Influence of Diabetes Mellitus on Long-Term (Five-Year) Outcomes of Drug-Eluting Stents and Coronary Artery Bypass Grafting for Multivessel Coronary Revascularization

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Diabetes mellitus is a major risk factor for coronary artery disease (CAD) and for diffuse and progressive atherosclerosis. We evaluated the outcomes of drug-eluting stent (DES) placement and coronary artery bypass grafting (CABG) in 891 diabetic patients (489 for DES implantation and 402 for CABG) and 2,151 nondiabetic patients (1,058 for DES implantation and 1,093 for CABG) with multivessel CAD treated from January 2003 through December 2005 and followed up for a median 5.6 years. Outcomes of interest included death; the composite outcome of death, myocardial infarction (MI), or stroke; and repeat revascularization. In diabetic patients, after adjusting for baseline covariates, 5-year risk of death (hazard ratio 1.01, 95% confidence interval 0.77 to 1.33, p = 0.96) and the composite of death, MI, or stroke (hazard ratio 1.03, 95% confidence interval 0.80 to 1.31, p = 0.91) were similar in patients undergoing DES or CABG. However, rate of repeat revascularization was significantly higher in the DES group (hazard ratio 3.69, 95% confidence interval 2.64 to 5.17, p <0.001). These trends were consistent in nondiabetic patients (hazard ratio 0.80, 95% confidence interval 0.55 to 1.16, p = 0.23 for death; hazard ratio 0.77, 95% confidence interval 0.56 to 1.05, p = 0.10 for composite of death, MI, or stroke; hazard ratio 2.77, 95% CI 1.95 to 3.91, p <0.001 for repeat revascularization). There was no significant interaction between diabetic status and treatment strategy on clinical outcomes (p for interaction = 0.36 for death; 0.20 for the composite of death, MI, or stroke; and 0.40 for repeat revascularization). In conclusion, there was no significant prognostic influence of diabetes on long-term treatment with DES or CABG in patients with multivessel CAD. **(Am J Cardiol 2012;109:1548–1557)**

Diabetes mellitus (DM) is a major risk factor for coronary artery disease (CAD), making patients prone to a diffuse, multiple, and rapidly progressive form of CAD.[1] About 25% of patients with significant CAD who undergo percutaneous coronary intervention or coronary artery bypass grafting (CABG) have DM,[2] and DM is significantly associated with higher rates of ischemic complications and recurrent revascularization in these patients.[3–8] CABG has been shown to be superior to percutaneous coronary intervention in diabetic patients with multivessel CAD,[9,10] indicating that DM is a major consideration in selecting an optimal revascularization strategy. However, these studies were conducted before the introduction of drug-eluting stents (DESs), which have markedly decreased the incidence of angiographic restenosis and repeat revascularization compared to bare-metal stents.[11] We therefore compared the long-term effects of treatment with DESs and CABG in diabetic and nondiabetic patients with multivessel CAD and evaluated the interaction between diabetic status and treatment procedure in these patients.

Methods

This study is a subgroup analysis of patients in the Asan Multivessel Registry with and without medically treated DM. The Asan Multivessel Registry is a single-center prospective study designed to evaluate the effects of percutaneous coronary intervention with DESs and CABG on patients with multivessel CAD in clinical practice.[12] Briefly, this registry included consecutive patients with multivessel CAD who received percutaneous coronary intervention with DESs, with or without other devices, or underwent isolated CABG at Asan Medical Center (Seoul, Korea) from January

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This study was supported in part by the Cardiovascular Research Foundation, Seoul, Korea, and Grant 0412-CR02-0704-0001 from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Seoul.

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0002-9149/12/$ – see front matter
doi:10.1016/j.amjcard.2012.01.377

Table 1
Baseline characteristics of patients according to diabetic status and treatment strategy

Variable	Diabetic Patients (n = 891)			Nondiabetic Patients (n = 2,151)		
	DES (n = 489)	CABG (n = 402)	*p* Value	DES (n = 1,058)	CABG (n = 1,093)	*p* Value
Age (years)	63.5 ± 9.3	62.8 ± 8.1	0.19	61.3 ± 10.5	61.4 ± 8.7	0.76
Men	304 (62.2%)	275 (68.4%)	0.06	769 (72.7%)	821 (75.1%)	0.20
Body mass index (kg/m^2)	25.3 ± 3.1	24.6 ± 3.0	0.001	24.9 ± 2.9	24.8 ± 3.0	0.43
Medically treated diabetes			0.66			
Oral hypoglycemic agent	403 (82.4%)	326 (81.1%)		—	—	—
Requiring insulin	86 (17.6%)	76 (18.9%)		—	—	—
Years with diabetes	9.9 ± 8.2	10.9 ± 8.4	0.08	—	—	—
Hypertension*	313 (64.0%)	247 (61.4%)	0.44	570 (53.9%)	320 (29.3%)	<0.001
Current smoker	113 (23.1%)	66 (16.4%)	0.02	344 (32.5%)	138 (12.6%)	<0.001
Hyperlipidemia†	105 (21.5%)	202 (50.2%)	<0.001	268 (25.3%)	272 (24.9%)	0.84
Previous coronary angioplasty	88 (18.0%)	59 (14.7%)	0.2	182 (17.2%)	90 (8.2%)	<0.001
Previous congestive heart failure	11 (2.2%)	28 (7.0%)	0.001	11 (1.0%)	40 (3.7%)	<0.001
Moderate or severe chronic obstructive pulmonary disease	6 (1.2%)	8 (2.0%)	0.42	10 (0.9%)	20 (1.83%)	0.08
Cerebrovascular or carotid artery disease	36 (7.4%)	69 (17.2%)	<0.001	49 (4.6%)	98 (9.0%)	<0.001
Peripheral vascular disease	17 (3.5%)	43 (10.7%)	<0.001	17 (1.6%)	71 (6.5%)	<0.001
Renal failure	26 (5.3%)	43 (10.7%)	0.004	16 (1.5%)	44 (4.0%)	<0.001
EuroSCORE	.7 ± 2.5	4.5 ± 2.7	<0.001	3.1 ± 2.3	3.7 ± 2.4	<0.001
Previous myocardial infarction			<0.001			<0.001
1–7 days before treatment	29 (5.9%)	21 (5.2%)		109 (10.3%)	63 (5.8%)	
≥8 days before treatment	6 (1.2%)	88 (21.9%)		12 (1.1%)	122 (11.2%)	
No previous myocardial infarction	454 (92.8%)	293 (72.9%)		937 (88.6%)	908 (83.1%)	
Electrocardiographic findings			0.82			0.01
Sinus rhythm	458 (93.7%)	381 (94.8%)		1,000 (94.5%)	1,059 (96.9%)	
Atrial fibrillation	17 (3.5%)	12 (3.0%)		31 (2.9%)	14 (1.3%)	
Others	14 (2.9%)	9 (2.2%)		27 (2.6%)	20 (1.8%)	
Ejection fraction (%)			<0.001			<0.001
<30%	9 (1.9%)	20 (5.1%)		5 (0.5%)	29 (2.7%)	
30%–40%	8 (1.7%)	40 (10.1%)		25 (2.4%)	57 (5.3%)	
40%–50%	58 (12.0%)	42 (10.6%)		86 (8.4%)	138 (12.8%)	
≥50%	407 (84.4%)	293 (74.2%)		910 (88.7%)	854 (79.2%)	
Data missing	7 (1.4%)	7 (1.7%)	0.79	32 (3.0%)	15 (1.4%)	0.01
Mean ejection fraction (%)	58.3 ± 9.2%	54.7 ± 12.2%	<0.001	59.0 ± 8.3%	56.8 ± 10.5%	<0.001
2-Vessel disease	258 (52.8%)	66 (16.4%)	<0.001	610 (57.7%)	277 (25.3%)	<0.001
With proximal left anterior descending coronary artery disease	89 (18.2%)	39 (9.7%)	<0.001	230 (21.7%)	107 (9.8%)	<0.001
Without proximal left anterior descending coronary artery disease	169 (34.6%)	27 (6.7%)	<0.001	380 (35.9%)	170 (15.6%)	<0.001
3-Vessel disease	231 (47.2%)	336 (83.6%)	<0.001	448 (42.3%)	816 (74.7%)	<0.001
With proximal left anterior descending coronary artery disease	106 (21.7%)	216 (53.7%)	<0.001	176 (16.6%)	442 (40.4%)	<0.001
Without proximal left anterior descending coronary artery disease	125 (25.6%)	120 (29.9%)	<0.001	272 (25.7%)	374 (34.2%)	<0.001
Left main coronary artery disease	46 (9.4%)	103 (25.6%)	<0.001	132 (12.5%)	269 (24.6%)	<0.001
Total occlusion	29 (5.9%)	189 (47.0%)	<0.001	81 (7.7%)	467 (42.7%)	<0.001
Discharge medications						
Aspirin	484 (99.0%)	385 (95.8%)	0.004	1,050 (99.2%)	1,061 (97.1%)	<0.001
Clopidogrel	481 (98.4%)	316 (78.6%)	<0.001	1,048 (99.1%)	716 (65.5%)	<0.001
Aspirin and clopidogrel	481 (98.4%)	316 (78.6%)	<0.001	1,048 (99.1%)	716 (65.5%)	<0.001
Statin	331 (67.7%)	230 (57.2%)	0.001	692 (65.4%)	506 (46.3%)	<0.001
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	214 (43.8%)	139 (34.6%)	0.006	347 (32.8%)	279 (25.5%)	<0.001
β Blockers	426 (87.1%)	112 (27.9%)	<0.001	925 (87.4%)	245 (22.4%)	<0.001
Calcium channel blockers	430 (87.9%)	321 (79.9%)	0.001	913 (86.3%)	894 (81.8%)	0.005
Nitrates	374 (76.5%)	369 (91.8%)	<0.001	809 (76.5%)	923 (84.4%)	<0.001

Table 1
(*continued*)

Variable	Diabetic Patients (n = 891)			Nondiabetic Patients (n = 2,151)		
	DES (n = 489)	CABG (n = 402)	*p* Value	DES (n = 1,058)	CABG (n = 1,093)	*p* Value
SYNTAX score in available cohort (n = 1,914)						
Number of patients	443	217		957	297	
Mean SYNTAX score	18.3 ± 7.9	30.4 ± 10.7	<0.001	17.0 ± 7.7	29.5 ± 10.5	<0.001
SYNTAX score category			<0.001			<0.001
Low (≤22)	324 (73.1%)	53 (24.4%)		744 (77.7%)	76 (25.6%)	
Intermediate (23–32)	95 (21.4%)	79 (36.4%)		179 (18.7%)	105 (35.4%)	
High (≥33)	24 (5.4%)	85 (39.2%)		34 (3.6%)	116 (39.1%)	

Data are reported as mean ± SD or number (percentage).
EuroSCORE = European System for Cardiac Operative Risk Evaluation.
* Defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or receiving antihypertensive treatment.
† Defined as total cholesterol >200 mg/dl or receiving antilipidemic treatment.

Table 2
Predictors of selection for drug-eluting stents: results of nonparsimonious logistic regression modeling used to develop the propensity score

Predictor	Diabetic Patients			Nondiabetic Patients		
	OR (95% CI)	Chi-Square	p Value	OR (95% CI)	Chi-Square	p Value
Age	1.00 (0.97–1.03)	1.66	0.95	1.01 (0.99–1.03)	0.18	0.20
Male gender	0.87 (0.56–1.37)	3.04	0.55	0.82 (0.61–1.09)	1.94	0.18
Body mass index (kg/m^2)	1.04 (0.98–1.11)	12.07	0.24	1.02 (0.98–1.06)	0.33	0.32
Hypertension*	1.21 (0.80–1.81)	0.02	0.37	3.32 (2.60–4.25)	137.53	<0.0001
Current smoker	1.77 (1.06–2.96)	13.61	0.03	4.81 (3.51–6.58)	127.88	<0.0001
Hyperlipidemia†	0.24 (0.16–0.36)	84.95	<0.0001	0.88 (0.67–1.15)	8.86	0.34
Insulin requiring diabetes	1.04 (0.60–1.80)	0.02	0.89	—	—	—
Years with diabetes	1.00 (0.97–1.03)	0	0.96	—	—	—
Previous coronary angioplasty	0.85 (0.51–1.40)	1.18	0.52	2.41 (1.67–3.49)	31.82	<0.0001
Previous congestive heart failure	1.14 (0.39–3.33)	5.50	0.82	0.50 (0.20–1.25)	9.71	0.14
Moderate or severe chronic obstructive pulmonary disease	0.45 (0.11–1.87)	2.08	0.27	0.61 (0.22–1.66)	1.74	0.33
Cerebrovascular or carotid artery disease	0.34 (0.15–0.80)	13.53	0.01	0.45 (0.25–0.80)	21.69	0.007
Peripheral vascular disease	0.49 (0.20–1.17)	10.51	0.11	0.23 (0.11–0.47)	33.51	<0.0001
Renal failure	0.46 (0.20–1.07)	2.22	0.07	0.52 (0.24–1.14)	6.06	0.10
EuroSCORE	1.09 (0.93–1.27)	7.51	0.31	1.03 (0.94–1.13)	10.47	0.58
Previous myocardial infarction	0.28 (0.15–0.52)	39.54	<0.0001	0.58 (0.40–0.84)	16.32	0.004
Ejection fraction (%)	1.00 (0.98–1.02)	1.90	0.92	1.01 (0.99–1.02)	5.95	0.48
2-Vessel disease	3.20 (2.11–4.86)	37.16	<0.0001	2.26 (1.78–2.87)	49.16	<0.0001
Proximal left anterior descending coronary artery disease	0.60 (0.41–0.89)	6.53	0.01	1.34 (1.05–1.71)	5.44	0.02
Left main disease	0.74 (0.44–1.27)	24.11	0.28	0.56 (0.41–0.76)	53.79	<0.0001
Total occlusion	0.12 (0.07–0.21)	71.00	<0.0001	0.21 (0.15–0.29)	97.80	<0.0001
SYNTAX score	0.91 (0.89–0.93)	194.10	<0.0001	0.90 (0.89–0.92)	524.77	<0.0001

* Defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or receiving antihypertensive treatment.
† Defined as total cholesterol >200 mg/dl or receiving antilipidemic treatment.
CI = confidence interval; OR = odds ratio. Other abbreviation as in Table 1.

1, 2003 through December 31, 2005. Patients who had previous CABG or underwent concomitant valvular or aortic surgery, had an acute myocardial infarction (MI) within 24 hours before revascularization, or presented with cardiogenic shock were excluded.

The decision to perform percutaneous coronary intervention or CABG depended on a physician's choice, considering available clinical and anatomic factors, and/or a patient's preference. During the study period, coronary stenting was performed exclusively with DESs. Percutaneous coronary intervention was performed according to current practice guidelines. Choice of a specific type of DES (i.e., sirolimus-eluting stent [CYPHER and CYPHER SELECT, Cordis, Johnson and Johnson, Bridgewater, New Jersey] or paclitaxel-eluting stent [TAXUS Express and TAXUS Liberté, Boston Scientific, Natick, Massachusetts])

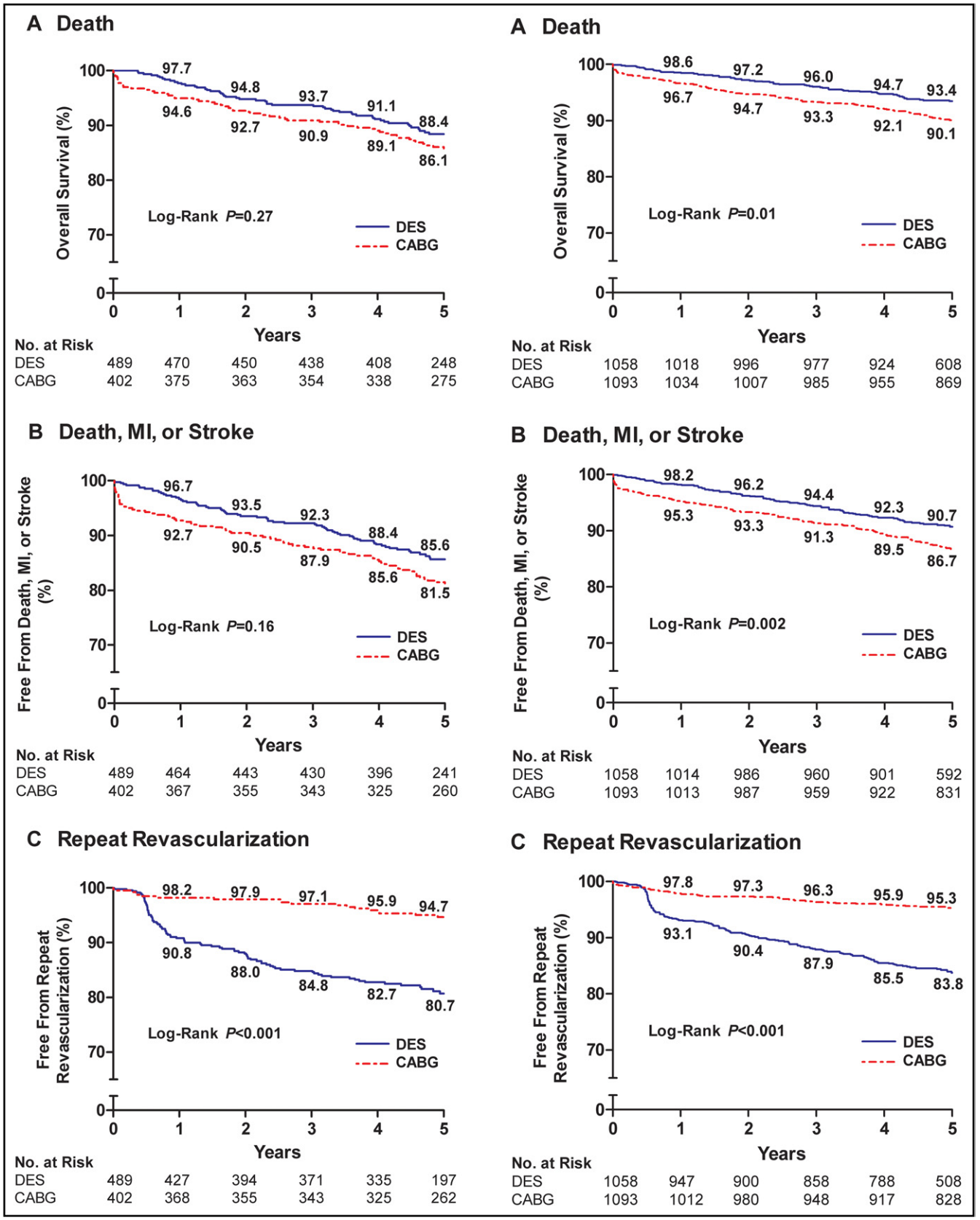

Figure 1. Kaplan–Meier event-free survival curves of 5-year outcomes according to diabetic status and treatment group in *(left)* diabetic patients and *(right)* nondiabetic patients: *(A)* death; *(B)* composite of death, myocardial infarction, or stroke; and *(C)* repeat revascularization.

Table 3
Hazard ratios for clinical adverse outcomes after drug-eluting stents compared to coronary artery bypass grafting according to diabetic status*

Outcomes	Total Number of Events/ Number of Patients		Unadjusted		Multivariable Adjusted†			Adjusted by IPTW		
	DES	CABG	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	Interaction *p* Value for Diabetic Status	HR (95% CI)	*p* Value	Interaction *p* Value for Diabetic Status
Death										0.36
Diabetic patients	57/489	60/402	0.82 (0.57–1.17)	0.27	1.37 (0.86–2.17)	0.19	0.32	1.01 (0.77–1.33)	0.96	
Nondiabetic patients	72/1,058	115/1,093	0.68 (0.51–0.91)	0.01	0.85 (0.63–1.15)	0.30		0.80 (0.55–1.16)	0.23	
Composite outcome (death, myocardial infarction, or stroke)							0.12			0.20
Diabetic patients	72/489	76/402	0.80 (0.58–1.10)	0.16	1.38 (0.92–2.08)	0.12		1.03 (0.80–1.31)	0.91	
Nondiabetic patients	99/1,058	158/1,093	0.67 (0.52–0.86)	0.002	0.79 (0.61–1.02)	0.07		0.77 (0.56–1.05)	0.10	
Repeat revascularization							0.46			0.40
Diabetic patients	91/489	22/402	3.88 (2.43–6.20)	<0.001	3.61 (2.25–5.77)	<0.001		3.69 (2.64–5.17)	<0.001	
Nondiabetic patients	168/1,058	65/1,093	3.12 (2.33–4.16)	<0.001	3.12 (2.34–4.17)	<0.001		2.77 (1.95–3.91)	<0.001	

* Hazard ratios are for the drug-eluting stent compared to the coronary artery bypass grafting group.

† Hazard ratios were adjusted for age; gender; diabetes; duration of diabetes; presence or absence of congestive heart failure; chronic obstructive pulmonary disease; cerebrovascular or carotid disease, peripheral arterial disease, and renal failure; European System for Cardiac Operative Risk Evaluation; history or no history of myocardial infarction before procedure; ejection fraction; 2- or 3-vessel disease; presence or absence of involvement of the proximal left anterior descending or left main coronary artery; total obstruction; and SYNTAX score.

HR = hazard ratio; IPTW = inverse probability-of-treatment weighting. Other abbreviation as in Table 2.

Table 4
Hazard ratios for clinical adverse outcomes after drug-eluting stents compared to coronary artery bypass grafting according to diabetic status and extent of diseased vessels*

Outcomes	Total Number of Events/Number of Patients		Unadjusted		Multivariable Adjusted†		
	DES	CABG	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	Interaction *p* Value for Diabetic Status
2-Vessel disease	868	343					
Death							0.68
Diabetic patients	19/258	9/66	0.56 (0.25–1.23)	0.15	0.68 (0.29–1.56)	0.36	
Nondiabetic patients	35/610	30/277	0.56 (0.35–0.92)	0.02	0.43 (0.25–0.75)	0.003	
Composite outcome (death, myocardial infarction, or stroke)							0.71
Diabetic patients	28/258	12/66	0.61 (0.31–1.21)	0.16	0.59 (0.30–1.16)	0.13	
Nondiabetic patients	52/610	33/277	0.77 (0.50–1.19)	0.24	0.86 (0.55–1.34)	0.49	
Repeat revascularization							0.64
Diabetic patients	50/258	5/66	2.82 (1.12–7.07)	0.028	1.04 (1.01–1.08)	0.024	
Nondiabetic patients	94/610	23/277	2.11 (1.33–3.34)	0.002	2.15 (1.35–3.40)	0.001	
3-Vessel disease	679	1,152					
Death							0.38
Diabetic patients	38/231	51/336	1.16 (0.76–1.77)	0.48	1.17 (0.76–1.81)	0.48	
Nondiabetic patients	37/448	85/816	0.83 (0.56–1.22)	0.34	1.06 (0.71–1.59)	0.77	
Composite outcome (death, myocardial infarction, or stroke)							0.09
Diabetic patients	44/231	64/336	1.04 (0.71–1.53)	0.85	1.21 (0.81–1.83)	0.35	
Nondiabetic patients	47/448	125/816	0.70 (0.50–0.97)	0.034	0.86 (0.61–1.22)	0.40	
Repeat revascularization							0.79
Diabetic patients	41/231	17/336	4.10 (2.32–7.23)	<0.001	4.67 (2.62–8.34)	<0.001	
Nondiabetic patients	74/448	42/816	3.84 (2.62–5.64)	<0.001	3.79 (2.58–5.57)	<0.001	

* Hazard ratios are for the drug-eluting stent compared to the coronary artery bypass grafting group.

† Hazard ratios were adjusted for age; gender; diabetes; duration of diabetes; presence or absence of congestive heart failure; chronic obstructive pulmonary disease; cerebrovascular or carotid disease, peripheral arterial disease, and renal failure; European System for Cardiac Operative Risk Evaluation; history or no history of myocardial infarction before procedure; ejection fraction; presence or absence of involvement of the proximal left anterior descending or left main coronary artery; total obstruction; and SYNTAX score.

Abbreviations as in Tables 2 and 3.

was at the discretion of the operator. At this time, second-generation DESs (i.e., zotarolimus-, everolimus-, and biolimus-eluting stents) were not available to the treating physicians. Antiplatelet therapy and periprocedural anticoagulation followed standard regimens. After the procedure, patients were prescribed aspirin indefinitely and clopidogrel for ≥6 months regardless of DES type. Treatment beyond this time was at the discretion of each physician. Surgical revascularization was performed using standard bypass techniques; whenever possible, the internal thoracic artery was used for revascularization of the left anterior descending coronary artery. When possible, complete revascularization was performed using arterial conduits or saphenous vein grafts. This study was approved by our local institutional review board.

End points of the study were death; composite of death, MI, or stroke; and repeat revascularization. Death was defined as death from any cause. A diagnosis of acute MI was defined as complications at index admission (defined as new pathologic Q waves after index treatment) or follow-up MI requiring subsequent hospitalizations (i.e., emergency admission with a principal diagnosis of MI), as described previously.[13] Stroke, as indicated by neurologic deficits, was confirmed by a neurologist based on imaging studies. Repeat revascularization included target vessel revascularization regardless of whether the procedure was clinically or angiographically driven and nontarget-vessel revascularization. In the DES group, stent thrombosis was defined as definite or probable events according to the Academic Research Consortium classification.[14] All outcomes of interest were carefully verified and adjudicated by independent clinicians. The diabetic subgroup was defined as all patients actively receiving treatment with oral hypoglycemic agents or insulin.

The registry prospectively contains information on patient demographics, coexisting clinical conditions, hemodynamic status, left ventricular function, extent of disease, details of procedures, and in-hospital and follow-up outcomes by independent research personnel. Patients were clinically followed 1 month and 6, and 12 months after the procedure and annually thereafter by office visit or telephone contact. The follow-up period was through January 31, 2010 to ensure that all patients had an opportunity for ≥4 years and up to approximately 7 years of follow-up. For validation of complete fol-

Table 5
Hazard ratios for clinical adverse outcomes after drug-eluting stents compared to coronary artery bypass grafting according to diabetic status and SYNTAX score*

Outcomes	Total Number of Events/Number of Patients		Unadjusted		Multivariable Adjusted†		
	DES	CABG	HR (95% CI)	p Value	HR (95% CI)	p Value	Interaction p Value for Diabetic Status
Low score (≤22)	1,068	129					
Death							0.40
Diabetic patients	30/324	5/53	0.98 (0.38–2.54)	0.97	1.05 (0.41–2.72)	0.92	
Nondiabetic patients	44/744	6/76	0.85 (0.34–2.15)	0.74	0.73 (0.31–1.74)	0.48	
Composite outcome (death, myocardial infarction, or stroke)							0.85
Diabetic patients	42/324	6/53	1.16 (0.49–2.72)	0.74	1.21 (0.51–2.85)	0.66	
Nondiabetic patients	67/744	6/76	1.24 (0.54–2.85)	0.62	1.13 (0.49–2.61)	0.78	
Repeat revascularization							0.11
Diabetic patients	58/324	1/53	10.37 (1.44–74.85)	0.02	10.37 (1.44–74.85)	0.02	
Nondiabetic patients	124/744	7/76	1.96 (0.92–4.20)	0.08	2.01 (0.94–4.31)	0.07	
Intermediate score (23–32)	274	184					
Death							0.38
Diabetic patients	14/95	14/79	0.90 (0.43–1.88)	0.77	1.01 (0.45–2.26)	0.98	
Nondiabetic patients	15/179	17/105	0.50 (0.25–0.99)	0.05	0.67 (0.33–1.37)	0.27	
Composite outcome (death, myocardial infarction, or stroke)							0.49
Diabetic patients	15/95	20/79	0.64 (0.33–1.25)	0.19	0.69 (0.34–1.41)	0.31	
Nondiabetic patients	18/179	22/105	0.45 (0.24–0.84)	0.012	0.53 (0.28–1.01)	0.06	
Repeat revascularization							0.88
Diabetic patients	21/95	7/79	2.79 (1.18–6.58)	0.019	2.79 (1.18–6.58)	0.019	
Nondiabetic patients	21/179	5/105	2.51 (0.94–6.66)	0.07	2.51 (0.94–6.66)	0.07	
High score (≥33)	58	201					
Death							0.60
Diabetic patients	5/24	13/85	1.41 (0.50–3.96)	0.52	1.19 (0.30–4.67)	0.80	
Nondiabetic patients	3/34	10/116	1.03 (0.28–3.73)	0.97	1.03 (0.28–3.73)	0.97	
Composite outcome (death, myocardial infarction, or stroke)							0.12
Diabetic patients	7/24	13/85	1.99 (0.79–4.98)	0.14	1.77 (0.65–4.87)	0.27	
Nondiabetic patients	3/34	15/116	0.67 (0.19–2.30)	0.52	0.42 (0.11–1.68)	0.22	
Repeat revascularization							0.12
Diabetic patients	5/24	2/85	11.36 (2.18–59.15)	0.004	11.36 (2.18–59.15)	0.004	
Nondiabetic patients	4/34	7/116	2.15 (0.63–7.40)	0.22	2.15 (0.63–7.40)	0.22	

* Hazard ratios are for the drug-eluting stent compared to the coronary artery bypass grafting group.

† Hazard ratios adjusted for age; gender diabetes; duration of diabetes; presence or absence of congestive heart failure; chronic obstructive pulmonary disease; cerebrovascular or carotid disease, peripheral arterial disease, and renal failure; European System for Cardiac Operative Risk Evaluation; history or no history of myocardial infarction before the procedure; ejection fraction; 2- or 3-vessel disease; presence or absence of involvement of the proximal left anterior descending or left main coronary artery; total obstruction; and SYNTAX score.

Abbreviations as in Tables 2 and 3.

low-up data on mortality, information about vital status was obtained through January 31, 2010 from the National Population Registry of the Korea National Statistical Office using a unique personal identification number.

Treatment-related differences in long-term outcomes between the 2 procedures were analyzed separately in patients with and without medically treated DM. Prevalence rates of risk factors and characteristics of the patients in the 2 treatment groups were compared using *t* test or Wilcoxon rank-sum test for continuous variables and with chi-square statistics or Fisher's exact test for categorical variables. Survival curves were constructed using the Kaplan–Meier method and compared using log-rank test.

Differences in risk-adjusted long-term rates of study outcomes between patients in the DES and CABG groups were assessed using multivariable Cox proportional hazards regression. Adjusted covariates included patient age and gender, presence or absence of different clinical and coexisting conditions, left ventricular function, and number and extent of diseased vessels. The proportional hazards assumption was confirmed by examination of log(–log [survival]) curves and by testing of partial (Schoenfeld) residuals, and

no relevant violations were found. To decrease the impact of treatment selection bias and potential confounding in an observational study, we also performed rigorous adjustment for baseline differences using weighted Cox proportional hazards regression models with inverse probability-of-treatment weighting.[15] Weights for patients undergoing CABG were the inverse of (1 – propensity score), and weights for patients undergoing stenting were the inverse of the propensity score. Propensity scores were estimated without regard to outcomes using multiple logistic regression analysis. We developed a full nonparsimonious model that included all variables listed in Table 1. Model discrimination was assessed with c-statistics, and model calibration was assessed with Hosmer–Lemeshow statistics. Treatment effects were evaluated separately in diabetic and nondiabetic patients. Then, interaction terms in the multivariate Cox model and weighted Cox model using the inverse probability-of-treatment weighting method were used to test for the statistical significance of the effects of the 2 treatment strategies according to diabetic status on clinical outcomes.

In addition, outcomes were analyzed based on extent of diseased vessels (2- or 3-vessel disease) and Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) score.[16]

All reported p values are 2-sided, and p values <0.05 were considered statistically significant. No adjustments were performed for multiple testing in several subgroups. SAS 9.1 (SAS Institute, Cary, North Carolina) and the R programming language (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

Results

From January 2003 through December 2005, 891 diabetic patients and 2,151 nondiabetic patients with multivessel CAD underwent percutaneous coronary intervention with DES implantation or CABG. Baseline characteristics of study patients are listed in Table 1. Compared to patients undergoing DES, diabetic and nondiabetic patients undergoing CABG had higher-risk profiles for clinical and angiographic characteristics. Of diabetic patients who underwent percutaneous coronary intervention, 77.1% received sirolimus-eluting stents and 22.9% received paclitaxel-eluting stents; in nondiabetic patients, 80.5% received sirolimus-eluting stents and 19.5% received paclitaxel-eluting stents. Median follow-up in the overall population was 5.6 years (interquartile range 4.6 to 6.3), with 97.4% undergoing complete follow-up for major clinical events including 97.7% of patients in the DES group and 97.0% in the CABG group ($p = 0.20$). Predictors of choice of revascularization strategy are listed in Table 2.

Unadjusted event-free survival curves are shown in Figure 1 and crude and adjusted risks according to treatment approach and diabetic status are presented in Table 3. After adjustment for differences in baseline risk factors between treatment procedures using multivariable Cox regression analysis and weighted Cox regression using inverse probability-of-treatment weighting methods, adjusted treatment-related risks of death and the composite of death, MI, or stroke did not differ significantly in diabetic and nondiabetic patients. Adjusted risk of repeat revascularization was consistently higher in the DES than in the CABG group. When we tested the interaction between diabetic status and treatment strategy on clinical outcomes, we found no statistically significant interactions after adjustment for possible confounders (Table 3).

Table 4 presents risks according to diabetic status and extent of diseased vessels. There were no significant differences of treatment effect in risks of death and composite of death, MI, or stroke in diabetic and nondiabetic patients with 3-vessel disease. In nondiabetic patients with 2-vessel disease, however, adjusted risk of mortality was significantly lower in the DES than in the CABG group. Risk of repeat revascularization was significantly lower in the CABG group among all subgroups.

During the study enrollment period, the SYNTAX score algorithm was not available to the physician. Retrospective retrieval of baseline angiogram for detailed measurement of the SYNTAX score was available in 63% of the overall cohort. Mean SYNTAX score and SYNTAX score category are listed in Table 1. Risks according to the SYNTAX score are presented in Table 5. After adjustment of covariates, risks of death and composite outcomes were similar between the DES and CABG groups in diabetic and nondiabetic patients with low, intermediate, and high scores, although adjusted hazard ratios nonsignificantly favored CABG in diabetic patients with a high score. Risk of repeat revascularization was significantly higher in diabetic patients but did not differ significantly in nondiabetic patients with low, intermediate, and high scores.

Discussion

The major findings of our study are that risk-adjusted long-term (5-year) rates of death and the composite outcomes of death, MI, or stroke were similar in patients with multivessel CAD undergoing DES implantation and CABG, whereas rates of repeat revascularization with CABG were significantly lower for diabetic and nondiabetic patients. These relative treatment effects were not significantly modified by diabetic status.

DM is a major determinant of poor clinical outcomes after percutaneous and surgical revascularizations in patients with multivessel CAD. Long-term mortality and incidence of restenosis and repeat revascularization were significantly lower in nondiabetic than in diabetic patients undergoing percutaneous coronary intervention.[9,17] Although DESs remarkably improves efficacy compared to bare-metal stents, the tendency toward poorer outcomes in patients with diabetes was also observed with DESs.[18–20] In addition, morbidity and mortality rates were higher in diabetic than in nondiabetic patients undergoing CABG.[21–23] Therefore, diabetic status is a major consideration when choosing the optimal revascularization strategy for patients with multivessel CAD. Previous studies have shown that CABG was superior to percutaneous coronary intervention in diabetic patients with multivessel CAD. For example, the Bypass Angioplasty Revascularization Investigation (BARI) showed that CABG was associated with a significantly higher survival rate compared to percutaneous coronary intervention in diabetic patients with multivessel

CAD.[9] A meta-analysis of data from 10 randomized trials of patients undergoing elective myocardial revascularization confirmed that CABG had an apparent survival advantage over percutaneous coronary intervention in diabetic patients with multivessel CAD.[10] Those studies, however, were performed before the introduction of DESs.

Several recent studies have compared outcomes of percutaneous coronary intervention using DESs to CABG in diabetic patients with multivessel CAD.[24–26] In a subgroup analysis of diabetic patients enrolled in the SYNTAX trial, there was no significant difference in the 1-year composite of death, MI, or stroke between patients who underwent percutaneous coronary intervention with paclitaxel-eluting stents and those who underwent CABG, whereas the rate of repeat revascularization was significantly higher in the percutaneous coronary intervention group.[24] This treatment effect was not modified by diabetic status. The Coronary Artery Revascularization in Diabetes (CARDia) trial also showed that 1-year rates of death and the composite of death, MI, or stroke were similar in the percutaneous coronary intervention and CABG groups, with a higher rate of repeat revascularization associated with stenting.[25] However, length of follow-up in these trials was insufficient to evaluate the long-term safety of DESs, including the propensity for late stent thrombosis and late-occurring clinical events,[27,28] and might be limited in reflecting "real-world" practice in which patients do not meet strict criteria.

Our study involved the consecutive recruitment of patients with multivessel CAD who required revascularization in routine practice and compared very long-term follow-up in patients with and without diabetes who underwent percutaneous coronary intervention with DESs or CABG. We found that the long-term mortality and serious composite outcomes rates were similar in the percutaneous coronary intervention with DES and CABG groups, with no significant interaction between DM and treatment methods on outcomes. Risk of revascularization was consistently higher with stenting irrespective of diabetic status. These findings suggest that the optimal clinical judgment of the physician provides long-term clinical equipoise between DES placement and CABG for multivessel CAD revascularization in terms of mortality and serious ischemic complications and that the prognostic influence of diabetic status on long-term treatment outcomes is minimal.

This study had several limitations, the first of which is its design as a nonrandomized observational cohort study. Although we rigorously adjusted for baseline covariates using inverse probability-of-treatment weighting methods, there were inherent limitations in choice of treatment procedure such as a potential bias from confounding by indication. In addition, unknown confounders may have affected our results. Second, because our results are mainly derived from subgroup analysis, they should be regarded as hypothetical and hypothesis-generating only and should not necessarily dictate any change in current practice patterns. Third, in our study, we did not thoroughly and prospectively measure the variable of completeness of revascularization according the detailed angiographic definition. Fourth, the direct application of our findings to current real-world practice using second-generation DESs is likely limited. The comparative long-term benefits of second-generation DESs and CABG should be evaluated in large prospective clinical studies.

Patients with multivessel CAD who underwent percutaneous coronary intervention with DES placement or CABG had similar long-term risks of mortality and the composite of serious ischemic complications, with these outcomes not substantially modified by diabetic status. Risk for repeat revascularization was consistently higher with percutaneous coronary intervention than with CABG irrespective of diabetic status.

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;241:2035–2038.
2. Hammoud T, Tanguay JF, Bourassa MG. Management of coronary artery disease: therapeutic options in patients with diabetes. *J Am Coll Cardiol* 2000;36:355–365.
3. Stein B, Weintraub WS, Gebhart SP, Cohen-Bernstein CL, Grosswald R, Liberman HA, Douglas JS Jr, Morris DC, King SB III. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation* 1995;91:979–989.
4. 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;94:1818–1825.
5. Elezi S, Kastrati A, Pache J, Wehinger A, Hadamitzky M, Dirschinger J, Neumann FJ, Schömig A. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol* 1998;32:1866–1873.
6. Thourani VH, Weintraub WS, Stein B, Gebhart SS, Craver JM, Jones EL, Guyton RA. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. *Ann Thorac Surg* 1999; 67:1045–1052.
7. Mehran R, Dangas GD, Kobayashi Y, Lansky AJ, Mintz GS, Aymong ED, Fahy M, Moses JW, Stone GW, Leon MB. Short- and long-term results after multivessel stenting in diabetic patients. *J Am Coll Cardiol* 2004;43:1348–1354.
8. West NE, Ruygrok PN, Disco CM, Webster MW, Lindeboom WK, O'Neill WW, Mercado NF, Serruys PW. Clinical and angiographic predictors of restenosis after stent deployment in diabetic patients. *Circulation* 2004;109:867–873.
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;335:217–225.
10. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrié D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kähler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009;373:1190–1197.
11. Stettler C, Allemann S, Wandel S, Kastrati A, Morice MC, Schömig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabaté M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, De Carlo M, Erglis A, Chechi T, Ortolani P, Schalij MJ, Diem P, Meier B, Windecker S, Jüni P. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ* 2008;337:a1331.
12. Park DW, Kim YH, Song HG, Ahn JM, Oh J, Kim WJ, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Yun SC, Jung SH, Choo SJ, Chung CH, Lee JW, Park SJ. Long-term comparison of drug-eluting stents and coronary artery bypass grafting for multivessel coronary revascularization: 5-year outcomes from the Asan Medical Center-Multivessel Revascularization registry. *J Am Coll Cardiol* 2011;57:128–137.
13. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, Higgins RS, Carlson RE, Jones RH. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med* 2008;358:331–341.
14. Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration

Center for Devices and Radiologic Health, December 7–8, 2006. *Circulation* 2007;115:2352–2357.
15. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550–560.
16. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; 360:961–972.
17. Abizaid A, Costa MA, Centemero M, Abizaid AS, Legrand VM, Limet RV, Schuler G, Mohr FW, Lindeboom W, Sousa AG, Sousa JE, van Hout B, Hugenholtz PG, Unger F, Serruys PW, Arterial Revascularization Therapy Study Group. 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;104:533–538.
18. Hong SJ, Kim MH, Ahn TH, Ahn YK, Bae JH, Shim WJ, Ro YM, Lim DS. Multiple predictors of coronary restenosis after drug-eluting stent implantation in patients with diabetes. *Heart* 2006;92:1119–1124.
19. Iijima R, Ndrepepa G, Mehilli J, Markwardt C, Bruskina O, Pache J, Ibrahim M, Schömig A, Kastrati A. Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era. *Am Heart J* 2007;154:688–693.
20. Billinger M, Beutler J, Taghetchian KR, Remondino A, Wenaweser P, Cook S, Togni M, Seiler C, Stettler C, Eberli FR, Lüscher TF, Wandel S, Jüni P, Meier B, Windecker S. Two-year clinical outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents in diabetic patients. *Eur Heart J* 2008;29:718–725.
21. 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;40:418–423.
22. 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:I454–I460.
23. Wit MA, de Mulder M, Jansen EK, Umans VA. Diabetes mellitus and its impact on long-term outcomes after coronary artery bypass graft surgery. *Acta Diabetol* 2010. [Epub ahead of print].
24. Banning AP, Westaby S, Morice MC, Kappetein AP, Mohr FW, Berti S, Glauber M, Kellett MA, Kramer RS, Leadley K, Dawkins KD, Serruys PW. Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. *J Am Coll Cardiol* 2010;55: 1067–1075.
25. Kapur A, Hall RJ, Malik IS, Qureshi AC, Butts J, de Belder M, Baumbach A, Angelini G, de Belder A, Oldroyd KG, Flather M, Roughton M, Nihoyannopoulos P, Bagger JP, Morgan K, Beatt KJ. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-Year results of the CARDIA (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol* 2010;55:432–440.
26. Lee MS, Yang T, Dhoot J, Iqbal Z, Liao H. Meta-analysis of studies comparing coronary artery bypass grafting with drug-eluting stenting in patients with diabetes mellitus and multivessel coronary artery disease. *Am J Cardiol* 2010;105:1540–1544.
27. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Jüni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007;369:667–678.
28. Lagerqvist B, James SK, Stenestrand U, Lindbäck J, Nilsson T, Wallentin L; SCAAR Study Group. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007;356: 1009–1019.