Short- and Long-Term Clinical Outcome After Drug-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease

Insights From the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH)

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Background—The impact of drug-eluting stent (DES) implantation on the incidence of major adverse cardiovascular events in patients undergoing percutaneous intervention for left main (LM) coronary disease is largely unknown.

Methods and Results—From April 2001 to December 2003, 181 patients underwent percutaneous coronary intervention for LM stenosis at our institution. The first cohort consisted of 86 patients (19 protected LM) treated with bare metal stents (pre-DES group); the second cohort comprised 95 patients (15 protected LM) treated exclusively with DES. The 2 cohorts were well balanced for all baseline characteristics. At a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of major adverse cardiovascular events was lower in the DES cohort than in patients in the pre-DES group (24% versus 45%, respectively; hazard ratio [HR], 0.52 [95% CI, 0.31 to 0.88]; P=0.01). Total mortality did not differ between cohorts; however, there were significantly lower rates of both myocardial infarction (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; P=0.006) and target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; P=0.004) in the DES group. On multivariate analysis, use of DES, Parsonnet classification, troponin elevation at entry, distal LM location, and reference vessel diameter were independent predictors of major adverse cardiovascular events.

Conclusions—When percutaneous coronary intervention is undertaken at LM lesions, routine DES implantation, which reduces the cumulative incidence of myocardial infarction and the need for target vessel revascularization compared with bare metal stents, should currently be the preferred strategy. (Circulation. 2005;111:1383-1389.)

Key Words: stents ■ angioplasty ■ arteries

Despite the recognition that coronary revascularization, in selected patients with multivessel disease, can presently be accomplished by either a surgical or a percutaneous approach with no significant difference in long-term mortality, coronary artery bypass grafting (CABG) is still considered the treatment of choice in patients with left main (LM) disease. Several trials have reported on the safety and feasibility of stent implantation to treat LM stenosis. However, particularly in this subset of patients, restenosis remains a major, and potentially fatal, complication, precluding more widespread use of percutaneous coronary intervention (PCI). In the first observational report of patients treated with a sirolimus-eluting stent (SES) for LM disease, a low rate of binary restenosis and a favorable clinical outcome were reported. However, the benefit of drug-eluting stents (DES) on the short- and long-term incidence of major adverse cardiovascular events in this setting, compared with bare metal stents (BMS), remains largely unknown.

The purpose of the present study was to investigate, in this subset of patients undergoing revascularization in a tertiary referral center, the differential impact of DES as opposed to conventional BMS on the occurrence of short- and long-term major cardiovascular events.
Methods

Study Design and Patient Population

Since April 16, 2002, SES (Cypher, Johnson & Johnson, Cordis unit) have been used as a default strategy for every PCI at our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, paclitaxel-eluting stents (PES) (Taxus, Boston Scientific Corporation) became commercially available, replacing SES as the strategy of choice in every PCI because of cost-effectiveness considerations, as part of the Taxus Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. As a policy, all elective patients presenting with significant (>50% by visual estimation) LM disease, referred to our institution for coronary revascularization, are evaluated by both interventional cardiologists and cardiac surgeons, and the decision to opt for PCI or surgery is reached by consensus on the basis of a comprehensive evaluation of the following items: suitable anatomy and lesion characteristics for stenting and size and quality of vessels distal to the disease and of arterial and/or venous conduits for grafting. Finally, patient and/or referring physician preferences for a percutaneous approach, with both aware of the procedural risks and contraindications to surgery on the basis of the presence of comorbidity as evaluated by a cardiac surgeon, are also considered.

From April 16, 2002, to December 31, 2003, a total of 95 consecutive patients were treated exclusively with ≥1 DES in the LM as part of an elective or nonelective revascularization procedure and constitute the DES group of the present report. Fifty-two patients were treated in the first cohort (of whom procedural details and medium-term follow-up were previously reported for 31), received SES exclusively (available, at that time, in diameters from 2.25 to 3.00 mm), whereas in the following group of 43 patients, PES (available in diameters from 2.25 to 3.5 mm) were implanted. A control group for comparison was composed of 86 consecutive patients who received conventional BMS (available in diameters from 2.5 to 5.00 mm) for LM treatment in the period immediately before the introduction of SES. The following BMS were used: BX Sonic or BX Velocity in 35% (Cordis, Johnson & Johnson Company), R-Stent in 29% (Orbus Medical Technologies), Multi-Link Penta in 28% (Guidant Corp), Multi-Link Tetra in 8% (Guidant Corp), and other stents in 4%. Therefore, the total study population comprised all 181 consecutive patients who underwent percutaneous LM treatment from April 2001 to December 2003 with either BMS or DES in the 2 study phases, respectively. To stratify the study population into high- and low-risk groups, the Parsonnet surgical risk score was calculated for each patient. A score >15 was used to identify patients at high risk, as previously suggested.6-9 Protected LM segment was defined as the presence of at least 1 patent arterial or venous conduit to at least 1 left coronary segment. Nonelective treatment was defined as the presence of comorbidity as evaluated by a cardiac surgeon, are also considered.

Procedures and Postintervention Medications

All interventions were performed according to current standard guidelines, and the final interventional strategy, including the use of glycoprotein IIb/IIIa inhibitors, was left entirely to the discretion of the operator, except for the stent utilization. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis in Myocardial Infarction (TIMI) 3 flow grade. All patients were advised to maintain the use of aspirin lifelong. One-month clopidogrel treatment (75 mg/d) was recommended for patients treated in the pre-DES phase. For patients treated with either SES or PES, clopidogrel was prescribed for 6 months.

End Point Definitions and Clinical Follow-Up

The primary outcome was the occurrence of major adverse cardiac events, defined as (1) death, (2) nonfatal myocardial infarction (MI), or (3) target vessel revascularization. Patients with >1 event have been assigned the highest ranked event, according to the previous list. All deaths were considered to be of cardiac origin unless a noncardiac origin was established clinically or at autopsy. MI was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB fraction. Target vessel revascularization was defined as a repeated intervention (surgical or percutaneous) to treat a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent, including the ostium of the left anterior descending artery (LAD) and/or circumflex artery. Information about in-hospital outcomes was obtained from an electronic clinical database for patients maintained at our institution and by review of hospital records for those discharged to referring hospitals (patients were referred from a total of 14 local hospitals). Postdischarge survival status was obtained from the Municipal Civil Registries. Information on occurrence of MI or repeated interventions at follow-up was collected by consulting our institutional electronic database and by contacting referring physicians and institutions and all living patients.

Statistical Analysis

Continuous variables are shown as mean±SD and were compared by Student unpaired t test. Categorical variables are presented as counts and percentages and were compared with the Fisher exact test. Survival curves were generated by the Kaplan-Meier method, and survival among groups was compared with the log-rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Univariate analysis was performed with the consideration of all variables reported in Tables 1 and 2. Multivariate analyses, with consideration of all variables with a value of P<0.10, were performed to identify independent predictors of adverse events. Probability was significant at a level of <0.05. All statistical tests were 2-tailed. Statistical analysis was performed with the use of Statistica 6.1 (Statsoft Inc).

Results

Baseline and Procedural Characteristics

Baseline and procedural characteristics are shown in Table 1 and Table 2. The 2 groups were well matched for all baseline characteristics, including comorbidities. Overall, the average left ventricular ejection fraction was slightly >40%, and approximately half of the patients in both groups were admitted with acute coronary syndromes. Acute MI was the indication to the procedure in 19%; 10% of the patients presented with severe hemodynamic compromise at entry. The distal LM was involved in two thirds of cases in both groups, whereas patients treated with DES had significantly more 3-vessel disease, more bifurcation stenting, a higher number of stents, and greater total stent length per patients. The nominal stent diameter, as a result of limited size availability, was on average smaller in the DES group, which explains the more common practice of postdilatation in this group of patients. Procedural success was 99% in patients receiving DES: in 1 patient who presented with acute MI and shock, a final TIMI 1 flow grade was obtained, and the patient died 3 hours after the procedure. The procedural success was 98% in patients treated in the pre-DES phase: in 2 patients with acute MI and TIMI 0 flow grade in the left coronary artery, the LM and proximal LAD were stented, and subsequently CABG was performed because of residual critical stenosis in the left circumflex artery.
TABLE 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-DES Group (n=86)</th>
<th>DES Group (n=95)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y *</td>
<td>66±10</td>
<td>64±12</td>
<td>0.18</td>
</tr>
<tr>
<td>Men, %</td>
<td>62</td>
<td>66</td>
<td>0.53</td>
</tr>
<tr>
<td>Body mass index, kg/m²*</td>
<td>26±4</td>
<td>27±4</td>
<td>0.31</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>22</td>
<td>30</td>
<td>0.23</td>
</tr>
<tr>
<td>Non-insulin-dependent, %</td>
<td>17</td>
<td>20</td>
<td>0.71</td>
</tr>
<tr>
<td>Insulin-dependent, %</td>
<td>5</td>
<td>10</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>57</td>
<td>53</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>55</td>
<td>56</td>
<td>0.88</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>9</td>
<td>18</td>
<td>0.8</td>
</tr>
<tr>
<td>Creatinine, μmol/L*</td>
<td>102±80</td>
<td>95±31</td>
<td>0.36</td>
</tr>
<tr>
<td>LVEF, %*</td>
<td>42±13</td>
<td>41±14</td>
<td>0.85</td>
</tr>
</tbody>
</table>

| Medical history, %                 |                      |                  |      |
| Protected LM                       | 22                   | 16               | 0.17 |
| PCI                                | 35                   | 28               | 0.42 |
| MI                                 | 41                   | 38               | 0.58 |
| Transient ischemic attack/stroke   | 8                    | 11               | 0.81 |
| Heart failure*                     | 16                   | 20               | 0.36 |
| Severe COPD†                       | 5                    | 8                | 0.38 |
| Peripheral arterial disease*       | 24                   | 22               | 0.86 |
| Carotid artery disease*            | 6                    | 6                | 0.98 |
| Clinical presentation, %           |                      |                  |      |
| Stable angina                      | 50                   | 48               | 0.8  |
| Unstable angina                    | 33                   | 33               | 1    |
| Acute MI*                          | 17                   | 20               | 0.70 |
| Cardiogenic shock at entry*        | 9                    | 12               | 0.66 |
| Parsonnet score                    | 16±11                | 19±12            | 0.17 |

LVEF indicates left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

*Parameters included in the Parsonnet classification.
†Resulting in functional disability or hospitalization, requiring chronic bronchodilator therapy, or forced expiratory volume in 1 second <75% of predicted.8

Thirty-Day Outcomes

There were no significant differences between the DES and the pre-DES groups in the incidence of major adverse cardiovascular events during the first 30 days (Table 3). In the DES group, all deaths except 3 occurred in patients presenting with ST-segment elevation acute MI and cardiogenic shock at entry. In all these patients except 4 with severe peripheral artery disease, an intra-aortic balloon was placed during PCI. In the elective population, a total of 2 deaths occurred; both patients presented with unstable angina with mild troponin elevation and were refused by surgeons because of old age (84 years), low left ventricular ejection fraction (≤30%), and diabetic chronic renal insufficiency in 1 patient and diffuse 3-vessel disease associated with small-caliber vessels in the second. In this second patient the right coronary artery was occluded. The reason for death was pulmonary infection, which developed 19 days after the procedure in the first patient, and cardiogenic shock, which developed during the intervention, resistant to hemodynamic support (left ventricular assist device) in the other patient. In the pre-DES group, all 6 deaths occurred in patients with ST-segment elevation acute MI, of whom 4 were in cardiogenic shock at entry. No documented thrombotic stent occlusion occurred in the first 30 days or thereafter.

Long-Term Outcome

After a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of major adverse cardiovascular events (death, MI, or target vessel revascularization) was significantly lower in the DES patients than in the pre-DES patients (24% versus 45%, respectively; hazard ratio

TABLE 2. Angiographic and Procedural Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-DES Group (n=86)</th>
<th>DES Group (n=95)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion location, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ostium</td>
<td>18</td>
<td>27</td>
<td>0.20</td>
</tr>
<tr>
<td>Body</td>
<td>40</td>
<td>37</td>
<td>0.31</td>
</tr>
<tr>
<td>Distal</td>
<td>66</td>
<td>65</td>
<td>0.9</td>
</tr>
<tr>
<td>Pure LM disease, %</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>LM plus 1-vessel disease, %</td>
<td>29</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>LM plus 2-vessel disease, %</td>
<td>42</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LM plus 3-vessel disease, %</td>
<td>27</td>
<td>59</td>
<td>0.003</td>
</tr>
<tr>
<td>Right coronary artery &gt;70% stenosis, %</td>
<td>27</td>
<td>53</td>
<td>0.02</td>
</tr>
<tr>
<td>Right coronary artery occlusion, %</td>
<td>13</td>
<td>19</td>
<td>0.43</td>
</tr>
<tr>
<td>No. of implanted stents</td>
<td>1.2±0.5</td>
<td>1.4±0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Nominal stent diameter, mm</td>
<td>3.6±0.5</td>
<td>3.1±0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total stent length per patient, mm</td>
<td>20±9</td>
<td>24±13</td>
<td>0.02</td>
</tr>
<tr>
<td>Predilatation, %</td>
<td>67</td>
<td>71</td>
<td>0.62</td>
</tr>
<tr>
<td>Cutting balloon, %</td>
<td>5</td>
<td>6</td>
<td>0.94</td>
</tr>
<tr>
<td>Rotational atherectomy, %</td>
<td>1</td>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>Directional atherectomy, %</td>
<td>6</td>
<td>0</td>
<td>0.007</td>
</tr>
<tr>
<td>Postdilatation, %</td>
<td>58</td>
<td>80</td>
<td>0.01</td>
</tr>
<tr>
<td>Larger balloon inflated, mm</td>
<td>4±0.6</td>
<td>3.9±0.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Maximal pressure, atm</td>
<td>17±2</td>
<td>17±3</td>
<td>0.85</td>
</tr>
<tr>
<td>Bifurcation stenting, %</td>
<td>10</td>
<td>26</td>
<td>0.02</td>
</tr>
<tr>
<td>Culotte*</td>
<td>11</td>
<td>36</td>
<td>0.4</td>
</tr>
<tr>
<td>T technique*</td>
<td>88</td>
<td>44</td>
<td>0.35</td>
</tr>
<tr>
<td>Crush*</td>
<td>0</td>
<td>12</td>
<td>0.56</td>
</tr>
<tr>
<td>Kissing technique*</td>
<td>0</td>
<td>8</td>
<td>0.91</td>
</tr>
<tr>
<td>Intravascular ultrasonography, %</td>
<td>23</td>
<td>27</td>
<td>0.36</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors, %</td>
<td>26</td>
<td>28</td>
<td>0.83</td>
</tr>
<tr>
<td>Intr-aortic balloon pump, %</td>
<td>16</td>
<td>15</td>
<td>0.88</td>
</tr>
<tr>
<td>Left ventricular assist device, %</td>
<td>0</td>
<td>2</td>
<td>0.52</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm,</td>
<td>1.05±0.59</td>
<td>1.09±0.44</td>
<td>0.58</td>
</tr>
<tr>
<td>preintervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal lumen diameter, mm,</td>
<td>2.97±0.6</td>
<td>2.83±0.49</td>
<td>0.09</td>
</tr>
<tr>
<td>postintervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference vessel diameter, mm,</td>
<td>3.37±0.6</td>
<td>3.25±0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>postintervention</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Relative to patients with bifurcation stenting.
Mortality was similar in the DES (14%) and pre-DES cohort (16%; HR, 0.79 [95% CI, 0.38 to 1.66]; P = 0.54) (Figure, B), whereas there was a significant reduction in both the rate of MI (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; P = 0.006) and composite death/MI (Figure, C) as well as in the need for target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; P = 0.004) (Figure, D) in the DES group. Seventy-four percent of the deaths were cardiac, whereas 3 of 13 in the DES group and 4 of 14 in the pre-DES phase were attributed to extracardiac reasons. In Table 4, the baseline and procedural characteristics of those patients in the DES group who underwent target vessel revascularization during follow-up are reported. In all cases, the lesion was located in the distal LM, in 50% of cases diabetes was present, and all except 1 were women. In 3 cases, in-stent restenosis occurred; in 2 patients intimal hyperplasia developed at the distal edge of the stent, whereas in 1 patient severe ostial side branch restenosis (circumflex artery) necessitated reintervention. In all cases, restenosis was focal (<10 mm in length) and was successfully treated with repeated PCI. In the pre-DES group, 13 cases of pure in-stent restenosis, of which 3 were focal, were treated with PCI (9 patients) or CABG (4 patients). In 2 patients, diffuse intimal hyperplasia associated with progression of atherosclerotic disease in other vessels was treated with CABG, and in 5 patients (3 with ST-segment elevation acute MI as the indication for LM intervention), staged reintervention with CABG (in 4 patients) and PCI (in 1 patient) was performed because revascularization remained incomplete at the time of the index procedure.

**TABLE 3. Thirty-Day Outcomes**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-DES Group</th>
<th>DES Group</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>6 (7)</td>
<td>10 (11)</td>
<td>0.60</td>
</tr>
<tr>
<td>Nonfatal MI, n (%)</td>
<td>8 (9)</td>
<td>4 (4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Death or nonfatal MI, n (%)</td>
<td>14 (16)</td>
<td>14 (15)</td>
<td>0.84</td>
</tr>
<tr>
<td>Target vessel revascularization, n (%)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Repeated PCI</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Any event, n (%)</td>
<td>16 (19)</td>
<td>14 (15)</td>
<td>0.56</td>
</tr>
<tr>
<td>Stent thrombosis, n (%)†</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
</tbody>
</table>

*By Fisher exact test.
†Angiographically documented.

[HR], 0.52 [95% CI, 0.31 to 0.88]; P = 0.01) (Figure, A). Mortality was similar in the DES (14%) and pre-DES cohort (16%; HR, 0.79 [95% CI, 0.38 to 1.66]; P = 0.54) (Figure, B), whereas there was a significant reduction in both the rate of MI (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; P = 0.006) and composite death/MI (Figure, C) as well as in the need for target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65];
Predictors of Adverse Events

The Parsonnet score, ranging from 2.5 to 55.5 (mean value, 18±2; interquartile range, 16.5) was 16±11 and 19±12 in the pre-DES and DES groups, respectively (P=0.17) (Table 1), with a trend toward a higher rate of patients considered at high surgical risk (58% versus 46%, respectively; P=0.13) in the DES compared with the pre-DES cohort.

On univariate analysis, Parsonnet classification, use of intra-aortic balloon pump, presence of shock at entry, lesion located in the distal LM, nonelective PCI, troponin elevation at entry, TIMI flow grade before and after PCI, reference vessel diameter, left ventricular ejection fraction, and the use of DES were identified as significant predictors of adverse events. On multivariate analysis, Parsonnet classification, troponin elevation at entry, lesions located at distal site, reference vessel diameter, and the use of DES were independent predictors of major adverse cardiovascular events (Table 5).

Discussion

Despite the feasibility and the high procedural success rate of percutaneous LM intervention, the long-term incidence of adverse events in the pre-DES “era” was often reported to be unacceptably high in this subset of patients.4,6 This reflected the inclusion of high-risk patients, such as those not considered “good surgical candidates,” as well as the dramatic impact of treated vessel failure in this specific anatomic context. In consecutive patients receiving elective BMS for unprotected LM treatment, the 3-year cumulative incidence of death was recently reported to be ≈16%.6 In that series, 28% of the population was at high surgical risk. More than 50% of our study population was at high surgical risk according to the Parsonnet classification, thus explaining the relatively high rate of adverse events we observed. In this setting, when patients treated with DES were compared with those treated with BMS, a marked benefit with respect to the rate of major adverse cardiac events, as evidenced by a 47% relative risk reduction, emerged in the former. This was mainly due to the difference in the incidence of MI (67% relative risk reduction) and target vessel revascularization (65% relative risk reduction), with no effect on mortality. The higher prevalence of 3-vessel disease and bifurcation stenting in the DES group makes the observed benefit even more convincing. The difference in the incidence of events between

TABLE 4. Characteristics of Patients in the DES Group Who Underwent Target Vessel Revascularization During Follow-Up

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
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<tr>
<td>Age, y</td>
<td>66</td>
<td>77</td>
<td>36</td>
<td>70</td>
<td>52</td>
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<td>Gender</td>
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<td>F</td>
<td>F</td>
<td>M</td>
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<tr>
<td>Diabetes</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lesion location</td>
<td>Distal</td>
<td>Distal</td>
<td>Distal</td>
<td>Distal</td>
<td>Distal</td>
<td>Distal</td>
</tr>
<tr>
<td>Severe calcification</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Stent type</td>
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<td>SES</td>
<td>PES</td>
<td>PES</td>
<td>PES</td>
<td>PES</td>
</tr>
<tr>
<td>Stent No.</td>
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<td>2</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Total stent length, mm</td>
<td>16</td>
<td>36</td>
<td>20</td>
<td>48</td>
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<td>Bifurcation stenting</td>
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<td>Technique</td>
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<td>Postdilatation</td>
<td>Yes</td>
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<td>Final kissing</td>
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<td>Gap between stents</td>
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<td>Stent underexpansion</td>
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<td>Restenosis location</td>
<td>In-stent</td>
<td>In-stent*</td>
<td>RS</td>
<td>In-stent</td>
<td>DER</td>
<td>DER*</td>
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<td>Revascularization type</td>
<td>PCI</td>
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<tr>
<td>QCA after PCI</td>
<td>Reference vessel diameter, mm</td>
<td>3.74</td>
<td>3.27</td>
<td>3.53</td>
<td>2.65</td>
<td>2.44</td>
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<tr>
<td>Minimal lumen diameter, mm</td>
<td>2.12</td>
<td>1.06</td>
<td>3.34</td>
<td>2.49</td>
<td>1.94</td>
<td>2.32</td>
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<tr>
<td>Lesion length, mm</td>
<td>13.4</td>
<td>19.7</td>
<td>13.5</td>
<td>21.3</td>
<td>8.9</td>
<td>18.9</td>
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<tr>
<td>QCA at follow-up</td>
<td>Reference vessel diameter, mm</td>
<td>3.87</td>
<td>3.43</td>
<td>3.21</td>
<td>2.32</td>
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<tr>
<td>Minimal lumen diameter, mm</td>
<td>1.23</td>
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<td>0.98</td>
<td>0.99</td>
<td>0.6</td>
<td>0.71</td>
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<td>Restenosis length, mm</td>
<td>5.8</td>
<td>9.06</td>
<td>3.6</td>
<td>5.48</td>
<td>7.72</td>
<td>9.5</td>
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</table>

QCA indicates quantitative coronary angiography; In-stent, restenosis located within the stent margins; RS, restenosis located in the side branch (the ostium of the circumflex artery); and DER, distal edge restenosis located within the 5-mm segment distal to the stent.

*More than 1 focal site.
Implantation to treat bifurcated lesions have been relatively
management of LM bifurcation. To date, the results of SES
usually located and did not directly involve the LAD or left
obstruction, and troponin status at entry. Therefore, our data
adjustment for the Parsonnet score, the anatomic site of
mechanism of action of DES on intimal hyperplasia.

The overall advantage of DES remained significant after
adjustment for the Parsonnet score, the anatomic site of
obstruction, and troponin status at entry. Therefore, our data
suggest that when percutaneous treatment of LM coronary
artery disease is undertaken, DES should be used as the
default strategy.

The LM bifurcation was frequently involved (>60%) in
our series, and even when the obstruction was more prox-
ially located and did not directly involve the LAD or left
circumflex artery ostia, its treatment often required the
management of LM bifurcation. To date, the results of SES
implantation to treat bifurcated lesions have been relatively
disappointing, with high rates of restenosis in the side
branch. Our present findings are in keeping with these
previous observations, confirming that in the DES era distal
LM location is an independent predictor of adverse events at
follow-up. Furthermore, because the strategy and technical
aspects of bifurcation management were left entirely to the
preference of treating physicians, no clear conclusions can be
drawn in this regard.

Inconsistent findings have been reported thus far with
regard to the effect of DES on long-term cumulative
incidence of MI. In the first randomized clinical trials
comparing SES or PES with BMS, no difference in the
incidence of MI was observed. Second-generation
randomized trials assessing the benefit of DES in patients
selected to be at intermediate risk for in-stent restenosis or
all-inclusive registries reported trends toward MI reduction
in the DES group, but none of them reached statistical
significance. Recently, a clear reduction in the cumu-
late incidence of MI in the DES group was reported in
the SES-SMART trial, in which a selected group of
high-risk patients has been evaluated. Similarly, in our
patient population, a reduced incidence of MI was
observed in the DES group. Of note, 2 and 1 cases of MI in
the pre-DES phase were related to target vessel revascu-
larization and not related to target vessel revascularization,
respectively. Whether this difference between studies is
the reflection of a type II error in studies enrolling patients
at low or intermediate risk remains unclear, but when the
retrospective nature of our investigation is considered, data
from prospective studies are needed to confirm our
findings.

Limitations of the Study
The present study is a single-center experience from a tertiary
referral center and lacks the clear advantages of a multicenter
randomized study. In keeping with the aim of our investiga-
tion, an “all-comers” population has been enrolled, clearly
resulting in a heterogeneous group of patients. Further stud-
ies, with larger sample sizes, are required to investigate the
differential impact of DES versus BMS in prespecified
subgroups, stratified according to clinical presentation (stable
versus unstable) or protected versus unprotected type of
treatment.

Despite the fact that the study was conducted over a relatively
short period, we cannot exclude the possibility that improve-
ments in technique or differences in drug prescription could have
partially accounted for the difference observed in terms of major
adverse cardiovascular events between groups. However, con-
ducting randomized trials that seek to assess the efficacy of DES
versus BMS in this specific subset of patients seems unlikely,
and our understanding of the benefit of drug-coated stents to
treat this group of patients will probably also rely in the near
future on well-conducted registries that are able to record and
monitor our daily clinical practice.

Conclusions
The use of DES as a default strategy to treat LM disease was
associated with a significant reduction in adverse events. The
effectiveness of DES persisted even after adjustment for
clinical and procedural variables, including the Parsonnet

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% CI)</th>
<th>$\chi^2$</th>
</tr>
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<tbody>
<tr>
<td>Distal LM disease</td>
<td>2.7 (4.8–1.53)</td>
<td>13.3</td>
</tr>
<tr>
<td>DES use</td>
<td>0.54 (0.9–0.32)</td>
<td>5.48</td>
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<td>Nonelective PCI</td>
<td>2.1 (3.5–1.3)</td>
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<td>Intra-aortic balloon pump use</td>
<td>2.9 (4.9–1.7)</td>
<td>14</td>
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<tr>
<td>LVEF, %</td>
<td>0.95 (0.97–0.93)</td>
<td>20</td>
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<tr>
<td>Parsonnet score</td>
<td>1.07 (1.09–1.05)</td>
<td>44</td>
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<tr>
<td>Reference vessel diameter</td>
<td>0.36 (0.58–0.32)</td>
<td>19</td>
</tr>
<tr>
<td>Shock at entry</td>
<td>4.48 (7.9–2.5)</td>
<td>21</td>
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<tr>
<td>TIMI flow before PCI</td>
<td>0.75 (0.96–0.58)</td>
<td>4.3</td>
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<tr>
<td>TIMI flow after PCI</td>
<td>0.58 (0.85–0.39)</td>
<td>4.7</td>
</tr>
<tr>
<td>Troponin T &gt;0.02 µg/L at entry</td>
<td>3.15 (5.26–1.9)</td>
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<tr>
<td>Distal LM disease</td>
<td>2.94 (5.5–1.57)</td>
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<tr>
<td>DES use</td>
<td>0.33 (0.57–0.19)</td>
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<tr>
<td>LVEF, %</td>
<td>0.98 (1.09–0.95)</td>
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</tr>
<tr>
<td>Parsonnet score</td>
<td>1.94 (1.07–1.01)</td>
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<tr>
<td>Reference vessel diameter</td>
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</tr>
<tr>
<td>Troponin T &gt;0.02 µg/L at entry</td>
<td>2.3 (4.4–1.2)</td>
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<tr>
<td>Distal LM disease</td>
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<tr>
<td>DES use</td>
<td>0.35 (0.6–0.20)</td>
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<tr>
<td>LVEF, %</td>
<td>0.95 (0.98–0.94)</td>
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<tr>
<td>Reference vessel diameter</td>
<td>0.48 (0.74–0.30)</td>
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</tr>
<tr>
<td>Shock at entry</td>
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<td>Troponin T &gt;0.02 µg/L at entry</td>
<td>2.27 (4.2–1.17)</td>
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</table>
surgical risk score. Our findings apply to a selected group of patients referred for percutaneous LM treatment and suggest that in this setting routine DES implantation, by reducing the cumulative incidence of major adverse cardiovascular events, should be currently regarded as the strategy of choice. Until new evidence is provided by randomized clinical trials directly comparing the surgical and percutaneous approaches, CABG should remain the preferred revascularization treatment in good surgical candidates presenting with LM coronary artery disease.

Acknowledgments
The authors express their gratitude to Dr Pedro A. Lemos for his major contribution to the RESEARCH Registry and acknowledge the expert statistical assistance of Dr Eric Boersma.

References


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