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Long-Term Mortality After Percutaneous Coronary Intervention With Drug-Eluting Stent Implantation Versus Coronary Artery Bypass Surgery for the Treatment of Multivessel Coronary Artery Disease

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Background—Although previous studies have compared the treatment effects of percutaneous coronary intervention and coronary artery bypass grafting (CABG), the long-term outcomes beyond 1 year among patients with multivessel coronary artery disease who underwent percutaneous coronary intervention with drug-eluting stents (DES) or CABG have not been evaluated.

Methods and Results—Between January 2003 and December 2005, 3042 patients with multivessel disease underwent coronary implantation of DES (n=1547) or CABG (n=1495). The primary end point was all-cause mortality. In a crude analysis, the rate of long-term mortality was significantly higher in patients who underwent CABG than in those who underwent DES implantation (3-year unadjusted mortality rate, 7.0% for CABG versus 4.4% for percutaneous coronary intervention; $P=0.01$). However, after adjustment for baseline differences, the overall risks of death were similar among all patients (hazard ratio, 0.85; 95% confidence interval [CI], 0.56 to 1.30; $P=0.45$), diabetic patients (hazard ratio, 1.76; 95% CI, 0.82 to 3.78; $P=0.15$), and patients with compromised ventricular function (hazard ratio, 1.39; 95% CI, 0.41 to 4.65; $P=0.60$). In the anatomic subgroups, mortality benefit with DES implantation was noted in patients with 2-vessel disease with involvement of the nonproximal left anterior descending artery (hazard ratio, 0.23; 95% CI, 0.01 to 0.78; $P=0.016$). The rate of revascularization was significantly higher in the DES than in the CABG group (hazard ratio, 2.81; 95% CI, 2.11 to 3.75; $P<0.001$).

Conclusions—For the treatment of multivessel coronary artery disease, percutaneous coronary intervention with DES implantation showed equivalent long-term mortality as CABG. (***Circulation*. 2008;117:2079-2086.**)

Key Words: bypass ■ coronary disease ■ mortality ■ stents

The treatment of multivessel atherosclerotic coronary artery disease has evolved significantly, in part as a result of advances in both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).[1,2] Several large, randomized clinical trials comparing CABG and PCI for the treatment of multivessel coronary disease showed consistent evidence of similar mortality rates and of an increased risk of subsequent revascularization after PCI.[3–9] In contrast, large clinical registries reported that compared with stenting, CABG was associated with long-term survival benefits.[10,11] The availability of drug-eluting stents (DES), however, has altered current clinical practice by significantly reducing the rates of angiographic restenosis and repeat revascularization, largely removing one of the major limitations of balloon angioplasty and bare metal stent implantation.[12–14]

Clinical Perspective p 2086

Because of advances in periprocedural and postprocedural medical care for both CABG and PCI with DES, new comparisons are required to determine the standard of care for multivessel coronary artery disease. Currently, limited data exist regarding the long-term outcomes among patients with multivessel disease who underwent CABG or PCI with DES. We therefore compared the long-term outcomes of coronary implantation with DES and CABG in patients with multivessel disease.

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Table 1. Baseline Characteristics of the Overall Patient Population

Variable	DES (n=1547)	CABG (n=1495)	P Unadjusted	P Adjusted*
Demographic characteristics				
Age, y	62.0±10.2	61.8±8.5	0.59	0.74
Male gender, n (%)	1073 (69.4)	1095 (73.3)	0.02	0.95
Clinical characteristics				
Body mass index, kg/m^2	25.1±2.9	24.8±3.0	0.02	0.82
Diabetes, n (%)	489 (31.6)	402 (26.9)	0.004	0.13
Hypertension, n (%)	883 (57.1)	716 (47.9)	<0.001	0.54
Current smoker, n (%)	457 (29.5)	502 (33.6)	0.02	0.82
Hypercholesterolemia, n (%)	373 (24.1)	474 (31.7)	<0.001	0.72
Previous MI, n (%)	60 (3.9)	248 (16.6)	<0.001	0.61
Previous coronary angioplasty, n (%)	270 (17.5)	149 (10.0)	<0.001	0.91
Chronic lung disease, n (%)	54 (3.5)	109 (7.3)	<0.001	0.74
Peripheral vascular disease, n (%)	56 (3.6)	86 (5.8)	0.005	0.52
Previous stroke, n (%)	53 (3.4)	118 (7.9)	<0.001	0.67
Renal failure, n (%)	42 (2.7)	87 (5.8)	<0.001	0.33
Unstable angina, n (%)	666 (43.1)	537 (35.9)	<0.001	0.75
Left ventricular function				
Mean ejection fraction, %	58.8±8.6	56.3±11.0	<0.001	0.21
Ejection fraction <40%, n (%)	61 (4.0)	170 (11.5)	<0.001	0.32
Data missing, n (%)	39 (2.5)	22 (1.5)	0.04	0.82
Angiographic characteristics, n (%)				
2-Vessel disease	868 (56.1)	343 (22.9)	<0.001	0.88
3-Vessel disease	679 (43.9)	1152 (77.1)	<0.001	0.88
Left main disease	178 (11.5)	372 (24.9)	<0.001	0.31
Proximal LAD disease	601 (38.8)	804 (53.8)	<0.001	0.98
Total occlusion ≥1	110 (7.1)	656 (43.9)	<0.001	0.84

Data are mean±SD when appropriate.
*Propensity score–adjusted probability value.

Methods

Study Population and Revascularization Procedures

The study population consisted of consecutive patients with multivessel coronary disease who underwent DES implantation or isolated CABG at the Asan Medical Center (Seoul, Korea) between January 1, 2003, and December 31, 2005. The decision to perform PCI or CABG was the physician's and/or patient's choice. Patients who had prior CABG, those who underwent concomitant valvular or aortic surgery, and those who had an acute myocardial infarction (MI) within 24 hours before revascularization or presented with cardiogenic shock were excluded.

Stent implantation methods have been described previously.[15,16] DES implantation was performed with an attempt to fully cover the diseased segment and to ensure complete stent apposition. The choice of the specific type of DES (ie, sirolimus-eluting [Cypher, Cordis, Johnson & Johnson, Miami Lakes, Fla] or paclitaxel-eluting [Taxus, Boston Scientific, Natick, Mass] stents) was left to the operator's discretion. Patients were prescribed aspirin indefinitely and clopidogrel for at least 6 months, regardless of DES type.[17] Treatment beyond this duration was at the discretion of the physician. Surgical revascularization was performed using standard bypass techniques[2]; whenever possible, the internal thoracic artery was preferentially used for revascularization of the left anterior descending artery (LAD). Complete revascularization was performed when possible with arterial conduits or saphenous vein grafts.

This study was approved by the local institutional review board.

Outcome Variables and Definitions

The primary end point was all-cause mortality. All-cause death is the most robust and unbiased index because no adjudication is required, thus avoiding inaccurate or biased documentation and clinical assessments.[18] Treatment-related differences in long-term mortality were analyzed in all patients and in the 2 major high-risk patient subsets: those with diabetes and poor ventricular function (defined as a left ventricular ejection fraction <40%).[10,19]

Secondary end points were repeat revascularization and the composite of death, Q-wave MI, and cerebrovascular events. Repeat revascularization included target vessel revascularization, regardless of whether the procedure was clinically or angiographically driven, and non–target vessel revascularization. Q-wave MI was defined as the documentation of a new pathological Q wave after index treatment.[3,5] Cerebrovascular events were defined as stroke, transient ischemic attacks, and reversible ischemic neurological deficits as determined by a neurologist and confirmed by imaging modalities. The occurrence of stent thrombosis was assessed by the Academic Research Consortium definitions.[20]

Data Collection

Clinical, procedural or operative, and outcome data were recorded in the dedicated PCI and surgical databases by independent research personnel. Clinical follow-up was performed via office visit or telephone contact. To ensure accurate assessment of clinical end points, additional information was obtained from visits or telephone

Table 2. Cox Proportional-Hazards Analyses of Time to Death After Implantation of DES Compared With CABG

	All Patients (n=3042)		Patients With Diabetes (n=891)		Patients With Poor LV Function (EF<40%) (n=231)	
Model	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Crude	0.65 (0.47–0.90)	0.01	0.82 (0.49–1.38)	0.45	0.64 (0.26–1.55)	0.32
Multivariable adjusted*	0.85 (0.56–1.30)	0.45	1.76 (0.82–3.78)	0.15	1.39 (0.41–4.65)	0.60
Propensity score adjusted	0.95 (0.72–1.53)	0.68	1.88 (0.89–3.97)	0.10	1.26 (0.42–3.81)	0.68
Stratified analyses based on propensity scores						
Quintile 1	2.23 (0.88–5.65)	0.09	3.67 (0.85–15.83)	0.08	…†	…†
Quintile 2	1.53 (0.58–4.01)	0.39	3.28 (0.40–26.62)	0.27	7.71 (0.72–82.43)	0.09
Quintile 3	1.06 (0.51–2.21)	0.87	1.40 (0.39–4.96)	0.60	1.17 (0.25–5.57)	0.84
Quintile 4	0.53 (0.23–1.21)	0.13	1.34 (0.30–6.06)	0.70	0.54 (0.06–4.84)	0.58
Quintile 5	0.22 (0.08–0.63)	0.004	0.36 (0.04–3.10)	0.35	Infinite	0.98
Summary‡	0.90 (0.59–1.37)	0.63	1.74 (0.80–3.78)	0.16	1.31 (0.45–3.84)	0.62

LV indicates left ventricular; EF, ejection fraction.

*Adjusted for age, sex, body mass index, diabetes, hypertension, current smoker, hypercholesterolemia, history of MI, coronary angioplasty, chronic lung disease, peripheral vascular disease, stroke, renal insufficiency, unstable angina, ejection fraction, 3-vessel disease, left main disease, proximal LAD disease, and total occlusion ≥1.

†Could not be estimated.

‡Likelihood ratio test for homogeneity; $P=0.10$ for all patients, $P=0.46$ for patients with diabetes, $P=0.36$ for patients with poor LV function.

contacts with living patients or family members and from medical records obtained from other hospitals as necessary. Data were carefully verified and adjudicated by independent clinicians.

For validation of complete follow-up data regarding mortality, information about vital status was obtained through March 31, 2007, from the National Population Registry of the Korea National Statistical Office through the use of a unique personal identification number.

Statistical Analysis

Continuous variables were compared with the *t* test or Wilcoxon rank-sum test, and categorical variables were compared with χ^2 statistics or Fisher's exact test as appropriate. Survival curves were constructed using Kaplan–Meier estimates and compared with the log-rank test. Adjusted survival rates were compared with multivariable Cox proportional-hazards regression.[21] Adjusted covariates included age, sex, body mass index, diabetes, hypertension, smoking, hypercholesterolemia, history of MI or coronary angioplasty, chronic lung disease, peripheral vascular disease, stroke, renal insufficiency, unstable angina, ejection fraction, 3-vessel disease, left main disease, proximal LAD disease, and total occlusion. The proportional-hazards assumption was confirmed by examination of log (−log [survival]) curves and by testing of partial (Schoenfeld) residuals,[22] and no relevant violations were found.

Additionally, a propensity score analysis was carried out to control selection biases and to determine causal effect of the type of revascularization on outcomes.[23] The propensity scores were estimated without regard to outcomes by multiple logistic regression analysis. A full nonparsimonious model was developed that included all the variables shown in Table 1. Model discrimination was assessed with c statistics, and model calibration was assessed with Hosmer-Lemeshow statistics. The individual propensity score was incorporated into the Cox regression model as a covariate and type of revascularization to calculate the propensity-adjusted hazard ratio (HR). In addition, the propensity score was subdivided into quintiles.[24] Treatment effect was estimated separately within each quintile, and quintile estimates were combined to measure an overall estimate of the treatment effect. For each of the 2 major subgroups (diabetes and poor ventricular function), a new propensity score for PCI versus CABG was incorporated into each analysis. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC). A 2-tailed value of $P<0.05$ was considered statistically significant.

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

Results

Revascularization Procedures and Baseline Characteristics

Between January 2003 and December 2005, 3042 patients with multivessel coronary disease were treated with DES implantation (n=1547) or CABG (n=1495). In the DES group, 1229 patients (79%) received sirolimus-eluting stents, and 318 (21%) received paclitaxel-eluting stents. The mean number of stents used per patient was 2.8±1.2; the mean total length of stents implanted was 65.6±31.5 mm; and the average stent diameter per patient was 3.2±0.3 mm. In the CABG group, 469 patients (31%) underwent off-pump surgery, and 1476 (99%) received at least 1 arterial conduit; of the latter, 1414 patients (96%) underwent revascularization of the LAD with an arterial conduit. The average number of grafts used per patient was 3.5±1.1 (2.8±1.1 arterial grafts and 0.7±0.8 venous grafts).

Baseline characteristics are summarized in Table 1. Compared with patients who received DES, patients who underwent CABG were more likely to be men and to have a significantly higher prevalence of smoking and hypercholesterolemia and were significantly more likely to have a history of MI, chronic lung disease, peripheral vascular disease, stroke, or renal failure. Patients with CABG also had significantly lower mean ejection fractions and a higher likelihood of 3-vessel disease and left main disease. In contrast, patients with DES had a higher prevalence of diabetes, hypertension, and prior coronary angioplasty and presented more often with unstable angina.

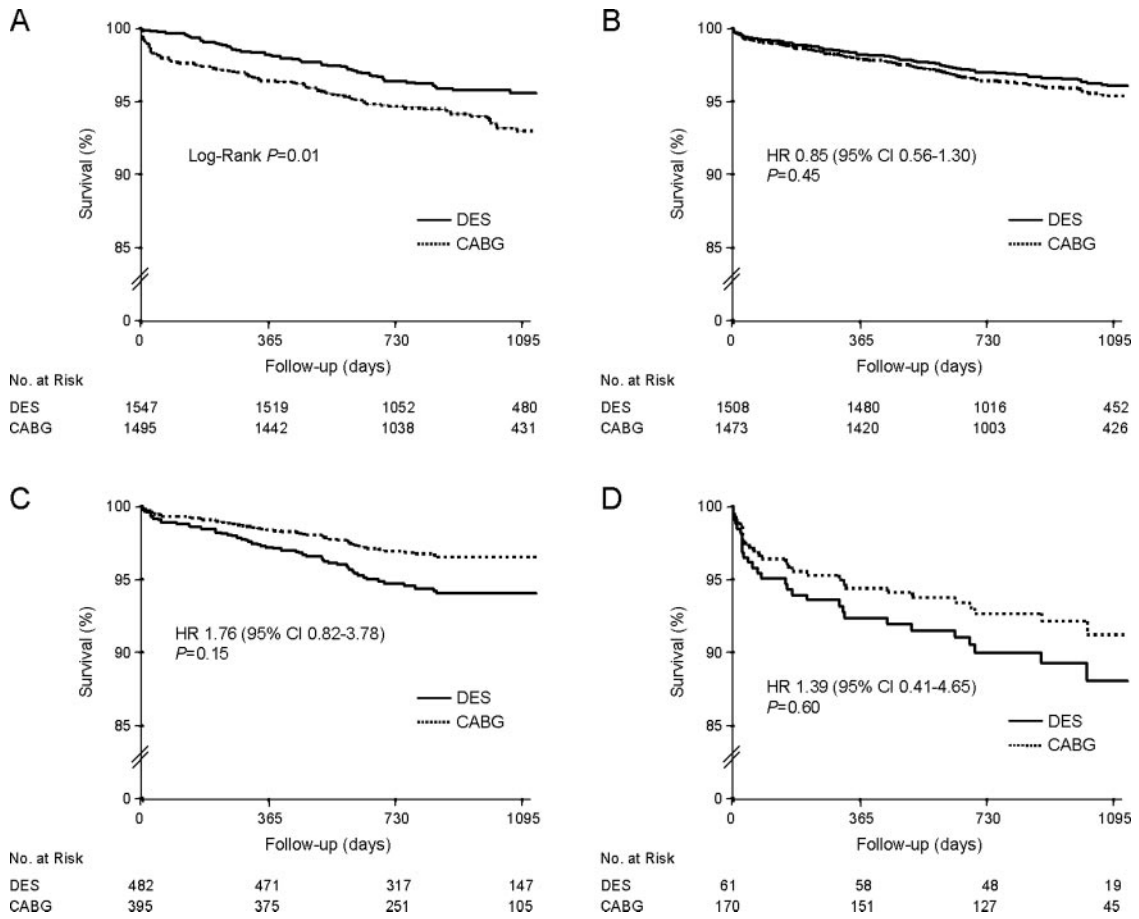

Figure 1. Unadjusted Kaplan–Meier survival curve of all study patients (A) and adjusted survival curves among all patients (B), patients with diabetes (C), and patients with poor ventricular function (D). Adjustments were made for age, sex, body mass index, diabetes, hypertension, current smoker, hypercholesterolemia, history of MI, coronary angioplasty, chronic lung disease, peripheral vascular disease, stroke, renal insufficiency, unstable angina, ejection fraction, 3-vessel disease, left main disease, proximal LAD disease, and total occlusion ≥1.

All-Cause Mortality

The median follow-up was 945 days (interquartile range, 693 to 1180 days) in the DES group and 933 days (interquartile range, 741 to 1164 days) in the CABG group. During the entire study period, 151 patients died (61 in the DES group, 90 in the CABG group). The unadjusted in-hospital morality was significantly higher in the CABG group than in the DES group (1.5% versus 0.6%; $P=0.01$). Table 2 and Figure 1 summarize overall mortality outcomes based on revascularization procedure. In a crude analysis, long-term morality was significantly higher in the CABG group than in the DES group (3-year unadjusted mortality rate, 7.0% for CABG versus 4.4% for PCI; $P=0.01$). However, after multivariable-adjusted Cox regression analysis, long-term mortality was similar in the 2 groups. The c statistic for the propensity score model was 0.86 (Hosmer-Lemeshow goodness of fit, $P=0.15$). All covariates differed nonsignificantly after propensity score adjustment (Table 1). In the propensity score– and propensity score quintile–adjusted analyses, the risk of death was similar in the 2 groups.

In the 2 major high-risk patient subsets with diabetes or poor ventricular function, there were no significant differences in long-term mortality between DES and CABG after multivariable- or propensity-adjusted analyses (Table 2 and Figure 1). Among 71 patients with severely depressed left ventricular function (ejection fraction <30%), there were 10 deaths, and the adjusted risk of long-term mortality was similar in the 2 groups (HR, 1.53; 95% CI, 0.25 to 9.50; $P=0.65$).

When we assessed cardiac mortality, the adjusted HRs for treatment were essentially unchanged among all patients (HR, 0.95; 95% CI, 0.50 to 1.81; $P=0.88$), diabetic patients (HR, 1.59; 95% CI, 0.57 to 4.43; $P=0.38$), and patients with poor ventricular function (HR, 1.99; 95% CI, 0.49 to 8.09; $P=0.34$).

New Revascularization and Serious Cardiovascular Events

During follow-up, 183 patients (11.8%) in the DES group (repeat PCI in 173, CABG in 10) and 69 patients (4.6%) in the CABG group (PCI in 57, repeat CABG in 12) had new revascularization. Unadjusted risk (Figure 2) and adjusted risk of repeat revascularization were significantly higher in patients treated with DES than in those treated with CABG (HR, 2.81; 95% CI, 2.11 to 3.75; $P<0.001$). This difference was more pronounced in the diabetic patients (Figure 2). During the study period, there were 33 Q-wave MIs (19 DES, 14 CABG patients) and 25 cerebrovascular events (8 DES, 17

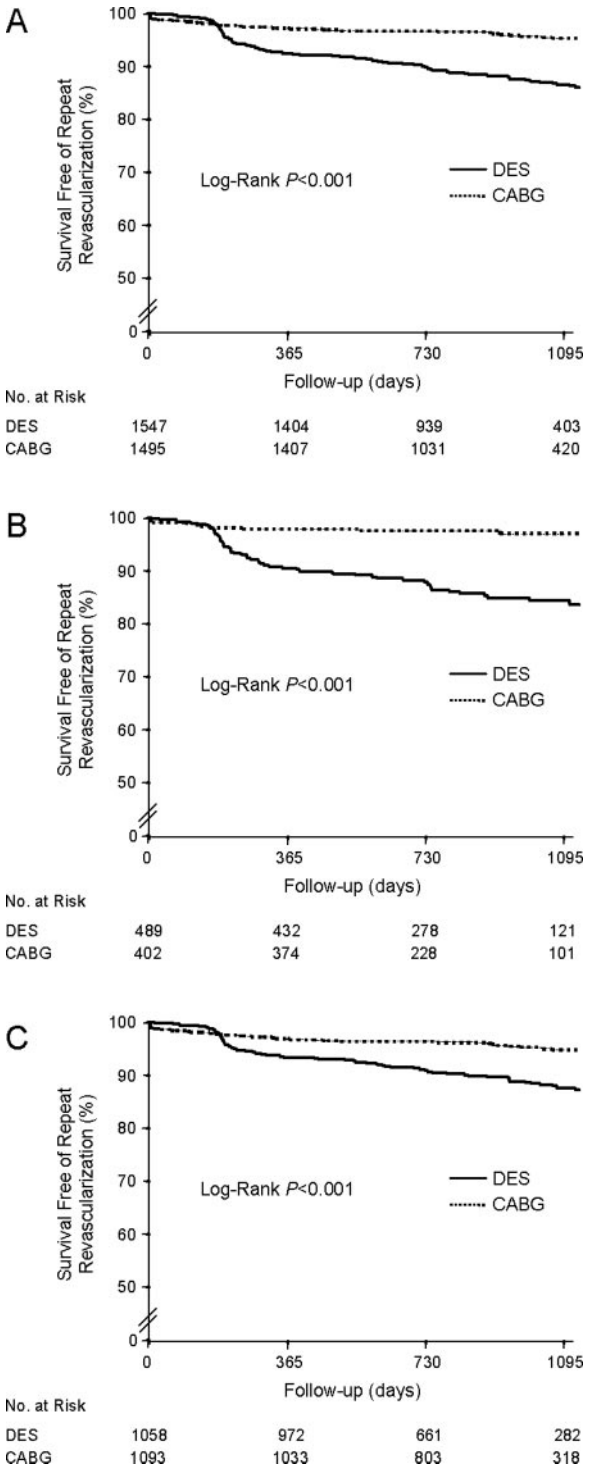

Figure 2. Kaplan–Meier curves for survival free of repeat revascularization in all patients (A), diabetic patients (B), and nondiabetic patients (C).

CABG patients). The adjusted risk for the composite of death, Q-wave MI, or cerebrovascular events was similar in the 2 groups (HR, 0.84; 95% CI, 0.57 to 1.23; $P=0.36$).

In the DES group, mean duration of clopidogrel use was 12.1±8.4 months. During follow-up, 10 patients had definite thrombosis, 2 had probable thrombosis, and 22 had possible thrombosis. At year 3, the incidence of definite or probable stent thrombosis was 1.1% (definite, 0.9%; any Academic Research Consortium criteria, 2.7%). Among 12 patients with definite or probable stent thrombosis, 1 patient had early, 3 had late, and 8 had very late thrombosis (5 occurring after 1 to 2 years, 3 occurring after 2 to 3 years). Of patients who had definite or probable thrombosis, 3 (25%) were on dual antiplatelet therapy, 3 (25%) were on aspirin monotherapy, and 6 (50%) were not on antiplatelet therapy at the time of stent thrombosis.

Mortality Among Special Clinical and Anatomic Subsets

Figure 3 shows treatment-related mortality based on high-risk clinical and various anatomic features in all patients, as well as in diabetic and nondiabetic patients. The adjusted mortality was comparable in the various clinical and anatomic subgroups. However, mortality benefit associated with DES implantation was noted in patients with 2-vessel disease, especially nondiabetic patients with nonproximal LAD involvement.

Discussion

In a large observational study of consecutive patients with multivessel coronary artery disease, we found that the adjusted long-term mortality risk was similar in patients who underwent PCI with DES implantation or CABG. In addition, although trends in HRs were different, patients with diabetes and those with left ventricular dysfunction had a similar risk of mortality. However, the subsequent revascularization rate was considerably higher after DES implantation than after CABG.

Randomized clinical trials comparing CABG and PCI with balloon angioplasty or bare metal stents have demonstrated that long-term survival was similar, but repeat revascularization was much more common with PCI.[25,26] In contrast, large observational studies have suggested a greater benefit of long-term mortality from CABG compared with PCI with bare metal stents and/or balloon angioplasty in patients with multivessel disease.[10,11] After adjustment for baseline differences, including mostly comorbidities associated with worse outcomes, survival was higher for CABG in all anatomic subgroups.[10]

The Arterial Revascularization Therapies Study II (ARTS-II) study, which compared outcomes with sirolimus-eluting stents and the surgical arm of the ARTS trial, showed that DES had 1-year outcomes similar to those of CABG.[27] In contrast, a recent report showed that in patients with multivessel disease, DES was associated with an increased 1-year mortality rate compared with CABG.[28] However, data regarding comparisons of long-term outcomes (beyond 1 year) of PCI with DES and CABG for multivessel disease are limited. Our findings suggested an equivalent long-term mortality and serious cardiovascular events of percutaneous revascularization with DES as surgical revascularization. Nevertheless, CABG was more effective than DES in reducing the need for repeat revascularization in complex settings such as multivessel disease.

Patients with diabetes are prone to a diffuse and rapidly progressive form of atherosclerosis, increasing the likelihood of cardiovascular events.[29] Diabetic patients with diffuse

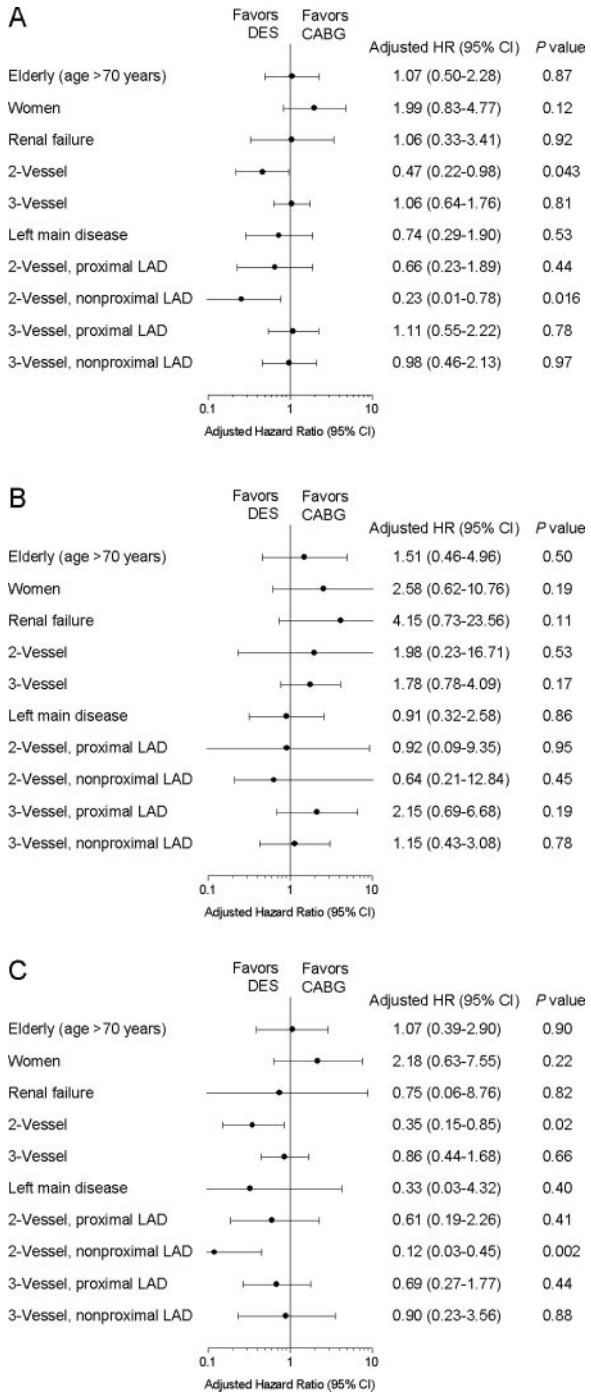

Figure 3. Adjusted HRs for mortality according to high-risk clinical and various anatomic subsets in all patients (A), diabetic patients (B), and nondiabetic patients (C). Adjustments were made for age, sex, body mass index, diabetes, hypertension, current smoker, hypercholesterolemia, history of MI, coronary angioplasty, chronic lung disease, peripheral vascular disease, stroke, renal insufficiency, unstable angina, ejection fraction, 3-vessel disease, left main disease, proximal LAD disease, and total occlusion ≥1.

disease have been reported to do better with CABG than with PCI with angioplasty or bare metal stents.[10,11,30] Recently, DES was found to significantly reduce the incidence of revascularization in diabetic patients, but the rate is higher than with CABG.[27] Our study showed that even with the more pronounced differences in repeat revascularization observed in diabetic patients, the overall long-term mortality was similar for the 2 treatments regardless of diabetic status. These results were consistent with previous studies.[31,32]

The choice of CABG or PCI for the treatment of multivessel disease depends on several factors, particularly the location and number of vessels involved. PCI generally is preferred in patients with 2-vessel disease not involving the proximal LAD, whereas CABG is usually the revascularization procedure of choice when a large amount of myocardium is at risk, as in unprotected left main disease and diffuse 3-vessel disease, particularly in diabetic patients.[2] However, there is increasing evidence of favorable clinical outcomes associated with DES in patients with unprotected left main disease or multivessel disease even in diabetes, comparable to rates observed with CABG.[33,34] In the present study, despite the possibility of insufficient statistical power, we observed no significant differences in long-term mortality in patients with left main disease and 3-vessel disease, regardless of diabetic status. Furthermore, DES implantation had survival benefits in nondiabetic patients with 2-vessel disease and nonproximal LAD involvement.

In our study, the long-term mortality rate of the DES group was relatively lower compared with recent reports.[28,35] These discrepancies may be explained is part by differences in patient populations, lesion characteristics, interventional practice, and ethnic groups.

Patient demographics, a variety of coexisting conditions, left ventricular function, and the severity of involved anatomy can frequently affect outcomes and can influence the choice of revascularization strategy. We performed propensity analysis to enable an even more rigorous adjustment for selection biases and confounding factors. Nonetheless, observational studies for the assessment of treatment effect can only partially control for actually measured factors, not for hidden biases. Therefore, a comparison of PCI with DES or CABG in patients with multivessel coronary disease awaits the results of ongoing randomized trials.[36–39]

Study Limitations

Our study evaluated nonrandomized, observational data. The choice of revascularization was at the discretion of the treating physician and/or patient. To adjust for selection bias, we used propensity score methods. Previous studies have suggested that well-designed observational studies provide valid results and do not systematically overestimate the magnitude of treatment effects compared with the results of randomized controlled trials.[40,41] Nevertheless, there are inherent limitations to using an observational population because of unmeasured confounding factors. In addition, given the risk of very late thrombosis with DES, a longer-term clinical follow-up is needed to assess the clinical safety of DES in these patients compared with CABG. In addition, our statistical analyses may have been underpowered to assess treatment effects in the various subgroups as a result of a limited number of patients in each subpopulation. Further research is needed to examine the relative long-term benefits of these interventions for each clinical or anatomic subset.

Conclusions

Our results suggest that compared with CABG, percutaneous revascularization with DES showed comparable long-term mortality for the treatment of multivessel coronary artery disease. However, repeat revascularization after index treatment was more common in patients treated with DES. Conclusions regarding a comparison of the 2 treatment strategies in these patients await the results of ongoing clinical trials.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Several studies have compared the treatment effects of coronary stenting and coronary artery bypass grafting (CABG) for multivessel coronary artery disease, but little information exists since the widespread availability of drug-eluting stents (DES). In the present study, we evaluated 1547 patients with multivessel disease who received DES and 1495 patients who underwent CABG. The primary end point was all-cause mortality. Other outcomes were repeat revascularization and the composite of death, Q-wave myocardial infarction, or cerebrovascular events. After adjustment for differences in baseline risk factors between patients receiving DES and undergoing CABG, the long-term risks of death were similar among all patients (hazard ratio, 0.85; 95% CI, 0.56 to 1.30; $P=0.45$), diabetic patients (hazard ratio, 1.76; 95% CI, 0.82 to 3.78; $P=0.15$), and patients with compromised ventricular function (hazard ratio, 1.39; 95% CI, 0.41 to 4.65; $P=0.60$) during 3 years of follow-up. The adjusted risk of hard end points (death, Q-wave myocardial infarction, or cerebrovascular events) also was similar (hazard ratio, 0.84; 95% CI, 0.57 to 1.23; $P=0.36$), whereas the risk of revascularization was significantly higher in the DES than in the CABG group (hazard ratio, 2.81; 95% CI, 2.11 to 3.75; $P<0.001$). Compared with CABG, coronary stenting with DES showed equivalent long-term mortality and serious composite outcomes but a higher rate of repeat revascularization for patients with multivessel coronary artery disease. Our findings need to be ascertained or refuted in ongoing, large randomized clinical trials, which may provide the answer to treatment effects between the 2 primary interventions.