Comparison of Bare-Metal Stenting With Minimally Invasive Bypass Surgery for Stenosis of the Left Anterior Descending Coronary Artery
A 5-Year Follow-Up

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Background—Randomized trials comparing stenting with minimally invasive direct coronary artery bypass surgery in patients with isolated proximal left anterior descending lesions have shown a significantly higher reintervention rate for stenting and similar results for mortality and reinfarction at short-term follow-up. Long-term follow-up data are sparse.

Methods and Results—Patients with isolated proximal left anterior descending stenosis were randomized to either surgery (n=110) or bare-metal stenting (n=110). At 5 years, follow-up data were obtained with respect to the primary end point of death, reinfarction, or repeated target vessel revascularization. Clinical symptoms were assessed by the Canadian Cardiovascular Society (CCS) classification. Follow-up information was completed for 216 patients (98.2%), and mean follow-up was 5.6±1.2 years. With respect to mortality (surgery, 12%; stenting, 10%; P=0.54) and reinfarctions (surgery, 7%; stenting, 5%; P=0.46), there were no differences between treatment strategies. The need for repeated target vessel revascularization was significantly higher after stenting (32%) compared with surgery (10%; P<0.001). Clinical symptoms improved significantly in both treatment groups compared with baseline; however, there was a favorable trend for surgery (stenting: CCS, 2.6±0.9 to 0.5±0.8, P=0.001; surgery: CCS, 2.6±0.9 to 0.3±0.6, P<0.001; P=0.05, stenting versus surgery).

Conclusions—At the 5-year follow-up, minimally invasive bypass surgery and bare-metal stenting showed similar results for the end points of mortality and reinfarctions. However, the reintervention rate is higher after stenting, and the relief in clinical symptoms is slightly better after surgery. (Circulation. 2005;112:3445-3450.)

Key Words: bypass ■ coronary disease ■ revascularization ■ stents ■ surgery

The prognosis of patients with untreated high-grade proximal stenosis of the left anterior descending (LAD) coronary artery is poor.1,2 Minimally invasive direct coronary artery bypass surgery and percutaneous coronary intervention with bare-metal stents are established treatment options that effectively relieve symptoms.3,4 In randomized trials comparing the 2 strategies, a significantly higher reintervention rate after stenting and similar results for mortality and reinfarction at a 6-month follow-up have been demonstrated.4-6 Because the high initial success rate is eroded over time by clinical events, the long-term follow-up is more appropriate to elucidate the merits of surgery or the interventional procedure.

In the present study, we report the 5-year follow-up of the largest randomized, prospective trial comparing minimally invasive bypass surgery with stenting for treatment of patients with isolated lesions of the proximal LAD.

Methods

The design and methods of this randomized trial have been described previously.4 In brief, patients with isolated high-grade lesions (>75% stenosis, no total occlusion) of the proximal LAD were included. Exclusion criteria were acute coronary syndromes, additional significant coronary lesions, valvular heart disease, and previous interventional or surgical treatment for coronary artery disease. A consensus on patient eligibility had to be obtained from both the cardiac surgeon and the cardiologist. The study was approved by the institutional ethics committee. After written informed consent was obtained, balanced randomization was performed, and patients were assigned to stenting or surgery.

Stenting Procedure

Stenting with bare-metal stents was performed according to standard practice.4 Patients received aspirin 100 mg/d indefinitely and ticlopidine or clopidogrel after a loading dose the day before the procedure for 4 weeks.
Minimally Invasive Direct Coronary Artery Bypass Surgery

Minimally invasive bypass surgery was performed through a left anterolateral minithoracotomy on the beating heart without cardiopulmonary bypass. The internal thoracic artery was used as bypass graft. Aspirin (100 mg/d) treatment was recommended indefinitely.

Follow-Up

Data were collected by a structured patient interview. Reported clinical events were confirmed by contact with the general practitioner and/or the treating hospital. Myocardial infarction was diagnosed if the creatine kinase-MB value was 3 times above the normal value or if the ratio of creatine kinase-MB to total creatine kinase exceeded 0.1. Additionally, standard ECG criteria were applied. Events were adjudicated by an event monitoring committee consisting of an experienced cardiologist and cardiovascular surgeon.

At the 6-month follow-up, a complete clinical workup, including symptom-limited exercise stress test and coronary angiography, was mandatory. For asymptomatic patients, no further noninvasive or invasive studies were performed at long-term follow-up. Repeated interventions were performed in case of recurrence of angina and/or a positive stress test. In these patients with repeated interventions, control angiography was recommended 6 months later. Quantitative angiography was not performed in these patients, except for the mandatory initial 6-month angiography. The choice of all recurrent revascularization procedures was left to the discretion of the investigator.

End Points

The primary composite end point was defined as freedom from major adverse cardiovascular events, defined as death, myocardial infarction, and the need for repeated target vessel revascularization. Secondary end points were each individual component of the primary end point. The clinical status was assessed by the Canadian Cardiovascular Society (CCS) classification, and the need for antianginal drugs at follow-up was documented.

Statistical Analysis

The sample size chosen to achieve 95% statistical power with a type I error of 5% by use of 2-sided Fisher’s exact test was based on the assumption that 30% of the patients treated by stenting and 9% treated by surgery would reach the combined primary end point. Accounting for losses to follow-up, we included 10 more patients in each group, resulting in a total of 220 randomized patients. All analyses were performed according to the intention-to-treat principle. After randomization, all events were counted. Patients lost to follow-up were excluded from further analysis (Figure 1). Continuous parameters were estimated as mean ± SD. The CCS classification as the ordinal scale is presented as median and interquartile range. Categorical variables are expressed as number and percentage of patients. Differences between the treatment groups were assessed by Fisher’s exact test or the 2 test for categorical variables with ordinal scales. For continuous data with normal distribution, Student’s t test was used. Event rates were compared by unconditional relative risks with 95% confidence intervals. Furthermore, the event rates were estimated by the Kaplan-Meier method and compared by means of the log-rank test. A 2-tailed probability value of P<0.05 was considered statistically significant.

Results

Between June 1997 and June 2001, 220 consecutive patients with isolated proximal LAD stenosis were randomized to either surgery (n=110) or stenting (n=110). All patients received the assigned treatment. Long-term follow-up was complete for 216 patients (98.2%) (Figure 1). Mean follow-up time was 5.6±1.2 years (range, 3.9 to 7.3 years).

Baseline characteristics were not different between the treatment groups (Table 1).

Primary Composite End Point

The primary composite end point occurred more frequently in patients assigned to stenting than to surgery (47% versus 29%, P=0.02; relative risk, 1.64; 95% confidence interval, 1.13 to 2.42). The cumulative event-free survival rate at 5 years was 53% after stenting and 71% after surgery (Figure 2). The incidence of major adverse cardiovascular events and each individual end point at long-term follow-up is shown in Table 2.

![Figure 1](Fig1.jpg)

Figure 1. Trial profile showing the numbers of patients included in the analysis. MIDCAB indicates minimally invasive direct coronary artery bypass surgery.

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of the Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Cardiovascular risk factors, n (%)</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Family history of coronary artery disease</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
</tr>
<tr>
<td>Angina class, n (%)</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
</tr>
<tr>
<td>Type B2 or C lesions, n (%)</td>
</tr>
</tbody>
</table>

MIDCAB indicates minimally invasive direct coronary artery bypass surgery.
Secondary End Points

Revascularization
The difference in the primary composite end point resulted from a higher rate of repeated target vessel revascularization after stenting (32% versus 10%; \(P<0.001\); relative risk, 3.18; 95% confidence interval, 1.67 to 6.39). Whereas at the 6-month follow-up 29% had already undergone repeated revascularization for recurrent angina and/or a positive stress test, only 3% required additional target vessel revascularization at long-term follow-up. However, some patients had multiple target vessel revascularizations. The mean rate was \(1.4 \pm 0.7\); 25 patients had 1, 8 had 2, 1 had 3, and 1 had 4 target vessel revascularizations.

In contrast to stenting, only 8% in the surgical group required target vessel revascularization at the 6-month follow-up, and this rate also was increased only marginally by 2% at the longer follow-up. The mean target vessel reintervention rate was \(1.2 \pm 0.6\); only 1 patient had >1 target vessel revascularization.

Although patients had single-vessel disease at randomization, the progression of coronary artery disease led to additional non–target vessel revascularization procedures in 16% (8 right coronary and 9 left circumflex artery lesions) after stenting and 8% (2 right coronary and 7 left circumflex artery lesions) after surgery (\(P=0.09\)).

Death and Myocardial Infarction
All-cause mortality did not differ between the 2 treatment groups (Figure 3). In addition, cardiac death rates were similar (Table 2). The cardiac deaths in the surgery group included 2 perioperative deaths from unknown cause, which were counted as cardiac death. In addition, 2 patients died of heart failure and 1 of acute myocardial infarction. The 4 cardiac deaths after stenting followed myocardial infarction in 2 and were a result of congestive heart failure in another 2 patients. The rate of myocardial infarction was not statistically different between surgery and stenting (\(P=0.46\)). Except for 2 patients who developed stent thrombosis during the 6-month follow-up, no infarctions were caused by subacute stent thrombosis at longer follow-up. Taken together, the event-free survival from death and myocardial infarction was 85% for stenting and 81% for surgery (Figure 4).

Anginal Symptoms and Antianginal Medication
After surgery, the median angina class improved from 2.0 (interquartile range, 2.0 to 3.0) to 0.0 (interquartile range, 0.0 to 0.0; \(P<0.001\), and 95% of patients were free from angina. In the intervention group, the CCS classification improved from 2.0 (interquartile range, 2.0 to 3.0) to 0.0 (interquartile range, 0.0 to 1.0; \(P<0.001\) versus baseline, \(P=0.05\) versus surgery), and 86% were free of angina (\(P=0.06\) compared with surgery).

Whereas at the 6-month follow-up fewer surgical patients required antianginal drug therapy (6% versus 19%; \(P=0.006\)), the rate of antianginal medication was not different at the long-term follow-up. Use of additional cardiac medication was similar between the 2 treatment groups (Table 3).

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**TABLE 2. Major Adverse Cardiac Events at Long-Term Follow-Up**

<table>
<thead>
<tr>
<th>Event</th>
<th>Stenting (n=108)</th>
<th>MIDCAB (n=108)</th>
<th>(P)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>11 (10)</td>
<td>13 (12)</td>
<td>0.54</td>
<td>0.85 (0.37–1.93)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>4 (4)</td>
<td>5 (5)</td>
<td>0.60</td>
<td>0.80 (0.18–3.35)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (5)</td>
<td>7 (7)</td>
<td>0.46</td>
<td>0.71 (0.20–2.43)</td>
</tr>
<tr>
<td>Myocardial infarction+death</td>
<td>16 (15)</td>
<td>20 (19)</td>
<td>0.34</td>
<td>0.80 (0.41–1.52)</td>
</tr>
<tr>
<td>TVR</td>
<td>35 (32)</td>
<td>11 (10)</td>
<td>&lt;0.001</td>
<td>3.18 (1.67–6.39)</td>
</tr>
<tr>
<td>Any MACE</td>
<td>51 (47)</td>
<td>31 (29)</td>
<td>0.02</td>
<td>1.64 (1.13–2.42)</td>
</tr>
</tbody>
</table>

MIDCAB indicates minimally invasive direct coronary artery bypass surgery; CI, confidence interval; TVR, target vessel revascularization; and MACE, major adverse cardiac event. Values are number of patients (%) per clinical event category. The number of patients with at least 1 event was counted. No double counting for multiple events within a category was done. Between categories, patients were double counted in case of multiple events. The probability value was calculated by the log-rank test.
be helpful for identifying patients who may preferentially
undergo invasive bypass surgery. In the 6-month angiographic follow-
up, 50% restenosis rate was observed in complex type C lesions as opposed to only 18% in type A lesions; lesion type was independent of subsequent restenosis in the surgical group. Predictive restenosis risk stratification models might be helpful for identifying patients who may preferentially benefit from surgery compared with stenting. This is of particular importance because only a minority of patients with apparent in-stent restenosis at 6-month follow-up will require subsequent target vessel revascularization.

The indication for repeated revascularization procedures was clinically and not angiographically driven. However, a higher rate of non–target vessel revascularizations was observed in the stenting group as a result of a closer clinical and angiographic follow-up. This might have uncovered otherwise undetected symptoms and silent ischemia, leading to a higher reintervention rate compared with surgery. The mandatory follow-up, including ergometry and angiographic control at 6 months, and different lesion types might have led to a slightly higher target vessel reintervention rate in this trial compared with other randomized trials.

At the time of this randomized trial, only bare-metal stents were available. Drug-eluting stents have been shown to reduce significantly the rate of restenosis and subsequently the need for reintervention procedures. Currently, data on the use of drug-eluting stents in proximal LAD lesions are limited, although these stents hold promise, with a 0% restenosis rate for a sirolimus-eluting stent. In contrast, higher restenosis rates of 7.3% were reported for the LAD when paclitaxel-eluting stents were used. An important finding of these trials is that the restenosis rate seems to be lower in the proximal portion of the LAD compared with more distal segments. The overall target vessel revascularization rate was as low as 7.9% and 9.0%, with a significant reduction of major adverse cardiac events at 1 year for the subgroup of patients with proximal LAD lesions (13.3% and 10.4%). Higher restenosis rates for drug-eluting stents were reported in diabetic patients, small vessels, and more complex lesions, but this might also impair the results of surgery. Another important issue is that long-term data on drug-eluting stents are very limited. Furthermore, the efficacy of drug-eluting stents, particularly in proximal LAD lesions, has not been tested in stent versus surgery trials. The design of such a trial should be quite similar to that of the present trial with the exception that drug-eluting stents are used for the interventional group. As a consequence of the anticipated similar major adverse cardiac event rates for surgery compared with drug-eluting stenting, such a trial should be designed as a noninferiority trial because a multicenter trial would have to include several thousand patients for superiority.

Multiple randomized trials have demonstrated equivalent mortality and myocardial infarction rates after surgery and percutaneous coronary intervention with or without stenting for either multivessel or single-vessel coronary artery disease. Our results with a cardiac death rate at the 5-year follow-up of 4% and 5% are in line with other trials in patients with isolated proximal LAD coronary artery lesions. The myocardial infarction rate after surgery at long-term follow-up was also similar to that in other trials.

Several studies have shown that internal mammary arterial grafts are better than vein grafts anastomosed to the LAD in terms of survival, freedom from recurrent infarction, angina, and repeated revascularization. The duration of benefit extends for >10 years, and the magnitude of benefit increases over time, stressing the importance of long-term follow-up of

### TABLE 3. Cardiovascular Medication at Long-Term Follow-Up

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Stenting (n=97)</th>
<th>MIDCAB (n=95)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blocker</td>
<td>78 (80)</td>
<td>79 (83)</td>
<td>0.77</td>
</tr>
<tr>
<td>ACE inhibitors/AT-1 receptors</td>
<td>72 (74)</td>
<td>72 (76)</td>
<td>0.94</td>
</tr>
<tr>
<td>Statins</td>
<td>74 (76)</td>
<td>70 (74)</td>
<td>0.80</td>
</tr>
<tr>
<td>Aspirin</td>
<td>81 (84)</td>
<td>70 (74)</td>
<td>0.15</td>
</tr>
<tr>
<td>Thienopyridines</td>
<td>11 (11)</td>
<td>6 (6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Nitrates</td>
<td>19 (20)</td>
<td>15 (16)</td>
<td>0.62</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>16 (17)</td>
<td>10 (11)</td>
<td>0.32</td>
</tr>
<tr>
<td>Antidiabetic medication</td>
<td>30 (31)</td>
<td>23 (24)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Values are n (%). MIDCAB indicates minimally invasive direct coronary artery bypass surgery; ACE, angiotensin-converting enzyme; and AT-1, angiotensin-1 receptor.
revascularization trials.27,28 The minimally invasive surgical approach has been developed to minimize surgical trauma by limiting access to the heart and avoiding cardiopulmonary bypass. Despite the more challenging access, similar patency rates compared with conventional bypass grafting have been reported.4 However, like in conventional surgery, this approach is associated with a small but consistent rate of perioperative complications, with early reoperation for acute graft failure, erroneously selected anastomotic sites, conversion to full sternotomy, pleural herniation, and wound healing problems.5-29 These perioperative complications do not affect long-term mortality and rate of infarctions.

In line with previous studies comparing balloon angioplasty and bypass surgery, the difference in anginal status at 6 months was attenuated during later follow-up because of additional revascularization procedures.21,24 In the present trial, there was still a strong trend in favor of surgery, which at longer follow-up might be further attenuated. The complete angina relief of 95% after surgery and 86% after stenting was higher than that reported for trials comparing angioplasty without stents (65% to 74%) and conventional bypass surgery using internal mammary arterial grafts (71% to 73%).24,25 In addition, these rates were higher than those reported in a randomized trial comparing minimally invasive bypass surgery (85%) with stenting (67%) at a 4-year follow-up.26 Cardiac medication, including antiplatelets, did not differ between treatment groups, and the rates of angiotensin-converting enzyme inhibitors, β-blockers, statins, and antiplatelets for chronic treatment of coronary artery disease reflect an excellent conservative treatment in both groups, which was better than in other trials.26,30

In conclusion, both stenting and minimally invasive bypass surgery are safe and effective treatment options for proximal high-grade LAD lesions at long-term follow-up. Stenting may be considered the first-line treatment option for low-to-intermediate-restenosis-risk lesions, whereas surgery provides excellent outcome regardless of lesion morphology, including chronic total occlusions. Therefore, treatment of isolated proximal LAD lesion requires an interdisciplinary approach with interdisciplinary patient information about alternative treatment options, individual success, and periprocedural event rates based on the morphology of the underlying lesion.

References


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