Mid-Term Results and Costs of Coronary Artery Bypass vs Drug-Eluting Stents for Unprotected Left Main Coronary Artery Disease

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Background: The optimal revascularization strategy for unprotected left main coronary artery (ULMCA) disease in the era of drug-eluting stents (DES) has become more controversial between coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).

Methods and Results: Since April 2004, 89 patients underwent CABG, including 82 (92.1%) off-pump procedures and 63 patients underwent PCI with DES for ULMCA disease. Major adverse cardiac and cerebrovascular events (MACCE: death, acute myocardial infarction, stroke and repeat revascularization) and hospitalization costs were compared. Patients in the CABG group were likely to have multivessel disease and higher euroSCORE. The mean follow-up was 2.2 ± 1.1 years in the CABG group and 1.6 ± 0.8 years in the DES group ($P < 0.001$). The overall survival rate did not differ ($P = 0.288$) between the groups (CABG: 93.4% and DES: 91.9% at 2 years). The MACCE-free survival rate was better ($P = 0.033$) in the CABG group (CABG: 82.2% and DES: 62.6% at 2 years). Total hospitalization costs were lower ($P = 0.013$) in the CABG group (median: 3,225 thousand yen) than in the DES group (median: 4,192 thousand yen).

Conclusions: CABG might be associated with cost-effectiveness and could be still the first revascularization strategy for ULMCA disease. (*Circ J* 2010; **74**: 449–455)

Key Words: Coronary artery bypass; Coronary artery disease; Drug-eluting stents; Percutaneous coronary intervention

Numerous studies have been conducted to compare the outcomes of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). In the era of bare metal stents (BMS), most studies reported that CABG was associated with a lower incidence of major adverse cardiac and cerebrovascular events (MACCE) in patients with multivessel coronary artery disease (CAD).¹ Some randomized or cohort studies demonstrated the survival advantage of CABG,² while others reported equivalent long-term mortality.³ Since the advent of drug-eluting stents (DES), the treatment for severe CAD has become much more controversial between CABG and PCI because DES reduce the rates of restenosis and repeat revascularization.⁴ Meanwhile, some investigators reported that CABG was still associated with lower mortality,⁵ MACCE⁶ or repeat revascularization rates^{7,8} in patients with multivessel CAD in the DES era. Moreover, some trials could not demonstrate the survival advantage of DES relative to BMS.⁹ Conversely, some investigators advocated PCI using DES for multivessel CAD or

even for unprotected left main coronary artery (ULMCA) disease.¹⁰ CABG has been considered the standard therapy for patients with ULMCA disease and is recommended by the current practice guidelines,¹¹ which state that PCI for ULMCA stenosis is usually restricted to patients who are not eligible for surgery or who require emergency intervention at angiography for hemodynamic instability. However, comparative data for the outcomes of CABG and PCI with DES for ULMCA disease are limited.

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On the other hand, surgical technologies for CAD have also been developed in the past decade or two. The off-pump technique has improved mortality and morbidity in patients undergoing CABG.¹² In Japan, off-pump CABG was performed in 63% of the total isolated CABG cases in 2007.¹³ It is essential to compare the clinical results of PCI using DES and CABG involving off-pump procedures for patients with

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Table 1. Patient Characteristics

	CABG	DES	P value
No. of patients	89	64	
Coronary risk factors			
Age	70±9	71±7	0.401
Female	13 (15%)	12 (19%)	0.494
Hypertension	70 (79%)	54 (84%)	0.270
Hypercholesterolemia	52 (58%)	29 (45%)	0.109
Diabetes mellitus	41 (46%)	31 (35%)	0.772
Obesity (BMI >25)	24 (27%)	14 (22%)	0.472
Smoking	58 (65%)	42 (66%)	0.953
Family history	26 (29%)	12 (19%)	0.140
Comorbidities			
Renal impairment (Cr >2.0 mg/dl)	12 (13%)	6 (9%)	0.437
Hemodialysis	6 (7%)	4 (6%)	0.903
Cerebrovascular accident	6 (7%)	4 (6%)	0.903
Chronic lung disease	5 (6%)	8 (13%)	0.132
Peripheral vascular disease	16 (18%)	11 (17%)	0.899
Diseased vessels			
LMCA+3VD	55 (62%)	31 (48%)	0.100
LMCA+2VD	26 (29%)	15 (23%)	0.426
LMCA+1VD	7 (8%)	18 (28%)	0.002
LMCA only	1 (1%)	0 (0%)	0.999
Average	2.5±0.7	2.2±0.9	0.014
%stenosis of LMCA			
50%	32 (36%)	36 (56%)	0.013
75%	38 (43%)	26 (41%)	0.798
90%	25 (28%)	2 (3%)	<0.001
99%	4 (4%)	0 (0%)	0.140
Average (%)	70±16	61±13	<0.001
Cardiac status			
Prior PCI	22 (25%)	25 (39%)	0.064
CCS III/IV	39 (44%)	18 (28%)	0.048
OMI	24 (27%)	9 (14%)	0.056
CHF	13 (15%)	4 (6%)	0.105
AMI	4 (4%)	3 (5%)	0.955
Shock	5 (6%)	1 (2%)	0.202
LVEF <40	11 (12%)	4 (6%)	0.210
EuroSCORE			
>10	27 (30%)	4 (6%)	<0.001
>5	42 (47%)	18 (28%)	0.017
Median	4.9	2.7	<0.001
Interquartile range	2.4–11.5	1.9–5.1	

CABG, coronary artery bypass grafting; DES, drug-eluting stent; BMI, body mass index; Cr, serum creatinine; LMCA, left main coronary artery; VD, vessel disease; PCI, percutaneous coronary intervention; CCS, Canadian Cardiovascular Society Grading Scale for Angina Pectoris; OMI, old myocardial infarction; CHF, congestive heart failure; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction.

ULMCA disease. Moreover, to evaluate optimal revascularization strategies, economic considerations should also be taken into account because the concerns about healthcare costs are now growing. Therefore, we compared the mid-term clinical results and medical costs of CABG and PCI with DESs for patients with ULMCA disease after DES became available in our hospital in April 2004.

Table 2. Procedural Characteristics

CABG group	
Procedure	
Off-pump CABG	81 (91.0%)
On-pump beating CABG	6 (6.7%)
Conventional CABG	1 (1.1%)
Emergency CABG	27 (30.3%)
Conduit use	
Left internal thoracic artery	79 (88.8%)
Right internal thoracic artery	11 (12.4%)
Radial artery	31 (34.8%)
Right gastroepiploic artery	11 (12.4%)
Saphenous vein graft	49 (55.1%)
Vein-only CABG	5 (5.6%)
Internal thoracic artery-LAD	84 (94.4%)
No. of distal anastomosis/patient	2.9±0.9 (1–5)
DES group	
DES to LMCA	64
Sirolimus-eluting stents	61
Paclitaxel-eluting stents	3
BMS to other lesions	8
Emergency procedures	7
No. of DES/patient	
DES to LMCA	1.7±0.8 (1–4)
Total DES	3.1±1.6 (1–8)
Single PCI	24
Staged PCI	40
No. of PCI/patient	1.9±0.9 (1–5)
Intravascular ultrasound use	62 (97%)
Rotablator use	7 (11%)
DCA use	6 (9%)

LAD, left anterior descending artery; BMS, bare metal stent; DCA, directional coronary atherectomy. Other abbreviations see in Table 1.

Methods

Between April 2004 and December 2007, 89 patients with ULMCA disease (diameter stenosis ≥50%) underwent primary isolated CABG (CABG group) and 64 patients underwent PCI with DES to the ULMCA (DES group) in The University of Tokyo Hospital. The decision to perform CABG or PCI was according to physician and/or patient choice. Patients who had previously undergone CABG were excluded from both groups; patients who underwent PCI using BMS to the ULMCA were also excluded. Staged PCI procedures were performed for the treatment of LMCA with multivessel CAD. The first PCI after diagnosis of ULMCA disease was set as the initial point of follow-up. The primary clinical endpoints of the study were MACCE (death, acute myocardial infarction (AMI), stroke and repeat revascularization) at mid-term follow-up. Death was defined as death from any cause. Myocardial infarction (MI) was defined as the documentation of a new abnormal Q wave and cardiac enzyme elevation 5-fold the upper limit of the normal or base line value within the first 7 days post intervention. Beginning 8 days after the intervention, either abnormal Q waves or enzymatic changes with cardiac symptoms were sufficient for a diagnosis of MI. Cerebrovascular event (stroke) was defined as any acute event related to the impairment of the cerebral circulation that resulted in irreversible brain damage or permanent body

impairment. Repeat revascularization did not include revascularization performed as a staged PCI but included target and nontarget vessel revascularization.

The cost of hospitalization, charged according to the Diagnosis Procedure Combination (DPC) system, was based on a flat payment system excepting the charges for procedure. The cost of hospitalizations was calculated from the universal medical insurance claim amount. Hospitalizations during the follow-up period included hospitalizations for the examination or treatment of ischemic or ischemia-related-heart disease. Postoperative angiography or coronary CT scans were routinely performed 1 or 2 weeks after CABG. Follow-up angiography was routinely performed 6–12 months after the initial PCI, except in patients with high risks for angiography. The Ethics Committee approved our study, and written informed consent was given by each patient.

Statistical Analysis

We calculated the means $\pm$ SD or the median with interquartile range for continuous variables in each group and compared them using Student's t-test or the Wilcoxon test. Binary variables are reported as counts and percentages, and differences between the 2 groups were assessed using the chi-square or Fisher's exact test. Cumulative event rates were estimated using the Kaplan-Meier method and differences were compared using the log-rank method.

Results

Patients' Characteristics

The baseline characteristics of the study patients are shown in **Table 1**. Patients undergoing CABG were more likely to

Table 3. MACCE

	CABG	DES	P value
n	89	64	
Follow-up (years)	2.2 $\pm$ 1.1	1.6 $\pm$ 0.8	<0.001
Any MACCE	16 (18.0%)	20 (31.3%)	0.056
Death	6 (6.7%)	5 (7.8%)	0.800
Within 30 days	1 (1.1%)	1 (1.6%)	0.999
In-hospital	2 (2.2%)	1 (1.6%)	0.736
Out-hospital	4 (4.5%)	4 (6.3%)	0.720
Non-cardiac death	3 (3.4%)	2 (3.1%)	0.999
AMI	0 (0%)	2 (3.1%)	0.173
Stroke	1 (1%)	0 (0.0%)	0.999
Repeat revascularization	10 (11.2%)	17 (26.6%)	0.014
PCI	10 (11.2%)	17 (26.6%)	0.014
CABG	0 (0.0%)	1 (1.6%)	0.418

MACCE, major adverse cardiac and cerebrovascular events. Other abbreviations see in Table 1.

have multivessel disease, greater stenosis of the LMCA, higher class of angina and higher euroSCORE. Procedural characteristics of the study patients are summarized in the **Table 2**. In the CABG group, 82 patients (92.1%) underwent off-pump surgery, including 1 minimally invasive direct coronary artery bypass procedure via left anterior mini-thoracotomy. Of the remaining 7 patients, 6 (6.7%) underwent on-pump beating CABG, including 2 patients converted from attempted off-pump surgery. Conventional CABG was performed under cardiac arrest in 1 patient (1.1%). In the DES group, emergency PCI was performed in 7 patients

Figure 1. Kaplan-Meier curves for the coronary artery bypass graft (CABG) group and drug-eluting stent (DES) group for unprotected left main coronary artery disease. MACCE, major adverse cardiac and cerebrovascular events.

	CABG	DES	P value
No. of hospitalizations	1 (1–1)	2 (2–3)	<0.001
No. of revascularizations	1 (1–1)	2 (1–3)	<0.001
Hospital stay (days)			
Total hospitalizations	23 (19–38)	25 (16–38)	0.327
Initial hospitalization	23 (19–35)	15 (11–22)	<0.001
Follow-up hospitalizations	0 (0–0)	7 (3–18)	<0.001
Costs of hospitalization (thousand yen)			
Total hospitalization	3,225 (2,654–4,126)	4,192 (3,031–6,311)	0.013
Initial hospitalization	3,190 (2,641–4,045)	3,624 (2,543–4,732)	0.357
Follow-up hospitalization	0 (0–0)	378 (202–1,480)	<0.001

Data are median (interquartile range).
Abbreviations see in Table 1.

Figure 2. Cost of hospitalization for left main coronary artery (LMCA) disease and the number of diseased vessels. Data are median. VD, vessel disease; CABG, coronary artery bypass; DES, drug-eluting stents; F/U, follow-up.

(10.9%), including 3 patients with acute occlusion of the right coronary artery and ULMCA disease. The mean number of DES implanted into the ULMCA lesions was 1.7 ± 0.8 (range 1–4). The primary success rate of PCI to the ULMCA lesions was 64/64 (100%). The mean number of DES implanted at the time of initial procedures was 3.1 ± 1.6 (range 1–8) per patient.

Clinical Outcomes

The follow-up rate was 100% in both groups. The follow-up period was significantly ($P < 0.001$) longer in the CABG group (2.2 ± 1.1 years) than in the DES group (1.6 ± 0.8 years) because of the increasing number of patients in the DES group each year. In the CABG group, 2 patients died of multiple organ failure at 29 days and 5 months, respectively. In the DES group, 1 patient died of heart failure 4 days after PCI. The in-hospital mortality rate did not differ between the groups (Table 3).

Four CABG group patients died during the follow-up period: 1 of heart failure and the others of cancer. In the DES group, 1 patient died of heart failure 4 days after PCI. Three DES group patients died during the follow-up period: 1 of heart failure, 1 of sudden death, 1 of interstitial pneumonia

and 1 of sepsis. The overall cumulative survival rate did not significantly differ between the groups ($P = 0.487$) and the rate at 1 and 2 years was 96.5% and 93.4% in the CABG group, respectively, and 95.3% and 91.9% in the DES group, respectively (Figure 1).

In the DES group 2 patients, including 1 with late stent thrombosis of the LMCA, had an AMI. Late stent thrombosis occurred in a 71-year-old male patient who underwent PCI with 4 sirolimus-eluting stents in 2004. Because of a skin rash caused by ticlopidine, the patient was treated with a dual platelet regimen including aspirin and cilostazol. Two years after the initial PCI, the patient presented with ST-elevation AMI, complicated by cardiogenic shock. Emergency coronary angiography revealed a thrombotic total occlusion in the mid-LMCA stented segment and emergency PCI was successfully performed. One patient (1.1%) had a stroke following postoperative atrial fibrillation 2 days after CABG, but there were no cases of this in the DES group.

In the CABG group, postoperative angiography was performed in 68 patients (76.4%) during the initial hospitalization. In this group, repeat revascularization with PCI was performed in 10 patients (11.2%). Five patients (5.6%) underwent PCI during initial hospitalization. No patient underwent

repeat CABG. In the DES group, follow-up angiography was performed in 51 patients (79.9%). Repeat revascularization with PCI was performed in 15 patients (23.4%) and repeat revascularization with CABG was performed in 1 patient (1.6%). The total number of implanted DES during all follow-up including the initial hospitalization was 3.5 ± 2.1 (range 1–12) per patient. The MACCE-free cumulative survival rate was better in the CABG group than in the DES group ($P=0.033$), and the rate at 1 and 2 years was 85.0% and 82.2% in the CABG group, respectively, and 69.8% and 62.6% in the DES group, respectively (Figure 1).

Medical Costs

The numbers of hospitalizations and revascularizations were lower in the CABG group. Hospital stay at the time of initial hospitalization was longer in the CABG group, whereas hospital stay during the follow-up period was longer in the DES group. Consequently, total hospitalization days did not differ between the groups. Total hospitalization costs were higher in the DES group than in the CABG group, particularly, the cost of follow-up hospitalization (Table 4). In the subgroup with 3-vessel disease, the cost of initial hospitalization was higher in the DES group (Figure 2).

Discussion

Recent ACC/AHA guidelines¹¹ recommend CABG for significant ULMCA disease in patients with unstable angina or non-ST-elevation MI at the level of evidence A with the class I recommendation, because CABG offers a well-documented survival benefit over medical therapy. In the BMS era, the APPROACH study¹⁴ revealed that CABG was associated with superior long-term (5 years) survival to PCI in the group with severe ULMCA disease. Since the advent of DES, some reports have been published that compare the outcome of these treatments. A single-center study in the USA¹⁵ compared conventional CABG (123 patients) with PCI using DES (50 patients) for ULMCA disease and reported that the MACCE-free survival rate and the freedom from target vessel revascularization at 1 year did not significantly differ between the 2 groups. The Bologna Registry¹⁶ for the treatment of ULMCA stenosis revealed no difference in the rate of mortality and MI between PCI (DES use: 59.9%) and CABG (off-pump: 9.7%) after a median follow up of 430 days. However, the rate of target vessel revascularization was higher in the PCI group. Another recent report from Taiwan¹⁷ reviewed 363 patients undergoing CABG (216 patients, off-pump: 8.3%), PCI with DES (94 patients) or PCI with BMS (patients 53) for ULMCA stenosis between January 2000 and March 2007. The revascularization-free survival rate was higher in the CABG group, but the cardiac death-free survival rate did not significantly differ among the 3 groups. A recent Korean cohort study¹⁸ of 1,102 patients with ULMCA disease revealed no significant difference found in rates of death for 3 years between patients receiving stents (DES 71%) and those undergoing CABG (off-pump 41%), however, stenting was associated with higher rates of target vessel revascularization than CABG. The 1-year results of the SYNTAX trial¹⁹ for 1,800 patients with 3-vessel or LMCA disease assigned to CABG (off-pump 15%) or PCI involving DES suggested that the rates of death were similar between the 2 groups (CABG 3.5% vs PCI 4.4%), but the rates of repeat revascularization were higher in the PCI group (5.9% vs 13.5%); stroke was more likely to occur with CABG (2.2% vs 0.6%).

In the present study, 30-day mortality (1.1%) of the CABG

group was satisfactory in patients with a median euroSCORE of 4.9. Off-pump procedures were performed in over 90% of patients. The off-pump technique has been considered effective in patients with high risks²⁰ or critical LMCA disease.²¹ Furthermore, 6 patients underwent on-pump beating CABG, which is effective in patients with unstable hemodynamics.²² Consequently, there was no difference in the 30-day mortality rates of the 2 groups, although the patients in the CABG group had more vessels affected, higher CCS angina class and higher euroSCORE. The overall mid-term survival rates also did not differ between the groups. PCI using DES might be an alternative to CABG in selected patients with ULMCA disease.²³ The MACCE-free survival was better in the CABG group. Higher MACCE rates in the DES group were mainly because of increased rates of repeat revascularization. These results are almost consistent with those of previous studies; however, in the present study, the rate of stroke might be less and the rate of repeat revascularization might be more in the CABG group. These results also could be associated with the higher percentage of off-pump procedures performed in the present study. Off-pump CABG has lower complication rates than standard on-pump CABG,¹² whereas graft patency and incomplete revascularization can be related to repeat revascularization.²⁴ Some cases of graft failure or incomplete revascularization might be attributed to the learning curve. Some might be caused by surgical strategies, such as a combined treatment with PCI.

One patient had late stent thrombosis of the LMCA 2 years after the initial procedure. Late stent thrombosis is a rare complication, even after DES implantation. However, as it can lead to fatal complications,²⁵ it must be taken into account, especially when the DES is implanted into the LMCA. Antiplatelet therapy is essential to prevent late DES thrombosis. The ACC/AHA recommends dual antiplatelet therapy with aspirin and clopidogrel for at least 1 year after PCI to mitigate the increased risk of late stent thrombosis.²⁶

The cost implications of coronary revascularization are now of concern. Several investigations have compared the cost-effectiveness of DES and BMS.^{27,28} The data suggest that DES are less cost-effective when used in a widespread, indiscriminate manner but might be cost-effective in selected PCI patients with the highest risk for restenosis. Compared with conventional CABG, the initial cost^{29,30} or the 1-year cost³¹ of PCI was lower in the era of BMS or balloon angioplasty. PCI with BMS might be less costly than CABG in high-risk patients for 5 years.²⁹ A recent Canadian study compared the 1-year costs of 4 revascularization procedures in patients with multivessel disease. The data revealed that PCI with BMS was the least costly procedure, followed by off-pump CABG, PCI with DES and on-pump CABG.³² The study also indicated that DES became the most costly procedure if 3.5 or more DES were used or if staged PCI was performed. The Study of Economics and Quality of Life in BARI participants³⁰ found that early differences between CABG and PCI with balloon angioplasty for multivessel disease, in terms of costs and quality of life, were no longer significant at 10–12 years of follow-up. A cost-effectiveness analysis of minimally invasive internal thoracic artery bypass vs PCI for isolated lesions of the left anterior descending artery in the UK suggested that CABG might be a more cost-effective medium- and long-term alternative to PCI with BMS.³³

Our study found that the cost of follow-up hospitalization was higher in the DES group. Secondly, the cost of initial hospitalization was higher in the DES group for those pa-

tients with ULMCA and 3-vessel disease. Thirdly, the initial hospitalization cost of the DES group was not lower than that of the CABG group, even in patients with LMCA and 1-vessel disease. Consequently, the total cost of hospitalization was significantly higher in the DES group. These data suggest that PCI with DES is more costly than CABG involving an off-pump technique for the treatment of LMCA disease. Additionally, PCI with DES might be more costly for patients with 3-vessel disease with or without LMCA disease. The number of implanted DES or the number of procedures for staged or repeated PCI could be contributing to the high cost.³² Meanwhile, off-pump CABG offers significant savings during the initial hospitalization, which may be sustained thereafter.³⁴ Considering the overall survival rate and MACCE-free survival rate for CABG and PCI in the present study, CABG mostly performed with an off-pump technique could be more cost-effective than PCI.

Study Limitations

The major limitation is that this was not a randomized or prospective study. The choice of treatment was according to physician/patient preference. Consequently, patients undergoing CABG were more likely to have a higher euroSCORE. However, this study reports 1 real-world outcome of the treatment of ULMCA disease in Japan. Each country has its own system for providing health insurance and covering medical expenses. In Japan, people are covered through the universal medical insurance system and medical fees and product prices are set by the Ministry of Health, Labour and Welfare. The price disparity³⁵ between Japan and foreign countries for medical devices or products can be associated with cost-effectiveness. Therefore, our results cannot be simply applied to all countries. Cost-effectiveness is often assessed by the cost per quality-adjusted-life-year gained,³³ and it can be also estimated by the cost per revascularization avoided^{27,28} or cost per life-year of survival.²⁹ Our data did not include out of hospital costs during follow-up. However, the need for extended clopidogrel therapy to prevent late stent thrombosis-related adverse events substantially increases the costs associated with the implementation of DES.²⁸

Conclusions

The mid-term survival rate of PCI with DES was comparable to that of CABG for the treatment of LMCA disease. PCI using DES might be an alternative to CABG in selected patients with ULMCA disease. However, CABG mostly performed using off-pump techniques showed better MACCE-free survival rates than PCI with DES. PCI with DES was more costly than CABG. These data suggest that CABG is more cost-effectiveness and still the first revascularization strategy for ULMCA disease.

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