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CLINICAL RESEARCH

Impact of Diabetes Mellitus on the Treatment Effect of Percutaneous or Surgical Revascularization for Patients With Unprotected Left Main Coronary Artery Disease

A Subgroup Analysis of the MAIN-COMPARE Study

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Objectives This study sought to investigate whether the outcome of drug-eluting stent (DES) treatment and that of coronary artery bypass grafting (CABG) differed in diabetic and nondiabetic patients with unprotected left main coronary artery (LMCA) disease.

Background Diabetes mellitus has been shown to be a risk factor for adverse events and a major determinant in selection of a revascularization strategy in patients with multivessel or LMCA disease.

Methods A total of 1,474 patients with unprotected LMCA stenosis who received DES (n = 784) or underwent CABG (n = 690) were examined. We compared the effects of these 2 treatments on long-term clinical outcomes (death; the composite of death, Q-wave myocardial infarction [MI], or stroke; and target vessel revascularization [TVR]), according to diabetic status.

Results After adjustment of covariates, the risk of death (hazard ratio [HR]: 0.95, 95% confidence interval [CI]: 0.62 to 1.46, p = 0.83) and the composite of death, Q-wave MI, or stroke (HR: 0.96, 95% CI: 0.65 to 1.42, p = 0.85) at 3 years were similar in the DES and CABG groups. However, the rate of TVR was significantly higher in the DES group (HR: 4.31, 95% CI: 2.28 to 8.15, p < 0.001). These trends were consistent in both diabetic and nondiabetic patients. We also did not observe a diabetes-associated excess risk of death ($p_{interaction}$ = 0.90 and 0.16), or a composite of death, Q-wave MI, or stroke ($p_{interaction}$ = 0.68 and 0.93), or TVR ($p_{interaction}$ = 0.23 and 0.92), between patients receiving either treatment.

Conclusions The prognostic impact of diabetes on long-term treatment with DES or CABG for patients with unprotected LMCA disease was minimal. (J Am Coll Cardiol Intv 2009;2:956–63) © 2009 by the American College of Cardiology Foundation

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Patients with diabetes are prone to a diffuse and rapidly progressive form of coronary artery disease (1,2). Together with coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) is an important component of revascularization strategy for diabetic patients with significant coronary artery disease (3,4). Percutaneous or surgical revascularization, however, has been associated with higher rates of short- or long-term complications in diabetic but not in nondiabetic patients (5–8).

See page 964

Previous studies have found that surgical revascularization resulted in better outcomes than percutaneous revascularization in diabetic patients with multivessel coronary disease (9), indicating that diabetic status is a major consideration in selection of a revascularization strategy in patients with multivessel disease. Although the impact of diabetes on treatment outcomes may be helpful in determining risk stratification and selecting an optimal strategy, the prognostic role of diabetes on CABG or PCI outcome in patients with unprotected left main coronary artery (LMCA) disease has not yet been determined. We therefore evaluated whether the outcome of PCI with drug-eluting stents (DES) or CABG in patients with unprotected LMCA disease was dependent on diabetic status.

Methods

Study population and procedures. The study population consisted of 1,474 consecutive patients with unprotected LMCA disease (defined as stenosis >50%) who received DES implantation (n = 784) or underwent CABG (n = 690) between May 2003 and June 2006 at 12 major academic institutions in Korea, within the MAIN-COMPARE (revascularization for unprotected left MAIN coronary artery stenosis: COMparison of Percutaneous coronary Angioplasty versus surgical REvascularization) registry (10). Patients with prior bypass surgery, concomitant valvular or aortic surgery, ST-segment myocardial infarction (MI), or cardiogenic shock were excluded.

Patients underwent PCI, rather than CABG, according to the preference of the patient or physician, taking into consideration the high risk associated with CABG (10). Starting in the second quarter of 2003, DES implantation has been the exclusive treatment for LMCA disease in all participating centers. The choice of sirolimus- (Cypher and Cypher Select, Cordis, Johnson & Johnson, Bridgewater, New Jersey) or paclitaxel- (Taxus Express and Liberté, Boston Scientific, Natick, Massachusetts) eluting stents was at the discretion of the physician. Stent implantation techniques for patients with LMCA disease have been described (10,11). Interventions for any other significant coronary artery disease were performed according to current practice guidelines. All patients receiving DES were prescribed aspirin (200 mg) plus clopidogrel 75 mg (after a loading dose of 300 or 600 mg) before or during the coronary intervention. After the procedure, aspirin was continued indefinitely and clopidogrel continued for at least 6 months (12). Extended use of clopidogrel beyond 6 months was at the discretion of the physician. Surgical revascularization was performed using standard bypass techniques (13). Whenever possible, the internal thoracic artery was preferentially used for revascularization of the left anterior descending artery.

This study was approved by the ethics committees of each hospital, which also permitted use of clinical data for this study.

Study end points and definitions. The end points of the study were death; the composite of death, Q-wave MI, or stroke; and target vessel revascularization (TVR). All events were based on clinical diagnosis by individual physicians and were centrally adjudicated by an independent group of clinicians at the University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

Death was defined as death from any cause. Q-wave MI was defined as documentation of a new abnormal Q-wave on electrocardiography and creatine kinase-MB levels >3× the upper limit of normal after the index treatment. Stroke, as indicated by neurologic deficits, was confirmed by a neurologist based on imaging studies. TVR was defined as repeat revascularization of the treated vessel, including any segments of the left anterior descending artery and the left circumflex artery (14). The diabetic subgroup was defined as all patients receiving active treatment with oral hypoglycemic agents or insulin. Diet-controlled diabetic patients were included only if there was documentation of an abnormal blood glucose level after an overnight fast or an abnormal glucose tolerance test during hospitalization for the revascularization procedure.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
IPTW = inverse probability of treatment weighting
LMCA = left main coronary artery
MI = myocardial infarction
PCI = percutaneous coronary intervention
TVR = target vessel revascularization

Data collection and follow-up. The MAIN-COMPARE registry holds data on all consecutive patients who underwent PCI or CABG for unprotected LMCA disease from 2000 to 2006 at 12 major cardiac centers (10). The registry is sponsored by the Korean Society of Interventional Cardiology, and there was no industry involvement in the design, conduct, or analysis of this study.

Clinical, angiographic, procedural or operative, and outcome data were collected using a dedicated internet-based reporting system. For validation of complete follow-up data,

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OCTOBER 2009:956–63

Table 1. Baseline Clinical and Procedural Characteristics

Variable	Overall (n = 1,474)			Diabetic Patients (n = 507)			Nondiabetic Patients (n = 967)		
	DES (n = 784)	CABG (n = 690)	p Value	DES (n = 251)	CABG (n = 256)	p Value	DES (n = 533)	CABG (n = 434)	p Value
Age (yrs)	64 (55–71)	66 (58–70)	0.004	64 (57–71)	66 (59–70)	0.37	63 (52–70)	65 (57–71)	0.006
Male sex	556 (70.9)	499 (72.3)	0.55	174 (69.3)	191 (74.6)	0.19	382 (71.7)	308 (71.0)	0.81
Treatment of diabetes mellitus			0.002			0.006			—
Insulin-requiring	64 (8.2)	68 (9.9)		64 (25.5)	68 (26.6)		—	—	
Oral hypoglycemic agents-requiring	160 (20.4)	179 (25.9)		160 (63.7)	179 (69.9)		—	—	
Diet-controlled	27 (3.4)	9 (1.3)		27 (10.8)	9 (3.5)		—	—	
Hypertension	418 (53.3)	343 (49.7)	0.17	160 (63.7)	153 (59.8)	0.36	258 (48.4)	190 (43.8)	0.15
Hyperlipidemia	241 (30.7)	254 (36.8)	0.014	87 (34.7)	108 (42.2)	0.082	154 (28.9)	146 (33.6)	0.11
Current smoker	166 (21.2)	21.9 (151)	0.74	44 (17.5)	59 (23.0)	0.12	122 (22.9)	92 (21.2)	0.53
Previous coronary angioplasty	160 (20.4)	79 (11.4)	<0.001	64 (25.5)	31 (12.1)	<0.001	96 (18.0)	48 (11.1)	0.003
Previous myocardial infarction	63 (8.0)	75 (10.9)	0.062	23 (9.2)	35 (13.7)	0.11	40 (7.5)	40 (9.2)	0.34
Previous congestive heart failure	20 (2.6)	22 (3.2)	0.46	11 (4.4)	17 (6.6)	0.27	9 (1.7)	5 (1.2)	0.49
Chronic obstructive pulmonary disease	20 (2.6)	18 (2.6)	0.94	5 (2.0)	4 (1.6)	0.75	15 (2.8)	14 (3.2)	0.71
Cerebrovascular disease	64 (8.2)	47 (6.8)	0.33	26 (10.4)	23 (9.0)	0.60	38 (7.1)	24 (5.5)	0.31
Peripheral vascular disease	14 (1.8)	31 (4.5)	0.003	4 (1.6)	17 (6.6)	0.004	10 (1.9)	14 (3.2)	0.18
Renal failure	26 (3.3)	24 (3.5)	0.86	16 (6.4)	19 (7.4)	0.64	10 (1.9)	5 (1.2)	0.37
Ejection fraction (%)	61 (56–67)	66 (58–70)	<0.001	60 (54–66)	58 (45–64)	0.002	62 (57–72)	60 (52–64)	<0.001
EuroSCORE	3.0 (2.0–5.0)	4.0 (3.0–6.0)	<0.001	4.0 (2.0–6.0)	5.0 (3.0–6.0)	0.001	3.0 (2.0–5.0)	4.0 (3.0–6.0)	<0.001
Electrocardiographic findings			0.67			0.62			0.77
Sinus rhythm	764 (97.4)	667 (96.7)		243 (96.8)	244 (95.3)		521 (97.7)	423 (97.5)	
Atrial fibrillation	18 (2.3)	21 (3.0)		6 (2.4)	10 (3.9)		12 (2.3)	11 (2.5)	
Other	2 (0.3)	2 (0.3)		2 (0.8)	2 (0.8)		0	0	
Clinical indication			<0.001			<0.001			0.002
Silent ischemia	27 (3.4)	13 (1.9)		11 (4.4)	5 (2.0)		16 (3.0)	8 (1.8)	
Chronic stable angina	267 (34.1)	156 (22.6)		78 (31.1)	46 (18.0)		189 (35.5)	110 (25.3)	
Unstable angina	405 (51.7)	448 (64.9)		124 (49.4)	171 (66.8)		281 (52.7)	277 (63.8)	
NSTEMI	85 (10.8)	73 (10.6)		38 (15.1)	34 (13.3)		47 (8.8)	39 (9.0)	
Involved location			<0.001			<0.001			<0.001
Ostium and/or midshaft	336 (42.9)	346 (50.1)		101 (40.2)	125 (48.8)		235 (44.1)	221 (50.9)	
Distal bifurcation	448 (57.1)	344 (49.9)		150 (59.8)	131 (51.2)		298 (55.9)	213 (49.1)	
Bifurcation lesion classification			<0.001			<0.001			<0.001
Isolated distal left main	145 (18.5)	20 (2.9)		49 (19.5)	6 (2.3)		96 (18.0)	14 (3.2)	
Distal LM + LAD os or LCX os	180 (22.9)	61 (8.8)		61 (24.3)	22 (8.6)		119 (22.3)	39 (9.0)	
Distal LM + LAD os and LCX os	123 (15.7)	263 (38.1)		40 (15.9)	103 (40.2)		83 (15.6)	160 (36.9)	
Extent of diseased vessel			<0.001			<0.001			<0.001
LM only	145 (18.5)	26 (3.8)		34 (13.5)	6 (2.3)		111 (20.8)	20 (4.6)	
LM plus single-vessel disease	182 (23.2)	54 (7.8)		50 (19.9)	14 (5.5)		132 (24.8)	40 (9.2)	
LM plus double-vessel disease	217 (27.7)	160 (23.2)		85 (33.9)	45 (17.6)		132 (24.8)	115 (26.5)	
LM plus triple-vessel disease	240 (30.6)	450 (65.2)		82 (32.7)	191 (74.6)		158 (29.6)	259 (59.7)	
Right coronary artery disease	333 (42.5)	538 (78.0)	<0.001	114 (45.4)	212 (82.8)	<0.001	219 (41.1)	326 (75.1)	<0.001
Restenotic lesion	27 (3.4)	6 (0.9)	0.001	9 (3.6)	2 (0.8)	0.030	18 (3.4)	4 (0.9)	0.011
Number of stents implanted	1.2 ± 0.5	—	—	1.3 ± 0.6	—	—	1.2 ± 0.5	—	0.004*
Total stent length (mm)	32.9 ± 22.0	—	—	36.1 ± 24.5	—	—	31.3 ± 20.5	—	0.008*
Stent diameter (mm)	3.3 ± 0.2	—	—	3.3 ± 0.3	—	—	3.3 ± 0.2	—	0.06*

The values are presented as medians (with interquartile ranges), mean ± SD, or n (%). *p values for diabetes versus nondiabetes.

CABG = coronary artery bypass graft; DES = drug-eluting stent; LAD os = ostium of the left anterior descending coronary artery; LCX os = ostium of the left circumflex coronary artery; LM = left main disease; NSTEMI = non–ST-segment elevation myocardial infarction.

information on vital status was obtained through July 15, 2007, from the National Population registry of the Korea National Statistical Office using unique patient personal identification numbers. Follow-up MI, stent thrombosis, and TVR were based on clinical diagnoses made by individual physicians and were centrally adjudicated.

Statistical analysis. Continuous variables were compared using Student *t* test or the Wilcoxon rank sum test, and categorical variables were compared using the chi-square test or Fisher exact test as appropriate. Unadjusted cumulative event rates were estimated by the Kaplan-Meier method and compared by log-rank tests.

Crude and adjusted risks for adverse outcomes were compared by univariate and multivariate Cox proportional hazards regression analyses. Multiple regression analyses using Cox proportional hazard models were tested with CABG group as the reference category and with DES group as the indicator variable. Variables with p values ≤ 0.20 and clinically relevant covariates irrespective of their statistical relevance in univariate analyses were candidates for inclusion in multivariate Cox proportional hazards models. The final models were determined by backward elimination.

To reduce the impact of treatment selection bias and potential confounding factors in an observational study, we used weighted Cox proportional hazard models with robust standard errors to compare hazard rates of outcomes between the DES and CABG groups. Weighted Cox's models were constructed using the inverse probability of treatment weighting (IPTW) approach (15). In this model, weights were stabilized by marginal probability for both treatment groups, respectively. Stabilized weights for patients who underwent CABG were the product of the marginal probability for CABG group and the inverse of (1 − propensity score), and stabilized weights for patients who underwent DES were the product of the marginal probability for DES group and inverse of the propensity score (16).

These treatments effects were evaluated in the total population, and in the diabetic and nondiabetic patients. Interaction terms in the multivariate Cox model and weighted Cox model using the IPTW method were used to test for the statistical significance of 2 treatment effects by diabetic status on clinical outcomes.

All reported p values were 2-sided, and p values <0.05 were considered statistically significant. SAS software, version 9.1 (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

Results

Baseline clinical and procedural characteristics. Of the 1,474 patients with unprotected LMCA disease receiving DES (n = 784) or CABG (n = 690), 507 (34%) had diabetes mellitus; of the latter, 251 (50%) patients received DES and

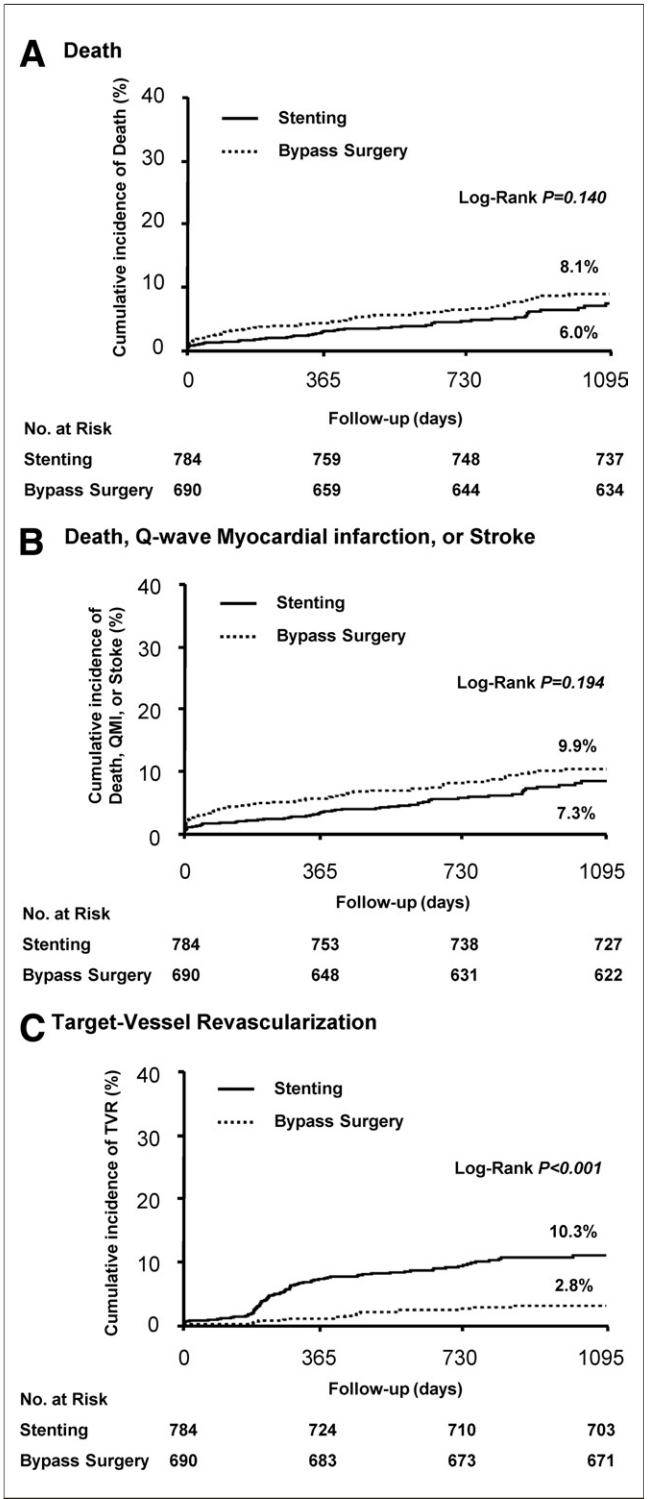

Figure 1. Cumulative Incidence of Outcomes in Overall Patients

Kaplan-Meier incidence curves of clinical outcomes up to 3 years in the overall population of patients with unprotected left main coronary artery lesions who received drug-eluting stents or underwent coronary-artery bypass grafting. **(A)** Death. **(B)** Composite of death, Q-wave myocardial infarction (QMI), or stroke. **(C)** Target vessel revascularization (TVR).

256 (50%) underwent CABG. Of the 967 (66%) nondiabetic patients, 533 (55%) received DES and 434 (45%) underwent CABG.

Clinical, angiographic, and lesional characteristics of overall, and diabetic and nondiabetic patients, who underwent DES and CABG, are shown in Table 1. Compared with patients who received DES, those who underwent CABG had a significantly higher prevalence of coexisting conditions (old age, peripheral vascular disease, lower ejection fraction, unstable angina, and higher EuroSCORE) and were significantly more likely to have 3-vessel disease (Table 1). Although DES patients had a significantly higher incidence of bifurcation lesions than CABG patients, most of them consisted of isolated and left main plus either ostial part of left coronary artery system, but complex bifurcation lesions were significantly higher in CABG than DES groups (Table 1).

Outcomes. Figure 1 and Table 2 summarize crude and adjusted outcomes of patients receiving DES versus CABG in the total population. Overall, the 3-year unadjusted risks of death (6.0% vs. 8.1%, p = 0.14) and the composite of death, Q-wave MI, or stroke (7.3% vs. 9.9%, p = 0.19) did not significantly differ between the DES and CABG groups. In contrast, the 3-year TVR rate was significantly higher in patients receiving DES (10.3% vs. 2.8%, p < 0.001). After multivariable adjustment using standard Cox regression and IPTW, these results were consistent.

In the diabetic population, the 3-year unadjusted risks of death (6.4% vs. 8.6%, p = 0.37) and the composite of death, Q-wave MI, or stroke (8.4% vs. 10.9%, p = 0.35) were similar in the DES and CABG groups (Fig. 2, Table 2). As with the overall population, the 3-year incidence of TVR was significantly higher in diabetic patients who underwent DES than in those who underwent CABG (11.2% vs. 2.0%, p < 0.001). In the nondiabetic population, the 3-year unadjusted rates of death (5.8% vs. 7.8%, p = 0.19) and the composite of death, Q-wave MI, or stroke (6.8% vs. 9.2%, p = 0.17) were similar in DES and CABG patients, but the rate of TVR was significantly higher in DES than in CABG patients (9.9% vs. 3.2%, p < 0.001) (Fig. 3, Table 2). After adjusting for possible confounders using a multivariate Cox regression model and weighted Cox regression using the IPTW method, these outcomes were consistent, showing that DES and CABG carried similar risks of death and the composite of death, Q-wave MI, or stroke, and higher risks of TVR, in the overall, diabetic, and nondiabetic populations (Table 2).

When we assessed whether the magnitude of the treatment effects for DES and CABG varied significantly according to diabetes status, we did not observe significant interactions between treatment outcomes and the presence or absence of diabetes after adjustment for covariates ($p_{interaction}$ = 0.90 by multivariate and $p_{interaction}$ = 0.16 by IPTW for death, $p_{interaction}$ = 0.68 by multivariate and $p_{interaction}$ = 0.93 by IPTW for the composite of death, Q-wave MI, or stroke, and $p_{interaction}$ = 0.23 by multivariate and $p_{interaction}$ = 0.92 by IPTW for TVR). Despite large differences in the hazard ratios (HRs) between diabetic and nondiabetic groups, the overlapping of confidence intervals

Table 2. Kaplan-Meier Cumulative Incidence and Crude and Adjusted HRs of Clinical Outcomes Over 3 Years*

	Crude		Multivariate Adjusted			Inverse Probability of Treatment Weighted		
Outcomes	HR (95% CI)	p Value	HR (95% CI)	p Value	Interaction p for Diabetic Status	HR (95% CI)	p Value	Interaction p for Diabetic Status
Overall								
Death	0.747 (0.507–1.101)	0.14	1.109 (0.735–1.674)	0.621†	0.902	0.954 (0.623–1.462)	0.828	0.156
Death, QMI, or stroke	0.737 (0.518–1.048)	0.089	1.070 (0.735–1.556)	0.724‡	0.684	0.962 (0.652–1.419)	0.846	0.934
TVR	3.863 (2.344–6.367)	<0.0001	5.102 (2.973–8.756)	<0.0001§	0.233	4.309 (2.278–8.151)	<0.0001	0.919
Diabetic patients								
Death	0.744 (0.391–1.417)	0.369	0.793 (0.396–1.586)	0.511		0.547 (0.24–1.245)	0.150	
Death, QMI, or stroke	0.764 (0.434–1.345)	0.351	0.926 (0.522–1.644)	0.793¶		0.782 (0.377–1.621)	0.509	
TVR	5.898 (2.277–15.275)	0.0003	6.213 (2.397–16.106)	0.0002#		7.668 (2.757–21.32)	<0.0001	
Nondiabetic patients								
Death	0.755 (0.464–1.229)	0.258	1.05 (0.623–1.768)	0.856**		1.004 (0.586–1.718)	0.989	
Death, QMI, or stroke	0.733 (0.467–1.149)	0.176	1.030 (0.636–1.670)	0.903††		0.963 (0.586–1.583)	0.882	
TVR	3.168 (1.758–5.710)	0.0001	4.273 (2.264–8.066)	<0.0001‡‡		2.943 (1.357–6.384)	0.006	

*Hazard ratios (HRs) for drug-eluting stents with reference to coronary artery bypass grafting; †adjusted for sex, insulin-requiring diabetes mellitus, extent of diseased vessel, and EuroSCORE; ‡adjusted for sex, insulin-requiring diabetes mellitus, previous congestive heart failure, extent of diseased vessel, and EuroSCORE; §adjusted for insulin-requiring diabetes mellitus, previous congestive heart failure, extent of diseased vessel, EuroSCORE, and bifurcation involvement; adjusted for age, insulin-requiring diabetes mellitus, previous congestive heart failure, peripheral vascular disease, and restenotic lesion; ¶adjusted for previous congestive heart failure, cerebrovascular disease, and EuroSCORE; #adjusted for insulin-requiring diabetes mellitus; **adjusted for sex, cerebrovascular disease, peripheral vascular disease, renal failure, extent of diseased vessel, and EuroSCORE; ††adjusted for sex, cerebrovascular disease, renal failure, extent of diseased vessel, and EuroSCORE; ‡‡adjusted for age, current smoker, previous coronary angioplasty, EuroSCORE, and bifurcation involvement.

CI = confidence interval; QMI = Q-wave myocardial infarction; TVR = target-vessel revascularization.

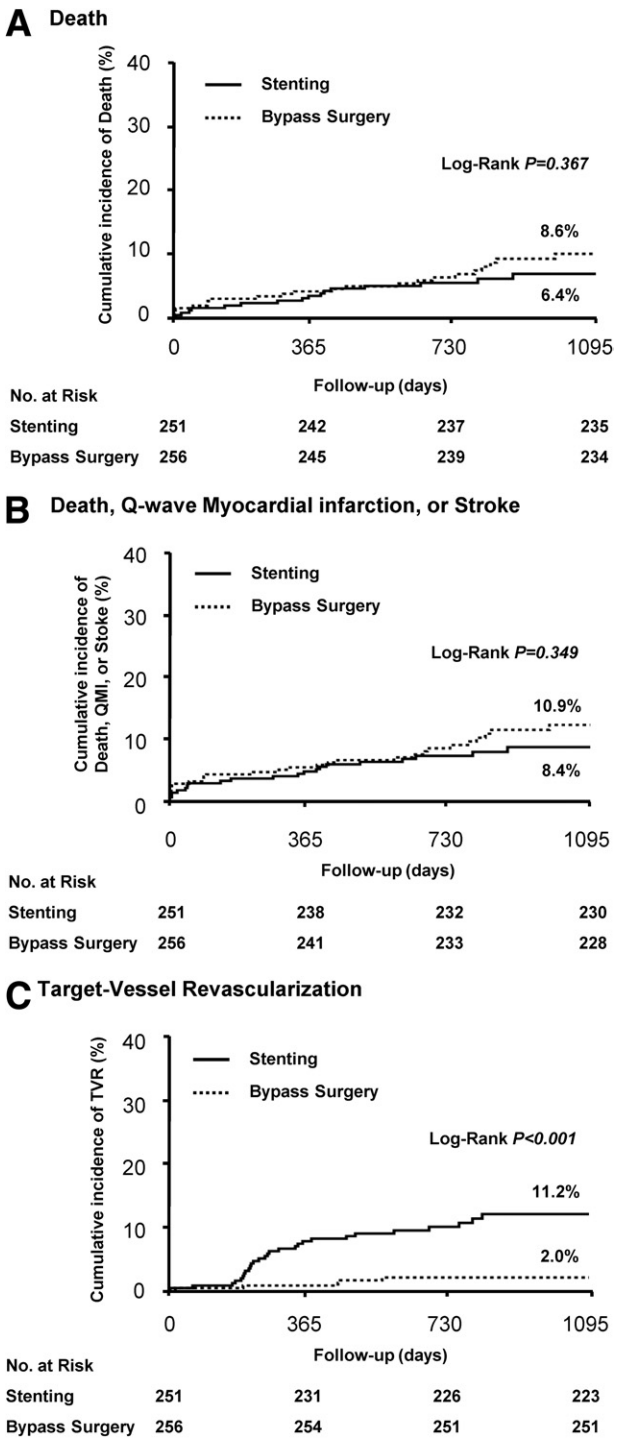

Figure 2. Cumulative Incidence of Outcomes in Diabetic Patients

Kaplan-Meier incidence curves of clinical outcomes up to 3 years in diabetic patients with unprotected left main coronary artery lesions who received drug-eluting stents or underwent coronary artery bypass grafting. **(A)** Death. **(B)** Composite of death, QMI, or stroke. **(C)** TVR. Abbreviations as in Figure 1.

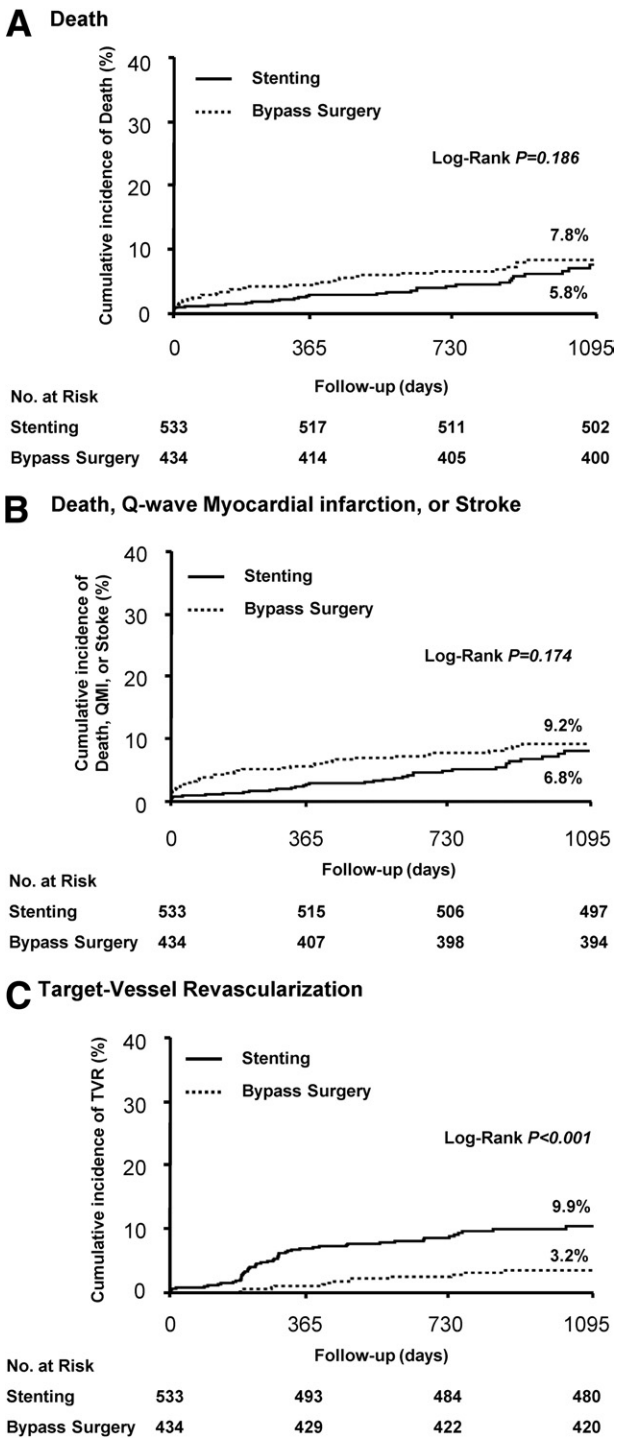

Figure 3. Cumulative Incidence of Outcomes in Nondiabetic Patients

Kaplan-Meier incidence curves of clinical outcomes up to 3 years in nondiabetic patients with unprotected left main coronary artery lesions who received drug-eluting stents or underwent coronary artery bypass grafting. **(A)** Death. **(B)** Composite of death, QMI, or stroke. **(C)** TVR. Abbreviations as in Figure 1.

(CIs) denoted statistical insignificance between the 2 groups (Table 2).

In addition, we directly compared TVR of diabetic with those of nondiabetic patients in the DES and CABG groups, respectively. After adjustment using multivariate Cox model and IPTW, the rates of TVR in diabetic over nondiabetic patients were similar in both DES (HR: 1.48, 95% CI: 0.81 to 2.71, p = 0.21 for multivariate Cox model; HR: 1.14, 95% CI: 0.69 to 1.87, p = 0.61 for IPTW) and CABG groups (HR: 1.75, 95% CI: 0.62 to 4.93, p = 0.29 for multivariate Cox model; HR: 1.36, 95% CI: 0.47 to 3.92, p = 0.57 for IPTW).

Discussion

The major findings of our study were that: 1) among patients with unprotected LMCA disease, the adjusted risks of death and the composite of death, Q-wave MI, or stroke were similar in patients who received DES or underwent CABG, whereas the risk of TVR was significantly higher in DES patients; 2) these findings were consistent in diabetic and nondiabetic patients; and 3) diabetes had a minimal prognostic impact on long-term treatment effects in patients who underwent DES or CABG.

Among patients with significant coronary artery disease undergoing CABG, periprocedural morbidity and mortality, long-term mortality, and the rates of repeat revascularization after CABG were found to be higher for diabetic than for nondiabetic patients (17–19). Diabetic patients receiving PCI also showed less favorable long-term survival and a higher incidence of restenosis and repeat revascularization than did nondiabetic patients (2,7,9,20). Compared with bare-metal stents, DES implantation has markedly reduced the need for repeat revascularization (21,22). A recent large meta-analysis of 10 randomized trials (23) showed that, despite substantial reductions in restenosis when DES were used, both in diabetic and nondiabetic patients, the presence of diabetes was associated with an increased risk of unfavorable clinical outcomes (5,6,22,24). Therefore, diabetic status has been regarded as both a major risk factor for adverse outcomes and an important clinical indicator in the choice of revascularization methods.

Several studies have compared PCI with CABG for multivessel disease treatment in diabetic patients. In diabetic subgroups from the ARTS (Arterial Revascularization Therapies Study) undergoing multivessel stenting using bare-metal stents and CABG, the incidence of death, MI, or stroke at 1 and 5 years did not differ between groups, but there was a higher incidence of repeat revascularization after stenting than after CABG (4,20). Even in the ARTS II trial, which compared DES with CABG, there were no significant differences in mortality, MI, and stroke, but higher rates of revascularization were observed after DES implantation (25). Although the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial could not compare PCI with CABG directly, patients who underwent CABG, but not PCI (DES, 35%), had significantly fewer major adverse cardiac events, as compared with patients who underwent optimal medical therapy (26).

Data comparing PCI and CABG in diabetic subsets with unprotected LMCA disease are, however, limited. Two ongoing large-scale randomized controlled studies comparing DES with CABG in patients with diabetes exclude patients with LMCA disease (27,28). A diabetic subgroup analysis of the SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) trial showed similar hard end points, including death, MI, or stroke, but higher repeat revascularization rates in patients with 3-vessel or LMCA disease (29). These results were similar to ours. We also found that treatment effects of the 2 primary interventions for patients with unprotected LMCA disease were consistent in diabetic and nondiabetic patients, without significant interactions. Similar trends were seen in previous randomized or registry studies comparing PCI with CABG in diabetic patients with multivessel coronary artery disease (20,22,25,30,31).

Study limitations. Our study had several limitations. Despite rigorous adjustment using standard and weighted Cox regression employing IPTW, it was an inherent limitation for the choice of treatment modality, which was based on the physician's or patient's preference, and otherwise unmeasured confounders or hidden bias may be present. Second, we may have inadequate statistical power to detect small outcome differences between the 2 revascularization strategies in diabetic and nondiabetic subgroups. Third, because our results are mainly derived from subgroup analyses, they should be regarded as exploratory in nature, and hypothesis-generating. Therefore, our findings should be confirmed or rebutted by large, prospective randomized clinical studies.

Conclusions

When the outcomes of 2 primary interventions (DES vs. CABG) for unprotected LMCA disease were compared, the adjusted risks of death and the composite of death, Q-wave MI, or stroke were similar, but the risk of TVR was significantly higher in DES patients. These findings were consistent in diabetic and nondiabetic patients, without significant interactions. Additional large clinical trials are warranted to evaluate the prognostic or clinical impact of diabetes in patients with multivessel coronary artery disease requiring revascularization procedures.

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REFERENCES

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA 1979;241:2035–8.
2. Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW. Coronary angioplasty in diabetic patients: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty registry. Circulation 1996;94:1818–25.
3. Rodriguez AE, Baldi J, Fernández Pereira C, et al. Five-year follow-up of the Argentine Randomized Trial of Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease (ERACI II). J Am Coll Cardiol 2005;46:582–8.
4. Serruys PW, Ong ATL, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005; 46:575–81.
5. Hong SJ, Kim MH, Ahn TH, et al. Multiple predictors of coronary restenosis after drug-eluting stent implantation in patients with diabetes. Heart 2006;92:1119–24.
6. Kumar R, Lee TT, Jeremias A, et al. Comparison of outcomes using sirolimus-eluting stenting in diabetic versus nondiabetic patients with comparison of insulin versus non-insulin therapy in the diabetic patients. Am J Cardiol 2007;100:1187–91.
7. Stein B, Weintraub WS, Gebhart SSP, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. Circulation 1995;91:979–89.
8. Thourani VH, Weintraub WS, Stein B, et al. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. Ann Thorac Surg 1999;67:1045–52.
9. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996;335:217–25.
10. Seung KB, Park DW, Kim YH, et al. Stents versus coronary-artery bypass grafting for left main coronary artery disease. N Engl J Med 2008;358:1781–92.
11. Park SJ, Kim YH, Lee BK, et al. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. J Am Coll Cardiol 2005;45:351–6.
12. Park DW, Park SW, Park KH, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol 2006;98:352–6.
13. Eagle KA, Guyton RA, Davidoff R, et al., American College of Cardiology/American Heart Association Task Force on Practice Guidelines Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery; American Society for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). J Am Coll Cardiol 2004;44:e213–310.
14. Chieffo A, Morici N, Maisano F, et al. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. Circulation 2006;113:2542–7.
15. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. Stat Med 2005;24:3089–110.
16. Robins JM. Marginal structural models. In: 1997 Proceedings of the American Statistical Association, Section on Bayesian Statistical Science. Alexandria, VA: American Statistical Association, 1998;1–10.
17. Carson JL, Scholz PM, Chen AY, Peterson ED, Gold J, Schneider SH. Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol 2002;40:418–23.
18. Sabik JF III, Blackstone EH, Gillinov AM, Smedira NG, Lytle BW. Occurrence and risk factors for reintervention after coronary artery bypass grafting. Circulation 2006;114:I-454–60.
19. Slaughter MS, Olson MM, Lee JTJ, Ward HB. A fifteen-year wound surveillance study after coronary artery bypass. Ann Thorac Surg 1993;56:1063–8.
20. Abizaid A, Costa MA, Centemero M, et al. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. Circulation 2001;104:533–8.
21. Roiron C, Sanchez P, Bouzamondo A, Lechat P, Montalescot G. Drug eluting stents: an updated meta-analysis of randomised controlled trials. Heart 2006;92:641–9.
22. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. BMJ 2008;337:a1331.
23. Stettler C, Allemann S, Egger M, Windecker S, Meier B, Diem P. Efficacy of drug eluting stents in patients with and without diabetes mellitus: indirect comparison of controlled trials. Heart 2006;92: 650–7.
24. Iijima R, Ndrepepa G, Mehilli J, et al. Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era. Am Heart J 2007;154:688–93.
25. Serruys PW, Ong ATL, Morice MC, et al. Arterial revascularization therapies study part II—sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. EuroIntervention 2005;1:147–56.
26. The BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–15.
27. Farkouh ME, Dangas G, Leon MB, et al. Design of the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial. Am Heart J 2008;155:215–23.
28. Kapur A, Malik IS, Bagger JP, et al. The Coronary Artery Revascularisation in Diabetes (CARDia) trial: background, aims, and design. Am Heart J 2005;149:13–9.
29. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
30. Park DW, Flaherty JD, Davidson CJ, et al. Prognostic influence of diabetes mellitus on long-term clinical outcomes and stent thrombosis after drug-eluting stent implantation in Asian patients. Am J Cardiol 2009;103:646–52.
31. Park DW, Yun SC, Lee SW, et al. 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. Circulation 2008;117:2079–86.

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