Comparison of Coronary Artery Bypass Surgery With Percutaneous Coronary Intervention With Drug-Eluting Stents for Unprotected Left Main Coronary Artery Disease

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OBJECTIVES
This study evaluated the clinical outcomes of consecutive, selected patients treated with coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) with drug-eluting stents (DES) for unprotected left main coronary artery (ULMCA) disease.

BACKGROUND
Although recent data suggest that PCI with DES provides better clinical outcomes compared to bare-metal stenting for ULMCA disease, there is a paucity of data comparing PCI with DES to CABG.

METHODS
Since April 2003, when DES first became available at our institution, 123 patients underwent CABG, and 50 patients underwent PCI with DES for ULMCA disease.

RESULTS
High-risk patients (Parsonnet score >15) comprised 46% of the CABG group and 64% of the PCI group (p = 0.04). The 30-day major adverse cardiac and cerebrovascular event (MACCE) rate for CABG and PCI was 17% and 2% (p < 0.01), respectively. The mean follow-up was 6.7 ± 6.2 months in the CABG group and 5.6 ± 3.9 months in the PCI group (p = 0.26). The estimated MACCE-free survival at six months and one year was 83% and 75% in the CABG group versus 89% and 83% in the PCI group (p = 0.20). By multivariable Cox regression, Parsonnet score, diabetes, and CABG were independent predictors of MACCE.

CONCLUSIONS
Despite a higher percentage of high-risk patients, PCI with DES for ULMCA disease was not associated with an increase in immediate or medium-term complications compared with CABG. Our data suggest that a randomized comparison between the two revascularization strategies for ULMCA may be warranted.

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patients who underwent PCI with DES and 123 patients who underwent CABG for ULMCA disease.

The primary clinical end points were freedom from major adverse cardiac and cerebrovascular events (MACCE) at 30-day and intermediate-term follow-up. We included patients with ULMCA stenoses or documented myocardial ischemia and ≥50% diameter stenosis of the ULMCA on angiography. The left main coronary artery was defined as unprotected if there were no CABGs to the left anterior descending artery and left circumflex artery. Patients were jointly evaluated by cardiac surgery and interventional cardiology consultants. The final decision of the method of revascularization was made after comprehensive review of all relevant factors. To be selected for PCI, a patient had to have one of the following characteristics: very high risk for CABG, limited life expectancy, patient refusal to undergo CABG with a preference for PCI, or patient deemed unsuitable for CABG by the cardiac surgeon. This study was approved by the Cedars-Sinai Medical Center Institutional Review Board.

PCI. Percutaneous coronary intervention was performed using the standard percutaneous transfemoral approach, except for two patients who underwent PCI via the transradial approach due to extensive peripheral vascular disease. Lesions in the ostium or body of the ULMCA without distal bifurcation involvement were usually treated with a single stent. Several techniques were used for the treatment of distal bifurcation disease. Stenting across the left circumflex artery, simultaneous kissing stenting, T stenting, and the crush technique have been previously described (12,13). The choice of a sirolimus-eluting stent or paclitaxel-eluting stent and antithrombotic agent was made by the operator. High-pressure stent deployment was performed using an initial inflation of 16 atm. Intravascular ultrasound was used to confirm optimal stent deployment. Post-dilation with additional balloons was performed for optimal stent apposition. Glycoprotein IIb/IIIa antagonists and intra-aortic balloon pump were used if clinically indicated. All patients received aspirin (325 mg/day) indefinitely and a loading dose of 300 mg of clopidogrel. Clopidogrel was continued for at least six months. Cardiac enzymes were not measured routinely unless there was a clinical suspicion of ischemia, and therefore was not a designated outcome of the study.

Bypass surgery. Standard bypass techniques included a left internal mammary artery for revascularization of the left anterior descending coronary artery whenever possible and cold potassium cardioplegia. Cardiac enzymes were not measured routinely unless there was a clinical suspicion of ischemia.

Definitions. Percutaneous coronary intervention procedural success was defined as Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 with a final residual stenosis of <30% without death, myocardial infarction, or emergency CABG before hospital discharge. Death was defined as any post-procedure death. A myocardial infarction was defined as ischemic symptoms associated with cardiac enzyme elevation ≥3 times the upper limit of the normal value. Target vessel revascularization was defined as a repeat revascularization to treat a luminal stenosis within the stent or within 5-mm distal and proximal segments adjacent to the stent, including the ostium of the left anterior descending artery and/or left circumflex artery. A cerebrovascular event was defined as stroke, transient ischemic attack, reversible ischemic neurologic deficit, or coma.

The Parsonnet score was used to stratify the risk of death at 30 days in patients undergoing cardiac surgery (14,15). A Parsonnet score >15 identified patients at high risk for surgical mortality.

Statistics. Continuous variables are presented as mean ± SD and were compared by Student t test (when the group distributions were symmetrical and mound) or Mann-Whitney U test (when the group distributions were skewed). The Satterthwaite adjustment was applied to the t test when there was evidence against equality of variance. The chi-square test (when all expected cell counts were ≥5) or Fisher exact test (when any expected cell count was <5) was used to determine the significance of differences in categorical variables. Survival curves were generated by the Kaplan-Meier method, and the differences were assessed by the log-rank test. Survival analyses were performed for the first 423 days of follow-up so that the comparison of CABG and PCI would be over the same time period. A multivariable Cox proportional hazard model was created with the use of baseline clinical and angiographic characteristics and procedure-related variables in order to identify independent predictors of MACCE. All statistical tests were two-tailed, and a significance level of 0.05 was used throughout. Statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics. Baseline clinical and demographic characteristics are listed in Table 1. Compared to the CABG group, the PCI group had less men (50% vs. 76%, p < 0.01), more patients with chronic renal insufficiency (16% vs. 5%, p = 0.02), and more patients with unstable angina as the presenting symptom (46% vs. 25%, p < 0.01). The average Parsonnet score was 13.7 ± 9.7 in the CABG group and 18.3 ± 10.9 in the PCI group (p < 0.01). High-risk patients (Parsonnet score >15) were present in 46% of the CABG group and 64% of the PCI group (p = 0.04).
Nine patients (18%) who underwent PCI were turned down for CABG after surgical consultation. All patients with isolated ostial or mid-body disease received one stent. A total of 60% in the PCI group had distal bifurcation disease.

**Procedural outcomes.** Procedural characteristics are presented in Table 2. The procedural success rate was 98% in the PCI group. Intra-aortic balloon pump was used in 32 patients (64%), and the TandemHeart percutaneous left ventricular assist device (CardiacAssist Inc., Pittsburgh, Pennsylvania) was used in 3 patients (6%). Forty-two patients (84%) underwent PCI with sirolimus-eluting stents and eight patients (16%) with paclitaxel-eluting stents. On average, 2.5 ± 1.4 stents were implanted with a total stent length of 43.2 ± 28.4.

In the CABG group, 3.0 ± 0.8 grafts per patient were used, with 96% of patients receiving an internal mammary artery conduit to the left anterior descending artery.

**30-day outcomes.** The 30-day clinical outcomes are summarized in Table 3. The cerebrovascular event rate was higher in the CABG group (8% vs. 0%, *p* = 0.03), but there was no statistically significant difference in mortality (5% vs. 2%, *p* = 0.34). In the CABG group, there were six in-hospital deaths (four from cardiac reasons, one from a stroke, and one from a pneumothorax). The one death in the PCI group occurred in a patient with a Parsonnet score of 41 who was turned down by cardiac surgery because the patient was considered a high-risk candidate for CABG. This patient underwent peripheral vascular surgery two days after PCI and died suddenly eight days after surgery.
MACCE rate was higher in the CABG group (17% vs. 2%, \( p < 0.01 \)).

There were also other significant post-operative complications in the CABG group. Eight patients (7%) required repeat operation for bleeding (1 for cardiac tamponade), 6 patients (5%) developed pneumonia, 5 patients (4%) required permanent pacemaker implantation, 8 patients (7%) developed pleural effusions requiring thoracocentesis, 2 patients (2%) developed renal failure requiring hemodialysis, and 11 patients (9%) developed ventricular tachycardia/ventricular fibrillation.

One patient in the PCI group developed a cardiac tamponade requiring emergent pericardiocentesis secondary to a wire perforation. No patient required permanent pacemaker implantation, developed acute renal failure requiring hemodialysis, or had vascular complications like major hematoma, pseudoaneurysm, or need for vascular repair at the access site.

Patients treated with CABG had significantly longer hospitalization compared with patients treated with PCI (7.6 ± 4.9 days vs. 3.9 ± 4.5 days, \( p < 0.01 \)).

Intermediate follow-up. The mean follow-up was 6.7 ± 6.2 months in the CABG group and 5.6 ± 3.9 months in the PCI group (\( p = 0.26 \)). The estimated MACCE-free survival at six months and one year was 83% and 75% in the CABG group versus 89% and 83% in the PCI group (\( p = 0.20 \)) (Fig. 1A). The estimated freedom from death at six months and one year was 87% and 85% in the CABG group versus 96% and 96% in the PCI groups (\( p = 0.18 \)). In the CABG group, there were seven deaths at intermediate follow-up (two from cardiac reasons, one from a stroke, one from an abdominal aortic aneurysm rupture, one from respiratory failure secondary to pneumonia, one from renal failure, and one from suicide). The second death in the PCI group was in a patient with a Parsonnet score of 23 who was a “do not resuscitate/do not intubate” patient who died after developing acute pulmonary edema following an outpatient blood transfusion (Fig. 1B). Angiographic follow-up in the PCI group was available in 21 patients (42%). The estimated freedom from target vessel revascularization at six months and one year was 99% and 95% in the CABG group versus 93% and 87% in the PCI group (\( p = 0.22 \)) (Fig. 1C).
that, in the ULMCA subset, PCI may provide a comparable outcomes in PCI with DES will be extended to patients at present, therefore, it is not known whether the improved increased need for repeat revascularization in the PCI arm. Multivariable analysis Parsonnet score <0.01 1.1 (1.0–1.1) Diabetes mellitus 0.03 2.2 (1.1–4.6) CABG (vs. PCI) 0.04 2.8 (1.0–7.4) CI = confidence interval; other abbreviations as in Table 1.

All three patients who underwent repeat PCI (two patients underwent balloon angioplasty and one patient underwent repeat PCI with DES) had distal bifurcation involvement. Two of these three patients returned with re-restenosis and underwent CABG. Two additional patients in the PCI group underwent repeat PCI for de novo lesions in the distal left anterior descending artery. The estimated freedom from death, myocardial infarction, and cerebrovascular events at six months and one year was 83% and 79% in the CABG group versus 96% and 96% in the PCI group (hazard ratio, 4.4 [95% confidence interval, 1.0 to 18.6]; p = 0.03) (Fig. 1D).

Predictors of intermediate MACCE. The following variables were entered into a stepwise multivariable Cox proportional hazard model for MACCE-free survival: age, gender, diabetes mellitus, Parsonnet score, ejection fraction, chronic renal insufficiency, myocardial infarction, and CABG. The significant univariate predictors were Parsonnet score, diabetes mellitus, and myocardial infarction (Table 4). In the final Cox model, the significant predictors of the hazard of MACCE were Parsonnet score, diabetes mellitus, and CABG.

DISCUSSION

The most important finding of our study is that in a pilot experience with ULMCA, treatment with PCI with DES resulted in outcomes equivalent to CABG. Patients in the PCI group were of comparable pre-operative risk using traditional cardiac surgery criteria.

Our study adds to the existing database comparing PCI to CABG in angiographic subsets of coronary artery disease. In several studies comparing PCI with bare-metal stents to CABG in multivessel coronary artery disease, no mortality benefit was demonstrable, although there was a lower requirement for target vessel revascularization with CABG (16–18). On the other hand, the Arterial Revascularization Therapies Study II (ARTS II) (19), a nonrandomized comparison of CABG and PCI with DES in patients with multivessel coronary artery disease, did not demonstrate an increased need for repeat revascularization in the PCI arm. At present, therefore, it is not known whether the improved outcomes in PCI with DES will be extended to patients with ULMCA disease. Our observational study suggests that, in the ULMCA subset, PCI may provide a comparable or lower rate of death, myocardial infarction, and cerebrovascular events compared to CABG, when patients are assigned to treatment by consensus of interventionalist and cardiac surgeon. On the other hand, we do not have long-term follow-up data, although long-term data (up to four years) in other angiographic subsets suggest that sirolimus-eluting stents have a low rate of in-stent restenosis (20). The ongoing prospective Synergy Between PCI and Taxus and Cardiac Surgery (SYNTAX) and Revascularization Comparing Surgery Versus Percutaneous Coronary Intervention for Unprotected Left Main Artery Stenosis Randomized Evaluation (REVASCULARIZE) trials will add more data for analysis of this issue, especially in bifurcation disease.

Our CABG 30-day (4.9%) and 6-month (11.4%) mortality rates are consistent with the published data for CABG for ULMCA disease. The Society of Thoracic Surgery reported an in-hospital mortality of 3.9% in patients with left main disease (21). The Cleveland Clinic Foundation reported 2.3% in-hospital mortality and 11.3% one-year mortality (22). In patients who were considered to be low surgical risk, with age <65 years and New York Heart Association heart failure class =2, the one-year mortality was 5.7%. d’Allonnes et al. (23) reported an early postoperative mortality of 4.7% in 106 patients with ULMCA stenosis who underwent CABG.

Although our patients were selected for either PCI or CABG based on consensus of clinical judgment of the cardiologist and surgeon, the surgical risk of the patient groups was comparable. Overall, patients with high Parsonnet scores constituted 51% of the patient population (64% in the PCI group and 46% in the CABG group). Included in the 50 PCI patients were patients with multivessel coronary artery disease, cardiogenic shock, orthotopic heart transplant, orthotopic lung transplant, and three patients on percutaneous left ventricular assistance. There was a relatively low 30-day mortality rate (2%) in the PCI group despite the majority of patients being at high surgical risk for mortality and no deaths in the PCI group with low-risk Parsonnet scores.

Intra-aortic balloon pumps were used in 64% of our patients who underwent PCI of ULMCA with DES compared to 4.9% in Park et al. (9), 21.2% in Chieffo et al. (10), and 15% in Valgimigli et al. (11). Three other patients underwent ULMCA PCI with the TandemHeart percutaneous left ventricular device. Hemodynamic support with the intra-aortic balloon pump and the percutaneous left ventricular assist device was frequently used because we chose to be very cautious in this early experience with PCI of ULMCA. With more experience, we currently do not use intra-aortic balloon pumps in low-risk patients with normal left ventricular function.

A total of 14% of patients received glycoprotein IIb/IIIa antagonists in our study compared to 7.8% in Park et al. (9), 28% in Valgimigli et al. (11), and 28.5% in Chieffo et al. (10). The impact of glycoprotein IIb/IIIa antagonists on

Table 4. Cox Proportional Hazard Model Results

<table>
<thead>
<tr>
<th>Variables</th>
<th>p Value</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>Myocardial infarction</td>
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<td></td>
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<tr>
<td>Parsonnet score</td>
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<tr>
<td>Diabetes mellitus</td>
<td>&lt;0.01</td>
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<tr>
<td>CABG (vs. PCI)</td>
<td>0.04</td>
<td>2.8 (1.0–7.4)</td>
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CI = confidence interval; other abbreviations as in Table 1.
patients undergoing ULMCA PCI has not been studied in a randomized clinical trial and is thus unknown.

One previously reported limitation of PCI in ULMCA that involves the distal bifurcation is the high incidence of restenosis at the ostium of the left circumflex artery (9 –11). Patients in our study with distal bifurcation disease also had a greater need for target vessel revascularization. All three of the cases of target vessel revascularization were in patients with distal bifurcation disease involving the ULMCA compared to no patients with ostial and mid-body lesions. Pathology studies of bifurcation lesions suggest that arterial branch points are predisposed to the development of atherosclerotic plaque, thrombus, and inflammation due to low shear and low flow velocities (24–26). Although the ideal PCI strategy for dealing with distal bifurcation lesions is still undefined, our preliminary experience suggests that in this condition, it may be difficult to match the clinical outcomes of a left internal mammary to the left anterior descending artery graft, which has a patency rate of more than 90% at 10 years and improves survival and freedom from further cardiovascular events (27,28).

The optimal treatment of restenosis after PCI of ULMCA with DES is unknown. The percentage of patients who underwent CABG as their mode of revascularization ranged from 0% to 50% (9 –11). In our study, two of three patients who underwent repeat PCI (one patient underwent balloon angioplasty and the other patient underwent repeat PCI with DES) returned with re-restenosis and subsequently underwent CABG. Because the outcomes of repeat PCI for restenosis of ULMCA are not well defined, it is reasonable to recommend CABG as the primary treatment modality for patients with restenosis after PCI with DES.

Potential clinical implications of data. Our data suggest that PCI in ULMCA disease is safe when patients are allocated by clinical judgment. Because PCI showed trends toward benefit in a number of outcome variables, it is possible that a large sample size might have revealed other statistically significant outcome variables. On the other hand, there may be an incidence of very late complications associated with DES that will be defined with longer-term follow-up. A randomized trial certainly seems indicated. It is important to recognize, however, that randomization, as with all trials comparing CABG to PCI, eliminates clinical judgment in patient selection and carries a potential for being misleading as a predictor of outcomes in actual clinical practice.

Study limitations. The nonrandomized nature of the study limits any direct comparisons of the two methods of revascularization. We included all patients with ULMCA disease, resulting in a heterogeneous population of patients. Although trial strategies often seek to determine if one option is superior to another, our trial cannot be interpreted in this manner. Rather, it demonstrates that comparable results can be obtained in clinical practice when consensus judgment is utilized. Another potential limitation is that almost all of the PCI of the ULMCA was performed by one primary operator. Thus, the results obtained in this study may not be applicable to the broad population of interventional cardiologists. The majority of the patients received Cypher stents (Cordis, Johnson & Johnson Corp.) (42 out of 50 patients). Therefore, the limited experience with Taxus stents may preclude extrapolating these data to all DES. Periprocedural cardiac enzyme levels were not serially drawn after PCI or CABG. The reported myocardial infarction rate in both revascularization strategies is only the post-hospitalization and/or clinical myocardial infarction rate and not the usually reported myocardial infarction rate in clinical trials. Absence of these data could be important, because creatine kinase-MB was considered to be a major predictor of clinical outcome in the CABG arm of the ARTS I trial, which compared PCI with bare metal stents to CABG in multivessel coronary artery disease (19). Our trial did not include any asymptomatic patients, so potential outcomes in this subset remain undefined. Our follow-up was somewhat less rigorous in the CABG group, because asymptomatic patients in this group were not subjected to routine follow-up angiography, and the length of follow-up is currently not quite equal in the two groups. Although we encourage follow-up angiography at three to six months, there was a low incidence of angiographic follow-up (42%) due to patients refusing repeat angiography. Currently, it is our policy not to offer ULMCA PCI to patients unless they agree to follow-up angiography. Finally, we did not conduct quantitative analysis of symptom or functional improvement in both groups.

Conclusions. In this observational study, PCI with DES was found to be a viable alternative to CABG, with no increase in short- and intermediate-term MACCE in patients with ULMCA disease compared with CABG, when clinical judgment was used for patient allocation. These results suggest a potential need for a large, multicenter, randomized study with long-term follow-up to provide a basis for re-evaluation of treatment guidelines for ULMCA disease.

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