Comparison of Drug-Eluting Stents and Coronary Artery Bypass Surgery for the Treatment of Multivessel Coronary Disease

Three-Year Follow-Up Results From a Single Institution

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Background—Numerous studies have compared the outcomes of coronary artery bypass grafting (CABG) surgery and coronary stenting for the treatment of multivessel coronary disease. In 2003, drug-eluting stents were introduced with the hope of reducing restenosis. However, limited information exists on the comparison of drug-eluting stents and CABG surgery. The long-term outcome of drug-eluting stents compared with that of CABG surgery is also unclear.

Methods and Results—We identified 3720 consecutive patients with multivessel disease who underwent isolated CABG surgery or received drug-eluting stents between April 1, 2004, and December 31, 2005, and we compared safety (total mortality, myocardial infarction, and stroke) and efficacy (target-vessel revascularization) during a 3-year follow-up. These outcomes were compared after adjustment for differences in baseline risk factors. Patients who underwent CABG (n=1886) were older and had more comorbidities than patients who received drug-eluting stents (n=1834). Patients receiving drug-eluting stents had considerably higher 3-year rates of target-vessel revascularization. Drug-eluting stents were also associated with higher rates of death (adjusted hazard ratio, 1.62; 95% confidence interval, 1.07 to 2.47) and myocardial infarction (adjusted hazard ratio, 1.65; 95% confidence interval, 1.15 to 2.44). The risk adjusted rate of stroke was similar in the 2 groups (hazard ratio, 0.92; 95% confidence interval, 0.69 to 1.51).

Conclusions—in a cohort of patients with multivessel disease, CABG was associated with lower rates of death, myocardial infarction, and target-vessel revascularization than drug-eluting stents. (Circulation. 2009;119:2040-2050.)

Key Words: coronary disease ■ follow-up studies ■ stents ■ surgery ■ survival

Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) have long been the definitive aggressive options for treating patients with coronary disease. Several randomized clinical trials and observational studies have examined the relative long-term benefits of these interventions.1–6 The past few years heralded the development of drug-eluting stents in an effort to suppress the recurrence of lesions and to reduce the rate of repeat revascularization, which has continued to be a problem associated with the use of bare-metal stents. Many trials presented consistent positive reports with drug-eluting stents.7–21 However, recent data suggested a higher rate of thrombotic occlusion with drug-eluting stents than with bare-metal stents, increasing the risk of myocardial infarction (MI) and mortality.22,23 Consequently, the Food and Drug Administration convened an advisory panel to address the safety of drug-eluting stents.24,25

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When we speak of evidence-based medicine, it is important to remember that previous data may be incomplete and of questionable relevance to patients excluded from randomized trials. Nowhere is this more apparent than in the controversies surrounding the use of drug-eluting stents in patients requiring multivessel revascularization. Could the relative outcomes reported in previous studies comparing CABG with PCI be reflective of current real-world practice? To what extent will these developments in coronary revascularization alter the conclusions of prior trials? With these considerations in mind, the aim of this study was to compare the safety (death, MI, and stroke) and efficacy (target-vessel revascularization [TVR]) in multivessel disease patients receiving drug-eluting stents and those undergoing CABG in our institution.
Methods

Study Population

The 2 primary databases used in the study were our institutional CABG registry and PCI registry. These registries were developed in 1999 and 2002, respectively, after the approval of the institutional review board, for the purpose of collecting information on all consecutive patients who had undergone CABG or PCI in our institution. Efforts to ensure the accuracy and completeness of these data have been described elsewhere. The 2 registries contain information on demographics, comorbidities, hemodynamic state, left ventricular function, diseased vessels and vessels for which bypass or angioplasty was attempted, operator identifiers, and in-hospital adverse outcomes. The PCI registry also contains information on the types of device used for each patient, including bare-metal stents and drug-eluting stents. Uniform definitions for these elements are used in our study. These clinical, angiographic, procedural or operative, and outcome data were collected with the use of a dedicated computer-based reporting system.

The present study includes consecutive patients with multivessel disease (defined as stenosis of ≥70% in at least 2 of the 3 main coronary arteries) who were treated with isolated CABG surgery or drug-eluting stents (with or without bare-metal stents) from April 1, 2004, to December 31, 2005. This strategy was chosen to avoid the start-up period for drug-eluting stents between October 2003 and March 2004 in our institution. Patients who had previously undergone revascularization, those with disease of the left main coronary artery (defined as stenosis of >50%), and those who had an acute MI within 24 hours before revascularization were excluded. The study group comprised 1886 patients who were treated with CABG and 1834 patients who were treated with drug-eluting stents.

Revascularization Procedures

Interventions for coronary artery disease were performed according to current practice guidelines. Insertion of drug-eluting stents was performed with an attempt to fully cover the diseased segment and to ensure complete stent apposition. The choice of the specific type of drug-eluting stents (ie, sirolimus-eluting or paclitaxel-eluting stents) was left to the interventionist's discretion. All patients undergoing PCI were prescribed aspirin plus clopidogrel (loading dose, 300 or 600 mg) before or during the coronary intervention. After the procedure, aspirin was continued indefinitely. Patients treated with drug-eluting stents were prescribed clopidogrel for at least 6 months, regardless of drug-eluting stent type. Clopidogrel beyond this duration was at the discretion of the physician.

CABG surgery was performed with the use of standard bypass techniques. When possible, the internal thoracic artery was used exclusively for revascularization. The left anterior descending (LAD) artery. Complete revascularization was performed when possible with atrial conduits or saphenous vein grafts.

Follow-Up and End Points

Clinical, procedural, or operative, and outcome data were recorded in the dedicated PCI and CABG database by independent research personnel. Clinical follow-up after CABG and after PCI was recommended at 1 month, 6 months, and 12 months and then annually thereafter, which was achieved via office visit or telephone contact. To ensure accurate assessment of clinical outcomes, additional information was obtained from visits or telephone/mail contacts with patients or family members, from their local physicians, and from medical records obtained from other hospitals as necessary. All follow-up outcomes were examined and classified by an events adjudication committee. Angiographic follow-up for patients treated with drug-eluting stents was recommended at 6 months after the procedure. Patients who were at high risk for procedural complications of angiography and had no symptoms or signs of ischemia did not undergo follow-up angiography. For patients who had undergone CABG, angiographic follow-up was recommended if ischemic symptoms or signs appeared during follow-up. For validation of complete follow-up data on vital status, information on deaths was obtained by matching the patients in each of the registries with the Chinese Population Registries of the National Statistic Office with the use of a unique personal identification number.

The end points of the study were death, MI, stroke, and TVR. All outcomes of interest were confirmed by source medical records or based on clinical diagnoses assigned by the patient’s physician and then were adjudicated by an independent events adjudication committee. Death was defined as death from any cause. Periprocedural MI was defined as the presence of a new significant Q wave in ≥2 contiguous leads or as the elevation of the serum levels of creatine kinase isoenzyme (CK-MB ≥3 times the upper limit of normal for PCI patients; CK-MB ≥5 times the upper limit of normal for CABG patients). MI during follow-up was defined as either documentation of a new abnormal Q wave after the index treatment or MIs at readmission (emergency admission with a principal diagnosis of MI). Stroke, as indicated by neurological deficits, was confirmed by a neurologist on the basis of imaging studies. TVR was defined as the need for either surgical or percutaneous revascularization of the target (treated) vessel.

Statistical Analysis

The primary purpose of the study was to compare differences in long-term outcomes between the 2 treatment types (CABG versus drug-eluting stents) after controlling for differences in patients’ procedural risk. A secondary purpose was to determine whether treatment-related differences existed in 4 patient subgroups (patients with diabetes mellitus, patients aged ≥70 years, patients with double-vessel disease, and patients with triple-vessel disease).

The prevalence rates of risk factors and characteristics (demographic features, hemodynamics, and comorbidities) of the patients were compared by the x2 test and the Fisher exact (for binary risk factors) test. Continuous variables were presented as mean±SD, and comparisons between means were performed with the use of Student t test or Wilcoxon rank sum test. Unadjusted survival curves were constructed with the use of Kaplan–Meier estimates and compared with the log-rank test.

The impact of treatment type (CABG or drug-eluting stents) on early and long-term outcomes was estimated with the use of the appropriate statistical methods for risk adjustment. The risk-adjusted odds ratios for in-hospital/30-day outcomes (death, MI, and stroke) were calculated with the use of stepwise logistic regression models with all candidate risk factors (Table 1) as independent control variables and treatment type included in the model as the independent study variable of interest. Differences in risk-adjusted long-term outcomes were investigated by developing separate stepwise Cox proportional hazards models for each of the end points. Candidate independent variables included all candidate variables listed in Table 1. Treatment type was also included into each model to obtain hazard ratios (HRs) and 95% CIs for drug-eluting stents versus CABG. Adjusted survival curves were constructed for each type of procedure with the use of the Cox proportional hazards models and methods for calculating adjusted survival. Cox proportional hazards models were also used to test for significance of the hazard ratios for 2 clinical subgroups (patients with diabetes and patients aged ≥70 years) and various anatomic subgroups defined by the number of the diseased vessels and by the presence of patients with triple-vessel disease and patients with double-vessel disease.

To reduce the effect of treatment-selection bias and potential confounding in this observational study, we conducted rigorous adjustment for significant differences in the baseline characteristics of patients with the use of propensity analysis. The propensity score was estimated without regard to outcomes by multiple logistic regression analysis. All prespecified covariates, which are listed in Table 1, were included in the final models for treatment with drug-eluting stents versus CABG. The resulting estimated probability of being treated with CABG is the propensity score. Model discrimination was assessed with c statistics, and model calibration was assessed with Hosmer-Lemeshow statistics. The propensity score was then subdivided into quartiles. Risk-adjusted HRs for drug-eluting stent versus CABG were computed for each quartile, and quartile estimates were combined to measure an overall estimate of the treatment effect. For each of the clinical and anatomic
subgroups, a new propensity score for PCI versus CABG was incorporated into each analysis, and the patients’ propensity scores were subdivided into quartiles to obtain the propensity stratification–adjusted HR.

All statistical tests were 2-tailed, and a significance level of 0.05 was used throughout. Statistical analyses were performed with the use of SPSS version 13.0 (SPSS Inc, Chicago, Ill) and MATLAB version 6.1 (MathWorks Inc, Natick, Mass).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 1. Risk Factors in Patients Treated With CABG or Drug-Eluting Stents

<table>
<thead>
<tr>
<th>Candidate Risk Factors (Variables)</th>
<th>CABG Group (n=1886)</th>
<th>Stenting Group (n=1834)</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.72</td>
</tr>
<tr>
<td>&lt;50 y</td>
<td>12.2</td>
<td>21.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59 y</td>
<td>32.8</td>
<td>31.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69 y</td>
<td>39.1</td>
<td>30.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70 y</td>
<td>15.8</td>
<td>16.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>60.75±8.81</td>
<td>58.38±10.37</td>
<td>&lt;0.001</td>
<td>0.73</td>
</tr>
<tr>
<td>Gender, %</td>
<td></td>
<td></td>
<td>0.111</td>
<td>0.85</td>
</tr>
<tr>
<td>Female</td>
<td>17.1</td>
<td>19.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>82.9</td>
<td>80.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.39±2.95</td>
<td>25.55±3.07</td>
<td>0.350</td>
<td>0.82</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>29.3</td>
<td>26.1</td>
<td>0.040</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>65.3</td>
<td>61.2</td>
<td>0.013</td>
<td>0.80</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>44.6</td>
<td>38.8</td>
<td>&lt;0.001</td>
<td>0.73</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>26.7</td>
<td>25.1</td>
<td>0.271</td>
<td>0.88</td>
</tr>
<tr>
<td>Cerebrovascular disease, %</td>
<td>18.1</td>
<td>13.0</td>
<td>&lt;0.001</td>
<td>0.68</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>11.7</td>
<td>5.9</td>
<td>&lt;0.001</td>
<td>0.59</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, %</td>
<td>15.5</td>
<td>6.4</td>
<td>&lt;0.001</td>
<td>0.61</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>44.6</td>
<td>43.2</td>
<td>0.410</td>
<td>0.92</td>
</tr>
<tr>
<td>Homodynamic instability or shock, %</td>
<td>2.1</td>
<td>0.2</td>
<td>&lt;0.001</td>
<td>0.71</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.65</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>1.9</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–50%</td>
<td>13.8</td>
<td>5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>84.3</td>
<td>93.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure (this admission), %</td>
<td>8.5</td>
<td>6.5</td>
<td>&lt;0.001</td>
<td>0.76</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, %†</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.72</td>
</tr>
<tr>
<td>&lt;60 mL/min per 1.73 m²</td>
<td>27.8</td>
<td>16.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–90 mL/min per 1.73 m²</td>
<td>48.3</td>
<td>48.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90 mL/min per 1.73 m²</td>
<td>23.9</td>
<td>35.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of diseased vessels, %‡</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.32</td>
</tr>
<tr>
<td>3 diseased vessels</td>
<td>82.0</td>
<td>23.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 diseased vessels</td>
<td>18.0</td>
<td>77.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal left anterior descending artery</td>
<td>77.0</td>
<td>37.2</td>
<td>&lt;0.001</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Values are percentages or mean±SD.
*Propensity score–adjusted P value.
†Estimated glomerular filtration rate was calculated on the basis of the Modification of Diet in Renal Disease equation.
‡Diseased vessels were defined by the presence of stenosis of at least 70%.

Results

Study Patients

Between April 1, 2004, and December 31, 2005, a total of 3720 patients with multivessel coronary disease met the criteria for inclusion. Of these, 1834 were treated with drug-eluting stents and 1886 with CABG. In the CABG group, 896 patients (47.5%) underwent off-pump surgery and 1850 patients (98.1%) received 1 internal thoracic artery that was used in revascularization of the LAD artery. The mean number of bypass grafts was 2.86 and the mean number of arterial distal anastomoses and 3.10 venous distal anastomoses. In the drug-eluting stents group, the mean total number of stents implanted in a patient was (2.25 drug-eluting stents and 0.43 bare-metal stents). The mean total length of the stents was 62.78±29.13 mm, and the mean stent diameter was 3.05±0.46 mm.
Baseline preprocedural characteristics of the study patients stratified by treatment type are listed in Table 1. Patients undergoing CABG were significantly older and appeared sicker with regard to having a higher prevalence of smoking, hypertension, hyperlipidemia, cerebrovascular disease, peripheral vascular disease, and chronic obstructive pulmonary disease. Patients undergoing CABG were also more likely to have lower ejection fractions, to have had previous MIs, to have had poorer renal function, to have had triple-vessel disease, and to have had involvement of the proximal LAD artery. With respect to the propensity score model, the c statistic was 0.79 (Hosmer-Lemeshow goodness of fit, $P=0.12$). All covariates differed nonsignificantly after propensity score adjustment (Table 1).

### In-Hospital/30-Day Outcomes

With respect to the unadjusted in-hospital/30-day mortality, 11 deaths occurred in the drug-eluting stents group and 22 deaths in the CABG group (0.60% versus 1.17%; $P=0.07$). After multivariate analysis, no significant differences were found between the 2 groups (drug-eluting stents versus CABG) in the risk-adjusted rates of in-hospital/30-day mortality (adjusted odds ratio, 0.547; 95% CI, 0.22 to 1.17; $P=0.20$). Patients treated with drug-eluting stents had a significantly lower unadjusted rate of in-hospital/30-day stroke (0.22% versus 0.95%; $P=0.02$). After adjustment for baseline risk factors, a benefit of drug-eluting stents was still found with respect to stroke (adjusted odds ratio, 0.75; 95% CI, 0.57 to 0.98; $P=0.03$). The unadjusted and adjusted rates of in-hospital/30-day MI were similar in the 2 groups (0.60% for drug-eluting stents versus 0.90% for CABG; adjusted odds ratio, 1.06; 95% CI, 0.35 to 3.28; $P=0.33$).

### Follow-Up and Long-Term Outcomes

The median follow-up was 33.1 months in the drug-eluting stent group and 38.9 months in the CABG group. Complete follow-up data for major clinical events were obtained in 98.9% of the overall cohort. During the entire study period, 128 patients died (61 in the drug-eluting stents group, 67 in the CABG group), and 103 MIs (52 drug-eluting stents patients, 51 CABG patients) and 84 strokes (29 drug-eluting stents patients, 55 CABG patients) occurred. During follow-up, 222 patients in the drug-eluting stents group and 23 patients in the CABG group underwent TVR. Among patients treated with drug-eluting stents, mean duration of clopidogrel use was 11.8±8.7 months. With respect to long-term efficacy, Figure 1 presents the 36-month unadjusted curves for TVR after the initial procedure for the entire cohort. The risk of TVR was considerably higher in the drug-eluting stent group than in the CABG group ($P<0.001$).

Cox multivariate proportional hazards analyses were performed to control for confounding variables. Table 2 presents the unadjusted and adjusted HRs (drug-eluting stents versus CABG) for long-term mortality, MI, stroke, and TVR. Fig-

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**Table 2.** HRs (Drug-Eluting Stents/CABG) and 95% CIs for Long-Term Outcomes

<table>
<thead>
<tr>
<th>Model</th>
<th>Death</th>
<th>MI</th>
<th>Stroke</th>
<th>TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>HR 95% CI</td>
<td>P</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.24</td>
<td>1.24 0.87–1.76</td>
<td>0.03</td>
<td>1.53 1.03–2.28</td>
</tr>
<tr>
<td>Multivariable-adjusted HR*</td>
<td>0.02</td>
<td>1.62 1.07–2.47</td>
<td>0.01</td>
<td>1.65 1.15–2.44</td>
</tr>
<tr>
<td>Propensity score-stratified analyses†</td>
<td>0.03</td>
<td>1.48 1.06–2.26</td>
<td>0.01</td>
<td>1.59 1.19–2.75</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, body mass index, current smoker, hypertension, hyperlipidemia, diabetes mellitus, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, previous MI, homodynamic instability or shock, left ventricular ejection fraction, congestive heart failure, estimated glomerular filtration rates, number of diseased vessels, and involvement of the proximal LAD artery.

†Cases were subdivided into quartiles on the basis of the propensity score, and then, for each adverse outcome, treatment effect was estimated separately within each quartile, and quartile estimates were combined to measure an overall estimate of the treatment effect.
ures 2 and 3 present the 36-month unadjusted and adjusted rates of overall survival and survival free from MI and survival free from stroke. As indicated in Table 2 and Figures 2A and 3A, although the unadjusted HR for mortality (unadjusted HR, 1.24; 95% CI, 0.87 to 1.76; \(P=0.24\)) suggested no significant difference between the 2 groups, CABG was associated with a lower 36-month rate of mortality after multivariable-adjusted Cox regression analysis (HR, 1.62; 95% CI, 1.07 to 2.47; \(P=0.02\)). Risk adjustment was also conducted with the use of propensity analysis to reduce the effect of treatment-selection bias and potential confounding variables. After the propensity score quartile-adjusted analyses, the difference in the 36-month rate of mortality was still present (HR, 1.48; 95% CI, 1.06 to 2.26; \(P=0.03\)). The similarity of these estimates is remarkable.

During the entire study period, the unadjusted risk and adjusted risk of MI (Table 2, Figures 2B and 3B) were significantly higher in patients treated with drug-eluting stents than in those treated with CABG (HR, 1.65; 95% CI, 1.15 to 2.44; \(P=0.01\)). In a crude analysis, as indicated in Figure 2C, a nonsignificant trend toward higher 36-month rate of stroke was found in the CABG group (log-rank \(P=0.086\)). However, after multivariable-adjusted Cox regression analysis, the long-term rate of stroke (Table 2 and Figure 3C) was similar in the 2 groups (HR, 0.92; 95% CI, 0.69 to 1.51; \(P=0.68\)). After propensity score quartile-adjusted analyses, the results were still consistent (Table 2).

Subgroup Analyses
Table 3 presents HRs (drug-eluting stents versus CABG) for long-term death and for the composite of death, MI, or stroke for 2 clinical subgroups of patients (patients with diabetes and patients aged ≥70 years) and various anatomic subgroups (triple- and double-vessel disease; with or without involvement of the proximal LAD artery) who were chosen at the outset of the study. As indicated, the rates of death were significantly higher in those treated with drug-eluting stents among patients with diabetes (adjusted HR, 1.56 for death; 95% CI, 1.06 to 3.19; \(P=0.03\)) and patients aged ≥70 years (adjusted HR, 1.62; 95% CI, 1.08 to 2.72; \(P=0.02\)). Adjusted HR also favored the CABG group over the drug-eluting stent group with respect to the composite of death, MI, or stroke among patients with diabetes (adjusted HR, 1.39; 95% CI, 1.04 to 2.86; \(P=0.02\)). However, the adjusted risk for the composite of death, MI, or stroke was comparable in patients aged ≥70 years (adjusted HR, 1.31; 95% CI, 0.90 to 2.91; \(P=0.10\)).

The majority of patients with triple-vessel disease underwent CABG surgery, whereas the majority of patients with double-vessel disease received drug-eluting stents. With regard to the risk of death and of the composite of death, MI, or stroke, the advantage of CABG was also quite consistent for each of the 2 major anatomic subgroups (triple- and double-vessel disease), with all of the 4 adjusted HRs being >1 and significant (Table 3). Among patients with triple-vessel disease, the mortality benefit associated with CABG surgery was also noted in patients with proximal LAD artery involvement, and a nonsignificant trend toward lower risk of death was found in CABG patients with proximal LAD involve-
ment. Among patients with double-vessel disease with proximal LAD involvement, a nonsignificant trend toward lower risk of death was noted in CABG patients, as indicated in Table 3.

Discussion
The 2 primary strategies for patients with multivessel coronary artery disease are CABG and PCI. The comparison of these 2 strategies remains an open question. Several randomized controlled trials1–6 have compared the long-term outcomes of these 2 strategies, but most of these studies might be outdated. In the era of drug-eluting stents, less information is available from previous studies on the comparison between bypass surgery and PCI with drug-eluting stents for multivessel revascularization with respect to long-term safety and efficacy. Hence, the intent of this study was to compare safety (death, MI, and stroke) and efficacy (TVR) among patients undergoing bypass surgery and those receiving drug-eluting stents.

Principal Findings
The principal findings of the study were that patients treated with CABG had lower risk for death, MI, and TVR than those treated with drug-eluting stents and that for most of the clinical and anatomic subgroups of patients (patients with diabetes, patients aged ≥70 years, patients with triple-vessel disease, and patients with double-vessel disease), our data still favored CABG for long-term safety.

Hopes and Fears Relative to Drug-Eluting Stents
In 2003, the Food and Drug Administration approved drug-eluting stents for the treatment of coronary artery disease with the hope that this device would reduce restenosis and possibly mortality by a drug that is released locally over time. Because of the magnitude of the treatment effect of drug-eluting stents in suppressing the recurrence of lesions, consistent positive reports from subsequent trials, and firsthand experiences, the use of drug-eluting stents has become the default strategy of PCI, with more fervent hope that it would trump bare-metal stents and perhaps, in the future, displace bypass surgery as the treatment for patients requiring coronary revascularization. The Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial,33 of which the hypothesis was that PCI with drug-eluting stents would not be inferior to bypass surgery in the management of patients with triple-vessel and/or left main disease, was an attempt to determine whether PCI with drug-eluting stents could be performed in higher-risk groups of patients (triple-vessel and/or left main disease) but with outcomes similar to those in earlier trials. However, the fear relative to drug-eluting stents has been that emerging data suggested a higher rate of thrombotic occlusion with drug-eluting stents than with bare-metal stents, increasing the risk of MI and mortality,34–37 and that evidence exists of very late stent thrombosis in patients receiving drug-eluting stents.22 Despite the fear about
higher stent thrombosis rates for drug-eluting stents, recent studies have suggested a lower or equivalent risk for mortality or MI with drug-eluting stents.38–41 Whether the hopes and fears relative to drug-eluting stents are real deserves further and continued study.

### Multivessel Revascularization: Drug-Eluting Stents Versus Bypass

Patients with multivessel coronary disease constitute a challenging group for cardiac care. Most of these patients have significant comorbidities; thus, coronary revascularization is associated with increased risk of death and other adverse cardiovascular outcomes, compromising the life expectancy and cost required. Owing to an aging population in Western countries and a higher incidence of coronary artery disease in the developing world, multivessel revascularization is increasing. The past decade heralded developments in both PCI and cardiac surgery, including drug-eluting stents and off-pump coronary bypass. To what extent will these developments alter the conclusions of prior trials comparing PCI and CABG for the treatment of multivessel disease?

Hannan et al42 compared outcomes for drug-eluting stents and CABG among patients with multivessel disease, using data on all patients in New York State who were undergoing CABG or PCI. That study, which examined the rates of death, death or MI, and repeat revascularization, found that for patients with multivessel disease, CABG continues to be associated with lower mortality rates than does PCI with drug-eluting stents and is also associated with lower rates of death or MI and repeat revascularization. Furthermore, among patients with 2-vessel disease in the New York State registries,42 CABG was also associated with significantly lower mortality either with involvement of the proximal LAD artery or without involvement of the proximal LAD artery. The results of these real-world registries affirmed the advantage of bypass surgery as the standard of care for patients who require multivessel coronary revascularization.

In the New York State registries,42 many of the repeat revascularizations for the patients receiving drug-eluting stents...
stents occurred within the first 60 days after the procedure, suggesting that these events were staged interventions and not failures of the target vessels. Our present study evaluated the risk of TVR and demonstrated that use of drug-eluting stents was still associated with significantly higher risk of TVR, suggesting target-vessel failure or late thrombosis associated with drug-eluting stents. However, a higher rate of follow-up angiography was found among patients treated with drug-eluting stents than among those treated with CABG. In our study, the angiographic follow-up among patients treated with drug-eluting stents was recommended at 6 months after the procedure. However, the angiographic follow-up among patients treated with CABG was clinically driven. During the study period, ≈60% of the patients treated with drug-eluting stents and <20% of patients with CABG surgery underwent angiographic follow-up. Therefore, the higher frequency of angiographic follow-up in the stent group may have increased the frequency of repeat revascularization procedures, and the rates of TVR and asymptomatic graft stenosis or occlusion may have been underestimated in the CABG group. Protocol-driven angiography has been demonstrated to have a powerful impact on the rates of repeat revascularization.43,44 Thus, protocol-driven angiography may have biased revascularization against the CABG group, thereby contributing to an overestimation of benefit with bypass surgery.

Is the advantage of CABG for multivessel revascularization explicable? First, concern has been raised recently about the possibility of an increased rate of late stent thrombosis observed with the use of drug-eluting stents. The improved clinical outcomes with a reduced rate of restenosis and subsequent repeat revascularization procedures may be neutralized by an increase in the rate of late stent thrombosis. Second, the difference in the approach to the coronary lesion may account for the superiori of CABG in patients with multivessel disease.45 PCI is targeted to the culprit lesion or lesions, whereas CABG is directed at the epicardial vessel, including the culprit lesion or lesions and future culprits, which are responsible for most of the adverse even if the rate of restenosis declines. Third, the past decade heralded advances in surgical, anesthetic, and perfusion procedures and postoperative intensive care. This progress led to CABG being regarded as a safe treatment option in patients requiring coronary revascularization. Furthermore, arterial grafting and complete revascularization have been performed whenever possible to provide long-term prognostic benefits.

The results of the much-awaited SYNTAX trial were released at the European Society of Cardiology Congress 2008 in Munich, Germany. A total of 1800 patients were randomized, 897 to CABG and 903 to PCI with drug-eluting stents. The results demonstrate that in patients with triple-vessel disease and/or left main disease, CABG was associated with lower risk for the primary end point of major adverse cardiac and cerebrovascular events at 12 months (CABG 12.1% versus drug-eluting stents 17.8%; \( P = 0.0015 \)), which were predominantly driven by the need for repeat revascularization in the drug-eluting stent group. However, no difference was found in the incidence of death (CABG 3.5% versus drug-eluting stents 4.3%; \( P = 0.37 \)) or MI (CABG 3.2% versus drug-eluting stents 4.8%; \( P = 0.11 \)) between the 2 groups at 12 months, and the incidence of stroke was significantly higher in the CABG group (2.2% versus 0.6%; \( P = 0.003 \)).

Stroke is a serious, devastating event and deeply influences the long-term prognosis of patients after coronary revascularization. Our present study demonstrated a nonsignificant trend toward higher rate of stroke among patients treated with CABG surgery. This worse long-term outcome after CABG may be primarily due to the fact that patients in the CABG group were significantly older, had a higher prevalence of peripheral vascular disease, and had worse heart and kidney function. However, we were unable to determine the extent to which the higher rate of stroke was related to revascularization strategy versus other risk factors. Therefore, a large randomized clinical trial is warranted to assess the influence of revascularization strategy on long-term cerebrovascular events.

In our study, the rates of clinical outcomes were different from recent reports.46,47 These discrepancies may be explained is part by differences in patient populations, lesion characteristics, interventional/surgical practice, and ethnic groups. Patient demographics, a variety of comorbidities, left ventricular function, and the severity of involved anatomy can frequently affect outcomes and can influence the choice of revascularization strategy. We performed propensity analysis to enable an even more rigorous adjustment for selection biases and confounding factors. Nonetheless, observational studies for the assessment of treatment effect can only partially control for actually measured factors, not for hidden biases. Therefore, a comparison of PCI with drug-eluting stents or CABG surgery in patients with multivessel coronary disease awaits the results of the ongoing randomized trials.36,48

**Potential Clinical Implications of Data**

First, because drug-eluting stents showed worse long-term results among patients with multivessel disease, large-scale randomized controlled trials are certainly indicated to compare the 2 interventions in this high-risk patient group. Randomization, as with all trials comparing stents with bypass surgery, eliminates clinical judgment in patient selection and carries a potential for being misleading as a predictor of outcomes in actual daily life. Large-scale randomized controlled trials with longer follow-up will provide complementary data and address some of the limitations of these current studies comparing drug-eluting stent with bypass surgery. Future longer-term follow-up results of the SYNTAX trial, as well as the results of other ongoing trials on this open question (eg, the Future Revascularization Evaluation in Patients With Diabetes: Optimal Management of Multivessel Disease [FREEDOM] and Coronary Artery Revascularization in Diabetes [CARDia] trials), are eagerly awaited for further resolution of this topic.

Second, the real world has many competitive pressures, and we confront clinical decisions that are less evidence based because of the absence of the totality of data. However, our decisions relative to indications for multivessel revascularization and the preferred method should be made in the interest of the patient and in an atmosphere of collegiality.
Such a goal would be enhanced by widespread participation of physicians in the decision-making process, including both interventional and noninterventional cardiologists and cardiovascular surgeons.45

Limitations
Observational data are of value because they shed light on the use of competing treatment options in current routine practice and because they include high-risk patients who are frequently not represented in randomized controlled trials. Previous studies have suggested that well-designed observational studies provide valid results and do not systematically overestimate the magnitude of treatment effects compared with the results of randomized controlled trials. Therefore, findings from observational studies and randomized trials can provide us with a panorama of the treatment effects. Despite this, the fundamental limitations of observational studies cannot be eliminated because of the nonrandomized nature and the unrecognized confounding factors.

With respect to our study, the major limitation is that the nonrandomized nature of the observational data limits any direct comparisons of the 2 revascularization strategies. Patients were subjected to a selection bias as the decision to proceed with drug-eluting stents versus CABG surgery was made either at the discretion of the treating physicians on the basis of anatomy and clinical findings or sometimes as the choice of the patients. We attempted to minimize this selection bias by propensity analyses, which demonstrate that the relative outcomes associated with the 2 procedures remained about the same, regardless of the propensity to choose one procedure versus the other, indicating that the results are not likely to be severely compromised by selection bias. However, only a limited number of potentially important baseline factors are presented in our study. Despite our efforts to eliminate selection bias as much as possible, the bias can still be present because of some undefined or unmeasured risk factors related to choice of treatment and to end points that were not present in our database. Target-vessel size, extent of disease in the target vessel, cancer, dementia, and alcohol use are examples of some of these factors. Hence, there are inherent limitations to using an observational population because of these unmeasured or undefined confounding factors. In an observational study, it is not possible to eliminate bias caused by the presence of patients who would not have been in a randomized controlled trial because they would have had contraindications or would have been deemed to be ineligible for 1 of the procedures or by the presence of pairs of patients who differ with respect to unmeasured risk factors not contained in the registries. Furthermore, factors precluding CABG include coexisting conditions that are linked to poor prognosis, whereas those precluding PCI are often lesion-based (eg, chronic total occlusion) and have a lesser effect on prognosis after CABG. Thus, the presence of these unmeasured factors may bias the outcome in favor of CABG.

Another important caveat is that the mean follow-up times for both treatments were only 3 years, a period that captures events driven by atherosclerosis of arterial or vein grafts, a process that begins several years after bypass surgery. It is possible that a longer-term follow-up might be more appropriate to evaluate the end points. However, the advantage of CABG might be maintained over the course of follow-up, both because New York State registries and our data showed evidence of that tendency and because evidence exists of very late stent thrombosis in patients receiving drug-eluting stents.22

In addition, our statistical analyses may have been underpowered to assess treatment effects in the various subgroups as a result of a limited number of patients in each subpopulation. Further studies are needed to examine the relative long-term benefits of these interventions for each clinical or anatomic subset. We also acknowledge that the specific expertise of the cardiac surgeons and interventional cardiologists who completed the procedures, as well as the particulars of clinical practice in our institution, may be different from other physicians and institutions, potentially limiting the reproducibility of these results in other settings.

Conclusion
We observed that for patients with multivessel disease, CABG was associated with lower rates of death, MI, and TVR than drug-eluting stents. Our study highlights the need for large-scale randomized controlled trials with longer-term follow-up to address some limitations of these current observational studies.

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Disclosures
None.

References


Numerous studies have compared the outcomes of 2 competing interventions for multivessel coronary artery disease: coronary artery bypass grafting and coronary stenting. However, little information has become available since the introduction of drug-eluting stents. In the present study, we identified 3720 consecutive patients with multivessel disease who received drug-eluting stents or underwent coronary artery bypass grafting to compare safety (death, myocardial infarction, or stroke) and efficacy (target-vessel revascularization) during a 3-year follow-up after adjustment for differences in baseline risk factors. Patients receiving drug-eluting stents had considerably higher 3-year rates of target-vessel revascularization. Drug-eluting stents were also associated with higher rates of death (adjusted hazard ratio, 1.62; 95% confidence interval, 1.07 to 2.47) and myocardial infarction (adjusted hazard ratio, 1.65; 95% confidence interval, 1.15 to 2.44). The risk-adjusted rate of stroke was similar in the 2 groups (hazard ratio, 0.92; 95% confidence interval, 0.69 to 1.51). Our findings need to be ascertained or refuted in ongoing, large randomized clinical trials, which may provide the answer to treatment effects between the 2 primary interventions.
Comparison of Drug-Eluting Stents and Coronary Artery Bypass Surgery for the Treatment of Multivessel Coronary Disease: Three-Year Follow-Up Results From a Single Institution
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