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Drug-Eluting Stents vs. Coronary-Artery Bypass Grafting in Multivessel Coronary Disease

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ABSTRACT

BACKGROUND

Numerous studies have compared the outcomes of two competing interventions for multivessel coronary artery disease: coronary-artery bypass grafting (CABG) and coronary stenting. However, little information has become available since the introduction of drug-eluting stents.

METHODS

We identified patients with multivessel disease who received drug-eluting stents or underwent CABG in New York State between October 1, 2003, and December 31, 2004, and we compared adverse outcomes (death, death or myocardial infarction, or repeat revascularization) through December 31, 2005, after adjustment for differences in baseline risk factors among the patients.

RESULTS

In comparison with treatment with a drug-eluting stent, CABG was associated with lower 18-month rates of death and of death or myocardial infarction both for patients with three-vessel disease and for patients with two-vessel disease. Among patients with three-vessel disease who underwent CABG, as compared with those who received a stent, the adjusted hazard ratio for death was 0.80 (95% confidence interval [CI], 0.65 to 0.97) and the adjusted survival rate was 94.0% versus 92.7% ($P=0.03$); the adjusted hazard ratio for death or myocardial infarction was 0.75 (95% CI, 0.63 to 0.89) and the adjusted rate of survival free from myocardial infarction was 92.1% versus 89.7% ($P<0.001$). Among patients with two-vessel disease who underwent CABG, as compared with those who received a stent, the adjusted hazard ratio for death was 0.71 (95% CI, 0.57 to 0.89) and the adjusted survival rate was 96.0% versus 94.6% ($P=0.003$); the adjusted hazard ratio for death or myocardial infarction was 0.71 (95% CI, 0.59 to 0.87) and the adjusted rate of survival free from myocardial infarction was 94.5% versus 92.5% ($P<0.001$). Patients undergoing CABG also had lower rates of repeat revascularization.

CONCLUSIONS

For patients with multivessel disease, CABG continues to be associated with lower mortality rates than does treatment with drug-eluting stents and is also associated with lower rates of death or myocardial infarction and repeat revascularization.

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Several studies have compared the long-term outcomes of coronary-artery bypass grafting (CABG) and coronary stenting.¹⁻⁵ In 2003, drug-eluting stents were introduced for the purpose of reducing restenosis, which has continued to be a problem associated with the use of bare-metal stents. Many randomized, controlled trials have documented lower rates of clinical and angiographic restenosis, target-lesion revascularization, and major adverse cardiac events with drug-eluting stents.⁶⁻²⁰ However, recent reports of the danger of late stent thrombosis among patients with drug-eluting stents^{21,22} led to a meeting of a Food and Drug Administration (FDA) advisory committee that addressed the safety of drug-eluting stents.^{23,24}

Consequently, it is not clear whether the relative outcomes reported in earlier studies that compared CABG with coronary stenting are reflective of current practice. The purpose of this study is to compare rates of death, death or myocardial infarction, and subsequent revascularization in patients receiving drug-eluting stents and those undergoing CABG in New York State.

METHODS

DATABASES

The two primary databases used in the study were the Cardiac Surgery Reporting System (CSRS) and the Percutaneous Coronary Intervention Reporting System (PCIRS) of the New York State Department of Health. These registries were developed in 1989 and 1991, respectively, for the purpose of collecting information on all residents of New York State who undergo CABG and percutaneous coronary intervention (PCI) in nonfederal hospitals in the state. The registries contain information on demographics, coexisting conditions, left ventricular function, hemodynamic state, diseased vessels and vessels for which surgery or angioplasty was attempted, hospital and operator identifiers, and in-hospital adverse outcomes. Uniform definitions for these elements are used in the databases. The PCIRS also contains information on the type or types of device used for each patient, including bare-metal stents and drug-eluting stents. Efforts to ensure the accuracy and completeness of these data have been described elsewhere.⁵

Information on deaths of residents of New

York State after discharge from the hospital was obtained by matching the patients in each of the registries with the state Vital Statistics Death file with the use of patient identifiers. CSRS and PCIRS were also linked with the state administrative acute care discharge-reporting system, the Statewide Planning and Research Cooperative System (SPARCS). The SPARCS contains information on patient demographics (age, sex, and race), diagnoses and procedures, admission and discharge dates, and discharge disposition for all patients discharged from nonfederal acute care hospitals in New York State. CSRS and PCIRS records were matched with SPARCS records by using unique hospital identifiers along with patient identifiers and dates of admission, surgery, and discharge. Subsequent emergency hospitalizations with myocardial infarction as the principal diagnosis were then identified.

STUDY GROUP AND END POINTS

The study includes patients who were treated with drug-eluting stents (with or without other devices) or CABG from October 1, 2003, to December 31, 2004. This strategy was chosen to avoid the start-up period for drug-eluting stents between April and September 2003.

Patients were excluded if they had previously undergone revascularization (6061 patients), had left main coronary artery disease (3188 patients), had had a recent myocardial infarction (within 24 hours before treatment) (1768 patients), or were not residents of New York State (678 patients). The remaining patients, who included 9963 patients receiving drug-eluting stents and 7437 patients undergoing CABG between October 1, 2003, and December 31, 2004, were followed through December 31, 2005, for myocardial infarction resulting in readmission, death, and repeat revascularization.

The end points of the study were death in the hospital or within 30 days after treatment and death, death or myocardial infarction, and revascularization up to 18 months after treatment. Myocardial infarctions as complications were defined as either complications at the index admission (defined as new Q waves in both the CSRS and the PCIRS) or myocardial infarctions at readmission (defined as an emergency admission with a principal diagnosis of myocardial infarction).

STATISTICAL ANALYSIS

The main purpose of the study was to compare differences in adverse outcomes between the two procedures. Another purpose, identified at the beginning of the study, was to compare adverse outcomes in subgroups of patients at high risk (patients with diabetes, patients 80 or more years of age, and patients with low left ventricular ejection fractions).

The prevalence rates of risk factors and characteristics (demographic features, left ventricular function, hemodynamics, and coexisting conditions) of the patients in the two treatment groups were compared by the chi-square test and Fisher's exact test. Kaplan–Meier estimates were used to plot the rates of subsequent revascularization; data from patients who died before subsequent revascularization were censored. The risk-adjusted odds ratios for in-hospital and 30-day mortality were calculated with the use of a stepwise logistic-regression model with patient risk factors as independent control variables and type of procedure included in the model as the independent study variable of interest.

Differences in risk-adjusted, long-term rates of death and of death or myocardial infarction between patients undergoing the two procedures were investigated by developing stepwise Cox proportional-hazards models after confirmation that the proportional-hazards assumption was justified.²⁵ Candidate independent variables included left ventricular function, hemodynamics, and coexisting conditions. Treatment type (drug-eluting stent or CABG) was included in each model in order to obtain hazard ratios for CABG as compared with drug-eluting stent after adjustment for covariates that are significant predictors of adverse outcomes. Separate models were developed for combinations of the two outcomes and four anatomical groups defined by the number of diseased vessels and by the presence or absence of disease in the proximal left anterior descending (LAD) coronary artery. Data from patients with two-vessel disease who had no LAD artery disease and from patients with two-vessel disease who had nonproximal LAD artery disease were combined because of sample-size considerations and similar outcomes. Separate models were developed for each of the outcomes for all patients with three-vessel disease and all patients with two-vessel disease. Disease was defined as stenosis of at least 70%.

Two-vessel disease was defined as disease in two of the three major epicardial vessels, and three-vessel disease as disease in all three vessels.

Adjusted Kaplan–Meier survival curves were constructed for each type of procedure for patients with two-vessel and three-vessel disease with the use of the Cox proportional-hazards models and methods for calculating adjusted survival.²⁶ Cox proportional-hazards models were also used to test for significance of the hazard ratios for three subgroups of patients: patients with diabetes, patients 80 or more years of age, and patients with left ventricular ejection fractions below 40%.

A propensity model was then used to test for selection bias.^{27,28} The significant predictors of type of procedure (CABG or drug-eluting stent) were identified by fitting a stepwise logistic-regression model with a binary dependent variable representing CABG versus drug-eluting stent, with candidate variables consisting of the patient-related predictors of the type of procedure used. For each anatomical group, the patients' propensity scores were subdivided into quartiles, and risk-adjusted hazard ratios for CABG versus drug-eluting stent were computed for each quartile. Hazard ratios were compared across quartiles. All reported P values are two-sided and are not adjusted for multiple testing. All analyses were performed with SAS software (version 9.1).

RESULTS

Table 1 presents the prevalence rates of risk factors among patients treated with CABG and among those treated with drug-eluting stents. Patients undergoing CABG were on average older (although more patients over 80 years of age were treated with stents than with CABG) and were more likely to be male, to be non-Hispanic, to be white, to have lower ejection fractions, to have had previous myocardial infarctions, to have other coexisting conditions, and to have three-vessel disease. There were no significant differences between the two groups in the risk-adjusted rates of in-hospital or 30-day mortality (adjusted odds ratio, 1.29; 95% confidence interval [CI], 0.92 to 1.81; $P=0.15$).

Figure 1 shows that the rate of revascularization within 18 months after the initial procedure was higher for patients receiving drug-eluting stents. Of patients who received drug-eluting

stents, 28.4% underwent repeat PCI (e.g., stenting or balloon angioplasty) and 2.2% underwent CABG within 18 months. The respective rates for patients undergoing CABG were 5.1% and 0.1%; both differences are statistically significant ($P<0.001$). Of patients who received drug-eluting stents, 12.5% underwent repeat PCI within 30 days and 18.3% underwent repeat PCI within 60 days. Many of these patients may have undergone planned PCI associated with incomplete revascularization during the index admission. Of the 28.4% of patients who underwent repeat PCI during the study period, only a little more than one quarter (7.0%) underwent target-vessel revascularization.

The mean follow-up times were 19.1 months

for patients undergoing CABG and 18.7 months for those receiving drug-eluting stents. Table 2 presents follow-up times according to treatment and anatomical group. Table 2 also presents adjusted hazard ratios (CABG vs. drug-eluting stent) for mortality among patients in six anatomical groups: all patients with three-vessel disease, those with three-vessel disease including proximal LAD artery involvement, those with three-vessel disease without proximal LAD artery involvement, all patients with two-vessel disease, those with two-vessel disease including proximal LAD artery involvement, and those with two-vessel disease without proximal LAD artery involvement. Figures 2 and 3 present the 18-month unadjusted and adjusted rates of sur-

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

Risk Factor	CABG (N=7437)	Stent (N=9963)	P Value
Age (%)			<0.001
<50 yr	7.6	9.7	
50–59 yr	20.7	23.1	
60–69 yr	30.2	27.6	
70–79 yr	31.3	26.9	
≥80 yr	10.2	12.7	
Median age (yr)	67.0	66.0	<0.001
Mean age (yr)	66.0±10.9	65.4±11.9	<0.001
Sex (%)			<0.001
Male	72.5	67.2	
Female	27.5	32.8	
Hispanic ethnic background (%) †	6.9	9.3	<0.001
Race (%) †			<0.001
White	87.7	82.1	
Black	7.1	10.1	
Other	5.2	7.9	
Ejection fraction (%)			<0.001
<20%	2.0	0.8	
20–29%	6.8	3.3	
30–39%	12.9	6.6	
≥40%	77.7	84.2	
Data missing	0.6	5.1	
Previous myocardial infarction (%)			<0.001
1–7 days before treatment	20.5	18.9	
8–20 days before treatment	5.6	2.5	
≥21 days before treatment	21.4	12.3	
No previous myocardial infarction	52.5	66.3	

Table 1. (Continued.)

Risk Factor	CABG (N=7437)	Stent (N=9963)	P Value
Cerebrovascular disease (%)	17.3	7.7	<0.001
Peripheral arterial disease (%)	10.7	7.0	<0.001
Hemodynamic instability or shock (%)	1.8	0.2	<0.001
Congestive heart failure (%)			<0.001
None	84.3	89.9	
At current admission	12.6	7.4	
Before current admission	3.1	2.7	
Malignant ventricular arrhythmia (%)	0.7	0.4	0.03
Chronic obstructive pulmonary disease (%)	17.4	6.6	<0.001
Diabetes (%)	38.2	32.7	<0.001
Renal failure (%)			0.01
Requiring dialysis	2.2	2.4	
Creatinine >2.5 mg/dl (220 μmol/liter)	2.0	1.4	
No renal failure	95.8	96.3	
No. of diseased vessels (%)‡			<0.001
3, with proximal LAD artery	51.5	11.8	
3, without proximal LAD artery	18.4	13.1	
2, with proximal LAD artery	20.0	26.1	
2, without proximal LAD artery	10.1	49.0	

* Plus–minus values are means ±SD. Because of rounding, percentages may not total 100. CABG denotes coronary-artery bypass grafting, and LAD left anterior descending.

† Race or ethnic group was reported by the Cardiac Surgery Reporting System and the Percutaneous Coronary Intervention Reporting System registries.

‡ Diseased vessels were defined by the presence of stenosis of at least 70%.

vival and survival free from myocardial infarction for patients with three-vessel disease treated with drug-eluting stents or CABG and for those with two-vessel disease treated with drug-eluting stents or CABG.

As indicated in Table 2 and Figure 3, CABG was associated with lower 18-month rates of death and of death or myocardial infarction than treatment with a drug-eluting stent for patients with three-vessel disease and for patients with two-vessel disease. Among patients with three-vessel disease who were treated with CABG, as compared with those who received stents, the adjusted hazard ratio for death was 0.80 (95% CI, 0.65 to 0.97), and the adjusted survival rate was 94.0% versus 92.7% (P=0.03); the adjusted hazard ratio for death or myocardial infarction among this group of patients was 0.75 (95% CI, 0.63 to 0.89), and the adjusted

rates of survival free from myocardial infarction were 92.1% versus 89.7% (P<0.001).

Among patients with two-vessel disease treated with CABG, the adjusted hazard ratio for death was 0.71 (95% CI, 0.57 to 0.89) and the adjusted survival rates were 96.0% versus 94.6% (P=0.003); the adjusted hazard ratio for death or myocardial infarction among this group of patients was 0.71 (95% CI, 0.59 to 0.87), and the adjusted rates of survival free from myocardial infarction were 94.5% versus 92.5% (P<0.001). CABG was also associated with significantly lower mortality in patients with two-vessel disease either with involvement of the proximal LAD artery (adjusted hazard ratio, 0.71; 95% CI, 0.53 to 0.96) or without involvement of the proximal LAD artery (adjusted hazard ratio, 0.69; 95% CI, 0.48 to 0.98).

Table 3 presents the rates of death and of

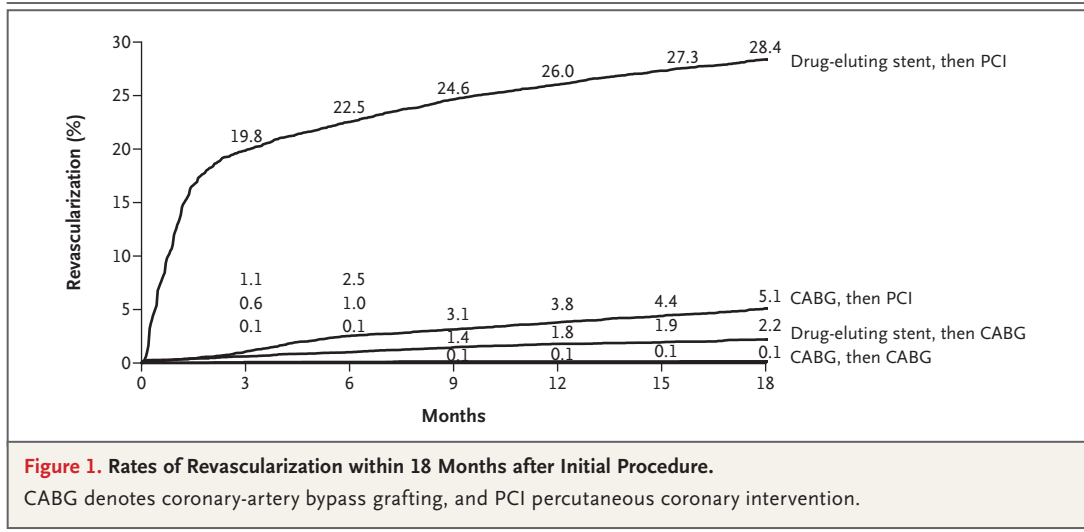
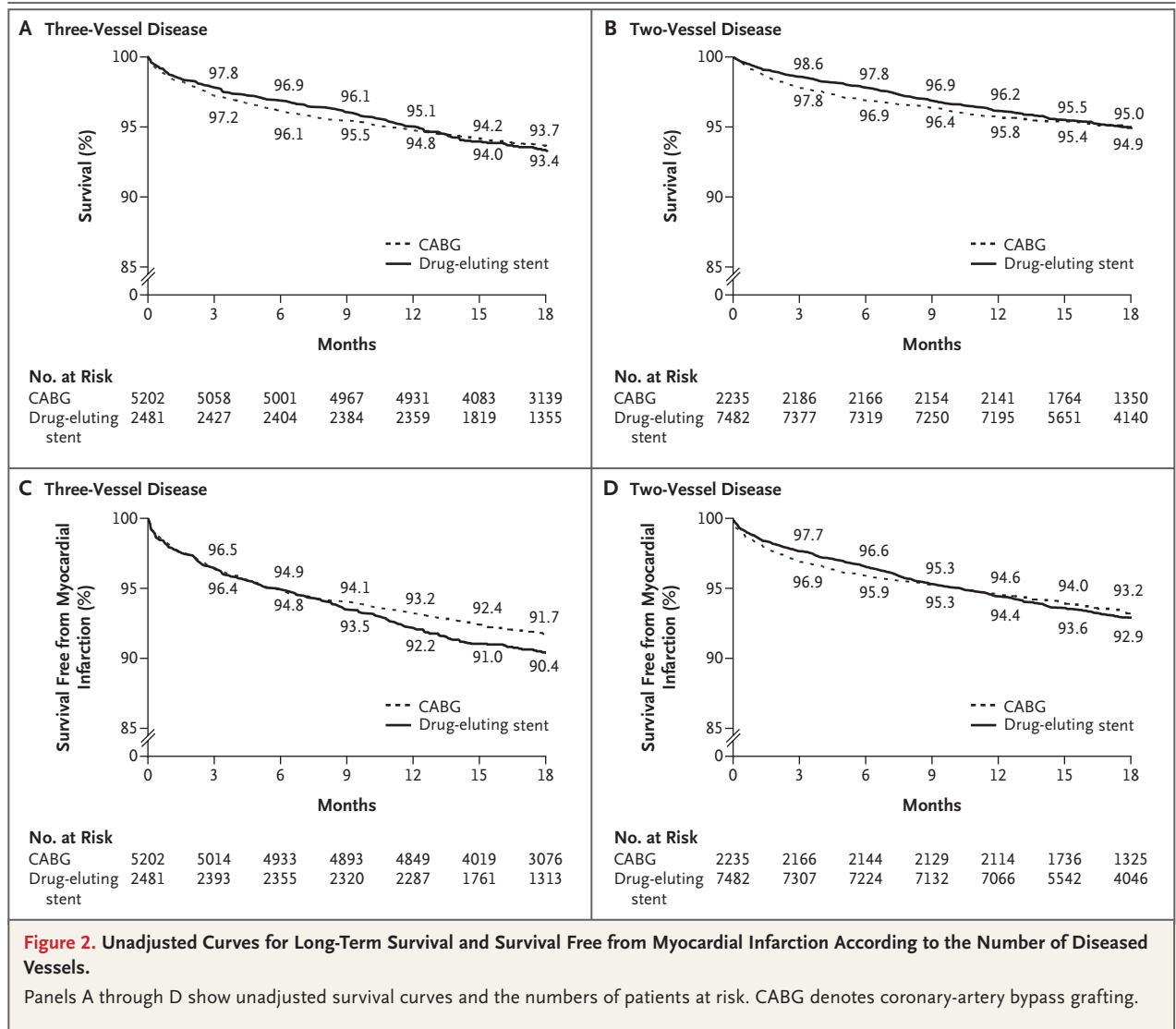


Table 2. Hazard Ratios for Death and for Death or Myocardial Infarction after CABG and after Treatment with a Drug-Eluting Stent, According to Number of Diseased Vessels.*

Variable	No. of Patients	Mean Follow-up <i>mo</i>	Death			Death or Myocardial Infarction		
			No. of Events	Adjusted Hazard Ratio (95% CI)†	P Value	No. of Events	Adjusted Hazard Ratio (95% CI)†	P Value
3 Diseased vessels								
With or without proximal LAD artery								
CABG	5202	19.1	346	0.80 (0.65–0.97)	0.03	449	0.75 (0.63–0.89)	<0.001
Stent	2481	18.5	171	Reference		249	Reference	
With proximal LAD artery								
CABG	3833	19.1	257	0.79 (0.61–1.02)	0.07	331	0.77 (0.61–0.96)	0.02
Stent	1178	18.5	85	Reference		117	Reference	
Without proximal LAD artery								
CABG	1369	19.1	89	0.79 (0.58–1.09)	0.15	118	0.69 (0.53–0.91)	0.008
Stent	1303	18.5	86	Reference		132	Reference	
2 Diseased vessels								
With or without proximal LAD artery								
CABG	2235	19.2	118	0.71 (0.57–0.89)	0.003	156	0.71 (0.59–0.87)	<0.001
Stent	7482	18.7	397	Reference		555	Reference	
With proximal LAD artery								
CABG	1486	19.2	80	0.71 (0.53–0.96)	0.02	105	0.72 (0.56–0.93)	0.01
Stent	2600	18.6	143	Reference		201	Reference	
Without proximal LAD artery								
CABG	749	19.1	38	0.69 (0.48–0.98)	0.04	51	0.71 (0.52–0.96)	0.03
Stent	4882	18.8	254	Reference		354	Reference	

* CABG denotes coronary-artery bypass grafting, and LAD left anterior descending.

† Hazard ratios are adjusted for age; sex; ejection fraction; hemodynamic state; history or no history of myocardial infarction before procedure; presence or absence of cerebrovascular disease, peripheral arterial disease, congestive heart failure, chronic obstructive pulmonary disease, diabetes, and renal failure; and involvement of the proximal LAD artery.



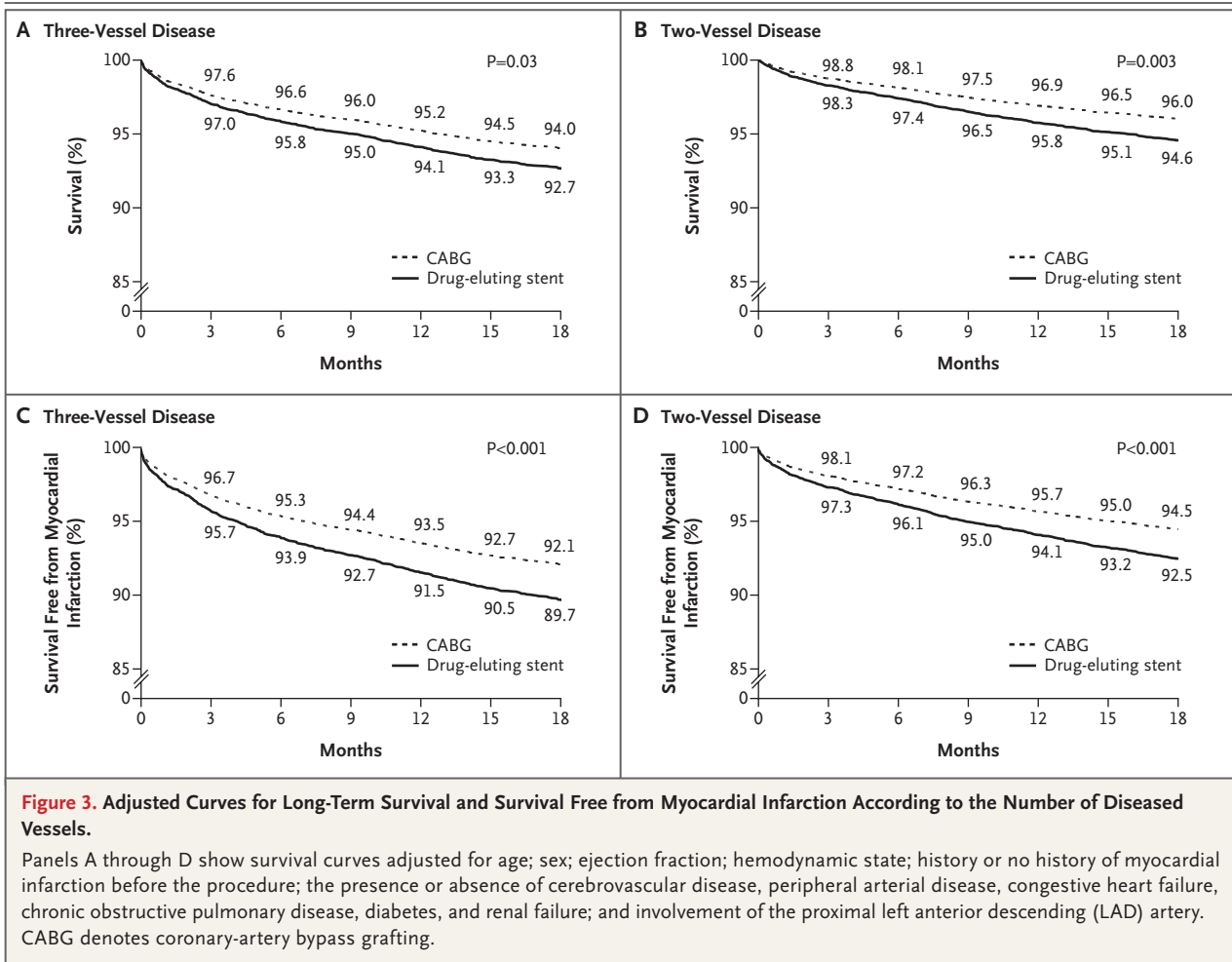
death or myocardial infarction for three subgroups of patients treated with drug-eluting stents or CABG who were chosen at the outset of the study. There were no significant differences in mortality among any of the subgroups. However, the rate of death or myocardial infarction was significantly lower for those treated with CABG among patients with ejection fractions below 40% (adjusted hazard ratio, 0.67; 95% CI, 0.53 to 0.84) and patients who were at least 80 years old (adjusted hazard ratio, 0.74; 95% CI, 0.56 to 0.96).

Significant covariates in the propensity analysis included age; sex; race; ethnic group; ejection fraction; history or no history of myocardial infarction; presence or absence of peripheral vas-

cular disease, hemodynamic instability, congestive heart failure, chronic obstructive pulmonary disease, and diabetes; and anatomical group (number of diseased vessels and the presence or absence of proximal LAD artery disease). For each of the 12 combinations of anatomical group and outcome (six anatomical groups and two outcome measures), the advantage of CABG was quite consistent, with only 11 of the 48 quartiles having adjusted hazard ratios that were larger than 1 and nonsignificant.

DISCUSSION

The two primary interventions for patients with multivessel coronary artery disease are CABG



and PCI. Several randomized, controlled trials and observational studies have compared the long-term outcomes of these two interventions, but these studies all preceded the introduction of drug-eluting stents.¹⁻⁵ Consequently, the findings of these studies are outdated and may no longer reflect current relative outcomes. For instance, many studies have compared the outcomes of drug-eluting and bare-metal stents, and the majority of these studies have concluded that drug-eluting stents compare favorably with bare-metal stents with regard to target-lesion stenosis, target-vessel stenosis, or both, or repeat-revascularization rates.⁶⁻²⁰ Conversely, two reports have warned about the danger of late stent thrombosis among patients with drug-eluting stents,^{21,22} leading to an FDA meeting that addressed the safety of drug-eluting stents.^{23,24} Thus, it is unclear how the long-term outcome of drug-eluting stents compares with that of CABG.

The purpose of this observational study was to compare rates of death and repeat revascularization among patients treated with CABG and among those treated with drug-eluting stents in New York State between October 1, 2003, and December 31, 2004, and in follow-up observations, to compare rates of death, death or myocardial infarction, and repeat revascularization in these two groups of patients through December 31, 2005. The major findings of the study were that among patients with three-vessel disease or two-vessel disease, those treated with CABG had significantly lower adjusted rates of death and of death or myocardial infarction than those treated with drug-eluting stents; that CABG was associated with lower rates of death or myocardial infarction for all subgroups of patients with multivessel disease defined by the presence or absence of proximal LAD artery disease; that for the mortality outcome, there were

Table 3. Hazard Ratios for Death and for Death or Myocardial Infarction after CABG and after Treatment with a Drug-Eluting Stent, According to Selected Subgroups of Patients.*

Variable	No. of Patients	Mean Follow-up <i>mo</i>	Death			Death or Myocardial Infarction		
			No. of Events	Adjusted Hazard Ratio (95% CI)†	P Value	No. of Events	Adjusted Hazard Ratio (95% CI)†	P Value
Diabetes								
CABG	2844	18.9	242	0.97 (0.77–1.20)	0.75	304	0.84 (0.69–1.01)	0.07
Stent	3256	18.5	224	Reference		343	Reference	
Ejection fraction <40%								
CABG	1614	18.6	181	0.77 (0.59–1.00)	0.05	213	0.67 (0.53–0.84)	<0.001
Stent	1059	17.8	144	Reference		183	Reference	
Age ≥80 yr								
CABG	760	18.0	107	0.74 (0.55–1.00)	0.05	125	0.74 (0.56–0.96)	0.03
Stent	1266	17.8	175	Reference		216	Reference	

* CABG denotes coronary-artery bypass grafting, and LAD left anterior descending.

† Hazard ratios are adjusted for age; sex; ejection fraction; hemodynamic state; history or no history of myocardial infarction before procedure; presence or absence of cerebrovascular disease, peripheral arterial disease, congestive heart failure, chronic obstructive pulmonary disease, diabetes, and renal failure; number of diseased vessels; and involvement of the proximal LAD artery.

no significant differences between drug-eluting stents and CABG for patients with three-vessel disease, with or without proximal LAD artery disease, but there was a trend in favor of CABG; and that in three high-risk subgroups of patients (patients with diabetes, patients with left ventricular ejection fractions below 40%, and patients 80 years of age or older), there were no significant differences in adjusted mortality rates between those undergoing CABG and those receiving drug-eluting stents, but patients with ejection fractions below 40% and patients who were at least 80 years old who underwent CABG had significantly lower rates of death or myocardial infarction. A caveat of the findings for the three high-risk subgroups is that there may be unmeasured confounding in the data. For example, data on the severity of diabetes and insulin dependence were not available, and to the extent that one treatment (e.g., CABG) is associated with more severe diabetes, the risk-adjustment process was unable to control for those differences.

Our earlier study conducted in New York State compared the outcomes of CABG and bare-metal stents.⁵ That study, which examined the rate of death but not the rate of death or myocardial infarction, found that the adjusted mor-

tality rates were lower for CABG than for bare-metal stents in all subgroups of patients defined on the basis of the number of diseased vessels and the presence or absence of proximal LAD artery disease. The hazard ratios ranged from 0.64 for patients with three-vessel disease including the proximal LAD artery to 0.76 for patients with two-vessel disease without involvement of the proximal LAD artery.⁵

The primary difference between the findings of this earlier study and the present study is that the earlier study found significantly lower death rates after CABG than after stenting in all subgroups of patients defined on the basis of location of disease, whereas we report here that two of these subgroups did not have lower death rates after CABG than after stenting. However, the current study did find lower rates of death or myocardial infarction after CABG than after stenting in all subgroups of patients.

An important caveat of the present study and the earlier one is that both were observational studies and are therefore subject to potential bias with respect to the relative preprocedural severity of illness among patients treated with CABG and drug-eluting stents. There are a few ways to test for and to minimize this bias, including propensity analyses and instrumental variables

in conjunction with adjustments to account for differences in measures of underlying preprocedural risk.²⁹ As in our earlier comparison of bare-metal stents versus CABG, we chose to use propensity analyses, whereby the existence of constant treatment effects can be tested for by subdividing patients into propensity groups on the basis of a score obtained from a logistic-regression model, with predictors of treatment type as independent variables and treatment type as a binary dependent variable.

Our propensity analyses demonstrate that the relative outcomes associated with the two procedures remained about the same, regardless of the propensity to choose one procedure over the other, indicating that the results are not likely to be severely compromised by selection bias. Furthermore, observational studies such as ours are of value because they shed light on the use of competing treatment options in current practice and because they include patients at high risk who are frequently not represented in clinical trials. Nevertheless, despite our efforts to eliminate bias as much as possible, in an observational study there is no way 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 one of the procedures, or by the presence of pairs of patients who differ with respect to unmeasured risk factors not contained in the registries.

Another caveat is that, as in our previous

study, we did not have access to data on deaths occurring outside of New York. We limited the study to residents of New York State and eliminated out-of-state patients who underwent the procedures in New York hospitals. However, if a New York resident moved from the state and died elsewhere, information on the death was not available to us. Consequently, it must be assumed that the likelihood of a patient's dying outside of New York was not associated with the type of procedure undergone by the patient.

Finally, we would like to have used a longer follow-up period, but more recent mortality data are not available at this time. Nevertheless, it would appear that the advantage of CABG would have persisted over the course of another year or two of follow-up, both because our earlier, longer study⁵ showed evidence of that tendency and because there is evidence of very late stent thrombosis in patients receiving drug-eluting stents.²¹

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The views expressed are those of the authors and do not necessarily reflect those of the New York State Department of Health.

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