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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

Duk-Woo Park, MD,* Young-Hak Kim, MD,* Hae-Geun Song, MD,* Jung-Min Ahn, MD,* Junhyok Oh, MD,* Won-Jang Kim, MD,* Jong-Young Lee, MD,* Soo-Jin Kang, MD,* Seung-Whan Lee, MD,* Cheol-Whan Lee, MD,* Seong-Wook Park, MD,* Sung-Cheol Yun, PHD,‡ Sung Ho Jung, MD,† Suk-Jung Choo, MD,† Cheol-Hyun Chung, MD,† Jae-Won Lee, MD,† Seung-Jung Park, MD*

Seoul, Korea

Objectives We performed the long-term (5-year) follow-up of a large cohort of patients who underwent drug-eluting stent (DES) or coronary artery bypass graft (CABG) surgery for multivessel revascularization.

Background Limited information is available on very long-term outcomes after multivessel DES treatment relative to CABG.

Methods We evaluated 3,042 patients with multivessel disease who received DES (n = 1,547) or underwent CABG (n = 1,495) between January 2003 and December 2005, and for whom complete follow-up data were available for a median 5.6 years (interquartile range: 4.6 to 6.3 years). We compared adverse outcomes (death; a composite outcome of death, myocardial infarction, or stroke; and repeat revascularization).

Results After adjustment for differences in baseline risk factors, 5-year risk of death (hazard ratio [HR]: 1.00; 95% confidence interval [CI]: 0.76 to 1.32, p = 0.99) and the combined risk of death, myocardial infarction, or stroke (HR: 0.97; 95% CI: 0.76 to 1.24, p = 0.81) were similar between the DES group and the CABG group. However, the rates of revascularization were significantly higher in the DES group (HR: 2.93; 95% CI: 2.20 to 3.90, p < 0.001). Similar results were obtained in comparisons of DES with CABG for high-risk clinical and anatomic subgroups with diabetes mellitus, abnormal ventricular function, age 65 years or more, and 3-vessel and left main disease. However, mortality benefit with DES implantation relative to CABG was noted in patients with 2-vessel disease (HR: 0.57; 95% CI: 0.36 to 0.92, p = 0.02).

Conclusions For patients with multivessel disease, DES treatment, compared with CABG, showed similar rates of mortality and of the composite safety outcomes, but higher rates of revascularization up to 5 years. (J Am Coll Cardiol 2011;57:128–37) © 2011 by the American College of Cardiology Foundation

Over the past few years, revascularization of patients with multivessel coronary artery disease (CAD) has improved significantly owing to advances in both coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI), contributing to reductions in mortality and morbidity (1,2). Especially, PCI involving drug-eluting stents (DES) is increasingly used to treat complex CAD, for which CABG has been regarded historically as the treatment of choice (3). Therefore, with technological advances and changes in clinical practice, the respective values and treatment effects of CABG and PCI needed to be reassessed.

Several studies have compared outcomes of PCI with DES and CABG for multivessel CAD (4–13). Most of these studies, however, were limited in duration, with follow-up within 1 to 3 years. That may result in a

From the *Division of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; †Division of Cardiac Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; and the ‡Division of Biostatistics, Center for Medical Research and Information, University of Ulsan College of Medicine, Seoul, Korea. This study was partly supported by the Cardiovascular Research Foundation, Seoul, Korea, and a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare, Korea (0412-CR02-0704-0001). The authors have reported that they have no relationships to disclose. Drs. Duk-Woo Park and Young-Hak Kim contributed equally to this work.

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disadvantage for CABG, because the apparent benefits of surgery over PCI in other settings are usually not fully evident until 1 to 5 years after the procedure. Furthermore, the long-term safety of DES has been questioned by recent reports suggesting increased risks of late stent thrombosis, mortality, and myocardial infarction (MI) (14,15). Therefore, very long-term follow-up after DES implantation, as compared to standard CABG, in a large cohort of patients with multivessel disease is clinically important.

The Asan-Multivessel (Asan Medical Center-Multivessel Revascularization) Registry was designed to investigate the "real-word" outcomes of PCI with DES and CABG for patients with multivessel CAD, and the median 3-year comparative outcomes were previously reported (5). To obtain a more reliable long-term treatment effect of DES and CABG, we have now extended the follow-up duration for the study patients, for whom follow-up data were available for at least 4 years and as long as 7 years.

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
CI = confidence interval
DES = drug-eluting stent(s)
EuroSCORE = European System for Cardiac Operative Risk Evaluation
HR = hazard ratio
LAD = left anterior descending artery
MI = myocardial infarction
PCI = percutaneous coronary intervention

Methods

Study population. The Asan-Multivessel Registry is a single-center, prospective study designed to evaluate the treatment effects of PCI and CABG for multivessel CAD in clinical practice (5). The registry prospectively contains information on patient demographics, coexisting and clinical conditions, hemodynamic status, left ventricular function, the extent of disease, details of the procedures, and in-hospital and follow-up outcomes. This analysis includes consecutive patients with multivessel CAD who received PCI with DES (with or without other devices) or underwent isolated CABG at the Asan Medical Center (Seoul, Korea) during the period from January 1, 2003, through December 31, 2005. The follow-up period was extended through January 31, 2010, to ensure that all patients had an opportunity for at least 4 years and approximately as many as 7 years of follow-up information.

Patients who had prior CABG, those who underwent concomitant valvular or aortic surgery, and those who had an acute MI within 24 h before revascularization or presented with cardiogenic shock were excluded. This study was approved by the local institutional review board.

Revascularization and pharmacologic treatment. The decision to perform PCI or CABG was dependent on physician and/or patient choice. During the study period, coronary stenting was performed exclusively with DES (16). The PCI was performed according to current practice guidelines. The choice of the specific type of DES (i.e., sirolimus-eluting stents [Cypher and Cypher Select, Cordis, Johnson & Johnson, Bridgewater, New Jersey] or paclitaxel-eluting stents [Taxus Express and Taxus Liberté, Boston Scientific, Natick, Massachusetts]) was left to the operator's discretion. At this time, second-generation DES (i.e., zotarolimus-, everolimus-, or 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 at least 6 months, regardless of DES type (5). Treatment beyond this duration was at the discretion of the physician. Surgical revascularization was performed using standard bypass techniques; whenever possible, the internal thoracic artery was preferentially utilized for revascularization of the left anterior descending artery (LAD). When possible, complete revascularization was performed using arterial conduits or saphenous vein grafts.

Study outcomes and follow-up. The end points of the study were death; the composite of death, MI, or stroke; and repeat revascularization. Death was defined as death from any cause. The diagnosis of acute MI were defined as either complications at the index admission (defined as new pathologic Q waves after index treatment) or follow-up MI requiring subsequent hospitalizations (defined as an emergency admission with a principal diagnosis of MI), as described previously (8). Stroke, as indicated by neurological deficits, was confirmed by a neurologist on the basis of 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 the definite or probable events, according to the Academic Research Consortium classification (17). All outcomes of interest were carefully verified and adjudicated by independent clinicians.

Clinical, angiographic, procedural or operative, and outcome data were prospectively recorded in the dedicated PCI and surgical databases by independent research personnel. Clinical follow-up was performed at 1 month, 6 months, and 1 year, and then annually thereafter, by office visit or telephone contact. For validation of complete follow-up data regarding 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.

Statistical analysis. Treatment-related differences in long-term outcomes between the 2 procedures were analyzed in all patients, as well as in high-risk clinical subsets (patients with diabetes, patients with abnormal left ventricular ejection fractions <50%, and patients older than 65 years of age), and in anatomic subgroups according to 2- or 3-vessel disease and the presence or absence of proximal LAD disease, and left main disease.

The prevalence rates of risk factors and characteristics of the patients in the 2 treatment groups were compared with the

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t test or Wilcoxon rank-sum tests (continuous variables) and with the chi-square statistics or Fisher exact test (categorical variables). Survival curves were constructed using Kaplan-Meier estimates and compared with the log-rank test.

Differences in risk-adjusted, long-term rates of study outcomes between patients undergoing the 2 procedures were assessed using multivariable Cox proportional-hazards regression (18). Adjusted covariates included the patient's age and sex, the presence or absence of a variety of clinical and coexisting conditions, left ventricular function, and the number and the 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 reduce the impact of treatment selection bias and potential confounding in an observational study, we also performed rigorous adjustment for baseline differences by use of the weighted Cox proportional-hazards regression models with the inverse-probability-of-treatment weighting (19). With that technique, the weights for patients undergoing CABG were the inverse of (1 − propen-

Table 1 Baseline Characteristics of the Patients According to Treatment

Variable	DES (n = 1,547)	CABG (n = 1,495)	p Value
Age, yrs			0.88
<55	357 (23.1)	299 (20.0)	
55 to 64	525 (33.9)	593 (39.7)	
≥65	665 (43.0)	603 (40.3)	
Median age, yrs	63.0	63.0	0.46
Sex			0.02
Male	1,073 (69.4)	1,095 (73.2)	
Female	474 (30.6)	400 (26.8)	
Body mass index, kg/m^2	25.1 ± 2.9	24.8 ± 3.0	0.02
Medically-treated diabetes			
Any	489 (31.6)	402 (26.9)	0.004
Requiring insulin	86 (5.6)	76 (5.1)	0.56
Hypertension	883 (57.1)	716 (47.9)	<0.001
Current smoker	457 (29.5)	502 (33.6)	0.02
Hyperlipidemia	373 (24.1)	474 (31.7)	<0.001
Previous coronary angioplasty	270 (17.5)	149 (10.0)	<0.001
Previous congestive heart failure	22 (1.4)	68 (4.5)	<0.001
Moderate or severe chronic obstructive pulmonary disease	16 (1.0)	28 (1.9)	0.05
Cerebrovascular or carotid artery disease	85 (5.5)	167 (11.2)	<0.001
Peripheral vascular disease	56 (3.6)	86 (5.8)	0.005
Renal failure	42 (2.7)	87 (5.8)	<0.001
Prior myocardial infarction			<0.001
1 to 7 days before treatment	138 (8.9)	84 (5.6)	
≤8 days before treatment	18 (1.2)	210 (14.0)	
No prior myocardial infarction	1,391 (89.9)	1,201 (80.3)	
Electrocardiographic findings			0.02
Sinus rhythm	1,458 (94.2)	1,440 (96.3)	
Atrial fibrillation	48 (3.1)	26 (1.7)	
Other	41 (2.7)	29 (1.9)	
Ejection fraction			<0.001
<30%	14 (0.9)	49 (3.3)	
30% to 40%	33 (2.2)	97 (6.6)	
40% to 50%	144 (9.5)	180 (12.2)	
≥50%	1,317 (87.3)	1,147 (77.9)	
Data missing	39 (2.5)	22 (1.5)	0.04
Median ejection fraction (%)	60.0	59.0	<0.001
2-vessel disease	868 (56.1)	343 (22.9)	<0.001
With proximal LAD disease	319 (20.6)	146 (9.8)	<0.001
Without proximal LAD disease	549 (35.5)	197 (13.2)	<0.001
3-vessel disease	679 (43.9)	1152 (77.1)	<0.001
With proximal LAD disease	282 (18.2)	658 (44.0)	<0.001
Without proximal LAD disease	397 (25.7)	494 (33.0)	<0.001
Left main disease	178 (11.5)	372 (24.9)	<0.001
Total occlusion	110 (7.1)	656 (43.9)	<0.001

Data are n (%) or mean ± SD.

CABG = coronary artery bypass graft surgery; DES = drug-eluting stent(s); LAD = left anterior descending artery.

sity score), and weights for patients receiving stenting were the inverse of the propensity score. The propensity scores were estimated without regard to outcomes, using multiple logistic regression analysis. A full nonparsimonious model was developed, which included all the variables shown in Table 1. Model discrimination was assessed with *c*-statistics, and model calibration was assessed with Hosmer-Lemeshow statistics. For each clinical or anatomic group, a separate propensity for PCI versus CABG was derived.

In addition, outcomes were analyzed on the basis of the EuroSCORE (European System for Cardiac Operative Risk Evaluation) value and the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score. The EuroSCORE value has been widely accepted as a clinical-scoring algorithm, with increasing values reflecting a higher predicted operative mortality (20); a low score was defined as 0 to 2, an intermediate score as 3 to 6, and a high score as >6. The SYNTAX score reflects a comprehensive anatomical assessment, with higher scores indicating more complex coronary disease (10); a low score was defined as ≤22, an intermediate score as 23 to 32, and a high score as ≥33. SYNTAX scores were calculated at the core laboratory (21).

All reported p values are 2-sided, and p values <0.05 were considered statistically significant. No adjustment was performed for multiple testing in several subgroups. The SAS software, version 9.1 (SAS Institute, Cary, North Carolina) and the R programming language were used for statistical analyses.

Results

Patient characteristics. From January 2003 through December 2005, 3,042 patients with multivessel CAD underwent PCI with DES (n = 1,547) or CABG (n = 1,495). The baseline characteristics of the study patients are listed in Table 1. The CABG patients had higher clinical and angiographic risk profiles than the PCI patients. The procedural characteristics of the patients in the Asan-Multivessel registry have been described previously (5), and selected features are as follows: 1) among PCI patients, 79% received sirolimus-eluting stents and 21% received paclitaxel-eluting stents; 2) the mean number of stents was 2.8 ± 1.2, and the mean total length of stents and the average stent diameter per patient were 65.6 ± 31.5 mm and 3.2 ± 0.3 mm, respectively; 3) among CABG patients, 31% underwent off-pump surgery; and 4) 95% underwent revascularization of the LAD with an arterial conduit.

Follow-up and outcomes. The median follow-up was 5.6 years (interquartile range: 4.6 to 6.3 years) for the overall patients. Complete follow-up for major clinical events was obtained in 97.4% of the overall cohort (97.7% for the DES group and 97.0% for the CABG group, p = 0.20). During overall follow-up, 304 patients (10.0%) died, of whom 149 (4.9%) died of a cardiovascular cause. A total of 56 (1.8%) had an acute MI, and 92 (3.0%) had a stroke. Repeat revascularization was performed in 346 patients (11.4%).

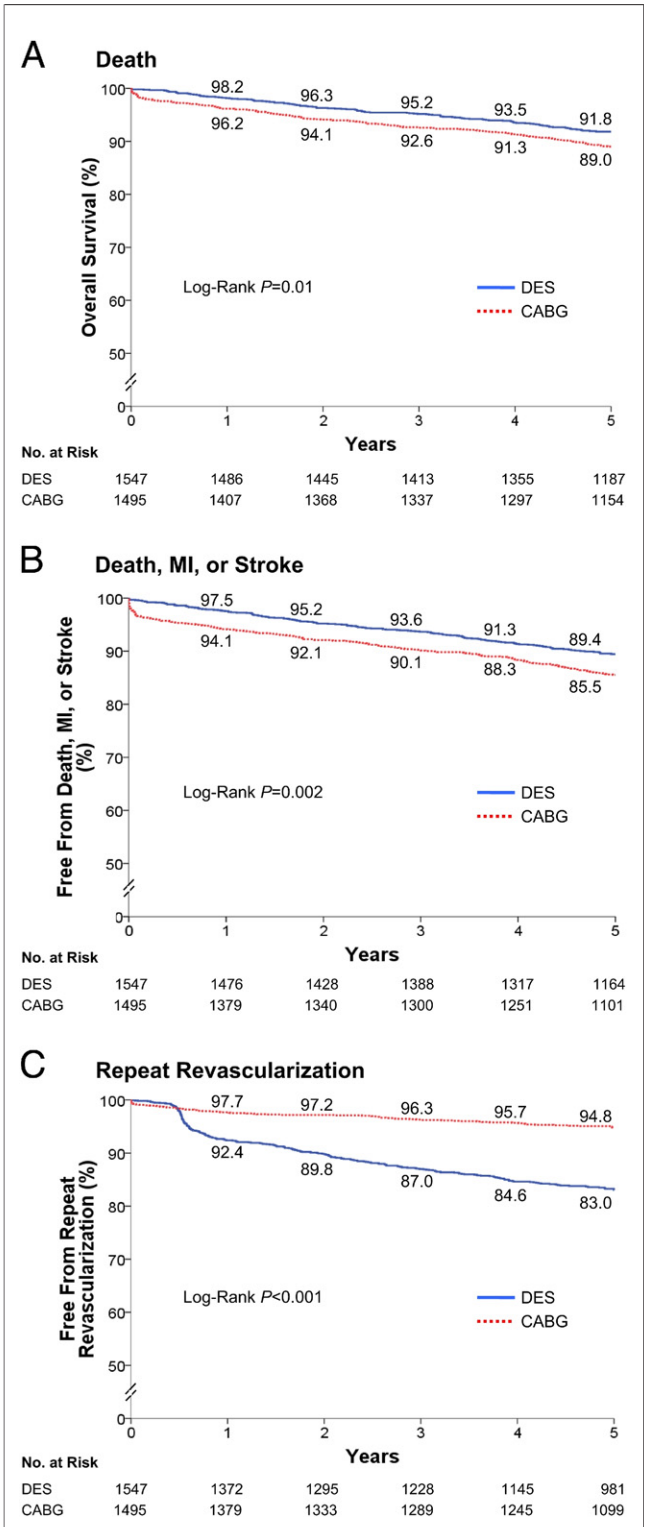

Figure 1 Kaplan-Meier Curves of 5-Year Outcomes for Overall Patients Who Received DES or CABG

(A) Overall survival. **(B)** Freedom from death, myocardial infarction (MI), or stroke. **(C)** Repeat revascularization. CABG = coronary artery bypass graft surgery **(red line)**; DES = drug-eluting stent(s) **(blue line)**.

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Table 2 Hazard Ratios for Clinical Outcomes After DES as Compared With After CABG in the Overall Population and in Selected Major Clinical Subgroups of Patients*

	No. of Patients/ Total No. of Events		Unadjusted		Multivariable Adjusted†		Adjusted by Inverse-Probability-of-Treatment Weights	
Outcome	DES	CABG	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Overall cohort (n = 3,042)	1,547	1,495						
Death	129	175	0.75 (0.60–0.94)	0.01	1.00 (0.76–1.32)	0.99	0.92 (0.70–1.20)	0.54
Composite outcome (death, MI, or stroke)	165	226	0.73 (0.59–0.89)	0.002	0.97 (0.76–1.24)	0.81	0.90 (0.91–1.14)	0.40
Repeat revascularization	259	87	3.35 (2.62–4.28)	<0.001	2.93 (2.20–3.90)	<0.001	2.78 (2.08–3.71)	<0.001
Diabetes mellitus (n = 891)	489	402						
Death	57	60	0.82 (0.57–1.17)	0.28	1.12 (0.72–1.76)	0.61	1.15 (0.73–1.80)	0.54
Composite outcome (death, MI, or stroke)	68	72	0.79 (0.57–1.11)	0.17	1.23 (0.81–1.85)	0.34	1.20 (0.80–1.81)	0.38
Repeat revascularization	91	22	3.88 (2.43–6.20)	<0.001	3.28 (1.94–5.54)	<0.001	3.48 (1.97–6.14)	<0.001
Abnormal LV function (n = 517)	191	326						
Death	30	66	0.78 (0.51–1.21)	0.27	1.21 (0.70–2.09)	0.49	0.89 (0.54–1.48)	0.66
Composite outcome (death, MI, or stroke)	36	82	0.74 (0.50–1.10)	0.13	1.15 (0.70–1.88)	0.59	0.92 (0.58–1.45)	0.71
Repeat revascularization	38	9	8.40 (4.04–17.51)	<0.001	9.20 (3.81–22.19)	<0.001	9.80 (4.51–21.32)	<0.001
Age >65 yrs (n = 1,268)	665	603						
Death	84	108	0.73 (0.55–0.97)	0.03	0.92 (0.64–1.32)	0.65	0.77 (0.55–1.09)	0.14
Composite outcome (death, MI, or stroke)	101	129	0.71 (0.55–0.93)	0.01	0.99 (0.71–1.37)	0.94	0.81 (0.59–1.11)	0.20
Repeat revascularization	96	23	4.31 (2.73–6.81)	<0.001	4.57 (2.66–7.87)	<0.001	4.28 (2.48–7.38)	<0.001

*Hazard ratios are for the DES group relative to the CABG group. †Hazard ratios are adjusted for age; sex; diabetes mellitus; presence or absence of congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular or carotid disease, peripheral arterial disease, and renal failure; history or no history of MI before procedure; ejection fraction; 2- or 3-vessel disease, presence or absence of involvement of the proximal left anterior descending artery or left main artery, and total obstruction.

CI = confidence interval; LV = left ventricle; MI = myocardial infarction; other abbreviations as in Table 1.

During 5 years of follow-up, the observed (unadjusted) event-free survival curve and the crude and adjusted relative risk according to treatment approach are presented in Figure 1 and Table 2. In the overall population, unadjusted rates of death and the composite of death, MI, or stroke were significantly lower in the DES group than in the CABG group, whereas the rate of revascularization was significantly higher in the DES group. After adjustment for baseline differences using multivariable-adjusted Cox regression analysis and the inverse-probability-of-treatment weighting, the 5-year risks of death and the composite of death, MI, or stroke were similar in the 2 groups. However, the adjusted risk of revascularization remained consistently higher in the DES group.

We also assessed the relative treatment effects in subsets of patients with major high-risk clinical factors, including diabetes mellitus, abnormal ventricular function, and age >65 years (Table 2). In these clinical subsets, there were no significant differences in the 5-year, adjusted rates of death, and the composite of death, MI, or stroke between the 2 groups, but the rate of repeat revascularization was consistently higher after DES treatment.

Table 3 presents unadjusted and adjusted hazard ratios for outcomes according to several anatomic groups. There were no significant differences of treatment effect in the rates of death and the composite of death, MI, or stroke among all subsets of patients with 3-vessel disease. These findings were consistent for patients with left main disease. However, in patients with 2-vessel disease, the adjusted risk of mortality was significantly lower in the DES group than in the CABG group. These trends were more prominent in patients with 2-vessel disease without proximal LAD disease. In each of these anatomic subgroups, patients undergoing CABG also had lower rates of repeat revascularization.

Of the 1,547 patients who received DES, 42 had definite or probable stent thrombosis. Among them, 1 patient had early thrombosis, 14 had late thrombosis, and 27 had very late thrombosis. At 5-year follow-up, the cumulative incidence of definite or probable stent thrombosis associated with DES was 2.6%.

Outcomes according to the EuroSCORE and SYNTAX score. The mean EuroSCORE value was 3.3 ± 2.4 in the DES group and 3.9 ± 2.5 in the CABG group ($p < 0.001$). There were no significant differences in observed (unadjusted) rates of death and the composite of death, MI, or stroke between 2 treatment groups in patients with low-risk and high-risk EuroSCORE values, except that these outcomes were better with DES in patients with intermediate EuroSCORE (Fig. 2, Table 4). After adjustment of other covariates, the risks of death and serious composite outcomes did not significantly differ. The rate of repeat revascularization was consistently higher after DES treatment.

During the study enrollment period, the SYNTAX score algorithm was not available for the physician. A retrospective retrieval of a baseline angiogram for a detailed measurement of the SYNTAX score was available in 1,915 patients (63%) of the overall cohort (91% in the DES group and 35% in the CABG group). The mean SYNTAX score was significantly lower in the DES group than in the CABG group (17.4 ± 7.8 and 29.9 ± 10.6, respectively; $p < 0.001$). The observed, long-term risk of death and the composite of death, MI, or stroke were similar between the 2 treatment groups among patients with low and high scores, except that these outcomes

Table 3 Hazard Ratios for Clinical Outcomes After DES as Compared With After CABG According to Extent of Diseased Vessels*

Outcome	No. of Patients/ Total No. of Events		Unadjusted		Multivariable Adjusted†		Adjusted by Inverse-Probability-of-Treatment Weights	
	DES	CABG	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
3-vessel disease								
Overall	679	1,152						
Death	75	136	0.99 (0.75–1.31)	0.94	1.26 (0.90–1.76)	0.18	1.18 (0.85–1.63)	0.32
Composite outcome (death, MI, or stroke)	87	182	0.83 (0.64–1.07)	0.15	1.06 (0.79–1.43)	0.71	1.00 (0.75–1.34)	0.99
Repeat revascularization	115	59	3.93 (2.86–5.40)	<0.001	3.57 (2.48–5.16)	<0.001	3.51 (2.46–5.02)	<0.001
With proximal LAD disease	282	658						
Death	35	90	0.96 (0.65–1.42)	0.83	1.07 (0.67–1.70)	0.77	1.08 (0.69–1.70)	0.75
Composite outcome (death, MI, or stroke)	40	111	0.86 (0.60–1.23)	0.40	1.05 (0.68–1.61)	0.83	1.06 (0.70–1.60)	0.79
Repeat revascularization	48	27	4.63 (2.88–7.44)	<0.001	5.54 (3.02–10.15)	<0.001	5.19 (3.09–8.70)	<0.001
Without proximal LAD disease	397	494						
Death	40	46	1.13 (0.74–1.73)	0.57	1.51 (0.91–2.50)	0.11	1.40 (0.86–2.27)	0.18
Composite outcome (death, MI, or stroke)	47	71	0.84 (0.58–1.22)	0.36	1.09 (0.72–1.67)	0.68	0.97 (0.64–1.47)	0.89
Repeat revascularization	67	32	3.31 (2.16–5.08)	<0.001	2.85 (1.78–4.57)	<0.001	2.57 (1.58–4.18)	<0.001
2-vessel disease								
Overall	868	343						
Death	54	39	0.58 (0.38–0.88)	0.01	0.57 (0.36–0.92)	0.02	0.60 (0.38–0.95)	0.03
Composite outcome (death, MI, or stroke)	78	44	0.75 (0.52–1.09)	0.13	0.74 (0.49–1.14)	0.17	0.80 (0.53–1.20)	0.28
Repeat revascularization	144	28	2.32 (1.54–3.49)	<0.001	2.03 (1.30–3.17)	0.002	1.89 (1.19–3.01)	0.008
With proximal LAD disease	319	146						
Death	20	15	0.62 (0.32–1.21)	0.16	0.60 (0.27–1.34)	0.21	0.64 (0.30–1.37)	0.25
Composite outcome (death, MI, or stroke)	30	16	0.89 (0.49–1.64)	0.72	0.91 (0.44–1.89)	0.80	0.97 (0.48–1.96)	0.93
Repeat revascularization	51	13	1.94 (1.05–3.58)	0.03	1.73 (0.87–3.45)	0.12	1.58 (0.81–3.10)	0.18
Without proximal LAD disease	549	197						
Death	34	24	0.55 (0.33–0.94)	0.03	0.59 (0.32–1.09)	0.09	0.54 (0.31–0.97)	0.04
Composite outcome (death, MI, or stroke)	48	28	0.67 (0.42–1.07)	0.09	0.67 (0.39–1.15)	0.15	0.66 (0.39–1.10)	0.11
Repeat revascularization	93	15	2.61 (1.51–4.51)	0.001	2.15 (1.19–3.90)	0.01	1.94 (1.04–3.64)	0.04
Left main disease	178	372						
Death	18	47	0.82 (0.48–1.42)	0.48	0.95 (0.51–1.80)	0.89	1.02 (0.57–1.85)	0.94
Composite outcome (death, MI, or stroke)	20	62	0.67 (0.40–1.11)	0.12	0.88 (0.49–1.58)	0.68	0.87 (0.50–1.51)	0.62
Repeat revascularization	23	23	2.27 (1.27–4.05)	0.006	2.16 (1.11–4.21)	0.02	2.10 (1.12–3.95)	0.02

*Hazard ratios are for the DES group relative to the CABG group. †Hazard ratios are adjusted for age; sex; diabetes; presence or absence of congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular or carotid disease, peripheral arterial disease, and renal failure; history or no history of MI before procedure; ejection fraction; 2-vessel or 3-vessel disease, presence or absence of involvement of the proximal LAD artery or left main artery, and total obstruction.

Abbreviations as in Tables 1 and 2.

were better for DES in patients with intermediate scores (Fig. 3, Table 4). After adjustment of other covariates, the risks of death and serious composite outcomes were similar, although adjusted hazard ratios nonsignificantly favor CABG in patients with high SYNTAX scores. The advantage of CABG was quite consistent for repeat revascularization.

Discussion

In this large cohort of patients with multivessel CAD, the clinical judgment ensured that risk-adjusted, long-term (5-year) rates of death and the composite outcome of death, MI, or stroke were similar between DES and CABG. The rate of repeat revascularization was significantly lower in the CABG group than in the DES group. These results were consistent among patients with high-risk clinical and anatomic subsets. In contrast, DES implantation showed a relative mortality benefit compared with CABG in patients with relatively less complex CAD, such as 2-vessel disease.

Several observational studies comparing DES and CABG for multivessel revascularization have shown inconsistent findings (4–9,13). Some studies indicated that mortality or safety outcomes were similar in the 2 groups (5–7,13); others registries found a lower rate of survival after PCI with DES than after CABG (4,8,9). The effect of unmeasured confounding related to case selection may explain the discordance between these registry results. The SYNTAX trial represent the most current and applicable evidence on multivessel revascularization (10). Although composite safety (death, MI, or stroke) was comparable at 1 year, the stroke rate was significantly higher in the CABG group, whereas DES was associated with more frequent revascularization. Recently, 2-year outcomes of the SYNTAX trial showed a significant increase of MI in PCI patients, compared to CABG patients, raising concerns about the long-term safety of multivessel DES treatment (22). However, the average follow-up duration in these clinical and observational studies was <3 years. Recent long-term,

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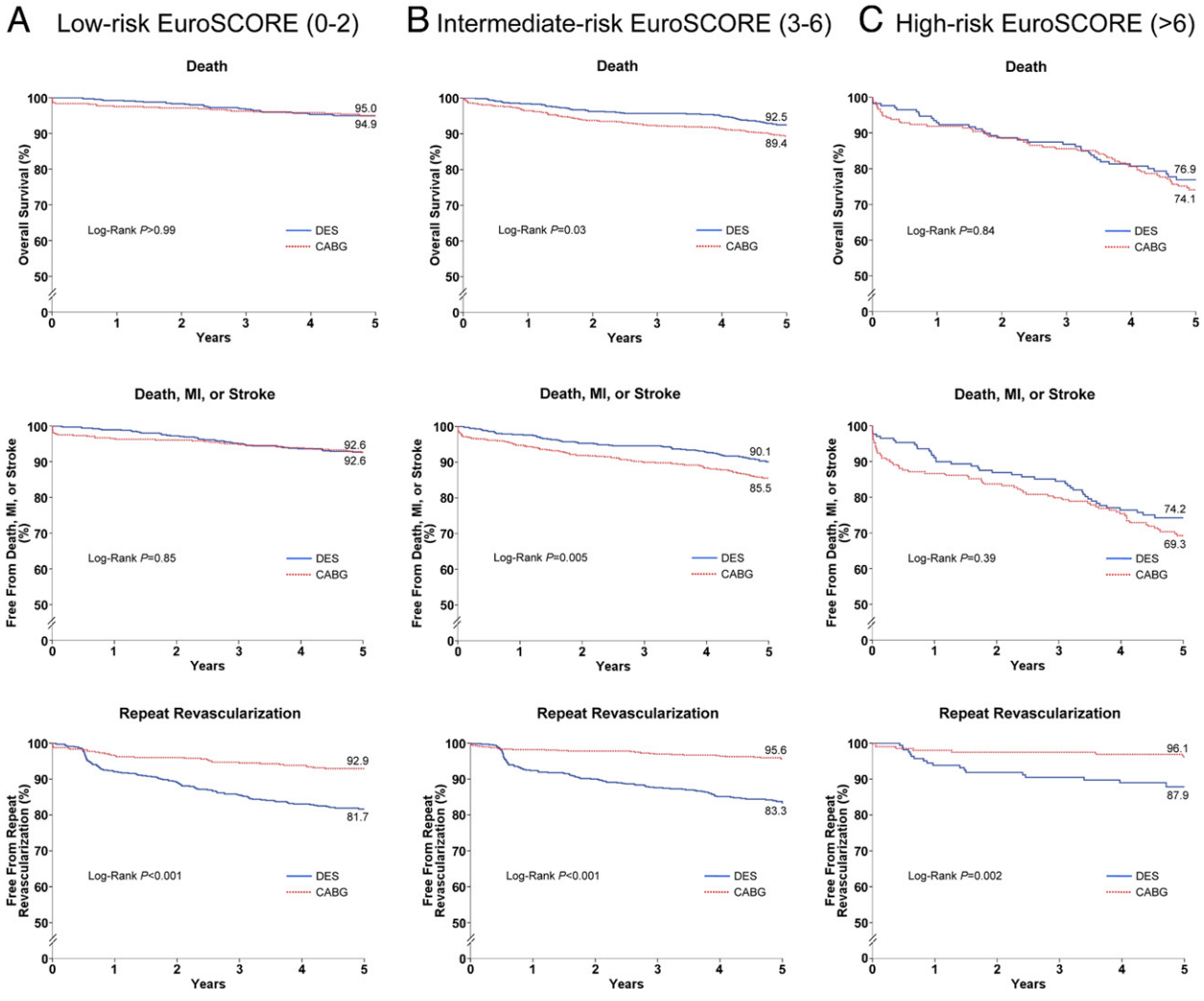

Figure 2 **Kaplan-Meier Curves of 5-Year Outcomes Among Study Patients According to Treatment Group and EuroSCORE Category**

(A) Outcomes for patients with low-risk EuroSCORE (European System for Cardiac Operative Risk Evaluation) (0 to 2). **(B)** Outcomes for patients with intermediate-risk EuroSCORE (3 to 6). **(C)** Outcomes for patients with high-risk EuroSCORE (>6). CABG **(red line)**; DES **(blue line)**. Abbreviations as in Figure 1.

pooled analysis involving bypass surgery or PCI with balloon angioplasty or bare-metal stents frequently include patients with follow-up durations of 5 or more years (23,24). So, our study is more long-term comparison of PCI with DES and CABG for multivessel CAD and therefore provides important information about the sufficiently long-term effect of DES relative to CABG.

In the diabetic subgroup of the SYNTAX and ARTS II (Arterial Revascularization Therapies Study–Part II) study and the CARDia (Coronary Artery Revascularization in Diabetes) trial, the mortality and safety composite were similar between the 2 treatments, whereas revascularization was significantly higher in the DES arm, which were consistent with our subgroup analysis (6,12,25). A recent meta-analysis suggests that CABG is associated with lower mortality than PCI for patients age 65 years or older (24). Other registry studies also revealed that CABG showed survival benefit in elderly patients compared with PCI with DES or BMS, which were contrary to our findings (8,26). In real-world clinical practice, it is likely that elderly patients with significant comorbidities tend to be more often referred for PCI because of its less invasive nature; thus, it might represent the residual effects of selection bias and otherwise unmeasured confounding, contributing to the discordant results in elderly patients among several studies. However, in our study, sicker patients with higher comorbidities were referred more to CABG than to DES. In addition, owing to the nature of subgroup analysis and the limited number of patients in each subgroup, these results of subgroup analyses must be interpreted with caution and must be confirmed with thorough, large clinical trials specifically targeting high-risk populations.

Table 4 Hazard Ratios for Clinical Outcomes After DES as Compared With After CABG, According to Clinical Scoring (EuroSCORE) and Anatomic Scoring (SYNTAX Score) Systems*

Outcome	No. of Patients/ Total No. of Events		Unadjusted		Multivariable Adjusted†	
	DES	CABG	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
EuroSCORE (n = 3,042)						
Low risk (0 to 2)	666	485				
Death	34	26	1.00 (0.60–1.67)	0.99	1.04 (0.57–1.89)	0.89
Composite outcome (death, MI, or stroke)	50	37	1.04 (0.68–1.60)	0.85	1.14 (0.69–1.88)	0.62
Repeat revascularization	119	41	2.49 (1.74–3.56)	<0.001	2.24 (1.49–3.38)	<0.001
Intermediate risk (3 to 6)	710	800				
Death	54	93	0.69 (0.49–0.96)	0.03	0.74 (0.49–1.10)	0.14
Composite outcome (death, MI, or stroke)	70	123	0.66 (0.49–0.88)	0.005	0.73 (0.51–1.04)	0.10
Repeat revascularization	121	39	4.15 (2.88–5.98)	<0.001	4.03 (2.62–6.20)	<0.001
High risk (>6)	171	210				
Death	41	56	0.96 (0.64–1.44)	0.84	1.33 (0.76–2.35)	0.32
Composite outcome (death, MI, or stroke)	45	66	0.85 (0.58–1.24)	0.39	1.19 (0.71–1.98)	0.51
Repeat revascularization	19	7	3.55 (1.49–8.45)	0.004	3.04 (0.91–10.19)	0.07
SYNTAX score (n = 1,915)						
Low risk (≤22)	1,068	129				
Death	74	11	0.84 (0.45–1.59)	0.60	1.14 (0.54–2.39)	0.74
Composite outcome (death, MI, or stroke)	106	12	1.12 (0.62–2.03)	0.71	1.25 (0.67–2.28)	0.47
Repeat revascularization	182	8	2.98 (1.47–6.04)	0.003	2.77 (1.31–5.85)	0.008
Intermediate risk (23 to 32)	274	185				
Death	29	32	0.62 (0.37–1.02)	0.06	0.78 (0.40–1.51)	0.46
Composite outcome (death, MI, or stroke)	33	42	0.52 (0.33–0.82)	0.005	0.74 (0.41–1.33)	0.31
Repeat revascularization	42	12	2.46 (1.29–4.68)	0.006	3.08 (1.44–6.58)	0.004
High risk (≥33)	58	201				
Death	8	23	1.23 (0.50–2.75)	0.61	1.76 (0.55–5.69)	0.34
Composite outcome (death, MI, or stroke)	10	27	1.30 (0.63–2.68)	0.48	1.64 (0.57–4.75)	0.36
Repeat revascularization	9	9	4.11 (1.62–10.40)	0.003	3.18 (0.94–10.78)	0.06

*Hazard ratios are for the DES group relative to the CABG group. †Hazard ratios are adjusted for age; sex; diabetes; presence or absence of congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular or carotid disease, peripheral arterial disease, and renal failure; history or no history of MI before procedure; ejection fraction; 2- or 3-vessel disease, presence or absence of involvement of the proximal LAD artery or left main artery, and total obstruction.

EuroSCORE = European System for Cardiac Operative Risk Evaluation; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; other abbreviations as in Tables 1 and 2.

Clinical registry studies have reported that patients with the least extensive CAD have better survival after PCI, whereas patients with the most extensive disease have better survival after CABG (27,28). Similarly, we found that PCI with DES had survival benefits over CABG in patients with 2-vessel disease. Therefore, some subsets of patients will do well or even better with DES, whereas other subsets will do better with CABG, with the extent of CAD being the strongest clinical factor affecting the choice between CABG and PCI, even in the DES era. The SYNTAX trial also suggested that PCI seemed to be even safer than CABG in more simple anatomic situations (i.e., low SYNTAX score), whereas the event rate was significantly lower in the CABG group among patients with high scores (10). In our study, the adjusted-risks for death and serious composite outcomes nonsignificantly favor CABG in patients with high SYNTAX score.

Long-term surveillance for stent thrombosis is particularly important, given the high average number of stent and long stent length after multivessel PCI with DES. In the current study, we noted a 5-year definite or probable stent thrombosis incidence of 2.6%, similar or even lower than rates reported in several observational studies (29,30). In addition, since second-generation DES show superior safety and efficacy to first-generation DES (31,32), the relative long-term benefits of new-generation DES compared to CABG should be reassessed soon for optimal multivessel revascularization.

Study limitations. The present study had the limitations inherent to a nonrandomized, single-center registry study. Despite appropriate statistical adjustments, unknown confounders may have affected the results. Second, for interpretation of several clinical and anatomic subgroup analyses, these exploratory results are to be considered hypothetical and hypotheses-generating only, and should not necessarily dictate any change in current practice patterns. Also, some of the multivariable models might be overfitted based on small numbers of end point events. Finally, the direct application of our findings to real-life practice predominantly using second-generation DES may be limited.

Conclusions

With optimal clinical judgment of the treating physician for appropriately selecting patients with multivessel CAD for

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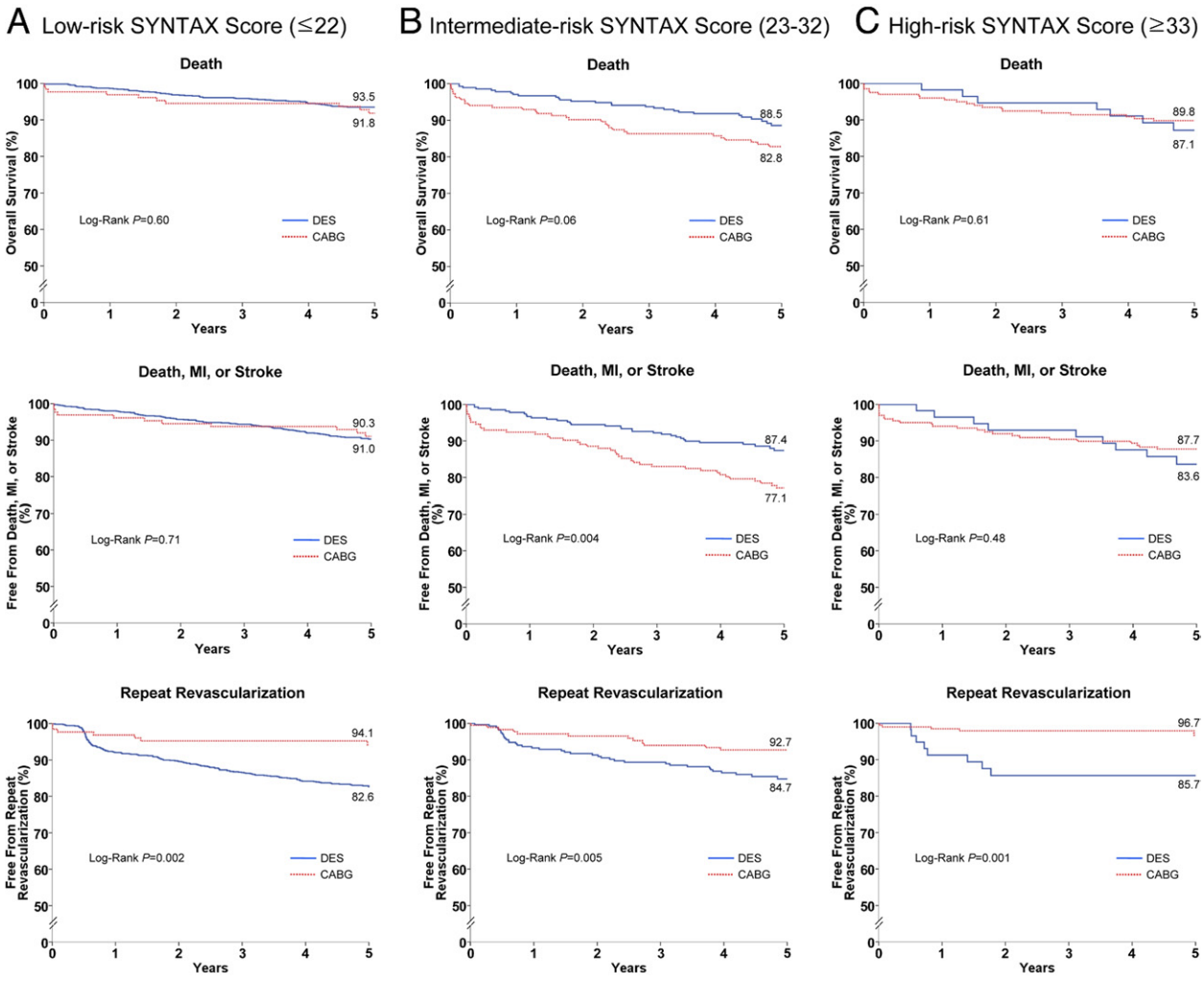

Figure 3 Kaplan-Meier Curves of 5-Year Outcomes Among Study Patients According to Treatment Group and SYNTAX Score Category

(A) Outcomes for patients with low SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) scores (≤22). **(B)** Outcomes for patients with intermediate SYNTAX scores (23 to 32). **(C)** Outcomes for patients with high SYNTAX scores (≥33). CABG **(red line)**; DES **(blue line)**. Abbreviations as in Figure 1.

PCI or bypass surgery, DES implantation is associated with similar long-term (5-year) rates of death and the composite end point of death, MI, or stroke, as compared with CABG. Rates of repeat revascularization were significantly higher among patients receiving DES. A large randomized comparison with longer-term follow-up of 5 or 10 years will provide more confidence in the long-term safety, durability, and efficacy of PCI with DES in reference to CABG.

Reprint requests and correspondence: Dr. Seung-Jung Park, Division of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea. E-mail: sjpark@amc.seoul.kr.

REFERENCES

1. Barner HB. Operative treatment of coronary atherosclerosis. Ann Thorac Surg 2008;85:1473–82.
2. Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. N Engl J Med 2006;354:483–95.
3. Frutkin AD, Lindsey JB, Mehta SK, et al. Drug-eluting stents and the use of percutaneous coronary intervention among patients with class I indications for coronary artery bypass surgery undergoing index revascularization: analysis from the NCDR (National Cardiovascular Data Registry). J Am Coll Cardiol Intv 2009;2:614–21.
4. Javaid A, Steinberg DH, Buch AN, et al. Outcomes of coronary artery bypass grafting versus percutaneous coronary intervention with drug-eluting stents for patients with multivessel coronary artery disease. Circulation 2007;116:I200–6.
5. 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.
6. Daemen J, Kuck KH, Macaya C, et al. Multivessel coronary revascularization in patients with and without diabetes mellitus: 3-year follow-up of the ARTS-II (Arterial Revascularization Therapies Study-Part II) trial. J Am Coll Cardiol 2008;52:1957–67.
7. Yang JH, Gwon HC, Cho SJ, et al. Comparison of coronary artery bypass grafting with drug-eluting stent implantation for the treatment of multivessel coronary artery disease. Ann Thorac Surg 2008;85:65–70.

8. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med 2008;358:331–41.
9. Li Y, Zheng Z, Xu B, et al. Comparison of drug-eluting stents and coronary artery bypass surgery for the treatment of multivessel coronary disease: three-year follow-up results from a single institution. Circulation 2009;119:2040–50.
10. 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.
11. Benedetto U, Melina G, Angeloni E, et al. Coronary artery bypass grafting versus drug-eluting stents in multivessel coronary disease. A meta-analysis on 24,268 patients. Eur J Cardiothorac Surg 2009;36: 611–5.
12. Kapur A, Hall RJ, Malik IS, et al. 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; 55:432–40.
13. 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;105:1540–4.
14. Daemen J, Wenaweser P, Tsuchida K, et al. 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;369:667–78.
15. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009–19.
16. 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.
17. 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;115:2352–7.
18. Cox D. Regression models and life tables J R Stat Soc B 1972;34: 187–220.
19. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550–60.
20. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European System for Cardiac Operative Risk Evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.
21. Kim YH, Park DW, Kim WJ, et al. Validation of SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score for prediction of outcomes after unprotected left main coronary revascularization. J Am Coll Cardiol Intv 2010;3:612–23.
22. Kappetein AP. Optimal revascularization strategy in patients with three-vessel disease and/or left main disease: 2 year outcomes of the SYNTAX trial. Paper presented at: ESC Congress; September 2, 2009; Barcelona, Spain.
23. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007;147: 7037–16.
24. Hlatky MA, Boothroyd DB, Bravata DM, et al. 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;373:1190–7.
25. Banning AP, Westaby S, Morice MC, et al. 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;55:1067–75.
26. Kimura T, Morimoto T, Furukawa Y, et al. Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. Circulation 2008;118 Suppl:199–209.
27. Malenka DJ, Leavitt BJ, Hearne MJ, et al. Comparing long-term survival of patients with multivessel coronary disease after CABG or PCI: analysis of BARI-like patients in northern New England. Circulation 2005;112:I371–6.
28. Smith PK, Califf RM, Tuttle RH, et al. Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. Ann Thorac Surg 2006;82:1420–8, discussion 1428–9.
29. Costa JR Jr., Sousa A, Moreira AC, et al. Incidence and predictors of very late (≥4 years) major cardiac adverse events in the DESIRE (Drug-Eluting Stents in the Real World)-Late Registry. J Am Coll Cardiol Intv 2010;3:12–8.
30. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol 2008;52:1134–40.
31. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201–9.
32. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–74.

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