Revascularization of Left Anterior Descending Coronary Artery in Patients With Single and Multivessel Disease*

Comparison Between Off-Pump Internal Thoracic Artery and Drug-Eluting Stent

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Study objectives: The left anterior descending artery (LADA), particularly when the proximal segment of the vessel is involved, is a challenging area for percutaneous coronary interventions (PCIs); therefore, coronary artery bypass grafting is often considered and sometimes performed even in patients with single-vessel disease involving the LADA. This study compares mid-term results of LADA revascularization with a drug-eluting stent (DES), with off-pump coronary artery bypass grafting (OPCAB) in patients with single-vessel or multivessel coronary artery disease (CAD).

Design: Matched-groups, retrospective cohort comparison between the DES and OPCAB.

Patients: From June 2002 to December 2003, 354 patients underwent myocardial revascularization of the LADA by OPCAB, and 168 by DES. After matching for age, sex, and extent of CAD, two groups (116 patients each) were used to compare the two revascularization modalities. The groups were similar; however, an ejection fraction of <30%, old myocardial infarction, and use of an intraaortic balloon pump were more prevalent in the OPCAB group.

Results: The average number of coronary vessels treated per patient in the two groups was similar (OPCAB, 1.97; DES, 1.6; p = 0.581). The 30-day mortality rate was 0.9% in the OPCAB group and 0% in the DES group (p = 0.329). The mean duration of follow-up was 12 months. There was one late death in each group. Angina returned in 31% of patients in the DES group and in 11.2% of the patients in the OPCAB group (p = 0.001). There were 12 reinterventions in the DES group compared to three reinterventions in the surgical group (p = 0.020). The only independent predictor (Cox proportional hazards regression model) of the return of angina (risk ratio [RR], 3.36; 95% confidence interval [CI], 1.57 to 7.14) and reintervention (RR, 3.9; 95% CI, 1.34 to 11.24) was assignment to the DES group.

Conclusions: The mid-term clinical outcome of OPCAB in patients with CAD, including multivessel disease, was better than that for PCIs with only one DES used in patients with similar extents of CAD.

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Key words: aortocoronary bypass; percutaneous administration; stents

Abbreviations: CABG = coronary artery bypass grafting; CAD = coronary artery disease; CI = confidence interval; DES = drug-eluting stents; EF = ejection fraction; ITA = internal thoracic artery; LADA = left anterior descending artery; MI = myocardial infarction; OPCAB = off-pump coronary artery bypass grafting; PCI = percutaneous intervention; PTCA = percutaneous transluminal coronary angioplasty; RR = risk ratio

Surgical revascularization of the left anterior descending artery (LADA) with the left internal thoracic artery (ITA) is still the only proven method of improving event-free survival of patients with multivessel coronary artery disease (CAD) having LADA stenosis.1,2 Percutaneous coronary intervention (PCI) has failed to match the outcome obtained with bypass grafting primarily due to the higher...
incidence of repeat interventions because of restenosis in patients with either isolated LADA disease (the Stenting vs Internal Mammary Artery trial)\(^3\) or multivessel disease.\(^4\)\(^5\) A considerable reduction of restenosis and reintervention rates has been reported\(^6\)\(^7\) with the introduction of drug-eluting stents (DESs). In a recent report\(^8\) of 459 patients with single LADA stenosis, the use of a DES significantly decreased restenosis and revascularization rates compared to the use of bare-metal stents.

A high percentage of patients with single-vessel or multivessel disease involving the proximal LADA segment who are referred for bypass surgery in our institution are operated on using the off-pump coronary artery bypass grafting (OPCAB) technique. We therefore decided to compare their outcomes with those of matched patients who had undergone PCIIs using a DES.

**Materials and Methods**

Between June 2002 and December 2003, 354 patients underwent OPCAB of the left ITA to the LADA, and 168 patients underwent PCIIs with DESs with LADA revascularization by means of a sirolimus DES (Cypher; Johnson & Johnson; New York, NY).

The baseline characteristics of the OPCAB and DES patients were not similar, as OPCAB patients were older, had increased prevalence of left main artery involvement (23% vs 1.7%, respectively; \(p = 0.000\)) and triple-vessel disease (58% vs 33%, respectively; \(p = 0.000\)), and decreased prevalence of single-vessel disease (13% vs 39%, respectively; \(p = 0.000\)). In order to control for these differences between OPCAB and DES patients, we decided to compare results between the two treatment modalities after matching for age, sex, and the extent of CAD (Table 1). Each of the two matched groups thus created contained 116 patients. The baseline characteristics of patients in both groups are depicted in Table 2.

During the study period, the selection criteria for surgery vs PCI were mainly technical. In principle, there was a preference to refer patients for surgery for the following reasons: (1) comorbid diseases such as diabetes or renal failure; (2) thrombosis of a coronary artery; (3) complex type C lesions (eg, calcified coronary arteries, lesion length of > 20 mm, twisted arteries, or suspicion of a thrombus in an artery), or bifurcation with major diagonal; (4) nonavailability of DES, including cases in which the patient was unable to fund a DES; (5) complete occlusion; and (6) patient preference.

During the study period, about one half of the patients who were treated surgically in our institution were operated on without extracorporeal circulation (ie, by OPCAB). The decision to perform the surgery without extracorporeal circulation is usually made intraoperatively. We prefer OPCAB surgery in patients who are > 70 years of age, patients with atheromatotic-calciified aortas, patients with damage to other systems (eg, kidneys, lungs, liver, or peripheral vascular disease), whereas surgery using a pump is preferred in patients with small coronary arteries or in those who have diffuse coronary disease that requires four or more anastomoses.

In the PCI group, stent implantation was performed after balloon angioplasty dilatation. All patients received aspirin (325 mg daily) before and after the procedure, and clopidogrel (Plavix; Sanofi-Aventis; Paris, France) [a loading dose of 300 mg the day before the procedure, and 75 mg daily for 3 months thereafter]. During the procedure, all patients were treated with IV heparin. IV platelet glycoprotein IIIb/IIIa inhibitor abciximab (Rheo-Pro; Eli Lilly; Indianapolis, IN) was used in only 16 patients in the PCI group. In most patients, only one DES was used for the LADA. However, more than one stent was used if required (eg, long lesion, dissection, or bifurcation). DESs, bare-stents, or percutaneous transluminal coronary angioplasty (PTCA) were used for non-LADA lesions. Acute myocardial infarction (MI) [within the previous 48 h], poor ejection fraction (EF) [< 25%], left main artery disease, calcification or thrombus within the LADA, long lesions (> 30 mm), and bifurcation lesions were major criteria for the exclusion of patients from the group treated with stents to the LADA. On the other hand, patients with diabetes or ostial LADA lesions were not excluded.

In the OPCAB group, all internal thoracic arteries were dissected as skeletonized vessels. In patients who needed only revascularization of the LADA system, we used the left ITA. In order to achieve the revascularization of the LADA and circumflex systems, our preferred approach was to create an anastomosis of the right ITA to the LADA, and the left ITA to the circumflex

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**Table 1—Extent of CAD and Number of Vessels Treated*\(^a\)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>OPCAB Group (n = 116)</th>
<th>DES Group (n = 116)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main artery</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>35</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>39</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>42</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Vessels treated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>43</td>
<td>66</td>
<td>0.660</td>
</tr>
<tr>
<td>Two</td>
<td>37</td>
<td>34</td>
<td>0.800</td>
</tr>
<tr>
<td>Three or more</td>
<td>36</td>
<td>16</td>
<td>0.002</td>
</tr>
<tr>
<td>Two internal thoracic</td>
<td>44 (38%)</td>
<td>33 (22.4%)</td>
<td>0.125</td>
</tr>
<tr>
<td>arteries or two DESs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2—OPCAB Characteristics*\(^a\)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>OPCAB Group (n = 116)</th>
<th>DES Group (n = 116)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70 yr</td>
<td>24 (20.7)</td>
<td>24 (20.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Female gender</td>
<td>17 (14.7)</td>
<td>17 (14.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34 (29.3)</td>
<td>32 (27.6)</td>
<td>0.771</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65 (56)</td>
<td>57 (49)</td>
<td>0.293</td>
</tr>
<tr>
<td>COPD</td>
<td>8 (6.9)</td>
<td>8 (6.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>6 (5.2)</td>
<td>4 (3.2)</td>
<td>0.518</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>21 (18)</td>
<td>14 (12)</td>
<td>0.191</td>
</tr>
<tr>
<td>Old MI</td>
<td>55 (47.5)</td>
<td>40 (34.5)</td>
<td>0.045</td>
</tr>
<tr>
<td>Acute MI (7 d)</td>
<td>12 (10.3)</td>
<td>6 (5.2)</td>
<td>0.141</td>
</tr>
<tr>
<td>EF &lt; 30%</td>
<td>6 (5.2)</td>
<td>1 (0.9)</td>
<td>0.055</td>
</tr>
<tr>
<td>Prior IABP</td>
<td>5 (4.3)</td>
<td>0 (0)</td>
<td>0.024</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>36 (31)</td>
<td>47 (40.5)</td>
<td>0.132</td>
</tr>
<tr>
<td>Emergency</td>
<td>11 (9.5)</td>
<td>5 (4.3)</td>
<td>0.120</td>
</tr>
<tr>
<td>Repeat operation</td>
<td>3 (2.6)</td>
<td>3 (2.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11 (9.5)</td>
<td>6 (5.2)</td>
<td>0.208</td>
</tr>
<tr>
<td>Preprocedural in-stent restenosis (in LADA)</td>
<td>9 (7.8)</td>
<td>18 (15.5)</td>
<td>0.065</td>
</tr>
</tbody>
</table>

*Values given as No. (%), unless otherwise indicated. IABP = intra-aortic balloon pump.

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artery. Our second choice was the create an anastomosis of the left ITA to the LADA, and either the free right ITA or the radial artery as a composite T-graft on the left ITA to the circumflex artery system. Right coronary system (ie, the posterior descending artery) revascularization was performed with saphenous vein grafts in 15 of the 44 patients treated through the bilateral ITA. Right coronary system revascularization in patients who were treated through the left ITA and radial artery (through a composite T-graft) was performed with the distal end of the radial artery (nine patients).

To decrease the risk of spasm of the arterial grafts, we treated all OPCAB patients with high dose of IV isosorbide mononitrate (Isoket; Schwartz Pharmaceuticals; Germany) of 4 to 20 mg/h during the first postoperative 24 to 48 h. Systolic BP was maintained at > 100 mm Hg. From the second postoperative day, all radial artery patients were treated postoperatively with the calcium channel blocker diltiazem (Cardizem; Teva, Israel), 90 to 180 mg/d orally. Similar to PCI patients, all OPCAB patients were treated postoperatively with clopidogrel (Plavix; Sanofi), 75 mg/d for 3 months.

Statistical Analysis

The follow-up of patients in both groups was performed with the aid of a telephone questionnaire. The patients were asked to describe their symptoms after intervention, including details regarding chest pain (ie, effort vs rest, quality of pain [particularly compared to preintervention], the response to therapy with sublingual nitroglycerin, the time interval between intervention and the recurrence of angina), and the results of any effort test or any reintervention performed after the procedure (ie, shortness of breath; functional class compared to preintervention, any signs of infection, and neurologic symptoms). Patients were also asked about any emergency department or hospital admissions. The data are expressed as the mean ± SD or proportions, as appropriate. The two groups were matched for age, sex, and extent of CAD. The χ² test and Fisher exact test were used to compare discrete variables. All p values < 0.050 were considered to be significant. The Cox proportional hazards regression model was used to evaluate the risk factors for the early return of angina and reintervention. This model could not be validated, as the DES stent was introduced to our center only in May 2002 and the vast majority of DES patients treated in our country during the study period were included in this study. However, it seems likely that the underlying assumptions for the Cox proportional hazards regression model hold, as the patients who were evaluated were independent of each other and were not selected for a specific pathognomonic condition. In addition, it seems that the hazards ratio did not vary much over time, as all patients were treated within a short time-frame by the same medical team, medical methods, and at the same hospital. The risk ratio (RR) and 95% confidence interval (CI) were given. All analyses were performed using a statistical software package (SPSS, version 9.0; SPSS Inc; Chicago, IL).

Results

After matching for age, sex, and extent of CAD (Table 1), the two groups were similar. However, old MI, poor EF (ie, < 30%), and preprocedural use of an intraaortic balloon pump were more prevalent in the OPCAB group (Table 2).

The average number of coronary vessels treated was similar (OPCAB group, 1.97 vessels; DES group, 1.6 vessels; p = 0.580). However, more patients in the DES group received only one stent, and more in the OPCAB group underwent revascularization of three vessels (Table 1). The 30-day mortality rate was 0.9% in the OPCAB group (one sudden death at home 20 days postoperatively) and 0% in the DES group (p = 0.322). The duration of follow-up ranged between 6 and 28 months (mean duration, 12 months). There was one late death in each group (one patient from the OPCAB group died of urosepsis 1 year after surgery, and one patient in the DES group sustained a fatal stroke 7 months after undergoing the PCI). Angina returned in 36 patients (31%) in the DES group compared to 13 patients (11.2%) in the OPCAB group (p = 0.001). During the follow-up period, 18 patients in the DES and 9 patients in the OPCAB group were referred for coronary angiography. There were 12 reinterventions (10.3%) in the DES group (10 coronary angioplasties [including 3 to the LADA] and 2 surgical interventions). Four of the reinterventions were due to restenosis or occlusion of a DES-stented LADA, while eight reinterventions were conducted in diseased vessels that had not been treated in the first instance. There were three reinterventions (PTCAs) [2.6%] performed in the surgical group (p = 0.020 [DES vs OPCAB]), and all were to non-LADA lesions.

A total of 86% (Kaplan-Meier test) of OPCAB patients experienced 18 months of angina-free survival compared to 40.5% of the PCI patients (p = 0.000 [log rank test]). After 18 months, OPCAB patients also had a significantly better reintervention-free survival rate (93.5% vs 84.2%, respectively; p = 0.007 [log rank test]; Fig 1). To determine whether the difference between groups in terms of the reoccurrence of angina and reinterventions is affected by the difference in baseline characteristics or the number of vessels treated, we performed a multivariable analysis (Cox proportional hazards regression model) using the patient group (ie, PCI or OPCAB) as an independent variable. We first included the variables to be controlled (ie, the number of vessels treated, old MI, poor EF, and preprocedure LADA in-stent restenosis) and then the treatment group.

The Cox proportional hazards regression model showed that after controlling for the above risk factors, the only independent predictor for the reoccurrence of angina was assignment to the DES group (RR, 3.36; 95% CI, 1.57 to 7.14). This group allocation was also the only independent predictor for reintervention (RR, 3.9; 95% CI, 1.34 to 11.24). Postprocedural major morbidity in the OPCAB group included stroke in one patient, deep sternal wound infection in one patient, perioperative MI in
one patient, late MI in one patient, and reoperations for bleeding in two patients. Minor adverse events included two superficial sternal wound infections and a worsening of renal function test results in four patients. In the DES group, in addition to the reoccurrence of angina and reintervention, major morbidity included one periprocedural and four late MIs, exacerbation of heart failure (pulmonary edema) in three patients, one life-threatening arrhythmia, and one pacemaker implantation. One patient required dialysis, and one patient, who underwent coronary artery bypass grafting (CABG) 3 months after DES implantation, sustained a deep sternal wound infection.

**DISCUSSION**

A trend for improved long-term survival with CABG in patients with multivessel disease and proximal LADA stenosis has been demonstrated in several retrospective studies comparing PCI and CABG. However, in later reports with more liberal use of stents to the proximal LADA, the only advantage of stenting the left ITA to the LADA was a lower rate of reintervention. The reported rate of restenosis and reintervention in patients undergoing PCI to the LADA with bare-stents ranged between 19% and 44%.

A tremendous reduction in the restenosis rate (from 41 to 2%) was recently reported in a group of 459 patients with single-vessel disease and LADA stenosis who were prospectively randomized for treatment with DES (Cypher) or bare-metal stents. At a mean follow-up period of 1 year, treatment with DES was also associated with considerably lower rates of reintervention (6% vs 23%, respectively; p < 0.001) and major adverse cardiovascular events (10% vs 25%, respectively; p < 0.001). Based on their results with the treatment of LADA in patients with single-vessel disease, these authors concluded that the reduced restenosis and reintervention rates may have narrowed the “reintervention gap” sufficiently to eliminate the historical major advantage of CAGB for LADA disease.

With the initial reported success of DES for single-vessel disease, more patients with multivessel disease and LADA stenosis are currently referred for PCI than for CABG. In this report, which represents the real-life situation in our catheterization laboratory, 82 of the patients studied (70%) with LADA stenosis were patients with multivessel disease, and in 24 of them more than one vessel was treated with DES. The survival rate was similar after a 12-month follow-up period, which is probably a long enough period for the development of in-stent restenosis.

However, a significant portion of the DES group (31%) experienced an early return of angina, and 10.3% required reintervention. These occurrences of return of angina and reintervention were considerably higher than those in the OPCAB group, and multivariable Cox proportional hazards regression model analysis showed that the only independent predictor of the reoccurrence of angina and reintervention was assignment to the DES group. Only 4 of the 12 reinterventions (1 surgical and 1 PCI) were performed on a DES-treated LADA, supporting...
previous observations of a decreased restenosis rate with the use of a DES.\textsuperscript{6,7,14}

Despite a similar extent of CAD and a similar mean number of vessels treated, more patients in the DES group underwent the revascularization of only one vessel, and more patients in the OPCAB group underwent the revascularization of three vessels. This, together with the fact that only four of the reinterventions were performed in the DES-treated vessel, may suggest that the reoccurrence of angina and reintervention in the DES group may be related to incomplete revascularization or revascularization of non-LADA vessels with PTCA or bare-metal stents. However, the number of vessels treated, as well as the relation between this number and the number of vessels involved (ie, the revascularization index) were entered as explanatory variables into the Cox proportional hazards model and did not emerge as independent predictors of the reoccurrence of angina or reintervention.

As a result of the matching protocol, the study population of the surgical group was not typical of the kind of patients who currently are referred for CABG in our institution. It includes a relatively high number of patients with single-vessel disease and relatively few patients with left main artery disease, triple-vessel disease, or patients who are > 70 years of age. Accordingly, a high proportion of the OPCAB patients were treated with a single graft (ITA to LADA). This explains the relatively low average number of grafts per patient (1.97) in the OPCAB group.

**Study Limitations**

This was a matched-groups, retrospective cohort comparison study that reflects the current treatment situation with the two revascularization techniques. The groups were matched for age, sex, and extent of CAD. They were also similar with regard to the incidence of diabetes mellitus, which is a major determinant of restenosis.\textsuperscript{14} However, other important covariates (mainly technical), such as vessel diameter, lesion length, occluded or thrombosed vessels, and bifurcation lesions, were not included in the analysis. These technical parameters, which are less important in the surgical group, may affect restenosis, the reoccurrence of angina, and reintervention in the PCI group. Larger prospective multicenter studies are required to determine their importance in patients who are selected for PCI or surgery in this evolving era of DES.

Another limitation of this study is that the mean follow-up period was only 1 year. There is certainly increasing evidence that the DES may develop delayed thrombosis related to delayed endothelialization, hypersensitivity to the polymer used in the stent, and the discontinuation of aspirin. Therefore, longer follow-up periods may be required in order to determine the true incidence of long-term DES complications.\textsuperscript{18,19}

**Conclusions**

In conclusion, the mid-term clinical outcome of OPCAB, which includes that of the left ITA to the LADA, is still better than that of PCI using only one DES to the LADA in patients with CAD, including those with multivessel disease. However, the reintervention gap between surgery and PCI may be further reduced by more extensive use of DESs in other vessels.

**References**