mm, and the loss index was 0.41 ± 0.41. Restenosis of the stented lesion was noted in 7 of the 40 patients (18%). Four restenotic lesions were dilated successfully by using repeat balloon angioplasty. Of these 7 restenotic lesions, 2 showed a focal pattern, 3 showed a diffuse pattern, 1 showed a proliferative pattern, and 1 showed total occlusion. Multivariate analysis of the predictors for restenosis identified diabetes mellitus (P = 0.041) and poststenting MLD (P = 0.028) as predictive factors. During a 6-month angiographic follow-up, 4 LIMA grafts were observed to be completely occluded, and 1 LIMA and 1 saphenous vein graft had lesions with ≥50% stenosis. Thus, 12 bypass grafts (15%) developed total occlusion and 3 (4%) developed ≥50% stenosis during the follow-up period. However, only 1 patient experienced both restenosis of LM stenting and total occlusion of the 2 bypass grafts during the follow-up period. This patient was successfully treated with repeat balloon angioplasty and recovered well thereafter.

Long-term Clinical Outcome

Long-term clinical outcome data are shown in Table 5. During the 135 ± 55–month follow-up period, 1 patient died of metastatic cancer of unknown origin. Two patients died of cardiac causes. One patient died because of decompensated congestive heart failure, and the other because of recurrent MI. Six patients (14%) developed angina, but there were no MIs. Five patients (12%) underwent balloon angioplasty at the original target site, and 4 patients (10%) underwent stenting at a new lesion site. Three patients (7%) experienced a nonfatal stroke. The overall TVF rate was 24%.

DISCUSSION

CABG and LMCA Stenosis

Since the description of LMCA disease by Herrick in 1912, this disease has been known to be of critical prognostic importance [Cohen 1975; Herrick 1983]. CABG is considered the standard treatment for LMCA because survival rates for surgery are greater than those for medical therapy. The VA Cooperative Randomized Trial showed that the survival rate was higher in surgically treated LMCA patients than in medically treated patients; the 1- and 3-year survival rates in these 2 groups were 87% vs. 67% and 82% vs. 60%, respectively [Takaro 1976]. The Collaborative Study in Coronary Artery Surgery (CASS) compared the 4-year cumulative survival rates in 1492 patients with LMCA disease who underwent surgical revascularization or medical therapy. Compared to medical therapy, CABG surgery significantly prolonged the 4-year cumulative survival rate (the 1-, 2-, 3-, and 4-year survival rates in the surgically and medically treated groups were 95% versus 85%, 93% versus 76%, 91% versus 69%, and 88% versus 63%, respectively) [Chaitman 1981]. However, the maximum survival benefit of CABG relative to medical treatment was noted at 7 years in the VA Cooperative Study. This benefit diminished

thereafter, reaching nonsignificance at 11 years [Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group 1984]. The CASS Registry also showed a disproportionate increase in the mortality rate at 15 years in the patients who underwent surgery [Caracciolo 1995]. This increase in late mortality in the patients treated surgically compared to those treated medically was attributed to accelerated disease progression in the native coronary arteries as well as graft occlusion due to atherosclerosis occurring in later years [Bourassa 1984]. Grafts using the IMA have been shown to have a higher long-term patency rate compared to vein grafts; therefore, LIMA, RIMA, or radial artery grafts were used in almost all patients included in the present study [Barner 1985].

Table 4. Angiographic Follow-up of Surgical Bypass Vessels

Vessel	LM Stenting		6-Month Follow-up		Total	
	Total Occlusion	≥50% Stenosis	Total Occlusion	≥50% Stenosis	Total Occlusion	≥50% Stenosis
LIMA (n = 40)	1 (3%)	1 (3%)	4 (10%)	1 (3%)	5 (13%)	2 (5%)
SVG (n = 34)	5 (15%)	0	0	1 (3%)	5 (15%)	1 (3%)
RA (n = 6)	1 (17%)	0	0	0	1 (17%)	0
RIMA (n = 3)	1 (33%)	0	0	0	1 (33%)	0
Total (n = 83)	8 (10%)	1 (1%)	4 (5%)	2 (2%)	12 (15%)	3 (4%)

Table 5. Clinical Events During Follow-up Period

Mortality	3 (7%)
Cardiac	2 (5%)
Noncardiac	1 (2%)
Reinfarction	0
STEMI	0
Non-STEMI	0
Recurrent angina	6 (14%)
TLR	5 (12%)
Stenting of a new lesion	4 (10%)
Nonfatal stroke	3 (7%)
TVF	10 (24%)

Stenting in LMCA Stenosis

BMS of the unprotected left main lesions is associated with variable outcomes [Ellis 1997; Park 2003]. The in-hospital mortality rate is higher in patients with surgical high-risk factors and ranges from 7.6% to 13.7%, whereas patients without these high-risk factors have an in-hospital mortality rate that ranges from 0% to 1.8% [Silvestri 2000; Black 2001; Tan 2001]. Park et al. studied the immediate and long-term results of unprotected BMS stenting in 270 patients with LMCA disease and normal left ventricular function, and reported a procedural success rate of 98.9% [Park 2003]. During hospitalization, there were 3 stent thromboses (1.1%), 3 Q-wave MIs (1.1%), 3 emergency bypass surgeries (1.1%), and 1 repeat coronary intervention (0.4%); none of the patients died during hospitalization. During a follow-up period of 32.3 ± 18.5 months, the target site and new lesion revascularization rates were 16.7% and 11.5%, respectively. The survival rates were 95.4 ± 1.3%, 93.6 ± 1.6%, and 92.1 ± 1.9% at 1, 2, and 3 years, respectively. The cumulative probabilities of MACE (cardiac death, nonfatal MI, and target lesion revascularization [TLR]-free survival) were 81.9% ± 2.4%, 78.4% ± 2.6%, and 77.7% ± 2.7% at 1, 2, and 3 years, respectively. Additional CAD and postprocedural MLD were predictors of MACE. The rate of restenosis of unprotected LM BMS is high, and ranged from 21% to 34% [Park 1998; Silvestri 2000; Suarez 2001]. A smaller reference diameter, bifurcated lesion, and need for longer stent coverings were predictors of restenosis, whereas a short lesion and longer LM artery were associated with a lower risk of restenosis [Suarez 2001]. In this study, the restenosis rate was 18% and the predictors of restenosis were diabetes and poststenting MLD. Over the past decade, drug-eluting stents (DESs) have further reduced the incidence of restenosis and the need for reintervention [Morice 2002]. However, increased repeat revascularization after the use of DESs in LMCA stenosis remains an ongoing problem and is the primary factor for noninferiority failure when compared with CABG (11). Several studies have demonstrated a TLR rate ranging from 2% to 38%, depending on the percentage of patients with distal LMCA disease [Park 2005; Chieffo 2005; Valgimigli 2005; Valgimigli 2006; Price MJ 2006; Kim 2009]. Distal bifurcated LMCA stenosis results in higher restenosis and TLR rates [Price 2006]. Furthermore, stent thrombosis with impaired endothelialization and healing is a potentially important limitation of DESs. Stent thrombosis is also associated with an increased risk of MI of up to 70% and an increased risk of mortality of up to 45% [Cutlip 2001; Chechi 2008]. In the setting of LMCA stenosis, stent thrombosis may have more critical outcomes.

Staged Therapy Combining CABG and Stenting for LMCA Stenosis

Based on the above disadvantages of CABG and stenting for patients with LMCA stenosis, we studied the safety and efficacy of a dual protection therapy. To the best of our knowledge, this study is the first study to report the outcomes of this dual protection therapy combining staged CABG and stenting for LMCA stenosis. In the present study, there was no perioperative mortality, which should be compared with the in-hospital mortality rate of 2.3% for standard bypass surgery [Ellis 1998]. This study showed that venous bypass grafting had higher early occlusion (15% at 2 weeks after bypass surgery), and arterial grafting had higher late occlusion (10% at 6 months after bypass surgery). These findings may indicate that arterial grafting is better than venous grafting at the early phase. However, this benefit will be offset by the competing blood flow between the bypass graft and the native coronary vessel opened after stenting, the latter of which induces a decrease in blood flow in the bypass graft. Competitive blood flow is a common finding in arterial grafting. Flow competition results from an equilibrium between the residual flow through the native coronary artery and the flow provided the bypass graft at the anastomosis. This situation occurs when the conductance of the graft closely matches that of the native circulation and is mainly dependent on the severity of stenosis and graft diameter and length. The native coronary artery blood flow, apart from arteriosclerosis, affects early arterial graft patency [Shimizu 2000]. Unlike saphenous veins, arteries are muscular and can autoregulate their lumen in response to metabolic demand. As proximal coronary artery stenosis decreases, the competitive flow increases and demand for arterial graft blood flow decreased. This process results in arterial graft constriction and possibly graft atrophy and occlusion [Sabik 2003, Sabik 2008]. Despite this disadvantage, the "double protection" strategy may protect patients from the fatal consequences of stent thrombosis and subsequent in-stent restenosis.

Study Limitations

There were a number of limitations of the present study. First, this was a single-arm study that did not compare the results with those of another group, and the sample size was small and may not be applicable to the entire range of LMCA stenosis patients. Second, IVUS guidance was not used, and IVUS could further decrease the rates of restenosis and TLR by improving stent deployment. Third, only BMS, without DES, was evaluated in this study. Fourth, the patients were enrolled over the past 15 years, and the techniques employed in the past are not likely to be representative of the current standards for interventions.

CONCLUSION

Dual protection therapy with staged CABG and stenting is not an appropriate therapeutic strategy because of an unacceptable graft patency rate. A higher rate of occlusion of the bypass grafts may result from decreased blood flow due to competing blood flow between the bypass graft and the native coronary vessel.

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