Cost-Effectiveness of Percutaneous Coronary Intervention With Drug Eluting Stents Versus Bypass Surgery for Patients With Diabetes Mellitus and Multivessel Coronary Artery Disease

Results From the FREEDOM Trial

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Background—Studies from the balloon angioplasty and bare metal stent eras have demonstrated that coronary artery bypass grafting (CABG) is cost-effective compared with percutaneous coronary intervention (PCI) for patients undergoing multivessel coronary revascularization—particularly among patients with complex coronary artery disease or diabetes mellitus. Whether these results apply in the drug-eluting stent (DES) era is unknown.

Methods and Results—Between 2005 and 2010, 1900 patients with diabetes mellitus and multivessel coronary artery disease were randomized to PCI with DES (DES-PCI; n=953) or CABG (n=947). Costs were assessed from the perspective of the U.S. health care system. Health state utilities were assessed using the EuroQOL 5 dimension 3 level questionnaire. A patient-level microsimulation model based on U.S. life-tables and in-trial results was used to estimate lifetime cost-effectiveness. Although initial procedural costs were lower for CABG, total costs for the index hospitalization were $8622 higher per patient. Over the next 5 years, follow-up costs were higher with PCI, owing to more frequent repeat revascularization and higher outpatient medication costs. Nonetheless, cumulative 5-year costs remained $3641 higher per patient with CABG. Although there were only modest gains in survival with CABG during the trial period, when the in-trial results were extended to a lifetime horizon, CABG was projected to be economically attractive relative to DES-PCI, with substantial gains in both life expectancy and quality-adjusted life expectancy and incremental cost-effectiveness ratios <$10000 per life-year or quality-adjusted life-year gained across a broad range of assumptions regarding the effect of CABG on post-trial survival and costs.

Conclusions—Despite higher initial costs, CABG is a highly cost-effective revascularization strategy compared with DES-PCI for patients with diabetes mellitus and multivessel coronary artery disease.


Key Words: coronary artery bypass grafting ■ cost-benefit analysis ■ diabetes mellitus ■ drug-eluting stents ■ percutaneous coronary intervention
well as medical therapy, have had an impact on the comparative clinical outcomes of the two revascularization strategies in both the short- and long-term. Nonetheless, most recent comparisons of revascularization outcomes in patients with diabetes mellitus in the bare metal and drug-eluting stent (DES) era have shown a trend toward more frequent major adverse cardiac and cerebrovascular events (MACCE) with percutaneous coronary intervention (PCI) relative to CABG.\textsuperscript{4,4} Whereas the rate of repeat revascularization procedures has been reduced with stenting and DES, rates have remained higher than for CABG.\textsuperscript{5,5} Moreover, economic analyses based on the available data (generally based on subset analyses of trials or observational studies) have suggested that CABG remains a cost-effective strategy.\textsuperscript{3,10-14}

The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial is the largest prospective randomized trial to compare the outcomes of multivessel coronary artery revascularization with drug-eluting stents versus CABG among diabetic patients.\textsuperscript{15} Recently, 5-year results from FREEDOM showed that CABG was associated with significantly lower rates of the primary end point of death, myocardial infarction, or stroke, compared with DES-PCI, with the benefit driven by reductions in both death and myocardial infarction.\textsuperscript{16} To provide additional insight into the relative value of these alternative revascularization strategies, we performed a prospective health economic evaluation alongside the FREEDOM trial, the results of which are the focus of this report.

**Methods**

The design and methods of the FREEDOM trial have been described previously.\textsuperscript{16} Between April 2005 and April 2010, 1900 patients with type 1 or 2 diabetes mellitus and angiographically confirmed multivessel CAD with a clinical indication for revascularization and who were deemed suitable for both DES-PCI and CABG were randomly assigned on a 1:1 basis to either technique. PCI procedures were performed using standard techniques. Given the timeframe of patient recruitment, both sirolimus-eluting stents (SES) and paclitaxel-eluting stents (DES) were the predominant stents used in the trial. The trial protocol recommended that patients randomized to PCI receive only 1 type of DES. Newer generation DES were allowed during the later phases of the trial, provided there was regulatory approval for use within the respective region. The use of abximab was recommended for patients undergoing PCI and was provided free of charge; at least 12 months of dual antiplatelet therapy with aspirin and clopidogrel was recommended after any DES procedure. Patients randomized to CABG underwent treatment according to standard techniques. After revascularization, optimal medical therapy including high-dose statin therapy, aggressive blood pressure control, and normalization of hemoglobin-A1c was recommended for both groups.

In-person assessments were performed at 1 month postprocedure, and 6 and 12 months postrandomization, and annually thereafter. In addition, telephone follow-up assessments were performed at 18 months and all subsequent semiannual time points. All sites obtained Institutional Review Board approval of the protocol, and all patients provided informed consent. The trial is registered at the National Institutes of Health website (http://www.clinical-trials.gov) as identifier NCT00086450.

**Estimation of Medical Care Costs**

Medical care costs for the index hospitalization and in-trial follow-up period were assessed using a combination of resource-based and event-based methods as described below. All costs were assessed from the perspective of the U.S. healthcare system and are reported in 2010 U.S. dollars.

**PCI and CABG Procedure Costs**

Detailed resource use was recorded for each revascularization procedure, and the cost for each item was estimated on the basis of the mean hospital acquisition cost for the item at 3 surveyed U.S. hospitals. Each DES was assigned a cost of $1500. Costs of antithrombotic therapy were based on the most current wholesale acquisition cost obtained from Micromedex Red Book.\textsuperscript{17} Costs of additional disposable equipment, overhead and depreciation for the cardiac catheterization laboratory and the operating room, and nonphysician personnel were estimated using data from the microcost accounting systems of Saint Luke’s Mid America Heart Institute and adjusted for actual procedure duration. Resource utilization and cost data for the initial PCI procedure and any planned staged PCI procedures were combined in the reporting of results for the index procedure.

**Postprocedure Hospitalization Costs**

Postprocedure costs for index hospitalizations were estimated using regression models based on FREEDOM-eligible Medicare patients who underwent either PCI (n=113921) or CABG (n=43866) and whose hospitalization data were included in the 2010 Medicare Provider and Review (MEDPAR) database. Total costs for these hospitalizations were estimated by multiplying hospital charges by the hospital and cost center–specific cost-to-charge ratio.\textsuperscript{18,19} Linear regression models were then developed, using total Medicare hospitalization costs as the outcome, and socioeconomic factors, comorbidities, and in-hospital complications (identified on the basis of ICD-9 codes) as predictors (see Table I in the online-only Data Supplement). Because of substantial variability in length of stay for revascularization procedures across the enrolling countries in FREEDOM, length of stay was not included as a predictor in these models. The final models for PCI and CABG were then used to predict nonprocedural costs for each index hospitalization as well as any subsequent hospitalizations that involved a coronary revascularization procedure. To avoid double-counting procedural costs, the intercept for each model was adjusted to remove the costs directly related to the revascularization procedures, themselves, based on national averages for procedure duration and resource use.\textsuperscript{11}

For follow-up hospitalizations that did not involve a revascularization procedure, Medicare Severity-Diagnosis Related Groups were assigned based on the primary indication for hospitalization and procedures performed during the hospitalization. Costs were then assigned based on mean 2010 Medicare reimbursement rates for the Medicare Severity-Diagnosis Related Group obtained from the Medicare Part A data files.\textsuperscript{20}

**Other Costs**

Physician fees for PCI procedures and CABG procedures (including those for the primary surgeon, surgical assistant, and anesthesiologist) were based on the 2010 national Medicare fee schedule. Nonprocedure-related physician fees for revascularization-related hospitalizations were estimated for U.S. patients on the basis of postprocedure ICU and non-ICU length of stay and Medicare payment rates; for non-U.S. patients, postprocedure length of stay after CABG and PCI was estimated from regression models developed using 2010 MedPAR data and the same covariates as used in the cost models (see Tables I and II in the online-only Data Supplement), and PCI and CABG-specific ratios of ICU versus total postprocedure length of stay estimated from the trial data for U.S. patients. Physician costs for all other hospitalizations were estimated as a percentage of hospital costs according to the Medicare Severity-Diagnosis Related Group.\textsuperscript{21,22} Costs for outpatient visits, tests and procedures, and inpatient rehabilitation and skilled nursing facility days were estimated using national average 2010 Medicare reimbursement rates. Because the length of stay in cardiac rehabilitation varied considerably at the country level, the average number of rehab days according to treatment group and follow-up year for U.S. patients was used to estimate the cost of rehabilitation stays for patients enrolled at non-U.S. sites.
Outpatient medication use was assessed at each follow-up visit, and costs were assigned using the most current average wholesale prices from Micromedex Red Book. To account for expected reductions in the cost of generic clopidogrel in the very near future, it was assigned a cost of $30/month.

Quality of Life
The EuroQOL 5 dimension 3 level questionnaire (EQ-5D) health status instrument was used to assess quality of life for each study patient at baseline, 1 month postprocedure, 6 and 12 months after randomization, and annually thereafter. Health state utility weights (range 0–1, higher=higher health) were obtained from the EQ-5D data using an algorithm developed from the U.S. population.

Statistical Analysis
Of the 1900 patients randomized in the FREEDOM trial, 36 patients assigned to CABG, and 9 patients assigned to PCI did not undergo any index procedure. All of these patients either died (n=3) or withdrew from the study (n=42) within 7 days of randomization. To avoid bias resulting from higher rates of withdrawal before CABG, the primary analytic population for the economic study consisted of all randomized patients who underwent ≥1 initial revascularization procedure, with patients categorized according to their assigned treatment (modified intention-to-treat [mITT] population, n=1855). A secondary analytic population included only those patients who underwent the revascularization procedure assigned (per protocol [PP] population, n=1832) and was used solely to examine initial treatment costs among those patients who actually underwent the specified procedures. Categorical data are reported as frequencies, and continuous data are reported as mean±standard deviation. Discrete variables were compared using Fisher exact test. Normally distributed continuous variables were compared using Student t test, and nonnormally distributed data were compared using the Wilcoxon rank-sum test. Treatment effects from Poisson regression models were used for the comparison of hospitalization rates. Kaplan–Meier survival curves and log-rank tests were used for the comparison of 5-year clinical events. Cost data are reported as both mean and median values, and confidence intervals for the differences in costs between treatment groups were obtained via bootstrapping.

Quality-adjusted life expectancy during the trial period was estimated for each patient as the time-weighted average of his or her utility value, using the midpoint between assessments as the transition between health states, starting at the 30-day visit. The baseline utility was applied to the time from randomization to the index procedure, and the 30-day utility value was applied to the period from the procedure through the midpoint between the 30 day and 6-month follow-up. Missing utility values were estimated using multiple imputation, with baseline patient characteristics, previous utility values, and previous in-trial clinical events informing the imputation.

In-Trial Analysis of Costs, Life-Years, and Quality-Adjusted Life-Years Gained
The prolonged recruitment period for the FREEDOM trial together with the fixed stopping point yielded a wide range of follow-up durations for enrolled patients. To accommodate this wide range of administrative censoring times, methods for the analysis of censored data were used to obtain estimates of cumulative costs and quality-adjusted life-years gained (QALY) over time. An inverse probability-weighted estimator was applied, whereby the time axis was divided into 3-month intervals, and costs for each interval were estimated as the observed costs during the interval for patients with complete data divided by the probability of not being censored within the interval. Similar methods were applied to estimation of quality-adjusted life expectancy. Life-years gained at annual time points were estimated as the difference in the area between the Kaplan–Meier survival curves for the 2 treatment groups. Confidence limits for the mean cumulative cost, life-year, and QALY estimates for each treatment group, as well as the difference between groups, were calculated using the bootstrap method.

Cost-Effectiveness
The cost-effectiveness of CABG versus PCI was assessed over a lifetime horizon using both life-years and QALYs as measures of health benefit; the study protocol specified that the analysis based on QALYs would be considered the primary analysis, consistent with current U.S. guidelines. This analysis was based on a combination of (1) observed data up to the time of last follow-up for each patient, from which in-trial costs, life-years, and QALYs were estimated, and (2) projections of post-trial costs, life expectancy, and quality-adjusted life expectancy obtained from a Markov disease-simulation model. In this model, each surviving patient was assumed to face a monthly risk of death, with estimates of this risk based on age-, sex- and race-matched risks of death obtained from U.S. life tables, calibrated to the observed 5-year mortality for the trial population.

For the PCI group, the comparison of the observed 5-year mortality for the trial population with that of an age, sex, and race-matched U.S. population yielded a mortality multiplier of 1.88. For the CABG group an additional multiplicative factor was applied to capture the prognostic benefit of CABG versus DES-PCI. This multiplier was based on the hazard ratio derived from a landmark analysis of all-cause mortality from the FREEDOM patients, starting at 1 year after randomization. Three sets of analyses were performed based on different assumptions regarding the duration of the survival benefit of CABG. The base case analysis assumed that the mortality hazard ratio for CABG versus DES-PCI increased in a linear fashion from year 5 to year 10, and that there was no survival benefit of CABG beyond year 10 (ie, hazard ratio=1). In sensitivity analyses, the survival benefit of CABG was assumed either (1) to remain constant through 10 years, with no further benefit beyond 10 years, or (2) to be in effect through 5 years only (ie, no further benefit beyond the observed trial period).

Patient-level costs and utility weights applied to each projected year of life beyond the trial observation period were derived from regression models developed from the in-trial data (see Tables III and IV in the online-only Data Supplement). All projected life-years, QALYs, and costs were discounted 3% annually based on time from randomization.

Uncertainty in the joint distribution of lifetime costs, life-years, and QALYs for each treatment group was estimated by the bootstrap method. To maintain consistency of the within-trial and post-trial CABG effect within each bootstrap sample, the effect of CABG on mortality from the 1-year postbaseline landmark analysis, was re-estimated for each bootstrap replicate.

All analyses of data from the trial period, and the analyses of cost-effectiveness based on the combined trial data and long-term projections, were performed using SAS 9.3 (SAS Institute, Cary, NC). The Markov model used for projection of life expectancy beyond the trial was developed using TreeAge Pro 2012 (TreeAge Software Inc, Williamstown, MA).

Results
Patient Population
A total of 1900 patients with diabetes mellitus and multivessel CAD were randomized to either CABG (n=947) or DES-PCI (n=953). Of these, 45 patients did not undergo any form of revascularization (36 CABG, 9 PCI) and were excluded from the primary population for the economic analysis (Figure 1). Baseline characteristics for patients in the economic study population (mITT) and the 45 excluded patients (non-mITT) are summarized in Table 1. Patients who withdrew from the trial and had no index procedure tended to be older and have higher SYNTAX scores than the mITT population; otherwise there were no significant differences. Among the mITT population, there were no significant differences in any observed characteristics between the CABG and PCI groups. Nineteen percent of the mITT patients were enrolled in the United States, >84% had 3-vessel CAD, and the median follow-up duration was 47 months.
Among patients in the mITT cohort assigned to PCI, 99.5% underwent initial PCI and 0.5% underwent CABG. Among patients assigned to initial CABG, 98% underwent CABG and 2% underwent PCI. Resource utilization and costs for the initial revascularization procedures (including any staged procedures) are summarized in Table 2. Thirty-three percent of index PCI procedures were staged, with 31% involving 2 procedures, and 2% involving 3 or 4. On average, the initial PCI procedures required 2.3 guiding catheters, 3.1 guidewires, 3.4 angioplasty balloons, and 4.1 drug-eluting stents (range 0–13). Although PCI procedure duration was considerably shorter than that for CABG, index procedure costs were significantly lower for CABG owing to the higher costs associated with stents and other consumable devices in the PCI group ($9739 versus $13014 for the per protocol population, \( P < 0.001 \)). For the mITT population, the difference was slightly smaller ($9776 versus $12998, \( P < 0.001 \)), because a small proportion of patients crossed over to the alternate treatment before revascularization.

Clinical events and resource use during the index hospitalization for the mITT population are summarized in Table 3. Costs associated with the postprocedure hospital stay were significantly greater in the CABG group ($19521 versus $9880, \( P < 0.001 \)) as were physician costs ($5170 versus $4600, \( P < 0.001 \)).

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Revascularized Patients (mITT)</th>
<th>Non-Revascularized Patients (non-mITT)</th>
<th>mITT vs non-mITT P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CABG (n=911)</td>
<td>PCI (n=944)</td>
<td></td>
</tr>
<tr>
<td>Sociodemographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62.9±9.2</td>
<td>63.1±8.9</td>
<td>0.67</td>
</tr>
<tr>
<td>Male, %</td>
<td>69.9</td>
<td>73.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.8±5.3</td>
<td>29.6±5.4</td>
<td>0.52</td>
</tr>
<tr>
<td>Enrolling country, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>19.1</td>
<td>18.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Rest of world</td>
<td>80.9</td>
<td>81.2</td>
<td>83.3</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>16.7</td>
<td>14.8</td>
<td>0.28</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>25.1</td>
<td>26.3</td>
<td>0.58</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>10.5</td>
<td>10.1</td>
<td>0.76</td>
</tr>
<tr>
<td>COPD, %</td>
<td>5.4</td>
<td>3.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior stroke, %</td>
<td>2.7</td>
<td>3.8</td>
<td>0.16</td>
</tr>
<tr>
<td>History of CHF, %</td>
<td>28.3</td>
<td>25.5</td>
<td>0.18</td>
</tr>
<tr>
<td>Angiographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD involvement, %</td>
<td>93.0</td>
<td>90.7</td>
<td>0.07</td>
</tr>
<tr>
<td>Three-vessel disease, %</td>
<td>84.3</td>
<td>82.1</td>
<td>0.21</td>
</tr>
<tr>
<td>SYNTAX score</td>
<td>26.0±8.8</td>
<td>26.2±8.4</td>
<td>0.71</td>
</tr>
<tr>
<td>SYNTAX score tertile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>36.6</td>
<td>34.7</td>
<td>0.375</td>
</tr>
<tr>
<td>23–32</td>
<td>43.3</td>
<td>46.5</td>
<td>0.411</td>
</tr>
<tr>
<td>≥33</td>
<td>20.1</td>
<td>18.8</td>
<td>0.058</td>
</tr>
<tr>
<td>Initial treatment received, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>2.0</td>
<td>99.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>98.0</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; SYNTAX, Synergy between PCI with TAXUS and Cardiac Surgery; and TIA, transient ischemic attack.

*Comparison of combined treatment groups for mITT vs non-mITT.
Follow-up clinical outcomes, resource utilization, and costs are summarized in Table 4. During the first year of follow-up, rates of repeat revascularization by either PCI or CABG were higher among patients assigned to initial PCI. Although costs for cardiovascular hospitalizations were thus greater for the PCI group, these higher costs were offset by higher costs for noncardiovascular hospitalizations, outpatient visits, and rehabilitation services for the CABG group such that total 1-year follow-up costs were similar for the 2 groups. During each subsequent year of follow-up, patients assigned to PCI continued to experience higher rates of cardiovascular-related hospitalizations, driven mainly in differences in rates of myocardial infarction and revascularization procedures. Costs for outpatient medications after PCI remained higher than those after CABG for the first 3 years (related mainly to higher rates of use of dual antiplatelet therapy) and then equalized. Annual medical care costs were thus substantially lower for the CABG group for each subsequent year, with annual differences ranging from $793 in year 2 to $1594 in year 5. As a result, the difference in cumulative medical care costs between the CABG and PCI groups narrowed progressively from $8622/patient after the completion of the index revascularization procedures to $3641/patient by the end of the 5-year follow-up period (Table 5 and Figure 2).

Utility Weights and QALYs
Utility weights as assessed by the EQ-5D are summarized in Table 6. Overall, utility weights improved substantially for both treatment groups over the course of the trial. Not surprisingly, utility weights at 1 month follow-up were substantially lower after CABG than PCI (0.81 versus 0.89, P<0.001), reflecting the more invasive nature and prolonged recovery of the former procedure. These differences were no longer apparent at 6 months, however, and utility weights remained similar for the 2 groups through the remainder of the 5-year follow-up period. As a result of these early differences, quality-adjusted life expectancy was lower with CABG than with PCI after the first year and remained lower through the first 4 years of follow-up (Table 5). However, owing to progressive differences in all-cause mortality, by the end of the 5-year follow-up period, life expectancy (4.665 versus 4.613 years) and quality-adjusted life expectancy (3.719 versus 3.688 QALYs) were actually greater with CABG than with PCI, although these differences were not statistically significant.

Cost-Effectiveness
Results from the lifetime cost-effectiveness analyses are summarized in Table 7. Based on the landmark analysis of outcomes from year 1 to 5, the estimated mortality hazard ratio for CABG versus PCI was 0.60 (95% confidence interval [CI], 0.42–0.86); CABG was associated with a reduction in follow-up costs of $1672/yr (95% CI, $942 to $2403); and there was no significant difference in follow-up utility weights (see Tables III and IV in the online-only Data Supplement). When these results were used to project clinical and economic outcomes beyond the trial period (Figure 3), we estimated that CABG would be associated with lifetime incremental costs of $5392 (95% CI, $399 to $10320) together with an increase in overall quality-adjusted life expectancy of 0.663 QALYs (95% CI, 0.177–1.132). The resulting incremental cost-effectiveness ratio (ICER) for CABG versus PCI was $8132/QALY gained, with 99.2% of bootstrap replicates below a societal willingness to pay threshold of $50,000/QALY (Figures 4 and 5, and Table 7, row 1). When outcomes were assessed in life-years, CABG was associated with a gain in life expectancy of 0.794 years and an associated ICER of $6791/life-year gained (Figure 5 and Table 7, row 2).

These results were robust across a wide range of alternative assumptions regarding the duration and magnitude of the benefit of CABG over PCI on both survival and costs beyond the timeframe observed in the trial. When we assumed that the observed benefits of CABG would be sustained through 10 years after initial treatment, the estimated QALY gains with CABG increased to 0.864 QALYs with an associated ICER of $8064/QALY gained—similar to the base case results. Even

$2967, P<0.001). As a result, total index hospitalization costs were significantly higher for CABG than for DES-PCI ($34,467 versus $25,845, P<0.001).

Table 2. Index Procedural Resource Utilization and Cost (Per Protocol Population)

<table>
<thead>
<tr>
<th></th>
<th>CABG (n=893)</th>
<th>PCI (n=939)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PCI procedures, %</td>
<td>66.6 (625/939)</td>
<td>30.9 (290/939)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedure duration, minutes</td>
<td>248±78</td>
<td>107±67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug-eluting stents</td>
<td>4.1±1.9</td>
<td>1.9±2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paclitaxel-eluting</td>
<td>3.4±2.6</td>
<td>2.1±2.4</td>
<td>0.01±0.6</td>
</tr>
<tr>
<td>Sirolimus-eluting</td>
<td>1.0±0.3</td>
<td>2.3 (22/939)</td>
<td>0.1±0.4</td>
</tr>
<tr>
<td>Other drug-eluting stents</td>
<td>0.0±0.3</td>
<td>1.0±0.4</td>
<td>0.1±0.4</td>
</tr>
<tr>
<td>Bare metal stents</td>
<td>2.3±1.3</td>
<td>3.1±2.3</td>
<td>3.4±2.6</td>
</tr>
<tr>
<td>Guiding catheters</td>
<td>2.3±1.3</td>
<td>3.1±2.3</td>
<td>3.4±2.6</td>
</tr>
<tr>
<td>Guidewires</td>
<td>0.0±0.3</td>
<td>1.0±0.4</td>
<td>0.1±0.4</td>
</tr>
<tr>
<td>Intravascular ultrasound catheters</td>
<td>0.0±0.3</td>
<td>1.0±0.4</td>
<td>0.1±0.4</td>
</tr>
<tr>
<td>Atherectomy devices</td>
<td>0.0±0.3</td>
<td>1.0±0.4</td>
<td>0.1±0.4</td>
</tr>
<tr>
<td>Contrast volume, ml</td>
<td>376±186</td>
<td>376±186</td>
<td>0.01±0.01</td>
</tr>
<tr>
<td>Antithrombotic agents used, %</td>
<td>87.2% (819/939)</td>
<td>16.0% (150/939)</td>
<td>1.1% (10/939)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>53.9% (506/939)</td>
<td>32.6% (269/939)</td>
<td>3.1±2.3</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>16.0% (150/939)</td>
<td>1.1% (10/939)</td>
<td>1.1% (10/939)</td>
</tr>
<tr>
<td>Other drug-eluting stents</td>
<td>0.0±0.3</td>
<td>1.0±0.4</td>
<td>0.1±0.4</td>
</tr>
<tr>
<td>Index procedure costs, $</td>
<td>9,739±2,453</td>
<td>13,014±5,173</td>
<td>$9,477</td>
</tr>
</tbody>
</table>

Values in brackets represent medians. CABG indicates coronary artery bypass graft; GP, glycoprotein; and IABP, intra-aortic balloon pump.
under the highly conservative assumption of no further benefit of CABG on either survival or costs beyond 5 years, the ICER remained relatively favorable at $27,022/QALY gained and was <$50,000/QALY in 82.4% of bootstrap replicates. Similar results were seen when the analysis was based on life-years rather than QALYs (see Tables V and VI in the online-only Data Supplement).

Subgroup Analyses

Results from prespecified subgroup analyses are presented in Table 8. Despite the greater uncertainty associated with reduced sample sizes, these results were generally consistent with our primary analysis. For all subgroups examined, with the exception of patients without left anterior descending artery involvement, our analysis demonstrated that CABG was associated with greater quality adjusted life expectancy than PCI with mean differences ranging from 0.28 to 1.16 QALYs. For two subgroups, age 60 to 69 and HgbA1c <7%, CABG was an economically dominant strategy, with lower lifetime costs and greater quality-adjusted life expectancy than PCI. For patients without left anterior descending artery involvement (n=150), PCI was associated with greater overall costs and quality-adjusted life expectancy with an ICER of $20,661/QALY gained relative to CABG. However, these results were relatively unstable owing to the small sample size of the subgroup. Estimated ICERs for all other subgroups were <$25,000/QALY gained with CABG, and most were <$10,000/QALY gained.

Discussion

This study is the first direct comparison of economic outcomes of DES-PCI versus CABG among patients with diabetes mellitus and multivessel CAD. Our results reveal that although CABG was associated with an increase in initial costs of ≈$9000/patient, these up-front costs were partially offset by lower costs in subsequent years principally as a result of a lower rate of repeat revascularization procedures (and, to a lesser extent, less use of cardiac medications). Over the first 5 years of follow-up, CABG improved life expectancy by ≈0.05 years and quality-adjusted life expectancy by ≈0.03 QALYs while increasing total costs by ≈$3600. When the observed in-trial results were extrapolated over a lifetime horizon, CABG was associated with much larger gains in quality-adjusted life expectancy relative to PCI (0.66 QALYs in the base case), whereas projected lifetime costs remained ≈$5400/patient higher with CABG. Thus, under our base case assumptions regarding the duration and magnitude of benefit of CABG over DES-PCI, we found that CABG was associated with a lifetime ICER of $8132/QALY gained. Although there are no universally accepted standards for cost-effectiveness in the U.S. health care system, ICERs <$50,000/QALY are considered to be reasonably cost-effective, and ICERs <$20,000/QALY are considered highly cost-effective.27 In our base case analysis, the probability that the ICER for CABG versus DES-PCI would be <$50,000/QALY was >99%. These findings thus suggest that compared with
DES-PCI, CABG is a highly attractive use of scarce societal healthcare resources. These results were robust to a broad range of sensitivity analyses. Importantly, the ICER for CABG remained <$50,000/QALY gained (and in most cases <$10,000/QALY) in all analyses except those that were restricted to the first 10 years of follow-up. Although an in-trial cost-effectiveness analysis would have demonstrated an ICER for CABG of $68,958 per life-year gained and $116,699 per QALY gained, such an analysis would be misleading by failing to account for the significant 5-year survival advantage with CABG over DES-PCI (89.3 versus 83.9%) and its impact on longer-term life expectancy. Indeed, our analysis demonstrates that the projected benefits of CABG on life expectancy and quality-adjusted life expectancy would be substantial even if there were no further prognostic benefit of CABG beyond the trial period. These findings underscore the importance of a long-term evaluation in understanding the clinical and economic benefits of procedures like CABG, where a higher initial cost must be balanced against clinical benefits that extend well into the future.

These results were also consistent across a wide range of subgroups defined by age, sex, angiographic extent of CAD (including SYNTAX score), and health care system (United States versus other countries). The only possible exception to this finding was the subgroup of patients without significant left anterior descending artery disease, for whom PCI was estimated to improve

### Table 4. Follow-Up Events, Resource Utilization, and Costs (mITT Population)

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>5-Year Cumulative*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG n=911</td>
<td>PCI n=944</td>
<td>CABG n=897</td>
<td>PCI n=845</td>
<td>CABG n=824</td>
<td>PCI n=784</td>
</tr>
<tr>
<td>Death, %</td>
<td>4.1</td>
<td>3.4</td>
<td>2.1</td>
<td>3.0</td>
<td>1.3</td>
</tr>
<tr>
<td>MI, %</td>
<td>3.7</td>
<td>5.8</td>
<td>0.8</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>1.9</td>
<td>0.8</td>
<td>0.7</td>
<td>0.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

### Table 5. Cumulative Costs, QALYs, and Life-Years for Years 1 to 5, After Adjusting for Censoring

<table>
<thead>
<tr>
<th>Time Since Randomization, y</th>
<th>Cumulative Costs ($)</th>
<th>Cumulative QALYs*</th>
<th>Cumulative Life-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CABG</td>
<td>PCI</td>
<td>Δ</td>
</tr>
<tr>
<td>1</td>
<td>41,855</td>
<td>33,976</td>
<td>7,878</td>
</tr>
<tr>
<td>2</td>
<td>47,111</td>
<td>40,025</td>
<td>7,086</td>
</tr>
<tr>
<td>3</td>
<td>51,848</td>
<td>45,596</td>
<td>6,251</td>
</tr>
<tr>
<td>4</td>
<td>56,551</td>
<td>51,316</td>
<td>5,235</td>
</tr>
<tr>
<td>5</td>
<td>60,501</td>
<td>56,860</td>
<td>3,641</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; and QALY, quality-adjusted life-years gained. Δ = difference between CABG and PCI groups.

*Cumulative costs, QALYs, and life-years adjusted for censoring (see Methods for details).
long-term survival at an ICER of $20,700/QALY gained relative to CABG. These findings were relatively uncertain, however, given the small sample size in this subgroup. Nonetheless, these results are broadly consistent with those of previous studies that have suggested that the prognostic benefit of CABG over PCI is restricted to patients who receive a left internal mammary artery graft to the left anterior descending artery.28

Comparison With Previous Studies

Overall, the cost and cost-effectiveness results from FREE- DOM are similar to those reported from the BARI trial, in which CABG was estimated to have a lifetime incremental cost-effectiveness ratio of $14,300/life-year gained compared with conventional balloon angioplasty.3 There are important differences in the results of these 2 studies, however. In BARI, most of the cost offsets for CABG accrued during the first 1 to 2 years of follow-up, as a result of relatively high rates of repeat revascularization procedures necessary to treat restenosis after conventional balloon angioplasty. In contrast, cost offsets were minimal during the first year in FREEDOM and accrued at a relatively constant rate throughout the 5-year follow-up period thereafter. Although detailed angiographic data were not assessed at the time of repeat revascularization in FREEDOM, it is likely that this event pattern reflects the fact that drug-eluting stents have led to dramatic reductions in restenosis compared with either balloon angioplasty alone or

Table 6. EQ-5D Utility Scores by Treatment (mITT Population)

<table>
<thead>
<tr>
<th>Time Point</th>
<th>CABG</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.779±0.185 [0.810]</td>
<td>0.782±0.188 [0.810]</td>
</tr>
<tr>
<td>1 mo</td>
<td>0.810±0.180 [0.827]</td>
<td>0.894±0.143 [1.000]</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.810±0.180 [0.827]</td>
<td>0.895±0.143 [1.000]</td>
</tr>
<tr>
<td>1 yr</td>
<td>0.810±0.180 [0.827]</td>
<td>0.881±0.160 [1.000]</td>
</tr>
<tr>
<td>2 yr</td>
<td>0.889±0.164 [1.000]</td>
<td>0.895±0.143 [1.000]</td>
</tr>
<tr>
<td>3 yr</td>
<td>0.895±0.162 [1.000]</td>
<td>0.891±0.161 [1.000]</td>
</tr>
<tr>
<td>4 yr</td>
<td>0.89±0.148 [1.000]</td>
<td>0.868±0.177 [0.854]</td>
</tr>
<tr>
<td>5 yr</td>
<td>0.876±0.175 [1.000]</td>
<td>0.884±0.132 [0.854]</td>
</tr>
</tbody>
</table>

Values in brackets represent medians. CABG indicates coronary artery bypass graft; and PCI, percutaneous coronary intervention.

Table 7. Lifetime Cost-Effectiveness Results for Base Case and Sensitivity Analyses

<table>
<thead>
<tr>
<th></th>
<th>Cost With CABG, $</th>
<th>Cost With PCI, $</th>
<th>∆ Cost ($) (95% CI)</th>
<th>QALYs With CABG</th>
<th>QALYs With PCI</th>
<th>∆ QALYs With CABG (95%CI)</th>
<th>ICER ($/QALY)</th>
<th>% Dominant</th>
<th>% Dominated</th>
<th>% &lt;$50K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapered CABG effect between 5 and 10 yr</td>
<td>114,571</td>
<td>109,179</td>
<td>5,392 (399, 10,320)</td>
<td>10,667</td>
<td>10,004</td>
<td>0.663 (0.177, 1.132)</td>
<td>8132</td>
<td>1.5</td>
<td>0.4</td>
<td>99.2</td>
</tr>
<tr>
<td>Base case</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime analysis, cost per life-year gained*</td>
<td>114,571</td>
<td>109,179</td>
<td>5392 (399, 10,320)</td>
<td>12,177*</td>
<td>11,383*</td>
<td>0.794* (0.202, 1.221)</td>
<td>6791*</td>
<td>1.5</td>
<td>0.2</td>
<td>99.7</td>
</tr>
<tr>
<td>Lifetime analysis, per protocol population</td>
<td>114,855</td>
<td>108,878</td>
<td>5976 (1207, 10,925)</td>
<td>10,688</td>
<td>9,980</td>
<td>0.708 (0.202, 1.221)</td>
<td>8440</td>
<td>0.7</td>
<td>0.2</td>
<td>99.3</td>
</tr>
<tr>
<td>10-yr time frame</td>
<td>81,710</td>
<td>80,295</td>
<td>1416 (−2061, 5017)</td>
<td>6,684</td>
<td>6,455</td>
<td>0.230 (−0.008, 0.457)</td>
<td>6156</td>
<td>22.8</td>
<td>1.7</td>
<td>95.8</td>
</tr>
<tr>
<td>Fixed CABG effect between 5 and 10 yr</td>
<td>121,244</td>
<td>109,179</td>
<td>12,045 (6933, 17,103)</td>
<td>10,667</td>
<td>10,004</td>
<td>0.663 (0.177, 1.132)</td>
<td>18,167</td>
<td>0.0</td>
<td>0.5</td>
<td>97.4</td>
</tr>
<tr>
<td>Lifetime analysis, no CABG effect on long term costs</td>
<td>116,147</td>
<td>109,179</td>
<td>6968 (1273, 12,327)</td>
<td>10,867</td>
<td>10,004</td>
<td>0.864 (0.278, 1.426)</td>
<td>8064</td>
<td>0.7</td>
<td>0.2</td>
<td>99.7</td>
</tr>
<tr>
<td>10-yr analysis</td>
<td>81,846</td>
<td>80,295</td>
<td>1551 (−1822, 5292)</td>
<td>6,704</td>
<td>6,455</td>
<td>0.249 (0.016, 0.519)</td>
<td>6229</td>
<td>18.8</td>
<td>1.4</td>
<td>96.7</td>
</tr>
<tr>
<td>No effect of CABG after 5 yr</td>
<td>118,664</td>
<td>109,179</td>
<td>9485 (4905, 13,995)</td>
<td>10,355</td>
<td>10,004</td>
<td>0.351 (−0.033, 0.713)</td>
<td>27,022</td>
<td>0.0</td>
<td>3.3</td>
<td>82.4</td>
</tr>
<tr>
<td>Lifetime analysis</td>
<td>87,155</td>
<td>80,295</td>
<td>6861 (3408, 10,230)</td>
<td>6,541</td>
<td>6,455</td>
<td>0.086 (−0.088, 0.254)</td>
<td>79,779</td>
<td>0.0</td>
<td>17.8</td>
<td>27.0</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; ICER, incremental cost-effectiveness ratio; PCI, percutaneous coronary intervention; and QALY, quality-adjusted life-years gained.

*Results presented in row 2 represent life-years (columns 6–8) and cost per life-year gained (column 9). **All costs, life-years, and QALYs discounted at 3% per year.
bare metal stents. Nonetheless, diabetic patients remain at substantial risk of events related to progression of CAD—events that are unrelated to restenosis and are unlikely to be prevented by inherently focal therapies such as stenting.

Another difference between the FREEDOM and BARI results that impacts the cost-effectiveness of therapy is the timing of the mortality benefit. In BARI, improved survival with CABG was evident in the first year of follow-up, with increasing benefits over time. As a result, CABG was already an economically attractive revascularization strategy within the first several years after initial treatment. In contrast, in FREEDOM, mortality was similar after DES-PCI or CABG through the first 3 years of follow-up with divergence of the survival curves only in years 4 and 5. These findings may relate to the following: (1) more complete and durable revascularization with DES-PCI in FREEDOM compared with plain old balloon angioplasty in BARI; (2) increased durability of left internal mammary artery grafts versus saphenous vein grafts, the former of which were used more often in FREEDOM; or (3) greater rate of use of preventive measures (including high dose statins, ACE-inhibitors or ARBs, and aggressive dual antiplatelet therapy) in FREEDOM which may have protected PCI patients from the progression of atherosclerosis and the development of atherothrombotic events in the earlier phases of follow-up.

**Limitations**

Our study should be considered in light of several important limitations. First, our economic analysis was carried out from a U.S. healthcare system perspective, although FREEDOM enrolled patients from 18 countries. To address these issues, costs associated with the index procedures were estimated from detailed resource use data which would not be expected to vary significantly by geographic region. Because hospital length of stay varies considerably between countries, we used costing methodology that was independent of length of stay and depends only on the assumption that clinical outcomes and procedural complications are similar across healthcare systems. In addition, our study was limited by the need to extrapolate results from 5 years of follow-up data to a lifetime horizon to capture the full benefits of the alternative revascularization strategies. Our approach to extrapolation required several assumptions regarding the impact of CABG versus PCI on long-term survival, health care costs, and quality of life that are not verifiable at the present time. Accordingly, we varied our assumptions of the magnitude and durability of the impact of CABG in a range of sensitivity analyses, the results of which demonstrated the robustness of the overall cost-effectiveness results to plausible variation in these key parameters.

Finally, most PCI patients in the FREEDOM trial received first-generation DES, which were the only DES available for use at the time. Recently, second-generation DES (primarily everolimus-eluting stents) have been shown to reduce rates of myocardial infarction and stent thrombosis relative to first generation DES. As a result, the cost results from our study.
Table 8. Lifetime Cost-Effectiveness Results for Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Cost With CABG, $</th>
<th>Cost With PCI, $</th>
<th>ΔICER Cost ($) (95% CI)</th>
<th>QALYs Gained With CABG</th>
<th>QALYs Gained With PCI</th>
<th>QALYs Gained</th>
<th>ICER</th>
<th>Cost ($ per QALY Gained</th>
<th>% Dominant</th>
<th>% Dominated</th>
<th>% &lt;$50K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n=1328)</td>
<td>107,527</td>
<td>104,468</td>
<td>3059 (−2,304, 8,406)</td>
<td>10,856</td>
<td>10,078</td>
<td>0.778 (0.205, 1.358)</td>
<td>3,932</td>
<td>10.3</td>
<td>0.0</td>
<td>99.8</td>
<td></td>
</tr>
<tr>
<td>Female (n=527)</td>
<td>131,295</td>
<td>122,046</td>
<td>9249 (−7,29, 18,900)</td>
<td>10,311</td>
<td>9,801</td>
<td>0.510 (−1,427)</td>
<td>18,135</td>
<td>0.6</td>
<td>11.0</td>
<td>77.3</td>
<td></td>
</tr>
<tr>
<td>Age &lt;60 (n=624)</td>
<td>136,342</td>
<td>125,152</td>
<td>11,190 (36,56, 18,572)</td>
<td>13,897</td>
<td>12,737</td>
<td>1.160 (0.526, 1.838)</td>
<td>9,647</td>
<td>0.3</td>
<td>0.0</td>
<td>99.8</td>
<td></td>
</tr>
<tr>
<td>Age 60–69 (n=621)</td>
<td>106,301</td>
<td>108,066</td>
<td>1765 (−9533, 5504)</td>
<td>9,947</td>
<td>9,671</td>
<td>0.276 (−0.486, 0.938)</td>
<td>CABG Dominant</td>
<td>45.7</td>
<td>1.1</td>
<td>80.5</td>
<td></td>
</tr>
<tr>
<td>Age ≥70 (n=610)</td>
<td>93,926</td>
<td>87,034</td>
<td>6892 (−30,18, 15,804)</td>
<td>6,853</td>
<td>6,459</td>
<td>0.349 (−1,159)</td>
<td>19,748</td>
<td>2.5</td>
<td>15.1</td>
<td>71.9</td>
<td></td>
</tr>
<tr>
<td>SYNTAX score &lt;23 (n=657)</td>
<td>113,201</td>
<td>104,417</td>
<td>8784 (753, 16,272)</td>
<td>10,883</td>
<td>10,477</td>
<td>0.407 (−1,110)</td>
<td>21,582</td>
<td>0.3</td>
<td>14.7</td>
<td>73.5</td>
<td></td>
</tr>
<tr>
<td>SYNTAX score 23-32 (n=828)</td>
<td>115,602</td>
<td>111,441</td>
<td>4160 (−36,70, 11,619)</td>
<td>10,728</td>
<td>9,731</td>
<td>0.977 (0.225, 1.699)</td>
<td>4,172</td>
<td>13.7</td>
<td>0.1</td>
<td>99.2</td>
<td></td>
</tr>
<tr>
<td>SYNTAX score &gt;32 (n=359)</td>
<td>114,220</td>
<td>113,247</td>
<td>973 (−10,177, 11,337)</td>
<td>10,177</td>
<td>9,883</td>
<td>0.315 (−1,373)</td>
<td>3,088</td>
<td>22.9</td>
<td>7.3</td>
<td>72.4</td>
<td></td>
</tr>
<tr>
<td>LAD (n=1695)</td>
<td>115,124</td>
<td>109,463</td>
<td>5661 (505, 10,981)</td>
<td>10,713</td>
<td>9,991</td>
<td>0.722 (0.203, 1.239)</td>
<td>7,841</td>
<td>1.7</td>
<td>0.3</td>
<td>99.4</td>
<td></td>
</tr>
<tr>
<td>No LAD (n=150)</td>
<td>105,875</td>
<td>108,189</td>
<td>2314 (−52,357, 10,225)</td>
<td>10,126</td>
<td>10,239</td>
<td>−0.112 (−6,313, 1.313)</td>
<td>Not estimable</td>
<td>18.0</td>
<td>8.6</td>
<td>43.7</td>
<td></td>
</tr>
<tr>
<td>2 vessel disease (n=310)</td>
<td>103,264</td>
<td>92,313</td>
<td>10,850 (−24,86, 21,181)</td>
<td>11,029</td>
<td>10,312</td>
<td>0.718 (−1,343, 1.739)</td>
<td>15,251</td>
<td>0.6</td>
<td>11.2</td>
<td>78.8</td>
<td></td>
</tr>
<tr>
<td>3 vessel disease (n=1534)</td>
<td>116,891</td>
<td>112,830</td>
<td>4061 (−13,67, 9,483)</td>
<td>10,634</td>
<td>9,937</td>
<td>0.697 (0.141, 1.248)</td>
<td>5,826</td>
<td>6.6</td>
<td>0.3</td>
<td>99.2</td>
<td></td>
</tr>
<tr>
<td>HgbA1c &lt; 7 (n=617)</td>
<td>103,579</td>
<td>103,852</td>
<td>273 (−8,879, 7,142)</td>
<td>10,262</td>
<td>9,934</td>
<td>0.328 (−0,482, 1,132)</td>
<td>CABG Dominant</td>
<td>34.6</td>
<td>2.0</td>
<td>80.8</td>
<td></td>
</tr>
<tr>
<td>HgbA1c ≥ 7 (n=1,096)</td>
<td>120,399</td>
<td>111,189</td>
<td>8507 (16,18, 15,266)</td>
<td>11,011</td>
<td>10,064</td>
<td>0.946 (0.297, 1,547)</td>
<td>8,993</td>
<td>0.5</td>
<td>0.4</td>
<td>99.5</td>
<td></td>
</tr>
<tr>
<td>US (n=351)</td>
<td>126,113</td>
<td>121,412</td>
<td>4701 (−7,997, 17,253)</td>
<td>10,796</td>
<td>9,676</td>
<td>1.120 (0.084, 2.033)</td>
<td>4,197</td>
<td>21.8</td>
<td>0.3</td>
<td>98.1</td>
<td></td>
</tr>
<tr>
<td>Non-US (n=1,504)</td>
<td>111,978</td>
<td>108,356</td>
<td>5622 (506, 10,653)</td>
<td>10,655</td>
<td>10,079</td>
<td>0.576 (0.006, 1,144)</td>
<td>9,760</td>
<td>1.0</td>
<td>2.0</td>
<td>96.5</td>
<td></td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; HgbA1c, hemoglobin A1C; ICER, incremental cost-effectiveness ratio; LAD, left anterior descending artery stenosis; PCI, percutaneous coronary intervention; QALY, quality-adjusted life-years gained; SYNTAX, Synergy between PCI with TAXUS and Cardiac Surgery; and US, United States enrollment.

*All subgroup analyses based on mITT population using base case assumptions for the relative effect of CABG on survival and costs.

may not be generalizable to a setting characterized by exclusive use of second-generation DES for PCI. No studies, however, have demonstrated a mortality reduction with second- versus first-generation DES,36 and it is the mortality reduction obtained from CABG that primarily drives the favorable cost-effectiveness results in our study.

Conclusions

In FREEDOM, the largest randomized trial to compare CABG versus DES-PCI for the treatment of diabetic patients with multivessel CAD, we found that CABG provides not only better long-term clinical outcomes than DES-PCI but that these benefits are achieved at an overall cost that represents an attractive use of societal health care resources. These findings suggest that existing guidelines that recommend CABG for diabetic patients with multivessel CAD remain appropriate in current practice and may provide additional support for strengthening those recommendations.

Acknowledgments

We thank Khaja Chinnakondepalli for his programming support for this analysis.

Sources of Funding

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Disclosures

Dr Magnuson has received grant support from Abbott Vascular, Astra Zeneca, Boston Scientific, Daiichi Sankyo, Edwards Lifesciences, Eli Lilly, and Medtronic. Dr Farkouh has received grant support from Eli Lilly and other research support from Boston Scientific, Bristol-Myers Squibb, Cordis, Eli Lilly, and Sanofi-Aventis. Dr Cohen has received grant support from Abbott Vascular, Astra Zeneca, Biomet, Boston
Scientific, Edwards Lifesciences, Eli Lilly, Janssen Pharmaceuticals, and Medtronic and consulting fees from Abbott Vascular, Astra Zeneca, Eli Lilly and Medtronic. The other authors report no conflicts.

References


Clinical results from the Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) Trial showed that for patients with diabetes and multivessel coronary artery disease, coronary artery bypass graft (CABG) versus percutaneous coronary intervention (PCI) with drug-eluting stents was associated with lower rates of death, myocardial infarction, or stroke, with the benefit driven by significant reductions in both death and myocardial infarction. This prospective economic evaluation was performed to provide additional insight into the relative value of CABG versus PCI in the drug-eluting stents era from the perspective of the US healthcare system. FREEDOM enrolled patients with complex coronary artery disease and approximately one-third of PCI patients required more than one index PCI procedure, with a mean of 4.1 drug-eluting stents implanted per patient. Total procedure costs were roughly $3000 higher with PCI ($13,000 versus $9,700), whereas postprocedure costs were twice as high with CABG, yielding total hospitalization costs that were $8,600 higher with CABG ($35,000 versus $26,000). Over the 5-year follow-up period, higher initial costs with CABG were offset by lower costs associated with the need for repeat revascularization, yielding incremental costs with CABG of $3600 at 5 years. Cost-effectiveness analysis based on lifetime projections of quality-adjusted life-years and costs demonstrated that CABG was a highly cost-effective treatment with an incremental cost-effectiveness ratio of roughly $8000 quality-adjusted life-year gained, and showed similarly favorable results across a broad range of sensitivity and subgroup analyses. These findings therefore provide additional support for existing guidelines that recommend CABG for diabetic patients with multivessel coronary artery disease.
Cost-Effectiveness of Percutaneous Coronary Intervention With Drug Eluting Stents Versus Bypass Surgery for Patients With Diabetes Mellitus and Multivessel Coronary Artery Disease: Results From the FREEDOM Trial
Elizabeth A. Magnuson, Michael E. Farkouh, Valentin Fuster, Kaijun Wang, Katherine Vilain, Haiyan Li, Jaime Appelwick, Victoria Muratov, Lynn A. Sleeper, Robin Boineau, Mouin Abdallah and David J. Cohen on behalf of the FREEDOM Trial Investigators

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http://circ.ahajournals.org/content/suppl/2012/12/30/CIRCULATIONAHA.112.147488.DC1

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# SUPPLEMENTAL MATERIAL

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<tr>
<td>Lifetime Cost-Effectiveness Results for Subgroups in Terms of Cost per Life Year Gained</td>
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## Supplemental Table 1. MedPAR Model: Hospital Cost Estimates (2010 US$)

<table>
<thead>
<tr>
<th>Model Variable</th>
<th>CABG (n= 43,866)</th>
<th>PCI (n= 113,921)</th>
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<td>Intercept* (uncomplicated hospitalization, non-procedure costs)</td>
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<td>6,227</td>
</tr>
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<td>Demographics</td>
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<tr>
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<tr>
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<td>622</td>
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<tr>
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<tr>
<td>COPD</td>
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<td>620</td>
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<tr>
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<td>Cardiogenic shock</td>
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*intercepts have been adjusted to exclude the cost of otherwise uncomplicated procedures
Supplemental Table 2. MedPAR Model: Hospital LOS Estimates

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**Supplemental Table 3. Linear Regression Prediction Model for Long-term Costs**

<table>
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<tr>
<th>Parameter</th>
<th>Coefficient Estimate ($)</th>
<th>p-value</th>
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<td>0.0009</td>
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<td>CABG</td>
<td>-1,672</td>
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</tr>
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<td>Age (years)</td>
<td>18</td>
<td>0.40</td>
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<tr>
<td>Female</td>
<td>1,068</td>
<td>0.0102</td>
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<tr>
<td>3 vessel disease</td>
<td>1,353</td>
<td>0.0058</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td>4,491</td>
<td>0.0003</td>
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<tr>
<td>History of peripheral artery disease</td>
<td>1,894</td>
<td>0.0041</td>
</tr>
<tr>
<td>MI during trial</td>
<td>3,526</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stroke during trial but &gt; 1 yr previously</td>
<td>4,810</td>
<td>0.05</td>
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<tr>
<td>Stroke within the past year*</td>
<td>16,575</td>
<td>&lt;0.0001</td>
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</table>

*this coefficient was eliminated in the patient-level prediction of annual long-term costs, which includes only the long term impact of stroke events that occurred during the course of the trial.

**Supplemental Table 4. Linear Regression Prediction Model for Follow-up Utility Weights**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient Estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.9312</td>
<td>&lt;0.0001</td>
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<td>Age (years)</td>
<td>-0.00028</td>
<td>0.22</td>
</tr>
<tr>
<td>Female</td>
<td>-0.0625</td>
<td>&lt;0.0001</td>
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<tr>
<td>History of MI</td>
<td>-0.0205</td>
<td>&lt;0.0001</td>
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<tr>
<td>History of Stroke</td>
<td>-0.0226</td>
<td>0.066</td>
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<tr>
<td>History of Cerebrovascular Disease</td>
<td>-0.0618</td>
<td>&lt;0.0001</td>
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<tr>
<td>History of Peripheral Artery Disease</td>
<td>-0.0304</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI during trial</td>
<td>-0.0419</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke during trial but &gt; 1 yr previously</td>
<td>-0.0663</td>
<td>0.014</td>
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<tr>
<td>Stroke within the past year*</td>
<td>-0.1033</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

*this coefficient was eliminated in the patient-level prediction of long-term utility, which includes only the long term impact of stroke events that occurred during the course of the trial.
Supplemental Table 5. Lifetime Cost-Effectiveness Results for Base Case and Sensitivity Analyses in Terms of Cost per Life Year Gained

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Cost ($ with CABG)</th>
<th>Cost ($ with PCI)</th>
<th>$ \Delta_{C,P}$ Cost ($) (95% CI)</th>
<th>Life Years with CABG</th>
<th>Life Years with PCI</th>
<th>Life Years Gained with CABG (95% CI)</th>
<th>ICER: Cost ($) per Life Year gained</th>
<th>% Dominant</th>
<th>% Dominated</th>
<th>% &lt; $50K</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base Case:</strong> Lifetime – ITT</td>
<td>114,571</td>
<td>109,179</td>
<td>5,392 (399, 10,320)</td>
<td>12.177</td>
<td>11.383</td>
<td>0.794 (0.243, 1.323)</td>
<td>6,791</td>
<td>1.5</td>
<td>0.2</td>
<td>99.7</td>
</tr>
<tr>
<td>Lifetime – Per Protocol</td>
<td>114,855</td>
<td>108,878</td>
<td>5,976 (1,207, 10,925)</td>
<td>12.202</td>
<td>11.351</td>
<td>0.851 (0.284, 1.432)</td>
<td>7,022</td>
<td>0.7</td>
<td>0.0</td>
<td>99.6</td>
</tr>
<tr>
<td>10 year analysis – ITT</td>
<td>81,710</td>
<td>80,295</td>
<td>1,416 (-2,061, 5,017)</td>
<td>7.626</td>
<td>7.339</td>
<td>0.287 (0.015, 0.550)</td>
<td>4,934</td>
<td>23.4</td>
<td>0.7</td>
<td>97.3</td>
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<tr>
<td>Lifetime - ITT, no CABG effect on long term costs</td>
<td>121,244</td>
<td>109,179</td>
<td>12,045 (6,933, 17,103)</td>
<td>12.177</td>
<td>11.383</td>
<td>0.794 (0.243, 1.323)</td>
<td>15,170</td>
<td>0.0</td>
<td>0.3</td>
<td>98.6</td>
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<td><strong>Tapered CABG Effect Between 5 and 10 Years</strong></td>
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<td><strong>Fixed CABG Effect Between 5 and 10 Years</strong></td>
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<tr>
<td>Lifetime analysis</td>
<td>116,147</td>
<td>109,179</td>
<td>6,968 (1,273, 12,327)</td>
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<td>11.383</td>
<td>1.023 (0.352, 1.660)</td>
<td>6,811</td>
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<td>99.8</td>
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<td>80,295</td>
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<td>7.339</td>
<td>0.309 (0.037, 0.619)</td>
<td>5,019</td>
<td>18.9</td>
<td>0.3</td>
<td>98.5</td>
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<tr>
<td><strong>No Effect of CABG after 5 Years</strong></td>
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<tr>
<td>Lifetime analysis</td>
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<td>109,179</td>
<td>9,485 (4,905, 13,995)</td>
<td>11.822</td>
<td>11.383</td>
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<tr>
<td>10 year analysis</td>
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<td>80,295</td>
<td>6,861 (3,408, 10,230)</td>
<td>7.463</td>
<td>7.339</td>
<td>0.124 (-0.073, 0.308)</td>
<td>55,331</td>
<td>0.0</td>
<td>9.6</td>
<td>42.5</td>
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</table>
Supplemental Table 6. Lifetime Cost-Effectiveness Results for Subgroups in Terms of Cost per Life Year Gained

<table>
<thead>
<tr>
<th>SUBGROUP ANALYSES BASED ON BASE CASE ASSUMPTIONS</th>
<th>Cost ($) with CABG</th>
<th>Cost ($) with PCI</th>
<th>$\Delta_{C-P}$ Cost ($) (95% CI)</th>
<th>Life Years with CABG</th>
<th>Life Years with PCI</th>
<th>Life Years Gained with CABG (95% CI)</th>
<th>ICER: Cost ($) per Life Year Gained</th>
<th>% Dominant</th>
<th>% Dominated</th>
<th>% &lt; $50K</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNTAX Score &lt;23 (n=657)</td>
<td>113,201</td>
<td>104,417</td>
<td>8,784 (753, 16,272)</td>
<td>12.429</td>
<td>11.939</td>
<td>0.491 (-0.526, 1.394)</td>
<td>17,890</td>
<td>0.3</td>
<td>13.3</td>
<td>77.9</td>
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<tr>
<td>SYNTAX Score 23-32 (n=828)</td>
<td>115,602</td>
<td>111,441</td>
<td>4,160 (-3,670, 11,619)</td>
<td>12.221</td>
<td>11.113</td>
<td>1.107 (0.266, 1.893)</td>
<td>3,758</td>
<td>13.6</td>
<td>0.1</td>
<td>99.2</td>
</tr>
<tr>
<td>SYNTAX Score &gt;32 (n=359)</td>
<td>114,220</td>
<td>113,247</td>
<td>973 (-10,177, 11,337)</td>
<td>11.663</td>
<td>11.095</td>
<td>0.568 (-0.713, 1.743)</td>
<td>1,713</td>
<td>29.5</td>
<td>3.0</td>
<td>83.5</td>
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<tr>
<td>Male (n=1328)</td>
<td>107,527</td>
<td>104,468</td>
<td>3,059 (-2,304, 8,406)</td>
<td>12.124</td>
<td>11.243</td>
<td>0.882 (0.241, 1.515)</td>
<td>3,468</td>
<td>10.3</td>
<td>0.0</td>
<td>99.9</td>
</tr>
<tr>
<td>Female (n=527)</td>
<td>131,295</td>
<td>122,046</td>
<td>9,249 (-729, 18,900)</td>
<td>12.383</td>
<td>11.766</td>
<td>0.618 (-0.621, 1.705)</td>
<td>14,966</td>
<td>0.6</td>
<td>10.8</td>
<td>79.3</td>
</tr>
<tr>
<td>Age &lt;60 (n=624)</td>
<td>136,342</td>
<td>125,152</td>
<td>11,190 (3,656, 18,572)</td>
<td>15.850</td>
<td>14.419</td>
<td>1.431 (0.745, 2.205)</td>
<td>7,820</td>
<td>0.3</td>
<td>0.0</td>
<td>100</td>
</tr>
<tr>
<td>Age 60-69 (n=621)</td>
<td>106,301</td>
<td>108,066</td>
<td>-1,765 (-9,533, 5,504)</td>
<td>11.319</td>
<td>11.003</td>
<td>0.316 (-0.567, 1.070)</td>
<td>44.7</td>
<td>0.6</td>
<td>79.8</td>
<td></td>
</tr>
<tr>
<td>Age ≥70 (n=610)</td>
<td>93,926</td>
<td>87,034</td>
<td>6,892 (-3,018, 15,804)</td>
<td>7.899</td>
<td>7.464</td>
<td>0.435 (-0.687, 1.306)</td>
<td>15,844</td>
<td>2.2</td>
<td>15.3</td>
<td>72.6</td>
</tr>
<tr>
<td>LAD (n=1695)</td>
<td>115,124</td>
<td>109,463</td>
<td>5,661 (505, 10,981)</td>
<td>12.229</td>
<td>11.363</td>
<td>0.866 (0.280, 1.436)</td>
<td>6,537</td>
<td>1.7</td>
<td>0.1</td>
<td>99.6</td>
</tr>
<tr>
<td>No LAD (n=150)</td>
<td>105,875</td>
<td>108,189</td>
<td>-2,314 (-52,357, 10,225)</td>
<td>11.562</td>
<td>11.723</td>
<td>-0.161 (-8.027, 1.420)</td>
<td>16.7</td>
<td>8.0</td>
<td>42.6</td>
<td></td>
</tr>
<tr>
<td>2 vessel disease (n=310)</td>
<td>103,264</td>
<td>92,313</td>
<td>10,950 (-2,486, 21,181)</td>
<td>12.580</td>
<td>11.712</td>
<td>0.867 (-1.516, 2.075)</td>
<td>12.630</td>
<td>0.5</td>
<td>10.1</td>
<td>82.0</td>
</tr>
<tr>
<td>3+ vessel disease (n=1534)</td>
<td>116,891</td>
<td>112,830</td>
<td>4,061 (-1,367, 9,483)</td>
<td>12.142</td>
<td>11.312</td>
<td>0.830 (0.233, 1.438)</td>
<td>4,893</td>
<td>6.6</td>
<td>0.1</td>
<td>99.9</td>
</tr>
<tr>
<td>HgbA1c &lt; 7 (n=617)</td>
<td>103,579</td>
<td>103,852</td>
<td>-273 (-6,879, 7,142)</td>
<td>11.610</td>
<td>11.263</td>
<td>0.347 (-0.609, 1.247)</td>
<td>33.9</td>
<td>2.1</td>
<td>78.4</td>
<td></td>
</tr>
<tr>
<td>HgbA1c ≥ 7 (n=1096)</td>
<td>120,399</td>
<td>111,893</td>
<td>8,507 (1,618, 15,266)</td>
<td>12.605</td>
<td>11.480</td>
<td>1.126 (0.381, 1.827)</td>
<td>7,555</td>
<td>0.5</td>
<td>0.3</td>
<td>99.5</td>
</tr>
<tr>
<td>US (n=351)</td>
<td>126,113</td>
<td>121,412</td>
<td>4,701 (-7,997, 17,253)</td>
<td>12.379</td>
<td>11.039</td>
<td>1.339 (0.176, 2.353)</td>
<td>3,511</td>
<td>22.1</td>
<td>0.3</td>
<td>99.0</td>
</tr>
<tr>
<td>Non-US (n=1504)</td>
<td>111,978</td>
<td>106,356</td>
<td>5,622 (506, 10,653)</td>
<td>12.151</td>
<td>11.462</td>
<td>0.689 (0.025, 1.348)</td>
<td>8,160</td>
<td>1.0</td>
<td>1.6</td>
<td>97.4</td>
</tr>
</tbody>
</table>